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FREE RADICAL CYCLISATIONS

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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by

TONY LAWRENCE, B.Sc. (Hons.)

Department of Organic Chemistry

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CONTENTS

SUMMARY

The following free radicals were generated in solution by the reaction of tri-n-butyltin hydride with the corresponding bromocompounds:

Hex-5-en-1-yl, 2-Methylhex-5-en-1-yl, 3-Methylhex-5-en-1-yl, 4-Methylhex-5-en-1-yl, 2,2-Dimethylhex-5-en-1-yl, 3-3-Dimethylhex-5-en-1-yl, 2,2,5-Trimethylhex-5-en-1-yl, 2,2-Dimethylpent-4-en-1-yl, 3,3-Dimethylpent-4-en-1-yl, 1-Methylhept-6-en-1-yl, Hex-5-yn-1-yl, Hept-6-yn-1-yl, Oct-7-yn-1-yl, and 5,6-Epoxyhexan-1-yl.

Under carefully controlled conditions each bromide was reduced with tri-n-butyltin hydride in benzene, and the relative yields of cyclic and acyclic hydrocarbon products were determined by gas liquid chromatographic analysis.

The rates of intramolecular cyclisation of each radical relative to its rate of hydrogen atom abstraction from tri-n-butyltin hydride were determined over a range of temperatures and reagent concentrations.

Energies of activation were calculated.

Structures of the cyclic transition states were studied by analysing the *cis* and *trans* isomer distributions of 1,2-dimethyl- and 1,3-dimethylcycloalkanes, which were formed by intramolecular additions of monomethylalkenyl radicals.

Where it appeared possible, attempts were made to relate these studies to earlier work in free radical cyclisation. The existing explanations for the selective *exo*-cyclisation of the hex-5-en-1-yl radical were evaluated in the light of present observations.

Summary of the results:

(1) To the extent that they do cyclise the above radicals undergo selective and irreversible *exo*-cyclisation, with the sole exception of the 2,2,5-trimethylhex-5-en-1-yl radical which undergoes both *exo*- and *endo*-cyclisations at comparable rates.

(2) Methylsubstitution at C2, or C3, or C4 increases the rate of intramolecular cyclisation of the hex-5-en-1-yl radical in direct relationship to the extent of the methyl induced gauche interactions. Lowered enthalpy of activation is observed with these rate enhancements without significant changes in the entropy of activation.

(3) Intramolecular cyclisation of the 2,2,5-trimethylhex-5-en-1-yl radical contradicts the hypothesis that selective 1,5-cyclisation of the hex-5-en-1-yl radical is caused by through space interactions of hydrogens at C2 and C6, which bar the formation of the transition state for 1,6-cyclisation.

(4) Monomethyl substitution of the hex-5-en-1-yl radical at either C2, or C3, or C4 exerts control in the selective formation of *cis* or *trans* stereoisomers of dimethylcyclopentane. This is consistent with a chair-like cyclic conformation of the transition state in which the methyl group is predominantly in an equatorial orientation.

(5) The following free radicals do not undergo intramolecular cyclisation: 2,2-Dimethylpent-4-en-1-yl, 3,3-Dimethylpent-4-en-1-yl, and 5,6-Epoxyhexan-1-yl.

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.

TONY LAWRENCE.

ACKNOWLEDGEMENTS

At its best the work presented in this thesis is but a small addition to the results of research in free radical cyclisations, which were available to me during my studies. Of particular relevance were the reports in free radical cyclisations by K.U. Ingold, C. Walling, M. Julia, and A.L.J. Beckwith. I have endeavoured to do my work as well as they did theirs.

This project was supervised by Professor A.L.J. Beckwith, and by Dr. G.E. Gream during the absence of Professor Beckwith in 1979.

The whole manuscript was proof-read by Dr. R.H. Prager.

Throughout its duration this work was supported by a Commonwealth Postgraduate Scholarship.

INTRODUCTION

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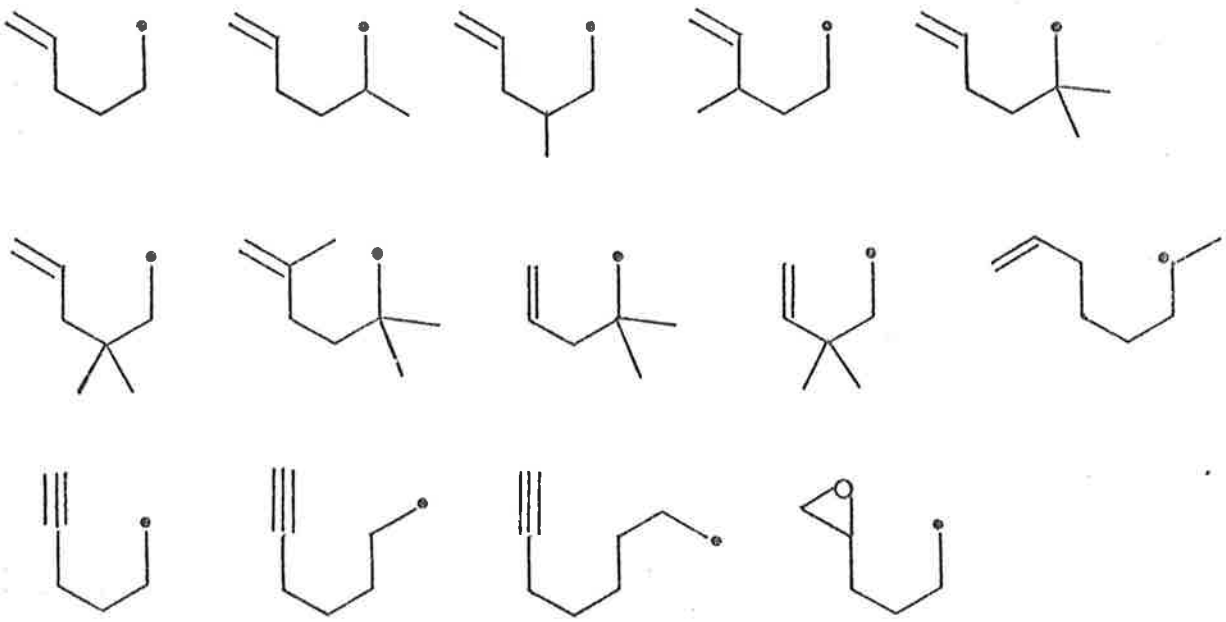
Background chemistry

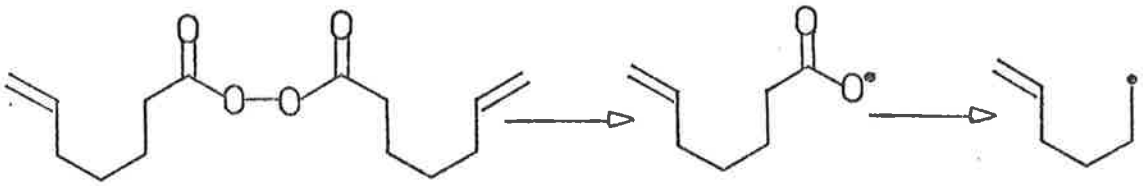
This is a study of carbon radicals. In all cases the unpaired electron is wholly centred on one carbon.* There is no delocalisation of the unpaired electron onto neighbouring groups by conjugation. There is no heteroatom within the molecule which could change the free spin density on the radical carbon. With but one exception all are primary carbon radicals, one being a secondary carbon radical. The following radicals were investigated in the course of this work.



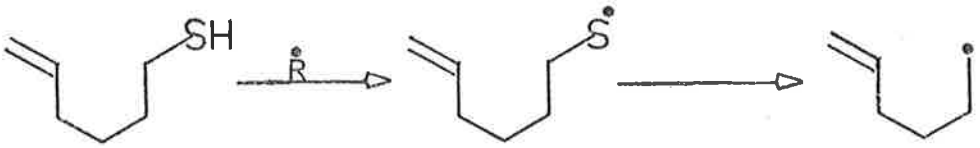
* To the extent that it does exist, electron delocalisation by hyperconjugation is unlikely to have significant influence upon the results of this work.

There are many ways to generate such free spin bearing reactive intermediates in solution. Some of the methods used to generate hex-5-en-1-yl radical - the first one listed above - involved the following reactions:

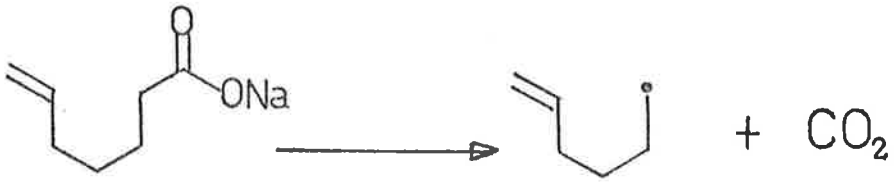
(1) Thermolysis of di-6-heptenoyl peroxide[1].



(2) Reduction of 6-mercapto-1-hexene with triethylphosphite[2].



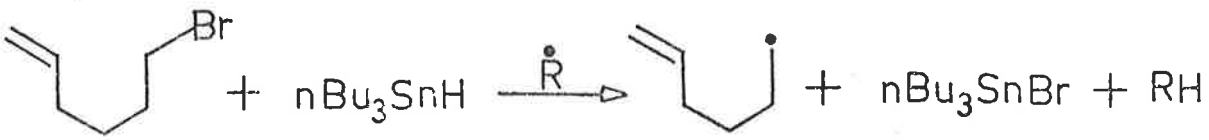
(3) Kolbe's electrolysis of 6-heptenoic acid[3].



(4) Reaction of 6-bromohex-1-ene with sodium naphthalene[4].

(5) Reaction of di-6-heptenoyl peroxide with copper acetate[5].

(6) Reduction of 6-chloro or 6-bromohex-1-ene with tri-n-butyltin hydride[6,31].



(7) Reaction of hex-5-enyl-1-mercuric bromide with sodium borohydride - reductive demercuration[7].

(8) Reduction of hex-5-enyl-1-mercuric bromide with tri-n-butyltin hydride[8].

Reduction of alkyl halides with tri-n-butyltin hydride is a simple and efficient method for generating free radicals in solution. It is the method of choice, and the only method employed for generating free radicals in this work. Some twenty years ago it was known that organotin hydrides react with alkyl halides[9,10] by replacing the alkyl halogen with the tin hydrogen, thus producing organotin halides and hydrocarbons. In 1962-64 Kuivila and co-workers undertook mechanistic studies in the reduction of alkyl halides by tri-n-butyltin hydride[11-13]. Their investigations led them to the conclusion that the reduction of alkyl halides by tin hydride involves free radical reactive intermediates. On the basis of their observations they proposed the following free radical chain mechanism[13].

Initiation Initiator + R-X ⟶ R·

Propagation R· + Bu_3SnH ⟶ RH + Bu_3Sn·

Bu_3Sn· + R-X ⟶ R· + Bu_3SnX

Termination R· + R· ⟶ R-R

R· + Bu_3Sn· ⟶ Bu_3Sn-R

Bu_3Sn· + Bu_3Sn· ⟶ Bu_3Sn-SnBu_3

Inactive products

Non-stabilized radicals of the hex-5-en-1-yl type are highly reactive. Their free spin bearing carbons are not sterically crowded, and such radicals will undergo coupling reactions at diffusion controlled rates. In a steady state process, where the concentration of free radicals is low and does not change with the reaction time, the extent of coupling reactions is likewise very low. Once generated a free radical in solution may undergo one or more of the following reactions:

(1) Disproportionation

(2) Intermolecular hydrogen atom abstraction

(3) Intramolecular hydrogen atom abstraction

(4) Intramolecular rearrangement

When a radical in solution undergoes two or more irreversible intermolecular reactions with reactants of identical concentrations the relative yield of each product is dependent only on the rate constant of its formation. Likewise the relative amounts of products from two or more irreversible intramolecular reactions of the same reactive intermediate are directly related to their respective rate constants.

Reduction of bromoalkenes with tri-n-butyltin hydride is a steady state process - the concentration of the free radical reactive intermediates is constant throughout the reaction. Here the extent of intramolecular rearrangements depend only on time and the reaction rate constants. High concentrations

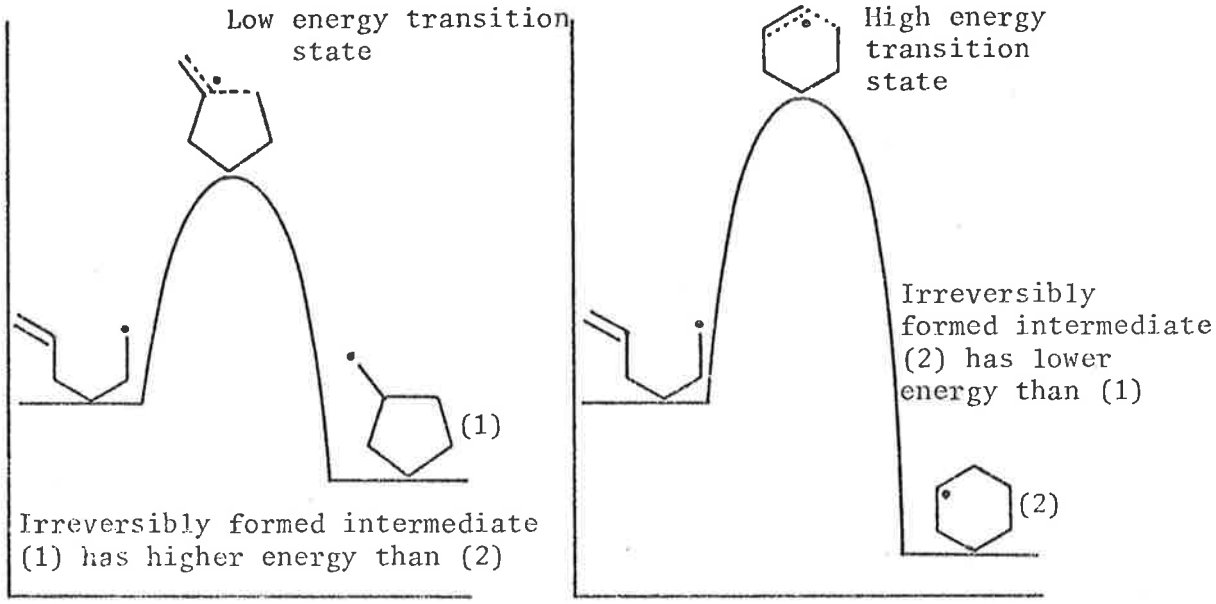
of reactants lead to an increased number of intramolecular collisions per unit time, and to relatively higher yields of products from irreversible intermolecular reactions. Low concentrations of reactants lead to high yields of products from intramolecular reactions.

These are elementary facts of chemical kinetics, but it is not amiss to mention them at the outset, because much of the work reported here involved manipulation of reactant concentrations in order to control the relative yields of products from the competing intermolecular and intramolecular reactions.

Free radical reactions are remarkably simple. It is in general true that a free radical reaction follows the most exothermic course. Thus the direction of a free radical reaction is predictable on the basis of free energy considerations - thermodynamically most stable products are formed. Another generalisation about free radicals describes the order of stability of alkyl radicals. That is, a primary radical is less stable than a secondary radical, which is less stable than a tertiary radical. These empirical generalisations are the first principles of free radical chemistry.

The notion of thermodynamic control is reasonably clear if one thinks in terms of the energies of the bonds broken and the bonds formed. When two or more products are possible then thermodynamic control depends on the reversibility of the reaction steps which lead to non-thermodynamic products. Irreversible reactions are under kinetic control and the proportion of each final product reflects its rate of formation. If a free radical (diagram page 7) can undergo either *exo* or *endo*-cyclisation and the competing reactions are under kinetic control, then the relative amount of each final product will be directly related to the rate constant of its irreversibly formed cyclic intermediate.

Implicit in the universal statement about exothermicity of free radical reactions are the assumptions that either all free radical reactions are reversible or that the irreversible step is the last one in the reaction sequence. Only then would always the final product be of the lowest free energy.



However stability of free radicals is an illdefined property. For example, the general conclusion inferred from the work of Hart and Wyman[14], in which they showed that under similar conditions cyclohexyl formyl peroxide decomposes 34 times as fast as cyclopentylacetyl peroxide, was that the cyclohexyl radical is more stable than the cyclopentylmethyl radical. It may well be asked whether the statement "Cyclohexyl radical is more stable than cyclopentylmethyl radical" is synonymous with the statement "cyclohexylformyl peroxide decomposes faster than cyclopentyl-acetyl peroxide"? To what extent have tautologies been confused for facts? The amount of conceptual and language confusion was recognised by Ingold[15] who went on to classify carbon centred radicals as being "stabilised", or "persistent", and defined physical parameters for

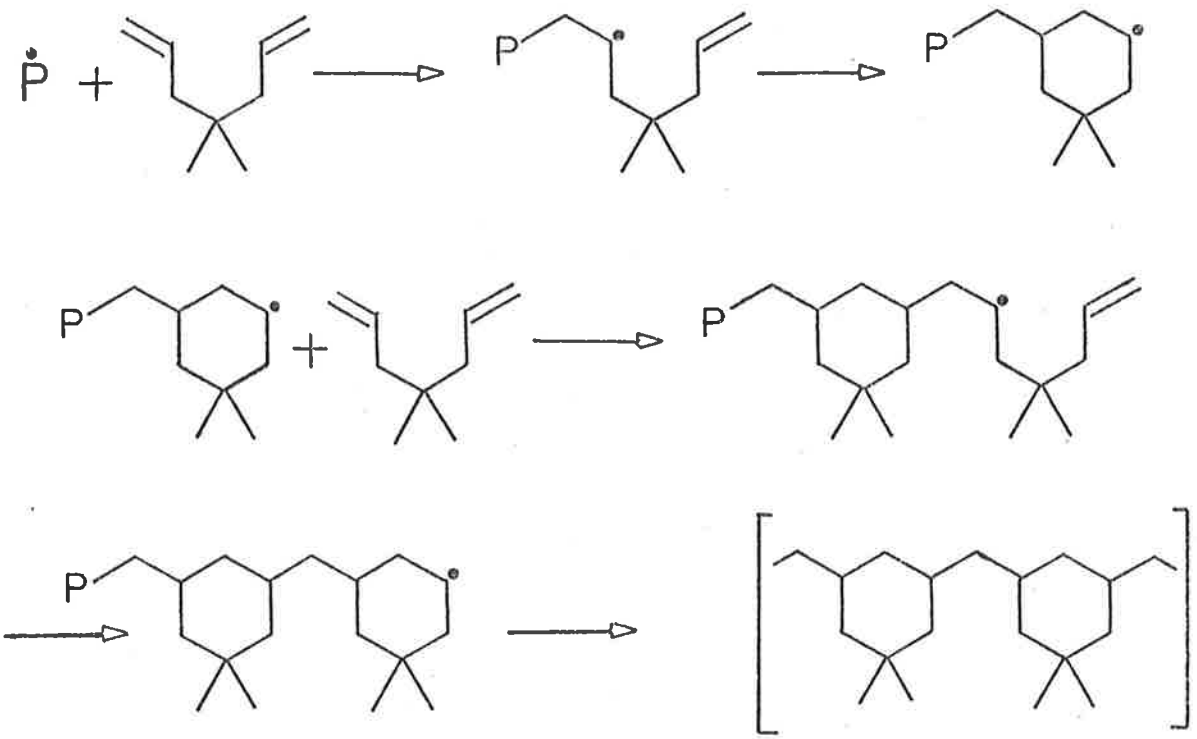
measuring the relative magnitudes of these properties. Ruchardt[16] attempted to correlate the structure of free radicals with their reactivity and thus re-evaluate the traditional concept about the stability of carbon centred radicals.

However vague, empirical generalisations about free radical chemistry have been used extensively, and, because of their predictive power, will continue to be applied in the future. About 22 years ago workers involved in free radical cyclopolymerisation postulated that the structure of soluble polymers from diallyl quaternary ammonium salts consisted of recurring 6-membered piperidine units[17,18]. Likewise free radical reactions of 1,6-heptadienes were reported to give products corresponding to intramolecular 1,6-cyclisations[19]. Assignment of cyclohexane ring structures to products from intramolecular cyclisations of hex-5-en-1-yl radicals were reported by other workers[20-22], who also based their conclusions on inferences from widely accepted generalisations. Workers on early cyclopolymerisation relied on inferences from empirical generalisations which in the main went as follows:

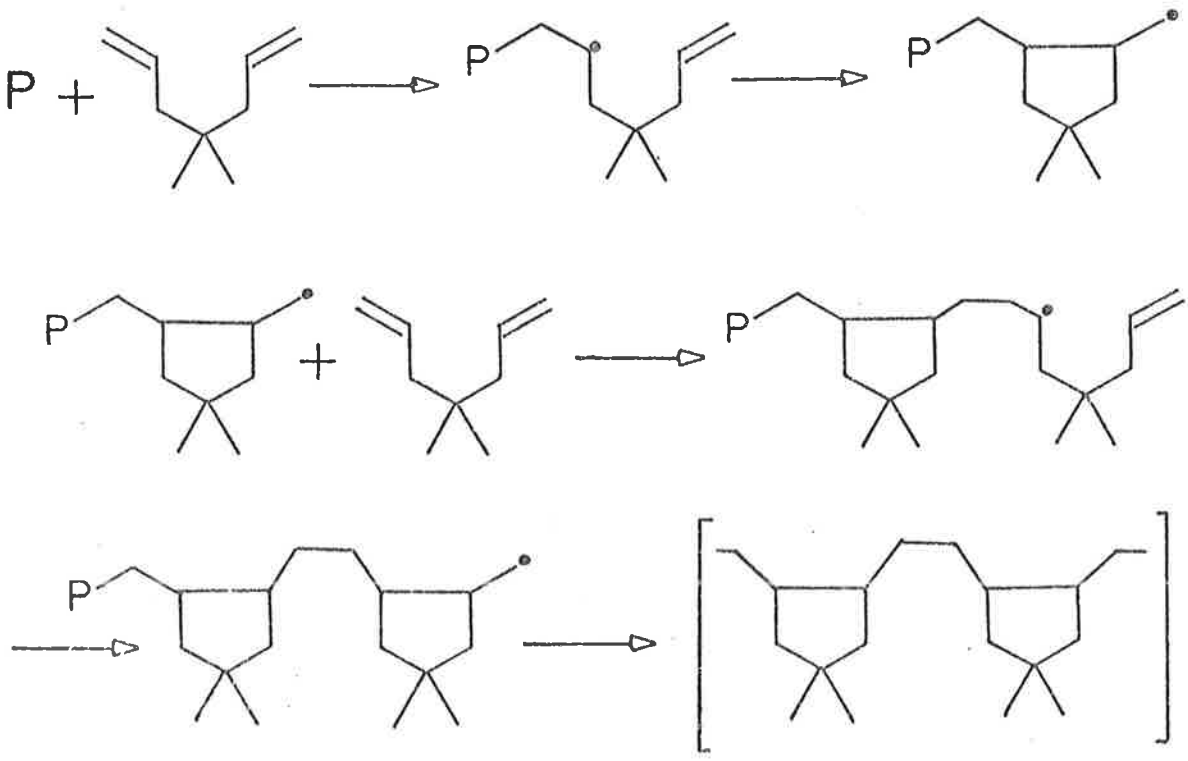
(1) A primary carbon centred radical is less stable than the isomeric secondary radical. Therefore reactions which generate secondary radicals must occur in preference to those generating primary radicals.

(2) Six-membered rings are of lower energy than five-membered rings. Therefore the former would form to the exclusion of the latter.

The following reaction mechanisms and product structures were postulated to occur on the basis of the above generalisations[17,18].



The following reaction mechanisms and product structures were excluded on the basis of the above generalisations[17,18].

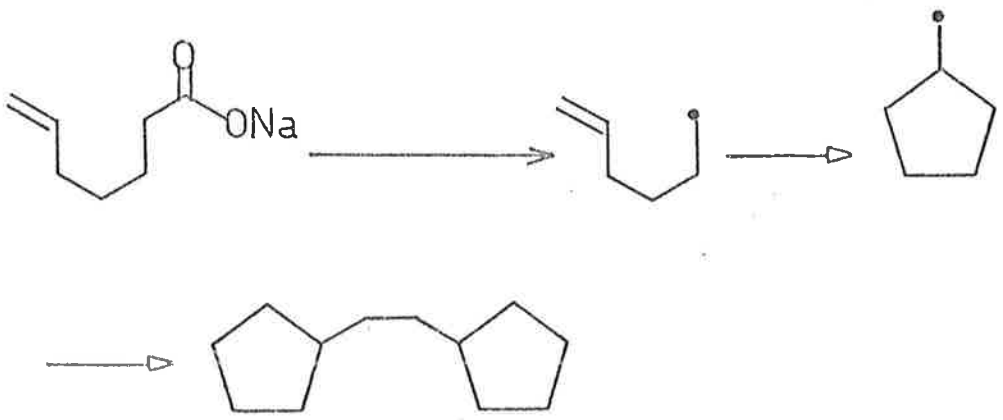


They were mistaken. Predictions based on well established generalisations did not hold.

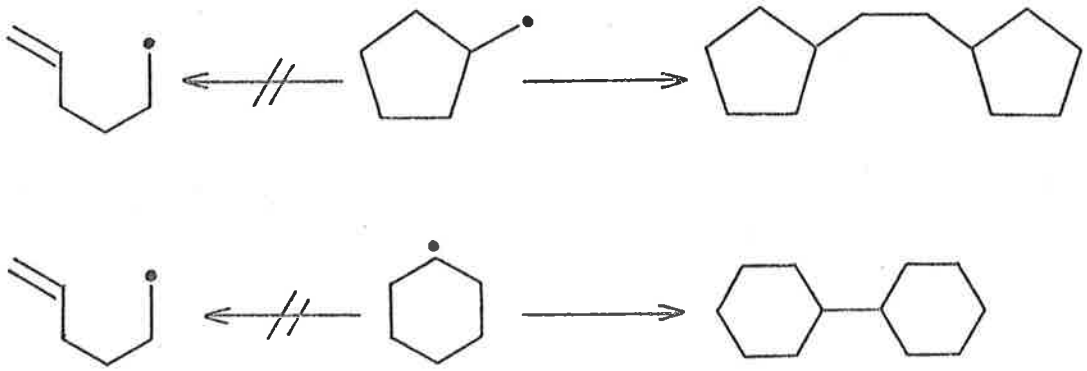
In 1963 it was noted that the hex-5-en-1-yl radical, which was generated by thermolysis of di-6-heptenoyl peroxide[1], underwent 1,5-intramolecular cyclisation. The researchers must have been puzzled by this observation when they wrote "It is difficult to justify the large yield of methylcyclopentane in the decomposition of 6-heptenoyl peroxide."

Then in 1964 Brace[23] showed that free radical chain reaction of 1,6-heptadiene with 1-iodoperfluoropropane resulted in the cyclisation of perfluoroalkylheptenyl radical exclusively to a methylcyclopentane structure. At the beginning of his report Brace wrote: "Surprisingly, cyclisation gave a five-membered ring rather that the anticipated cyclohexane derivatives." The paper ended with a line: "An investigation into this unusual cyclisation is underway."

In 1965 Garwood[3] and coworkers published their findings in the Kolbe's electrolysis of 6-heptenoic acid. In their report are summarised the essential features of the hex-5-en-1-yl radical in solution. From product analysis they concluded that the hex-5-en-1-yl radical underwent intramolecular 1,5-cyclisation.



The cyclisation was not reversible since cyclopentylacetic acid and cyclchexane carboxylic acid underwent Kolbe coupling without detectable ring opening.



By 1968, when Carlson and Ingold[24] published their work on the kinetics and rate constants for the reduction of alkyl halides by organotin hydrides, the behaviour of hex-5-en-1-yl radical in solution was well established[25]. Using a rotating sector method Carlson and Ingold[24] confirmed the validity of the free radical chain mechanism, which was postulated earlier by Kuivila[13]. Kinetic and mechanistic conclusions, particularly relevant to the study of hex-5-en-1-yl radical, which emerged from their research, are summarised below:

(1) The rates of reduction of alkyl halides by tri-n-butyltin hydride show first order dependence on the concentration of either the alkyl halide, or the tri-n-butyltin hydride.

(2) The reactions proceed normally throughout their course until one of the reactants is consumed.

(3) For the reduction of alkyl bromides the rate controlling step is the hydrogen atom abstraction from tri-n-butyltin hydride. Chain termination occurs by coupling of alkyl radicals.

(4) For the reduction of alkyl chlorides the rate controlling step is the chlorine atom abstraction from the alkyl chloride. Chain termination occurs by the coupling of two tri-n-butyltin radicals.

(5) The rates of hydrogen atom abstraction from tri-n-butyltin hydride by alkyl radicals show little variation with the extent of alkyl substitution at the free radical centre (Table 1).

Table 1 Absolute rate constants (k_H) for hydrogen atom abstraction by alkyl radicals from nBu_3SnH at 25°.[24]

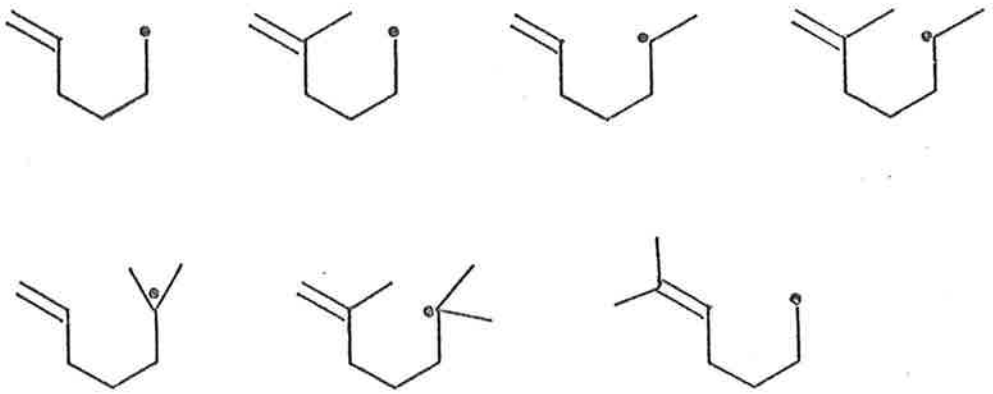
Radical	k_H $M^{-1}sec^{-1}$
t-Butyl, $(CH_3)_3C^{\bullet}$	$.74 \times 10^6$
cyclohexyl, $(CH_2)_5\dot{C}H$	1.2×10^6
hexyl, $CH_3(CH_2)_4\dot{C}H_2$	1.0×10^6

Having determined the rate constant (k_H) for hydrogen atom abstraction in the reaction of tri-n-butyltin hydride and n-hexyl radicals, and having established that n-hexyl radicals are equally reactive towards tri-n-butyltin hydride, Carlsson and Ingold combined the findings of Walling[6] with their own and determined the absolute value of the rate constant (k_c) for 1,5-intramolecular cyclisation of the hex-5-en-1-yl radical. Prior to their work Walling[6] *et al* had reduced 6-bromohex-1-ene with known concentrations of tri-n-butyltin hydride and determined the ratios of the acyclic to cyclic products — hex-1-ene to methylcyclopentane. Carlsson and Ingold found that at 25° $k_c = 1 \times 10^5$ sec^{-1}.

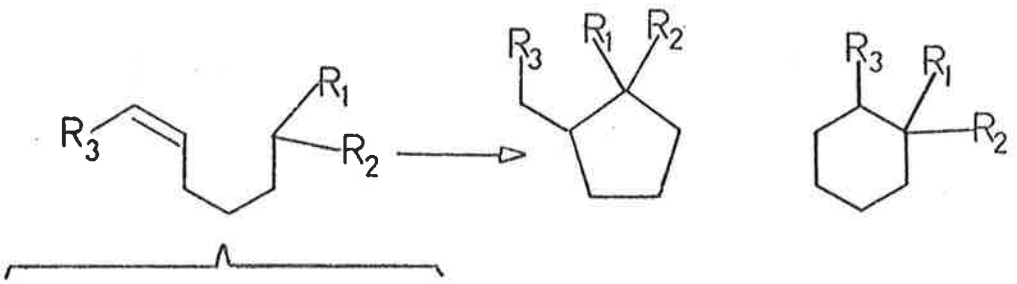
The work of Carlsson and Ingold had made it possible to study the rates of intramolecular additions of hexenyl radicals relative to their rates of hydrogen atom abstractions. A further important contribution to the research of hex-5-en-1-yl radicals in solution came from Kochi and Krusic in 1969[26], and was expanded on by Sheldon and Kochi in 1970[27]. They developed a method for producing specific alkyl radicals in solution in the cavity of the electron spin resonance (e.s.r.) spectrometer by photolysis of diacyl peroxides at low temperatures. This enabled them to observe intense spectra of a variety of alkyl radicals. Photolysis of 6-heptenoyl peroxide at -75° gave a well defined e.s.r. spectrum of the 5-hexenyl radical. When the temperature was raised to -35° the e.s.r. spectrum of only cyclopentylmethyl radical was observed. At -55° both 5-hexenyl and cyclopentylmethyl radicals were present. Photolysis of cyclopentylacetyl peroxide even at 0° showed no 5-hexenyl radical. It was earlier demonstrated that hex-5-en-1-yl radical undergoes 1,5-cyclisation irreversibly[3], but Kochi and Krusic had directly observed this one way rearrangement, and shown that cyclopentylmethyl radical exists as a discrete reactive intermediate.

In further conformational studies of alkyl radicals in solution by e.s.r. spectroscopy Edge and Kochi[28] observed pronounced line broadening in the e.s.r. spectrum of the hex-5-en-1-yl radical, which they associated with a coiled conformation in which the terminal unsaturated linkage lies over the radical centre. Such lower energy conformational alignment appeared consistent with 1,5-intramolecular cyclisation. However, as Kochi pointed out, the observed conformational orientation of the double bond and the free radical centred carbon is not essential for intramolecular cyclisation. Rearrangement of but-3-en-1-yl[29,30] radical goes through a cyclic state in which the conformation for cyclisation places the γ

carbon in an eclipsed position relative to the radical centre. By 1974 particularly prominent studies of hex-5-en-1-yl radicals were carried out by Walling[31], Julia[32-34], and Beckwith[25,35]. Walling, and Beckwith studied the kinetics of the simple unsubstituted hex-5-en-1-yl radical, and they also investigated the direction of ring closure of several alkyl substituted hex-5-en-1-yl radicals. The alkyl substituents were located at C1, C5, and C6 positions. Radicals which they investigated included the following:

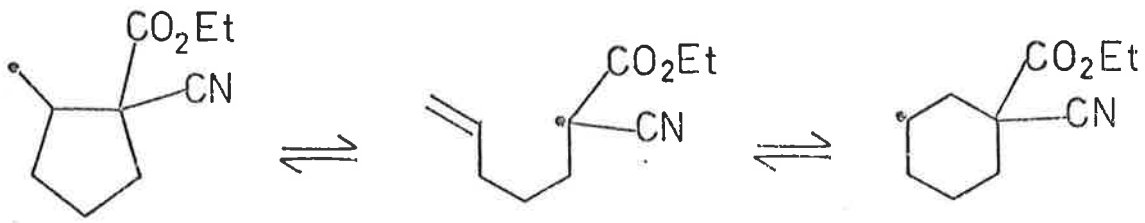


Both Walling, and Beckwith found the cyclisation of the above radicals to be under kinetic control - the intramolecular ring closure was irreversible. They also discovered that methyl substitution at C5 retarded the rate of 1,5-cyclisation, which in turn led to the relative increase in cyclohexane ring products. Julia's investigations[32] showed that the extent of 1,6-cyclisation of hex-5-en-1-yl radicals is a function of C1 substituent stabilisation of the acyclic radical. Relative yields of cyclised products from some of the investigated radicals are shown below[32-34].



R_1	R_2	R_3	%	%
H	H	H	100	0
CN	H	H	100	0
$COCH_3$	H	H	72	28
CO_2Et	H	H	56	44
CN	CO_2Et	H	16	84
CN	CO_2Et	CH_3	0	100

When cyclopentylcarbinyl radical, which carried suitable substituents for stabilizing its acyclic isomer, was generated the products observed were those corresponding to 1,6-cyclisation of hex-5-en-1-yl radical[32].



This demonstrated that when hex-5-en-1-yl radical is stabilised by appropriate substituents at C1 its intramolecular cyclisation is under thermodynamic control.

In order to explain the fast intramolecular 1,5-cyclisation of hex-5-en-1-yl radicals, which are not resonance stabilised, three main hypotheses were proposed:

(1) 1,5-Ring closure is entropy controlled. Entropy change favours the formation of the smaller ring - methylcyclopentane[36].

(2) 1,6-Ring closure is sterically hindered by through space interactions between the pseudo-axial hydrogen at C2 and the *trans*-hydrogen at C6. This explanation in terms of steric control was upheld by Julia[34].

(3) The hypothesis of Beckwith[25,38,39] states that intramolecular cyclisation of hex-5-en-1-yl radical is under stereoelectronic control. Stereoelectronic requirements of the transition state leading to 1,5-cyclisation involve lower strain energy than those of the transition state of 1,6-cyclisation. The lowest energy transition state involves maximum overlap of the "p" orbital bearing the unpaired electron and the vacant π^* orbital.

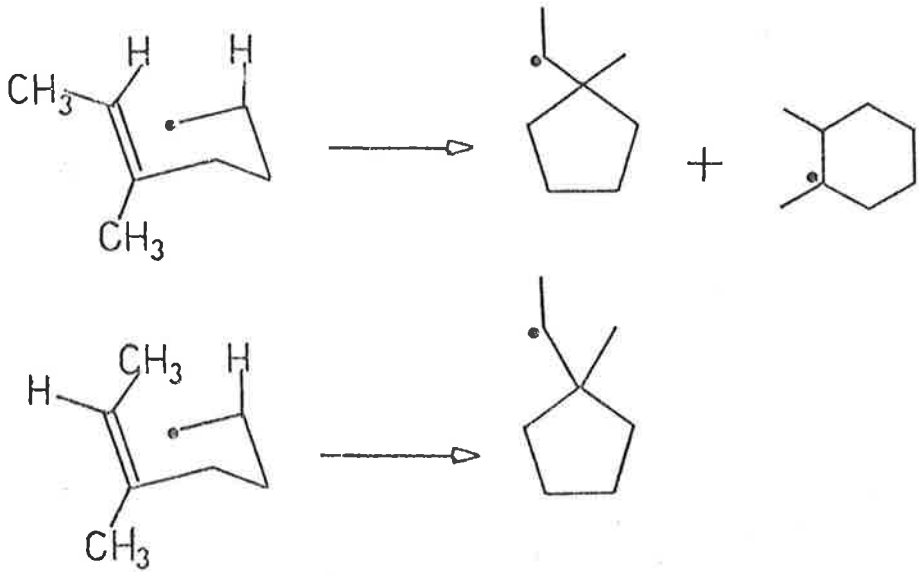
We shall examine these three hypotheses in some detail.

A recent work of Bischof[40] proposes to support the explanation that 1,5-cyclisation of the hex-5-en-1-yl radical is an entropy driven process. Close scrutiny of the calculated enthalpies and entropies of activation reveals that the entropy difference of 3 cal/mole/$^{\circ}$K between 1,5 and 1,6-cyclisation is too low to account for the observed difference of the corresponding rate constants. On the basis of calculated activation parameters[40] hept-6-en-1-yl radical is predicted to undergo 1,7-cyclisation, whereas 1,6-intramolecular addition is observed as the major cyclisation process[41]. Energies of activation parameters[41], which were calculated from experimental kinetic data for intramolecular cyclisation of hex-5-en-1-yl and hept-6-en-1-yl radicals, are not in agreement with those calculated from theoretical considerations using statistical thermodynamics[40,42] and the MINDO/3 - UHF methods[40,43].

Calculations based on experimental observations[41] show that although a small difference (3 cal/mole/°K) in the entropy of activation does favour the 1,5-cyclisation over 1,6-cyclisation, it is the difference in the enthalpy of activation (1.7 K cal/mol) which drives the 1,5-cyclisation process.

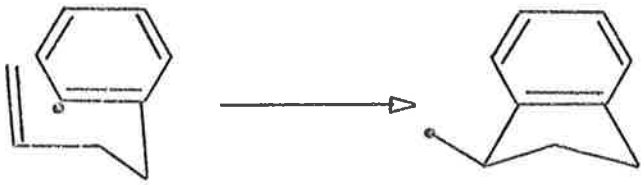
Because it is incompatible with experimental evidence, the hypothesis which ascribes the 1,5-intramolecular addition of hex-5-en-1-yl radical to the entropy of activation is unacceptable.

Julia's hypothesis of through space interactions between substituents at C2 and C6 rests in the main upon the evidence that the *cis*-5,6-dimethylhex-5-en-1-yl radical undergoes both 1,5- and 1,6-cyclisation; whereas the *trans*-5,6-dimethylhex-5-en-1-yl radical, in which 2,6-interactions are expected to be more pronounced, undergoes only 1,5-cyclisation[37].



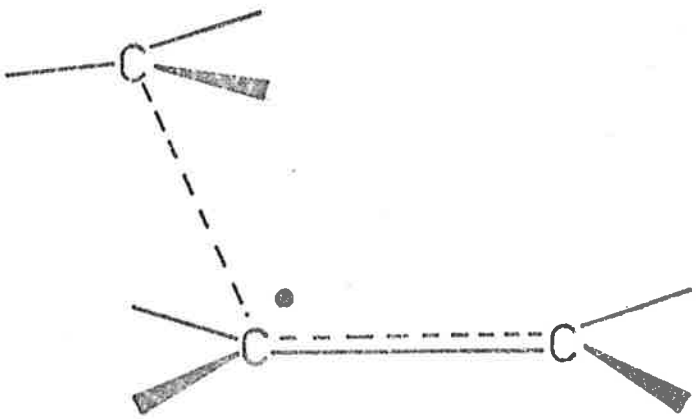
An obvious difficulty with Julia's hypothesis has been the total absence of quantitative evaluation of the magnitude of through space repulsions between C2 and C6 hydrogens in the transition state of the cyclising radical. After all such nonbonded interactions, to the extent

that they do exist, may have no causal influence on the intramolecular cyclisation of the hex-5-en-1-yl radical. Indeed, it has been shown that the alkenylaryl radical below, which has no substituents at C2, undergoes fast and exclusive 1,5-cyclisation[39,44]. A good feature of



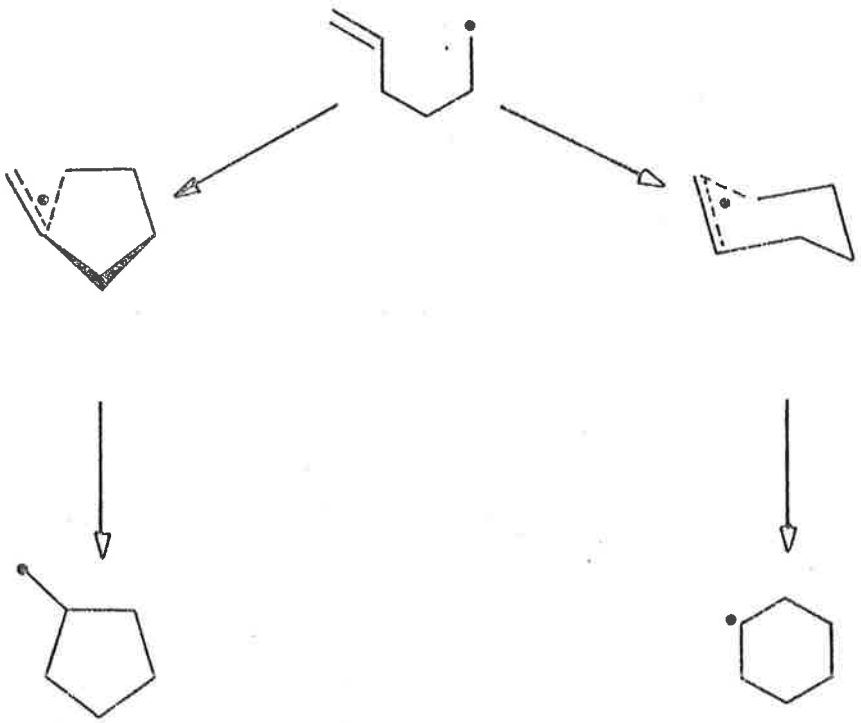
Julia's hypothesis is that it renders itself to experimental verification. Thus if hydrogens at C2 were replaced by methyl groups, and the rate of 1,6-cyclisation did not decrease, Julia's explanation would be false.

In its geometry the mechanism of stereoelectronic control, as proposed by Beckwith[25,35], is analogous to the model of the transition complex for addition of the methyl radical to ethylene[45,46].



Three carbons are involved in this model. They are situated at the vertices of an obtuse triangle. The plane of the triangle is orthogonal to the σ framework of the olefin. Formation of the transition complex involves an overlap of the semi-occupied 2p orbital with the unoccupied π^* orbital. It appears reasonable to assume that the transition state for intramolecular addition of a carbon centred free radical to a double bond would resemble that of intermolecular addition.

Since intramolecular reactions are subject to steric restraints, there must be a conformational orientation of lowest energy from which a particular intramolecular reaction can take place. Examination of models[35] indicated that the conformational geometry which is compatible with stereoelectronic requirements leads to 1,5-intramolecular cyclisation of the hex-5-en-1-yl radical. Such a conformation involves less structural strain than the alternative one leading to 1,6-cyclisation.



Although it is not readily evident from model examination that the cyclopentane-like conformation of the hex-5-en-1-yl radical is less strained than the cyclic structure resembling cyclohexane, strain difference between the transition states of the cyclopentane and cyclohexane cyclic structures has been calculated[159]. Calculations of geometric probability factors have indicated that the transition state leading to 1,5-cyclisation is of lower energy than the corresponding transition state for 1,6-cyclisation[159]. However on pages 16-17 it was argued that calculations are no substitute for experimental evidence, and it was pointed out that the relative magnitudes of calculated energy parameters[40-43] for intramolecular cyclisations of hexenyl and heptenyl radicals were not in agreement with experimental kinetic data[41]. Unlike Julia's hypothesis of steric control, Beckwith's hypothesis of stereoelectronic control is difficult to test hence difficult to falsify by experimental evidence. In principle this is a defect in terms of scientific philosophy.

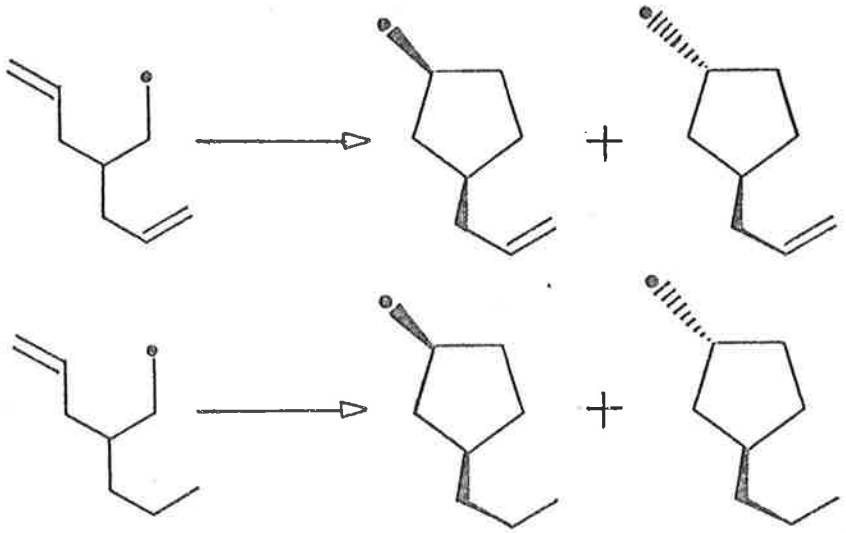
In their investigations of alkyl substituted hex-5-en-1-yl radicals Beckwith and Moad[47] observed that increase in the rate of intramolecular cyclisation was induced by mono-alkyl substitution at C3. When corrections were allowed for the statistical factor due to the two-fold concentration of identical double bonds within the molecule, 3-allyhex-5-en-1-yl radical cyclised about three times faster than its unsubstituted analogue. This rate enhancement was at first attributed[47] to through space interactions - homoconjugation-of the two double bonds. This explanation was consistent with earlier reports that double bonds in 1,6-heptadienes were more reactive in free radical reactions than isolated terminal double bonds[48,49]. Increased reactivity of 1,6-dienes in polymerisation[50,51], and the bathochromic shift in their U.V. spectra[52-54] gave further support for the hypothesis of through space interactions of the double bonds. Examination of models encouraged this line of reasoning - to quote: "An examination of Dreiding models of 1,6-heptadiene

indeed shows that a very favourable conformation exists for the across space homoconjugation, which leads to 5-membered ring closure and where a strong Π-Π interaction of the nodal planes of all p-orbitals is possible."[55]

Thus it appeared that homoconjugative interaction in the 3-allylhex-5-en-1-yl radical was the cause of its increased rate of cyclisation relative to the unsubstituted hex-5-en-1-yl radical[47]. This was thought to be brought about by stabilising conformations favourably disposed for intramolecular reaction, and by lowering the energy of the orbital involved in the formation of the new bond[47]. The hypothesis of homoconjugation, as an explanation of the reactivity of 3-allylhex-5-en-1-yl radical was well reasoned out. Its fault was that it was an argument from analogy. Even though all the premises (increased reactivity of 1,6-dienes, U.V. bathochromic shift, and conformational folding of Dreiding models) may have been true, the inference that homoconjugation was the cause of the rate increase of 1,5-cyclisation of the 3-allylhex-5-en-1-yl radical was invalid. It is an ever present risk with highly experimental sciences like chemistry to draw explanatory conclusions from analogy. In terms of formal logic all arguments from analogy are invalid irrespective of the truth or falsity of their conclusions. While most predictions concerning chemical reactions are made by analogy to earlier observations as a matter of practical necessity, such predictions are no more than convenient guides for conducting experimental research. Predictions about the outcome of experiments need not be, and mostly are not, based on theoretical considerations, because they tell what might happen, and not why or how it happens in terms of physical mechanisms. On the other hand explanations involve scientific descriptions of the physical causes

preceeding observed facts. Scientific explanations make predictions on the basis of theoretical considerations, not by analogy to recorded observations. The essence of the philosophy of science is that all scientific explanations must be experimentally refutable[56]. Until experimentally tested an explanation is hardly more than a convenient conjecture, which postulates the existence of a certain physical phenomenon. The homoconjugation explanation was a legitimate scientific hypothesis[56], because it was experimentally verifiable.

Subsequent investigation of 3-propylhex-5-en-1-yl radical[57] showed similar increase in the rate of cyclisation, and similar product stereochemistry to those observed with the 3-allyhex-5-en-1-yl radical.



The hypothesis of homoconjugation was rejected. The homoconjugation explanation is of interest here because:

(1) It closely resembles the early arguments by which 1,6-intramolecular cyclisation of the hex-5-en-1-yl radical was inferred, and which led to a false conclusion.

(2) The homoconjugation explanation parallels the hypothesis of stereoelectronic control by its dependence on conformational folding of Dreiding[47,55] models, and its analogy to intermolecular reactions[45,46]. This of course does not imply the falsity of the stereoelectronic control hypothesis, but it does illustrate the weakness of its deductive logic. It also emphasises the possibility that if it were verifiable this hypothesis might turn out to be false.

(3) When it was found[57] that n-propyl substitution at C3 has the same effect as the allyl substitution had on the rate of 1,5-intramolecular cyclisation of the hex-5-en-1-yl radical it became apparent that the explanation for the observed rate enhancement had to be sought in the gauche interactions of the cyclising radical intermediates. Further investigation into how alkyl substituents affect the kinetics and stereochemistry of cyclisation became warranted. Hence the main part of the work presented here is a continuation of the work on 3-propylhex-5-en-1-yl and 3-allyhex-5-en-1-yl radicals.

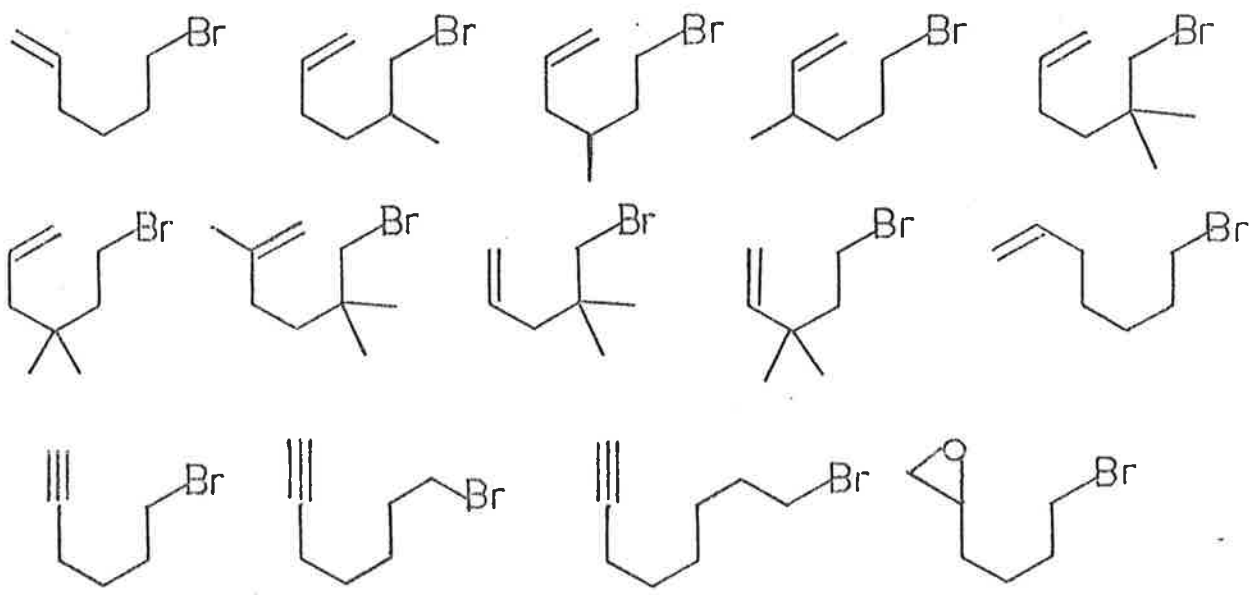
At the end of 1975 we knew a little about how a single monoalkyl substitution at C3 affected the chemistry of the hex-5-en-1-yl radical. We knew nothing about the consequences of alkyl substitution at C2 and C4, and also we wanted to know more about alkyl substitution at C3. We also were interested in intramolecular free radical addition to acetylenic bonds. Besides the scientific interest from the point of view of pure organic chemistry, we thought that intramolecular free radical addition to triple bonds may involve free radical mechanisms by which biochemical systems introduce *exo*-cyclic methylene groups. Whilst looking at free radical cyclisations, which may be occurring in living cells, we decided to enquire into intramolecular reactivity of free radicals

with 1,2-epoxy groups.

The choice of the research project was justifiable by the need for further knowledge in the chemistry of hexenyl radicals. Intramolecular cyclisation has aroused much interest in organic chemistry[58,59]. It is beyond the scope of this report to give a full review of the published works on the chemistry of hex-5-en-1-yl radicals; but if the references cited here are followed up they shall lead to many diverse reports on free radical cyclisation not mentioned in this thesis. Intramolecular cyclisation of hex-5-en-1-yl radicals is important in **industrial** cyclopolymerisation[60-62], and additional knowledge in this field is desirable for both applied and theoretical purposes. Free radical cyclisation has a broad application in mechanistic and synthetic chemistry, some of which was well summarised by Julia[33,34]. Nevertheless, primary importance must always be assigned to discoveries in pure natural sciences irrespective of the range of immediate applicability to which any part of such knowledge may be put.

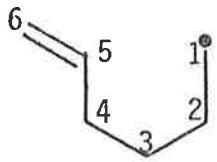
Outline of the research project.

(1) Synthesis of the following bromocompounds:

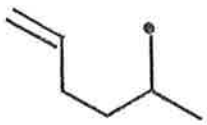


(2) Synthesis of reference compounds for identifying the products from the free radicals listed in (3) below.

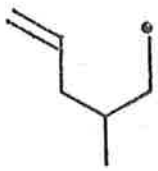
(3) Investigation of the kinetics of intramolecular addition of the following radicals:



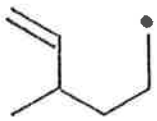
Hex-5-en-1-yl



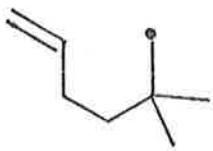
2-Methylhex-5-en-1-yl



3-Methylhex-5-en-1-yl

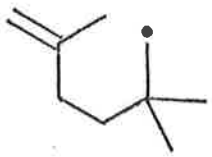


4-Methylhex-5-en-1-yl

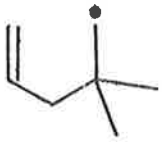


2,2-Dimethyhex-5-en-1-yl

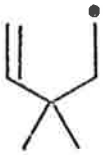
3,3-Dimethylhex-5-en-1-yl



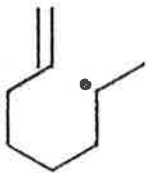
2,2,5-Trimethylhex-5-en-1-yl



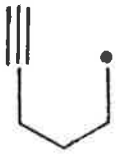
2,2-Dimethylpent-4-en-1-yl



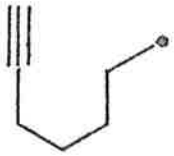
3,3-Dimethylpent-4-en-1-yl



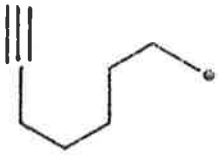
Oct-7-en-2-yl



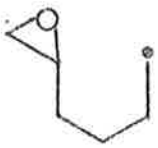
Hex-5-yn-1-yl



Hept-6-yn-1-yl



Oct-7-yn-1-yl



5,6-Epoxyhexan-1-yl

(4) Determination of the energies of activation for intramolecular addition of the above radicals.

(5) Attempt to verify or refute experimentally Julia's[34,37] hypothesis of steric control, and Beckwith's[25,35] hypothesis of stereoelectronic control, both of which propose to explain the predominance of 1,5-intramolecular cyclisation of the hex-5-en-1-yl radical.

Rates of cyclisation.

In the reduction of alkyl halides by tri-n-butyltin hydride the rate constants (k_H) for hydrogen atom abstraction from tri-n-butyltin hydride by tertiary, secondary, and primary radicals were found to be similar[24] (Table 1, page 12). The k_H difference between the primary hexyl radical and the secondary cyclohexyl radical was so small as to be within experimental error. On the basis of such small k_H differences between tertiary, secondary, and primary radicals, it appears reasonable to assume that there could be no significant difference in k_H values between similar primary alkyl radicals in general.

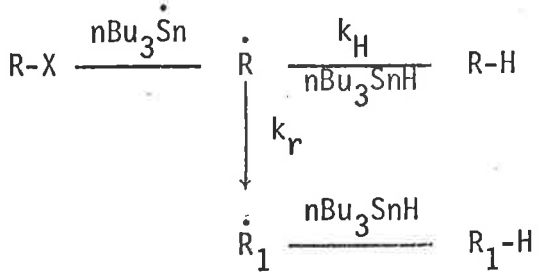
If the following assumptions are made:

(1) Hydrogen atom abstraction by alkyl radicals from tri-n-butyltin hydride is irreversible.

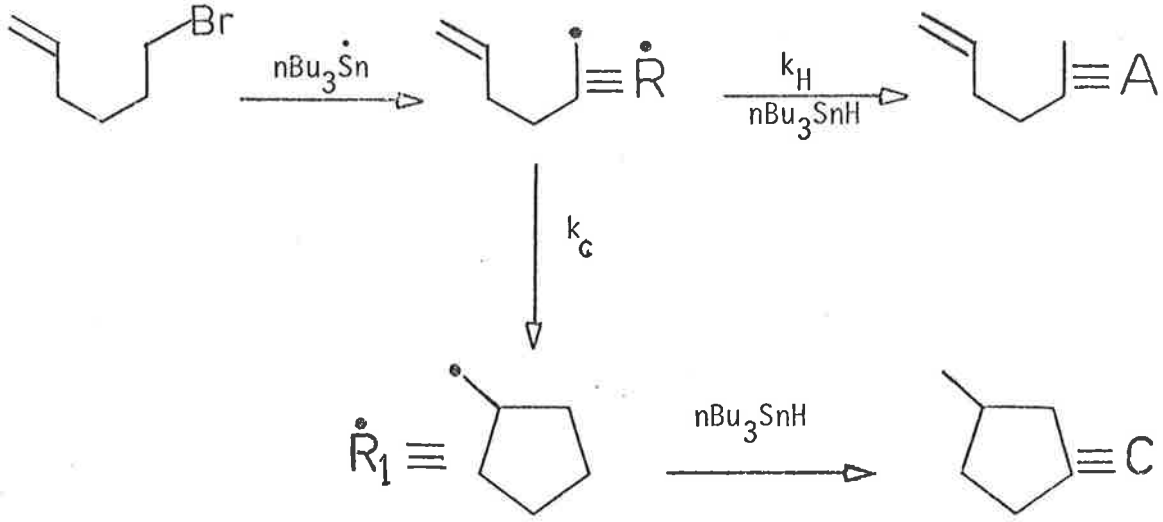
(2) Alkyl radicals abstract hydrogen atoms from tri-n-butyltin hydride at similar rates.

Then the relative rate of any irreversible free radical rearrangement, which competes with hydrogen atom abstraction, can be calculated.

Thus in general



And in particular



With the knowledge of the mean tin hydride concentration ($[nBu_3SnH]_m$) during the reaction, and the concentrations of the acyclic (A) and the cyclised (C) products the ratio of the rate constants (k_c/k_H) for the above reaction can be estimated.

(1) Since all the reaction steps are irreversible:

$$\frac{d[\dot{R}_1]}{dt} = k_c[\dot{R}] = \frac{d[C]}{dt}$$

(2) $$\frac{d[A]}{dt} = k_H[nBu_3SnH]_m[\dot{R}]$$

$$(3) \quad \frac{d[C]}{d[A]} = \frac{[C]}{[A]} = \frac{k_c}{k_H} \cdot \frac{1}{[nBu_3SnH]_m}$$

$$(4) \quad \frac{k_c}{k_H} = \frac{[C]}{[A]} \cdot [nBu_3SnH]_m$$

$$(5) \quad \text{If } [nBu_3SnH]_m = \frac{[nBu_3SnH]}{2}$$

$$(6) \quad \text{Then } \frac{k_c}{k_H} = \frac{[C]}{[A]} \cdot \frac{[nBu_3SnH]}{2} \qquad \text{Approximate value}$$

Because the mean concentration of tri-n-butyltin hydride ($[nBu_3SnH]_m$) cannot be determined its value, is taken as 50% of its initial concentration ($[nBu_3SnH]/2$). Since the bromide is in excess its concentration may be left out of these calculations.

Thus calculated, the values of the rate constants (k_c) for intramolecular cyclisation of the radicals investigated in this work relative to the rate constants (k_H) for hydrogen atom abstraction from tri-n-butyltin hydride were found to be within 10% plus or minus of the values calculated by computer methods (see below).

When the following assumptions hold true:

(1) Intramolecular cyclisation is irreversible.

(2) The reduction is a long-chain process.

(3) Throughout the reduction free radical intermediates are formed at the rate they are consumed.

Then by application of steady state principles the following integrated rate equation can be derived[6,63]:

$$\Sigma[C] = \Sigma k_c/k_H\{\ln([S]_o + \Sigma k_c/k_H) - \ln([S]_f + \Sigma k_c/k_H)\}$$

where $\Sigma k_c/k_H$ = the sum of the rate constants for all cyclisations relative to the rate of hydrogen atom transfer in l/mole.

$\Sigma[C]$ = total final concentration of the cyclised products in mol/l.

$[S]_o$ = initial concentration of nBu_3SnH in mol/l.

$[S]_f$ = final concentration of nBu_3SnH is mol/l.

The above equation can be solved for $\Sigma k_c/k_H$ by computer methods using an iterative procedure.

Where two or more irreversible intramolecular rearrangements compete with each other their respective k_c/k_H (or k_r/k_H) values are directly proportional to concentrations of their final products. All rate constants k_c/k_H were determined by accurately measuring the reactant (nBu_3SnH) and product concentrations and solving the above integrated rate expression by computer methods.

Note: *For calculation purposes concentrations of cyclised products were worked out using an assumption that the overall yield of products was 100%. Overall product yield varied over the range of 80-95%. No evidence was found that this assumption introduced significant errors into the rate constants.*

Energies of activation.

Having determined the values of the rate constants, k_c/k_H, at known temperatures, one can calculate the values of the activation parameters for intramolecular cyclisation by solving the following equation:

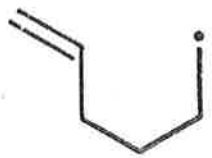
$$\frac{k_c}{k_H} = e^{\frac{-\Delta\Delta H^{\#}}{RT}} \cdot e^{\frac{\Delta\Delta S^{\#}}{R}}$$

where $\Delta\Delta H^{\#} = \Delta H_c^{\#} - \Delta H_H^{\#}$ kcal/mole,

and $\Delta\Delta S^{\#} = \Delta S_c^{\#} - \Delta S_H^{\#}$ cal/mol/^{o}K

Since both $\Delta S_H^{\#}$ and $\Delta S_c^{\#}$ are negative, and $\Delta S_H^{\#}$ has a larger negative value, $\Delta\Delta S^{\#}$ is positive.

In this work the above equation was solved by a least squares method, which minimises the scalar error in $\ln k_C/k_H$. An ACTENG[64] computer program was used. The program was modified for use of a ratio of rate constants.



HEX-5-EN-1-YL RADICAL

Hex-5-en-1-yl Radical

The principal aim of the work presented in this thesis is the study of the effects of alkyl substitutents on intramolecular cyclisation of hex-5-en-1-yl radicals. At a given temperature unsubstituted hex-5-en-1-yl radical undergoes intramolecular cyclisation with a definite rate, which, prior to commencement of this work, was expected to vary with the position and extent of alkyl substitution[47,57]. Thus the effects of a single methyl substitution at C2 on the rate of intramolecular addition and the stereochemistry of the product, 1,3-dimethylcyclopentane, may be different from those of a single methyl at C3. Likewise *gem*-dimethyl substitution was predicted[57] to enhance the rate of cyclisation more than a single methyl substitution on the same carbon. Evaluations of substituent effects on the rate of intramolecular cyclisation are essentially related to the kinetics shown by unsubstituted hex-5-en-1-yl radical.

Previously reported magnitudes of the rate constants, k_c/k_H, for intramolecular cyclisation of the hex-5-en-1-yl radical under similar experimental conditions differ by up to 32% (Table 2).

Table 2 Comparison of k_c/k_H values for the cyclisation of hex-5-en-1-yl radical at 70° (Scheme 1, page 35).

$\Sigma k_c/k_H$ ℓ/mol	Reference
.15	31
.17	34,37
.22	41
.20	65

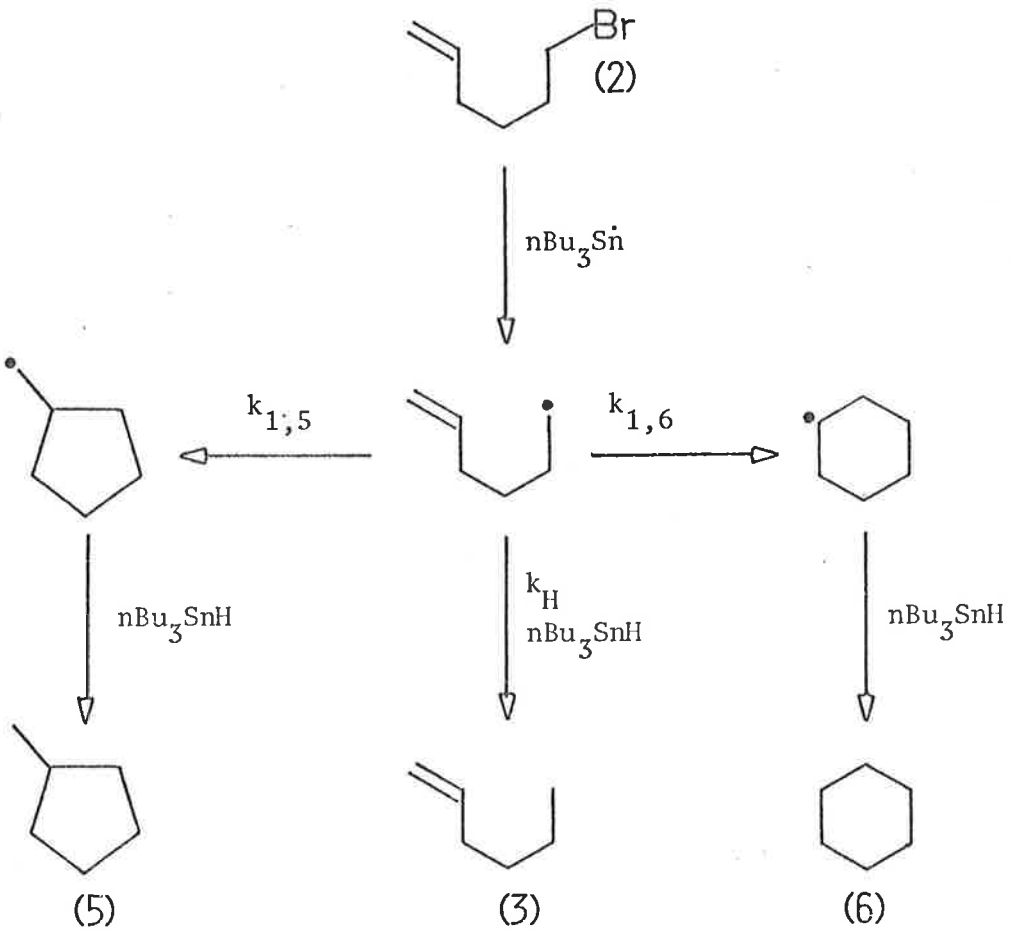
The likely causes of these differences are unknowingly introduced experimental errors - for there are many ways to err in this work. The main source of errors lies in the determination of the initial reactant concentrations. Apart from weight and volume inaccuracies the prepared solution of reactants may be contaminated with oxygen, which reacts with tributyltin hydride and lowers its effective concentration in the reaction mixtures, or it may have contaminated the tributyltin hydride during synthesis and storage of this reagent. Another serious cause of errors may occur in the assessment of the relative concentrations of cyclic and acyclic hydrocarbons, which are the final products of the reduction of 6-bromohex-1-ene with tributyltin hydride. Errors in either reactant or product concentrations enter into kinetic calculations, and the rate constants, k_c/k_H, thus obtained deviate from their true values in direct proportions to the magnitudes of concentration inaccuracies.

Hence for the purpose of this work it was imperative to re-investigate the kinetics of the hex-5-en-1-yl radical in order to reduce deviations in measurements caused by experimental differences subjective to individual researchers. It is thus unlikely that herein observed relative reactivity changes of alkyl substituted hex-5-en-1-yl radicals, or for that matter any radical, are significantly attributable either to experimental errors or to subjective fluctuations of experimental conditions. Whatever errors were introduced they were consistent throughout the work.

Reduction of 6-bromohex-1-ene with tributyltin hydride proceeds by the mechanism outlined in scheme 1.

Scheme 1

Reduction of 6-bromohex-1-ene with Bu_3SnH.



The above scheme may be taken as a generalised form of the reduction mechanism of 6-bromohex-1-enes, where the generated free radical intermediates either cyclise **irreversibly**, or abstract hydrogen atoms from tributyltin hydride. At a given temperature the extent of rearrangement is inversely related to the collision frequency of the unrearranged radical with the hydrogen atom donor, that is, intramolecular cyclisation is inversely dependent on the concentration of tributyltin hydride.

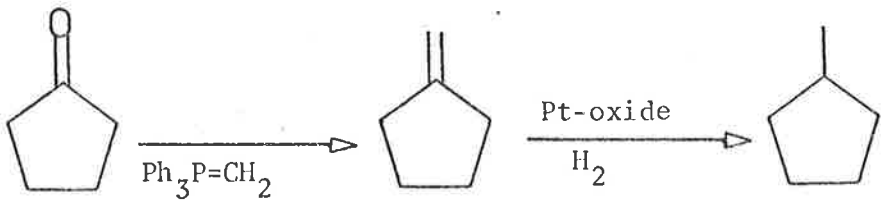
Since all steps (Scheme 1) in the reduction of 6-bromohex-1-enes with tributyltin hydride are irreversible, the amount of cyclisation is controlled by the concentration of tributyltin hydride in the reaction mixture. As a rule of thumb the concentration of stannane (mol/ℓ) which gives 50% cyclised product is equal to $2(k_c/k_H)$ at that temperature (page 29).

Synthesis

6-Bromohex-1-ene, the precursor for the hex-5-en-1-yl radical, was prepared by partial hydrogenation of 6-bromohex-1-yne, which was synthesised as outlined in scheme 40. Both tributyltin hydride and tributyltin deuteride were prepared from suitable reagents and freshly distilled under nitrogen. The reference compounds hex-1-ene, and cyclohexane were available as commercial reagents. Methylcyclopentane was prepared as outlined in scheme 2.

Scheme 2

Synthesis of methylcyclopentane.



(4) (5)

Reduction - Results and Discussion

6-Bromohex-1-ene was reduced in benzene at 25°, 60°, 80° and 100° using both tributyltin hydride and tributyltin deuteride at concentrations listed in Tables 1 and 2. In all reactions the bromide was present in an excess of 20%.

Overall yields and relative yields of hydrocarbons were determined by gas liquid chromatographic analysis.

Twenty reactions in sealed ampoules were run at each temperature and each concentration of reactants. The mean values of overall yields and product distributions are listed in Tables 3 and 4.

Table 3 Distribution of products in the reduction of 6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/ℓ	Relative Yield %			Total Yield %
		(3)	(5)	(6)	
25	.0984	33.9	63.8	2.3	78
25	.1954	45.0	53.1	1.9	83
25	.6057	68.0	30.8	1.2	87
60	.0775	17.3	79.8	2.9	84
60	.2613	39.1	58.7	2.2	88
60	.3466	45.0	53.0	2.0	88
80	.0775	14.0	83.0	3.0	85
80	.2653	33.8	63.9	2.4	92
80	.2653*	33.7	63.9	2.4	92
80	.4542	45.1	53.0	1.9	95
100	.1683	21.3	76.0	2.7	93
100	.1683*	21.1	76.1	2.8	94
100	.2998	31.3	66.3	2.4	94
100	.5821	45.0	53.1	1.9	96

* Free radical initiator (AIBN) was not used.

Table 4 Distribution of products in the reduction of 6-bromohex-1-ene with nBu_3SnD.

Temp. °C	$[nBu_3SnD]$ mol/ℓ	Relative Yield %			Total Yield %
		(3)	(5)	(6)	
25	.1469	26.8	70.1	3.1	80
25	.2868	38.3	59.1	2.6	82
25	.4001	45.0	52.7	2.3	86
60	.1664	19.7	76.9	3.4	88
60	.2885	28.9	68.0	3.1	87
60	.4021	35.5	61.8	2.7	93
80	.1643	16.6	79.8	3.6	89
80	.2246	21.1	75.5	3.4	95
80	.2976	26.0	70.8	3.2	95
80	.4260	32.4	64.7	2.9	96
100	.1718	14.7	81.6	3.7	90
100	.2907	22.1	76.6	3.3	94
100	.8961	43.7	53.7	2.4	92

At all temperatures the ratio of methylcyclopentane to hexane remained at about 27:1 in the reduction with tributyltin hydride, and approximately 22:1 in the reduction with tributyltin deuteride. Accurate assessment of the relative concentrations of methylcyclopentane and cyclohexane was not possible with such a small yield of the latter. There was no way of adjusting the reaction conditions, or the resolution of the gas chromatograph which could improve measurements of the relative concentrations of cyclic products for the purpose of determining the rate constants $k_{c_{1,6}}/k_H$ and $k_{c_{1,6}}/k_D$ to within the degree of accuracy required for calculations of energies of activation for 1,6-cyclisation.

This problem has no significant affect on the kinetic measurements of 1,5-cyclisation, and small amounts (1-3%) of products from *endo*

cyclisations are introduced into the kinetics of *exo*-cyclisations.

From the data in Tables 3 and 4 the rates of cyclisation (k_c) relative to the rates of hydrogen and deuterium atom abstractions (k_H and k_D) from tributyltin hydride and tributyltin deuteride were calculated and are listed in tables 5 and 6.

Table 5 $\Sigma k_c/k_H$ values for the reduction of 6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mols/ℓ	k_c/k_H ℓ/mole	Mean Value $\Sigma k_c/k_H$ ℓ/mole	St. Dev. %
25	.0984	.0965		
25	.1954	.0981		
25	.6057	.0983	.0977	1.0
60	.0775	.1732		
60	.2613	.1725		
60	.3466	.1737	.1732	.34
80	.0775	.2271		
80	.2653	.2264		
80	.2653*	.2273		
80	.4542	.2271	.2270	.17
100	.1683	.2877		
100	.1683*	.2903		
100	.2998	.2910		
100	.5821	.2923	.2903	.67

Mean values of $k_{c_{1,6}}/k_H$

25 ≈ .004
60 ≈ .006
80 ≈ .008
100 ≈ .010

* Free radical initiator (AIBN) was not used.

Table 6 $\Sigma k_c/k_D$ values for the reduction of 6-bromohex-1-ene with nBu_3SnD.

Temp. °C	$[nBu_3SnH]$ mol/ℓ	$\Sigma k_c/k_D$ ℓ/mole	Mean Value $\Sigma k_c/k_H$ ℓ/mole	St. Dev. %
25	.1649	.2029		
25	.2868	.1971		
25	.4001	.2010	.2003	.15
60	.1664	.3155		
60	.2885	.3165		
60	.4021	.3166	.3162	.19
80	.2246	.3882		
80	.2246	.3882		
80	.2976	.3831		
80	.4260	.3899	.3876	.80
100	.1718	.4728		
100	.2907	.4717		
100	.8961	.4723	.4723	.12

The rate constants, k_c/k_H, obtained in this work are significantly higher than those obtained by Walling[31] and Julia[34,37], about 10% lower than those of Beckwith[41] and not significantly different from the values found by Moad[65] (Table 7).

Table 7 $\Sigma k_c/k_H$ values for the reduction of 6-bromohex-1-ene at 70°.

	$\Sigma k_c/k_H$ ℓ/mole	$\Delta\Delta S^{\#}$ cal/mole/°K	$\Delta\Delta H^{\#}$ kcal/mole
Walling[31]	.15	3.3	2.4
Julia[34,37]	.17	-	-
Beckwith[41]	.22	5.7	3.0
Moad[65]	.20	6.3	3.3
This work	.199	6.1 ± .12	3.2 ± .04

Although the k_c/k_H value at 70° obtained in this work is almost identical with that of Moad, the k_c/k_H values at 60° and 80° differ from Moad's by 4% and 2% respectively, and the calculated activation parameters vary accordingly (Table 7).

The rate constants $\Sigma k_c/k_D$, (Table 6) exceed the corresponding rate constants, $\Sigma k_c/k_H$, by 62-104%; and the kinetic isotope effect is 1.63 at 100° , 1.71 at 80°, 1.83 at 60°, and 2.04 at 25°.

The activation parameters, which correspond to the obtained rate constants $\Sigma k_c/k_H$ and $\Sigma k_c/k_D$ are listed in Table 8.

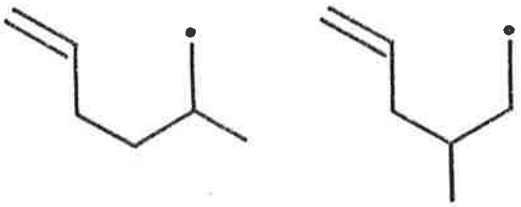
Table 8 Energies of activation for the cyclisation of hex-5-en-1-yl radical relative to hydrogen or deuteride atom abstraction from nBu_3SnH or nBu_3SnD.

	$\Delta\Delta S^{\#}$ cal./mole/°K	$\Delta\Delta H^{\#}$ kcal./mole
$\Sigma k_c/k_H$	$6.1 \pm .12$	$3.2 \pm .04$
$\Sigma k_c/k_D$	$5.3 \pm .12$	$2.5 \pm .04$

The difference in $\Delta\Delta S^{\#}$ of 0.8 cal/mole/°K between hydrogen and deuteride abstractions from tributylstannane may well be due to slight errors (1-3%) in the evaluated rate constants, $\Sigma k_c/k_D$. The enthalpy of activation calculations are not significantly affected by k_c/k_D fluctuations of such magnitudes, and the difference in $\Delta\Delta H^{\#}$ of .68 kcal/mole represents the isotope effect in the abstraction of the deuterium atom from tributyltin deuteride. The isotope effect of 2.04 at 25° is lower than 2.7 reported in literature[24]. A deuterium isotope effect of 1.66 at 100° was obtained in the reduction of 2,5,5-trimethyl-6-bromohex-1-ene with tri-n-butyltin deuteride, and 1.76 in the reduction of 7-bromohex-1-yne at 80°. These are similar to the isotope effects observed with

6-bromohex-1-ene at the same temperatures.

The values of the rate constants, $\Sigma k_c/k_H$, established in this work, are used as standards for evaluating the effects of alkyl substituents on intramolecular cyclisation of hex-5-en-1-yl radicals.



2-METHYLHEX-5-EN-YL and 3-METHYLHEX-5-EN-1-YL RADICALS

2-Methylhex-5-en-yl and 3-methylhex-5-en-1-yl radicals.

There were two aims in studying 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals:
First was the investigation of the effects of single methyl substitution at C2, and C3 on the kinetics of intramolecular cyclisation; the second aim was determination of the stereochemistry of the cyclised product - 1,3-dimethylcyclopentane.

On the basis of earlier observations[47,57] the rates of cyclisation were expected to increase, relative to unsubstituted hex-5-en-1-yl radical, as a consequence of methyl substitution at C2, and C3.

Methyl group induced gauche interactions may either lower the enthalpy of activation by destabilising the acyclic free radical, or such interactions may restrict internal rotation about C2-C3 and C3-C4 bonds in a way which leads to increase of rotomer populations resembling cyclic transition states, or both enthalpy and entropy factors may contribute to rate enhancement of intramolecular cyclisation.

The stereochemistry of 1,3-dimethylcyclopentane must represent the ring conformation of the transition states of the two radicals during the irreversible intramolecular cyclisation. If the transition state for intramolecular cyclisation of hex-5-en-1-yl radical resembled a chair conformation of cyclohexane then, as a consequence of non-bonded interactions of axial substituents, a methyl group at C2 or C3 would in each case assume predominantly equatorial orientation. If, on the other hand, the cyclic transition state resembled a puckered conformation of cyclopentane, then in both cases the methyl substituent would be found predominantly on the same side as the methylene group. Because the cyclisation is irreversible the stereochemistry of the final products of

1,5-cyclisation reflects the conformation and stereochemistry of the transition states of the cyclising 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals, and not the free energies of *cis* and *trans*-1,3-dimethylcyclopentanes.

In the study of 3-propylhex-5-en-1-yl[57] and 3-allylhex-5-en-1-yl[47] radicals a predominance of *cis*-1-methyl-3-propyl- and *cis*-1-methyl-3-allylcyclopentane isomers was noted. Formation of *cis*-1-methyl-3-allylcyclopentane, as well as the enhancement of the rate of cyclisation, was initially explained by postulating through space interaction of the allyl double bond with the double bond involved in intramolecular reaction with the free radical centre[47]. Later, when the idea of homoconjugation was disproved by studies of 3-propylhex-5-en-1-yl radical[57] (which showed similar rates of intramolecular cyclisation and similar proportions of *cis*:*trans* 1,3-dialkylcyclopentane to those observed with 3-allyhex-5-en-1-yl radical), preferential formation of *cis*-1-methyl-3-propylcyclopentane was explained[57] by analogy to 1,3-dimethylcyclopentane in terms of free energy differences between *cis*- and *trans*-1,3-dialkylcyclopentanes[66].

If the transition states of the cyclising 2-methylhex-5-en-1-yl, and 3-methylhex-5-en-1-yl radicals had chair-like or half-chair (envelop-like) conformations, then the methyl group of each radical would tend to take up an equatorial orientation. 2-Methylhex-5-en-1-yl radical would thus cyclise predominantly to *trans*-1,3-dimethylcyclopentane. If, on the other hand, *cis*-1,3-dimethylcyclopentane were formed in excess of the *trans* isomer this would imply a puckered cyclopentane ring-like transition state. However, formation of *cis*-1,3-dimethylcyclopentane as the main isomer from 3-methylhex-5-en-1-yl would be consistent with either a puckered cyclopentane or a chair-like conformation of the transition state, while the prevalence of *trans*-1,3-dimethylcyclopentane would be inconsistant with both.

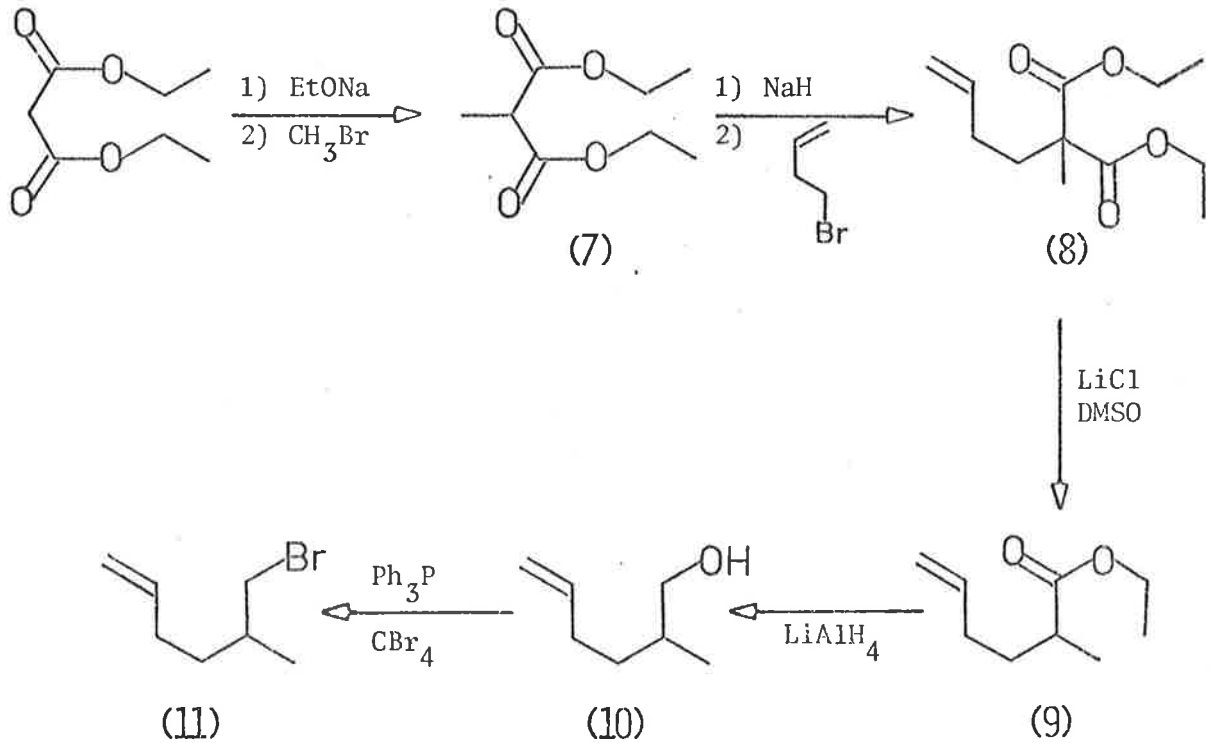
Thus for understanding the stereochemistry and conformation of the transition state during 1,5-cyclisation, a study of the 2-methylhex-5-en-1-yl radical is more informative than that of 3-methylhex-5-en-1-yl radical.

Synthesis

5-Methyl-6-bromohex-1-ene and 4-methyl-6-bromohex-1-ene, the precursors for 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals, were prepared by the synthetic routes outlined in schemes 3 and 4.

Scheme 3

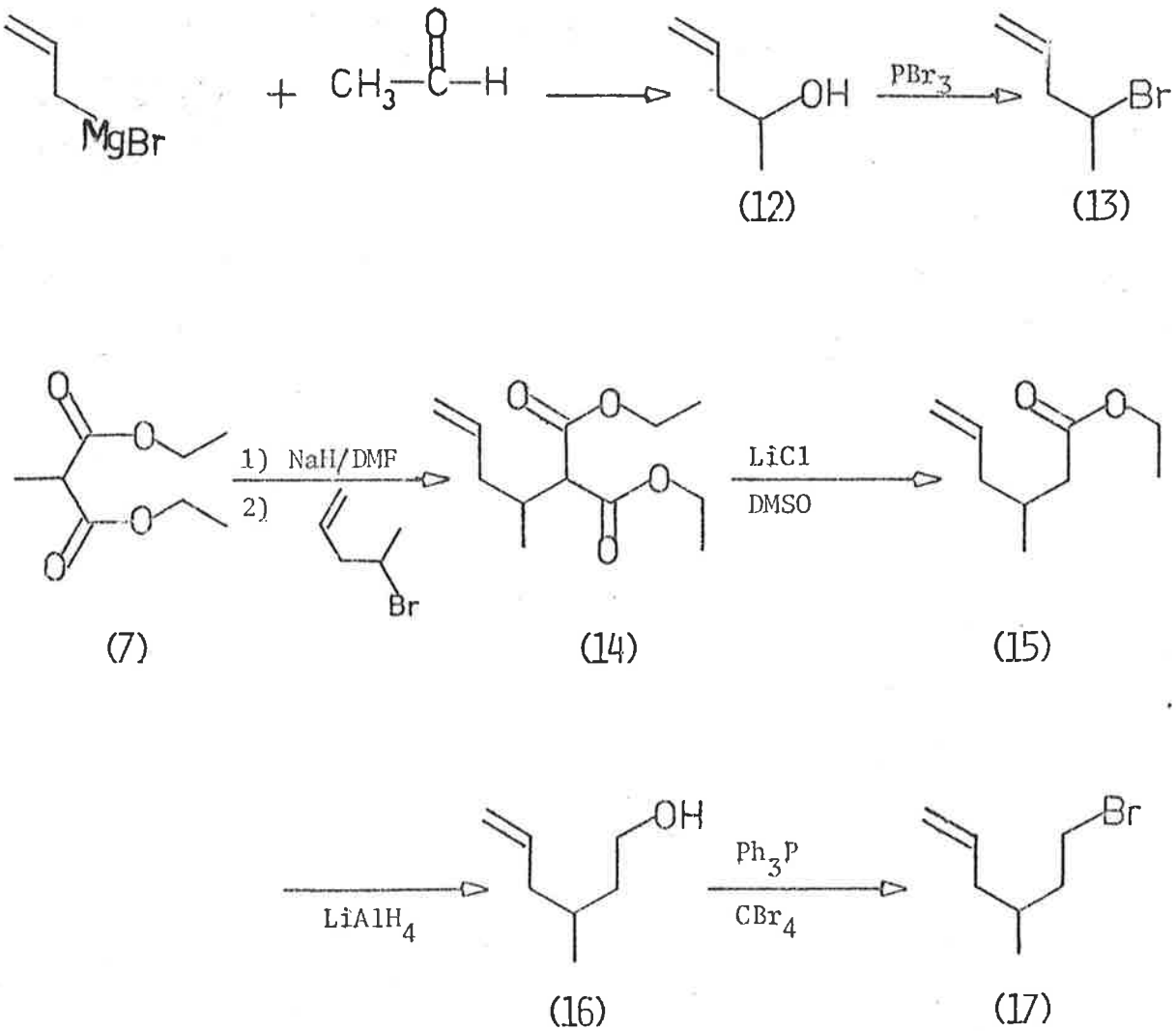
Synthesis of 5-methyl-6-bromohex-1-ene.



All reactions proceeded in yields greater than 70%. Generation of the anion from methyldiethyl malonate[7] with sodium ethoxide was slow (19 h.), and the reaction of 4-bromobut-1-ene with the generated anion was likewise slow (15 h.). Both reactions proceeded much faster when DMF was used as solvent in place of ethanol, and sodium hydride in lieu of sodium ethoxide.

Scheme 4

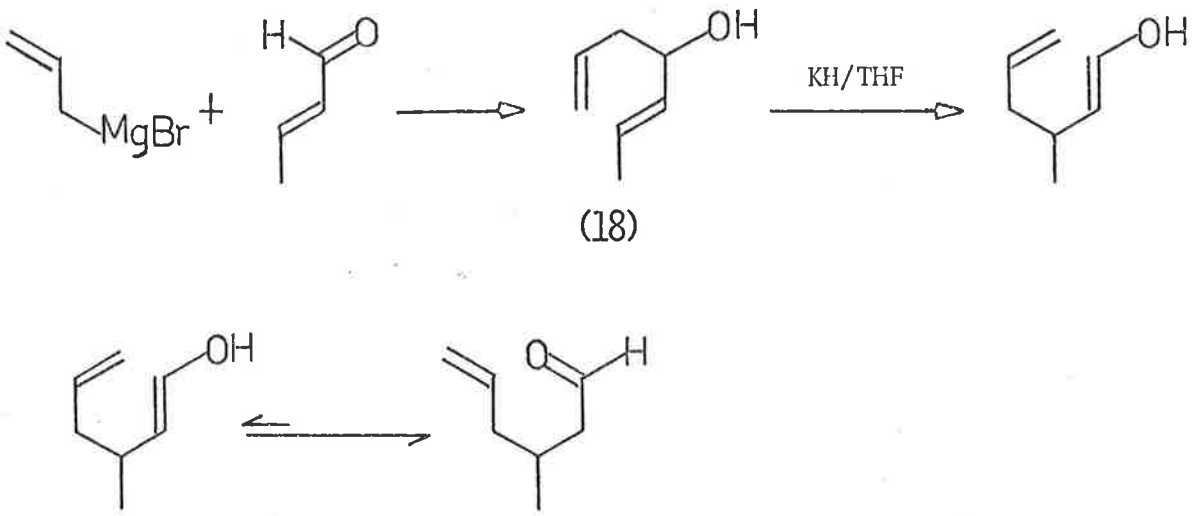
Synthesis of 4-methyl-6-bromohex-1-ene.



All reactions proceeded in yields greater than 70%. Prior to undertaking the synthesis outlined in scheme 4, preparation of 3-methylhex-5-en-1-al was attempted by an oxy-Cope type rearrangement of 1,5-heptadien-4-ol by the route outlined in scheme 5.

Scheme 5

Attempted synthesis of 3-methylhex-5-en-1-al.

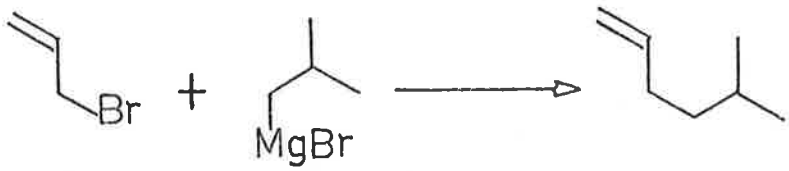


This shorter route to 4-methyl-6-bromohex-1-ene was unsuccessful. The reaction was run for 100 hours under reflux, and its progress followed by g.l.c. The reaction was run under conditions reported[67] to induce fast and efficient oxy-Cope rearrangment of similar heptadienols. After the work up only the starting 1,5-heptadien-4-ol (46%) was recovered. No products could be distilled.

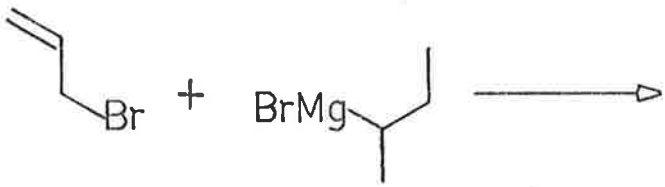
For the gas chromotographic identification of the products predicted by schemes 8 and 9 reference compounds 5-methylhex-1-ene, 4-methylhex-1-ene, and 1,3-dimethylcyclopentane were prepared as shown in schemes 6 and 7. Methylcyclohexane was available as a commercial reagent.

Scheme 6

Synthesis of 5-methylhex-1-ene and 4-methylhex-1-ene



(19)

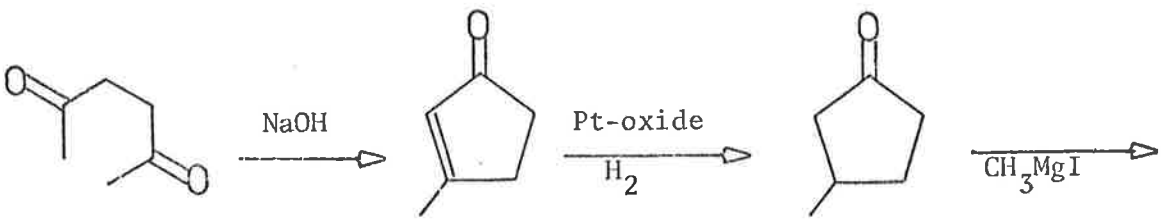


(20)

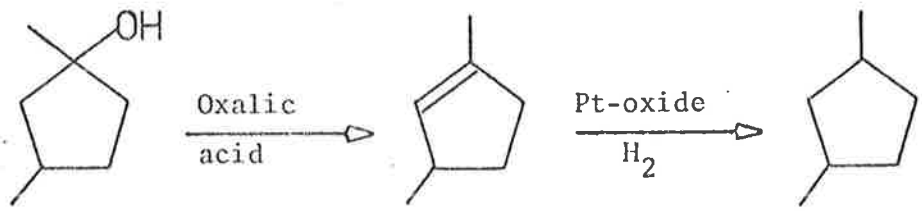
Both Grignard reagents coupled to allyl bromide with yields in excess of 75%.

Scheme 7

Synthesis of 1,3-dimethylcyclopentane.



(21) (22)



(23) (24) (25)

All reactions in scheme 7 proceeded well. Both hydrogenation steps were fast - the reactions were over in a matter of minutes. The ^{13}C n.m.r. spectrum of the final product showed resonance peaks with chemical shifts corresponding to those reported for *cis*- and *trans*-1,3-dimethylcyclopentane[68], and no others. The intensities of the peaks belonging to *cis*-isomer were 7.6 times greater than those of the corresponding *trans*-isomer peaks. This showed that *cis*-1,3-dimethylcyclopentane was in excess over its *trans*-isomer, which is consistent with the method of conversion of 1,3-dimethylcyclopentene to 1,3-dimethylcyclopentane. It is known that hydrogenation of a cyclic olefin over palladium on carbon produces the *cis*-isomer as the main product[69].

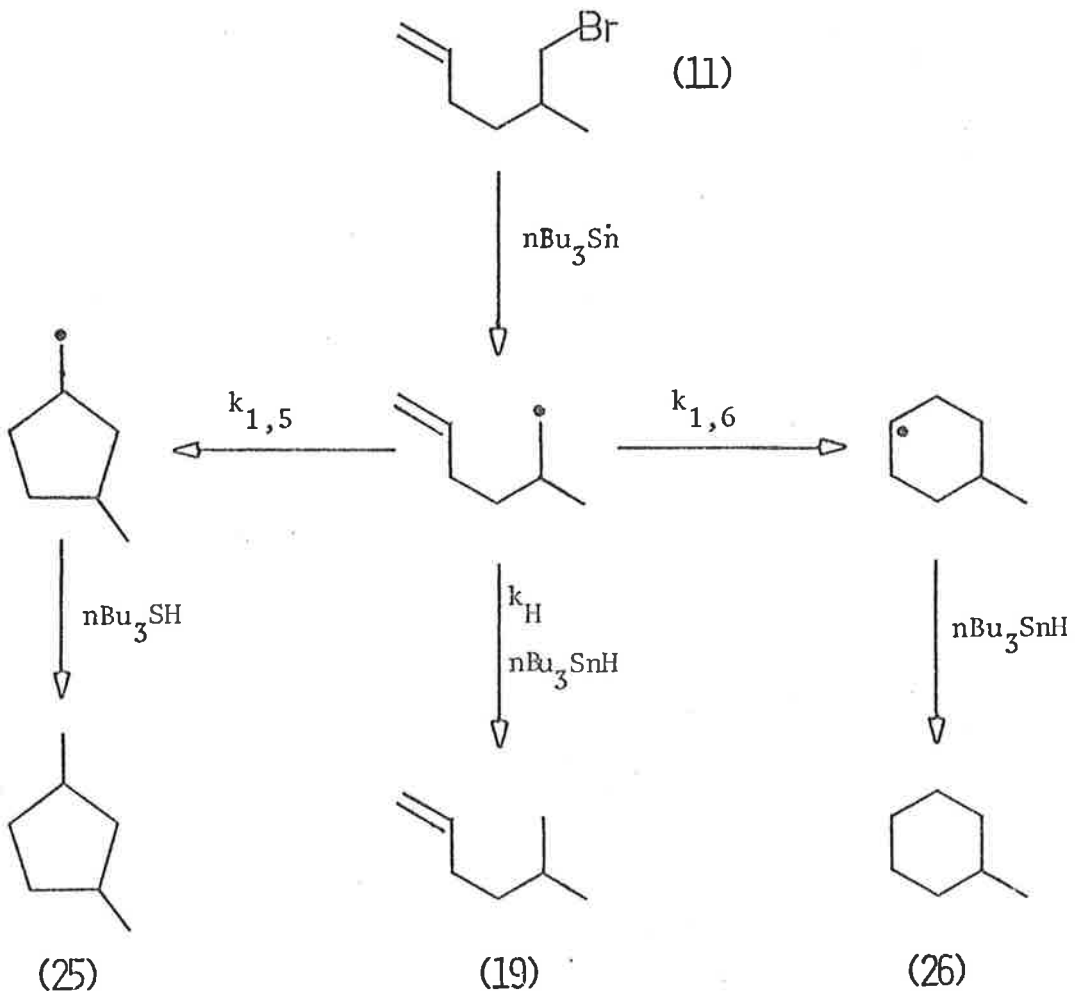
Now the two isomers of 1,3-dimethylcyclopentane, prepared via scheme 7, were identifiable on a g.l.c. spectrum by their peak sizes. Subsequently *cis*-1,3-dimethylcyclopentane, and *trans*-1,3-dimethylcyclopentane were separated by analytical gas liquid chromatography.

REDUCTION - RESULTS AND DISCUSSION

By analogy to 6-bromohex-1-ene, reductions of 5-methyl-6-bromohex-1-ene and 4-methyl-6-bromohex-1-ene were expected to proceed irreversibly through mechanisms outlined in schemes 8 and 9.

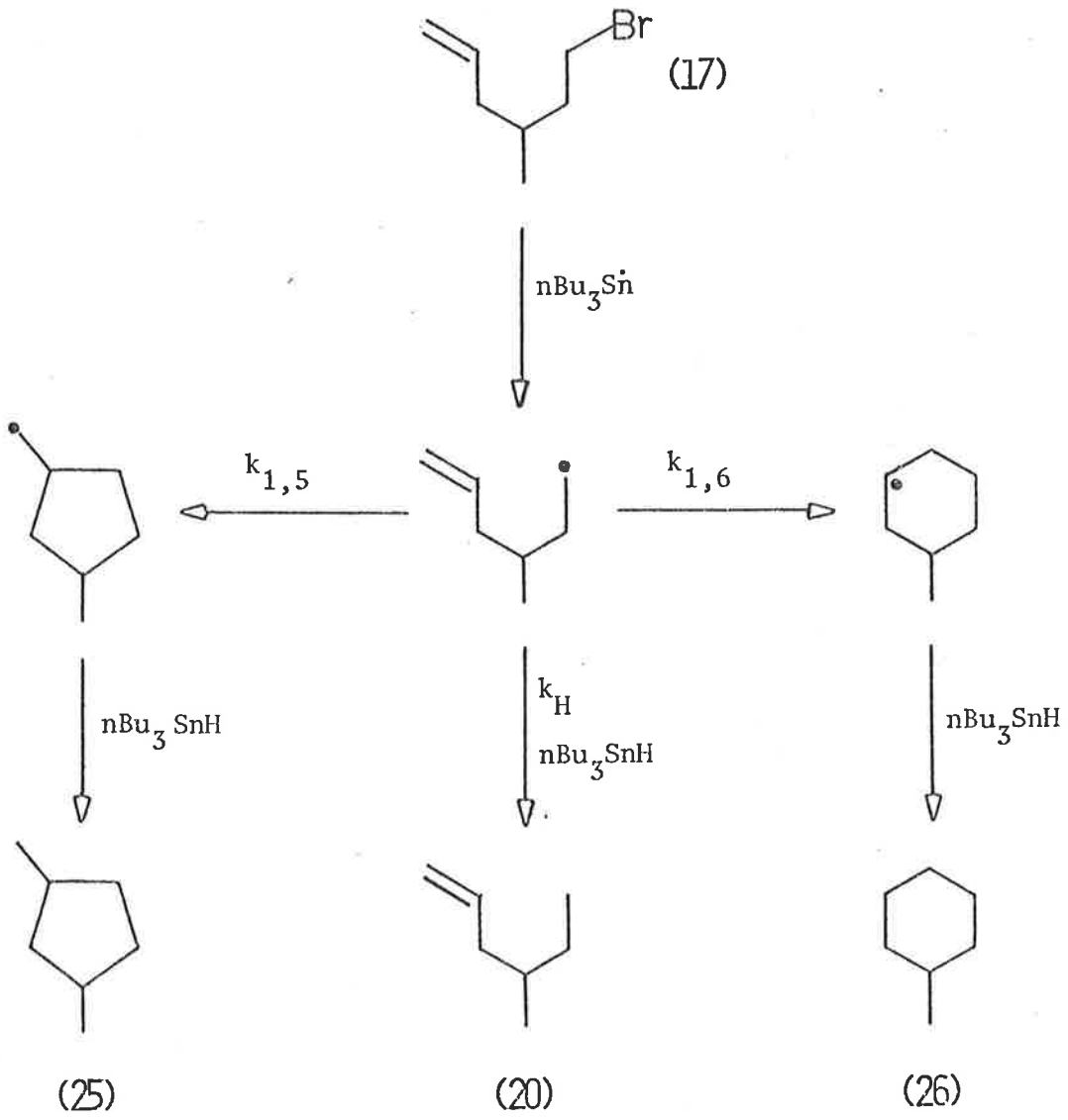
Scheme 8

Reduction of 5-methyl-6-bromohex-1-ene with nBu_3SnH.



Scheme 9

Reduction of 4-methyl-6-bromohex-1-ene with nBu_3SnH.



5-Methyl-6-bromohex-1-ene and 4-methyl-6-bromohex-1-ene were reduced with tri-n-butyltin hydride at temperatures of 45°, 60°, 80°, and 100°, and the stannane concentrations shown in tables 9 and 10.

Distribution of the products from both reductions is listed in tables 9 and 10.

Table 9 Distribution of products in the reduction of 5-methyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	Relative yield %				Total Yield %
		(19)	(25) *trans*	(25) *cis*	(26)	
45	.0983	10.9	56.0	31.8	1.3	85
45	.2064	20.0	50.4	28.2	1.4	88
45	.5692	38.6	38.8	21.7	1.0	88
60	.1021	9.6	56.7	32.4	1.3	87
60	.1799	15.5	53.0	29.9	1.6	90
60	.2778	21.6	49.4	27.6	1.4	94
80	.1574	11.5	55.0	32.3	1.2	86
80	.2738	18.0	50.6	30.1	1.3	91
80	.4608	26.3	45.6	26.8	1.3	95
100	.0986	6.4	56.8	35.5	1.3	86
100	.1430	9.0	54.7	34.5	1.9	90
100	.2741	15.5	51.3	31.7	1.6	93

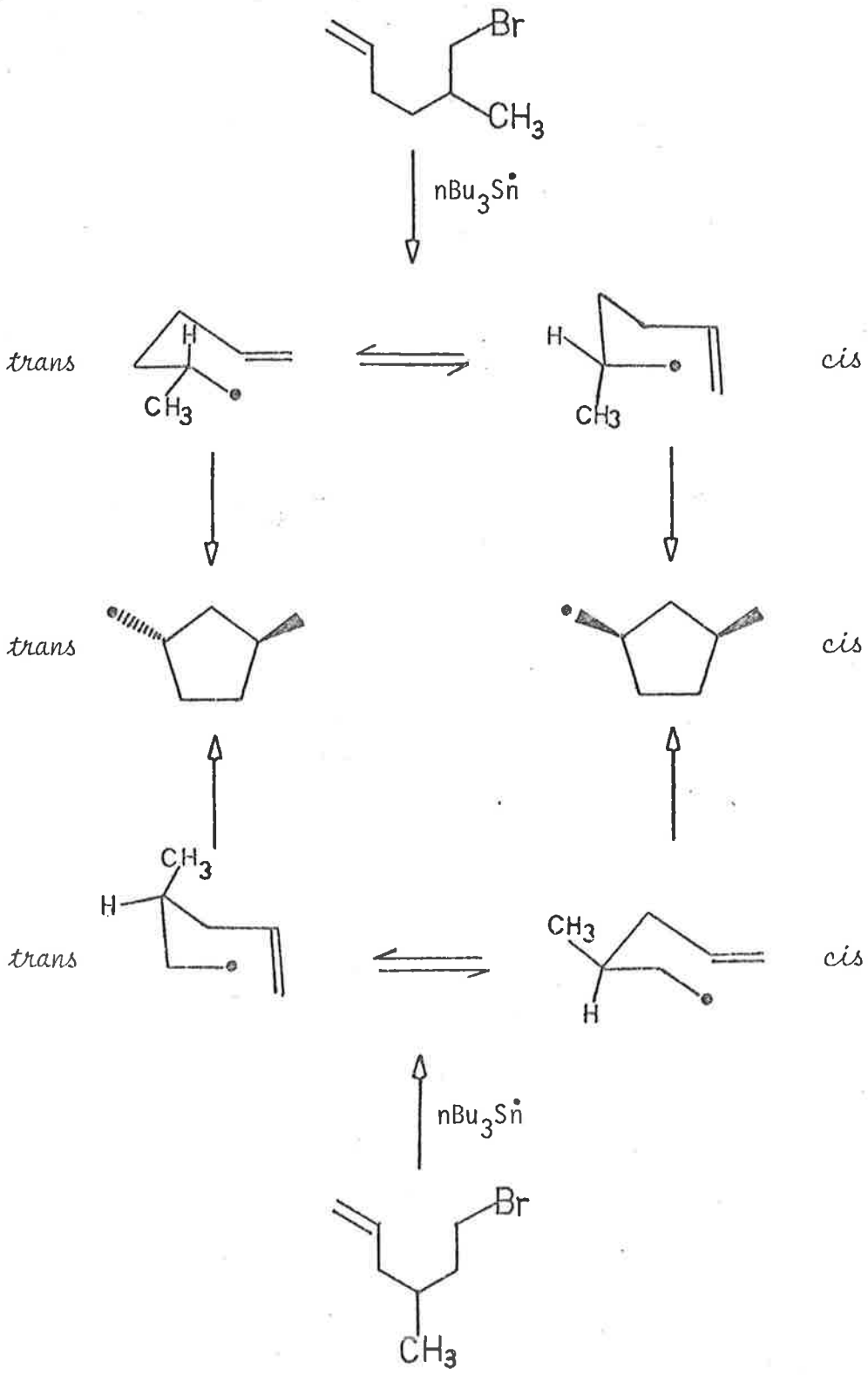
Table 10 Distribution of products in the reduction of 4-methyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	Relative yield %				Total Yield %
		(19)	(25) *trans*	(25) *cis*	(26)	
45	.1651	13.5	23.1	62.3	1.1	87
45	.2893	20.8	21.0	57.2	.9	89
45	.5110	30.8	18.1	50.2	.9	92
60	.2778	17.6	22.0	59.6	.8	89
60	.5258	27.9	19.2	52.0	.9	94
60	.8467	37.3	16.7	45.3	.8	95
80	.2738	14.8	23.5	60.6	1.0	90
80	.5165	23.9	20.9	54.3	.9	93
80	.8254	32.5	18.5	48.1	.9	96
100	.2699	12.5	24.8	61.5	1.1	91
100	.5254	21.2	22.3	55.5	.9	95
100	1.2438	37.1	17.9	44.3	.8	96

In both sets of reductions at any one temperature the extent of cyclisation has inverse linear dependence on the concentration of tri-n-butyltin hydride. This observation confirms that cyclisation is irreversible. In both cases methylcyclohexane, formed by intramolecular cyclisation, was present in concentrations too low (1.0 - 2.0% of the total cyclised product) to be measured with the accuracy required for kinetic calculations.

The *trans*:*cis* ratio of 1,3-dimethylcyclopentane, formed by intramolecular 1,5-cyclisation of 2-methylhex-5-en-1-yl radical, was 1.78 at 45°, 1.77 at 60°, 1.70 at 80°, and 1.60 at 100°. The *cis*:*trans* isomer ratio of 1,3-dimethylcyclopentane, from intramolecular 1,5-cyclisation of 3-methylhex-5-en-1-yl radical, was 2.73 at 45°, 2.71 at 60°, 2.59 at 80°, and 2.48 at 100°.

The conformation and stereochemistry of the acyclic 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals just prior to cyclisation are postulated below:



The isomer ratios of 1,3-dimethylcyclopentane from the two reductions represent the ratios of their rate constants, which in turn reflect the differences of the corresponding energies of activation.

The rate constants, calculated from the data in tables 9 and 10 by the methods described under "Rates of cyclisation" (page 29) are listed in tables 11 and 12.

Table 11 Values of k_c/k_H for the reduction of 5-methyl-6-bromohex-1-ene with nBu_3SnH.

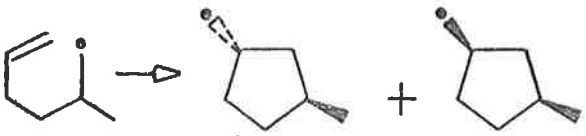
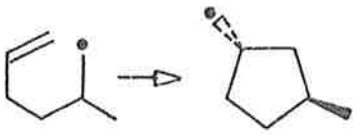
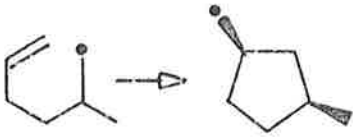
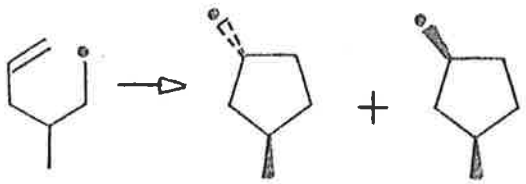
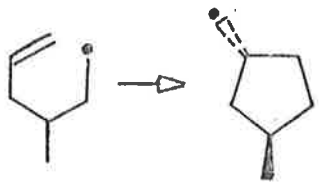
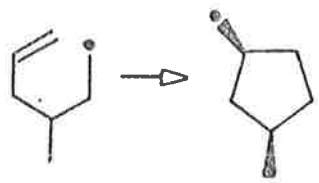
Temp ^oC	nBu_3SnH mol/ℓ	$k_{c_{1,5\text{-}trans}}/k_H$ ℓ/mole	$k_{c_{1,5\text{-}cis}}/k_H$ ℓ/mole	$\Sigma k_c/k_H$ ℓ/mole
45	.0983	.2461	.1395	.3856
45	.2064	.2451	.1371	.3822
45	.5692	.2478	.1382	.3860
60	.1021	.2969	.1696	.4665
60	.1799	.2964	.1676	.4640
60	.2778	.2984	.1665	.4649
80	.1574	.3722	.2188	.5809
80	.2738	.3673	.2182	.5855
80	.4608	.3681	.2156	.5837
100	.0986	.4368	.2733	.7101
100	.1430	.4352	.2749	.7101
100	.2741	.4384	.2708	.7092

Table 12 Values of k_c/k_H for the reduction of 4-methyl-6-bromohex-1-ene with nBu_3SnH.

Temp °C	nBu_3SnH mol/ℓ	$k_{c_{1,5\text{-}trans}}/k_H$	$k_{c_{1,5\text{-}cis}}/k_H$	$\Sigma k_c/k_H$ ℓ/mole
45	.1651	.1365	.3675	.5040
45	.2893	.1366	.3715	.5081
45	.5110	.1343	.3728	.5071
60	.2778	.1639	.4444	.6083
60	.5258	.1642	.4449	.6091
60	.8467	.1642	.4457	.6099
80	.2738	.2086	.5371	.7461
80	.5165	.2087	.5425	.7512
80	.8254	.2084	.5435	.7519
100	.2699	.2585	.6410	.8995
100	.5254	.2584	.6420	.9004
100	1.2438	.2605	.6444	.9049

Energies of activation parameters are listed in table 13. These were calculated from the data in tables 11 and 12 by methods described under "Energies of Activation" (page 30).

Table 13 Energies of activation for intramolecular cyclisations of 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals.

REACTION	$\Delta\Delta S^{\#}$ cal/mole/^{o}K	$\Delta\Delta H^{\#}$ kcal/mole
	6.3 ± .2	2.6 ± .1
	4.9 ± .2	2.5 ± .1
	5.2 ± .2	2.9 ± .1
	6.4 ± .2	2.5 ± .1
	4.8 ± .2	2.8 ± .1
	5.4 ± .2	2.3 ± .1

Where $\Delta\Delta S^{\#} = \Delta S^{\#}_{C} - \Delta S^{\#}_{H}$, and $\Delta\Delta H^{\#} = \Delta H^{\#}_{C} - \Delta H^{\#}_{H}$

Conclusions

The following inferences may be drawn from the observations:

1. Radicals 2-methylhex-5-en-1-yl, and 3-methylhex-5-en-1-yl cyclise irreversibly.

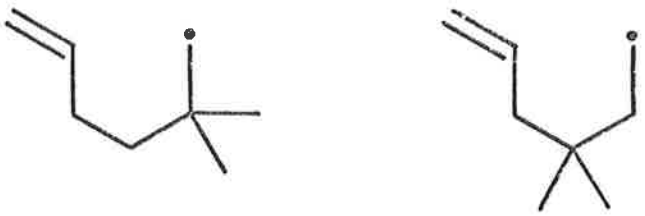
2. Both radicals undergo almost exclusive 1,5-cyclisation. Only traces of products from 1,6-cyclisation are formed.

3. 2-Methylhex-5-en-1-yl radical undergoes intramolecular 1,5-cyclisation 2.6 times as fast as its unsubstituted analogue, hex-5-en-1-yl.

4. 3-Methylhex-5-en-1-yl radical undergoes intramolecular 1,5-cyclisation at 3.3 times the rate of unsubstituted hex-5-en-1-yl radical.

5. Methyl substitutions at C2, and C3 lower the enthalpy of activation for the overall process of 1,5-cyclisation without significantly changing the entropy of activation. The rate enhancement is caused by the lower enthalpy of activation.

6. In both radicals the transition states leading to 1,3-dimethyl-cyclopentane have predominantly chair-like conformations with the methyl groups in equatorial positions.



2,2-DIMETHYLHEX-5-EN-1-YL AND 3,3-DIMETHYLHEX-5-EN-1-YL RADICALS

Having established that a single methyl substituent at either C2, or C3 causes an increase in the rate of intramolecular cyclisation of 2-methylhex-5-en-1-yl and 3-methylhex-5-en-1-yl radicals, and that this kinetic effect of the methyl groups is due to the lowering of the enthalpy of activation for intramolecular cyclisation, it appeared desirable to investigate the effects of gem-dimethyl substitution in 2,2-dimethylhex-5-en-1-yl and 3,3-dimethylhex-5-en-1-yl radicals.

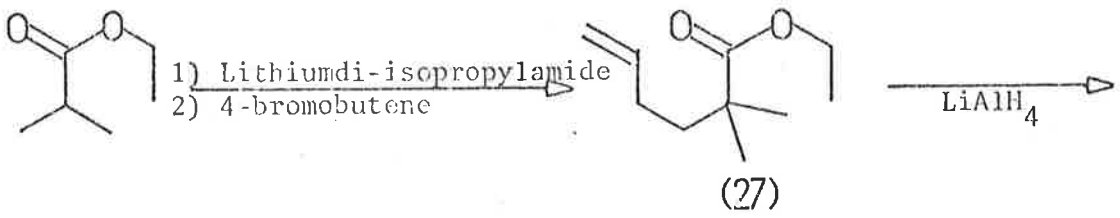
In the study of these two radicals the main aim was the evaluation of the effects of gem-dialkyl substitution on the kinetics and direction of intramolecular cyclisation. Stereochemistry of the cyclised products could give no meaningful information. If increase in the rates of cyclisation did occur, this may be a consequence of changes in the enthalpy or the entropy of activation, or both.

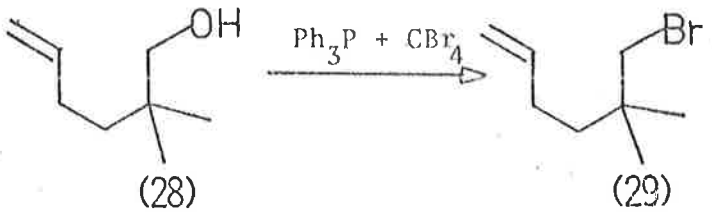
Synthesis

5,5-Dimethyl-6-bromohex-1-ene, the precursor for 2,2-dimethylhex-1-yl radical, was prepared as outlined in scheme 10.

Scheme 10

Synthesis of 5,5-dimethyl-6-bromohex-1-ene.



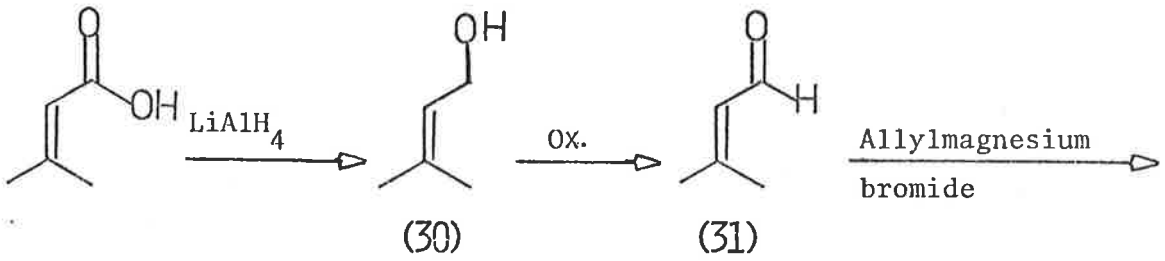


All reactions in scheme 10 gave yields of isolated products in excess of 70%. The ester (ethyl 2,2-dimethylhex-5-en-1-oate), and the alcohol (2,2-dimethylhex-5-en-1-ol) were analytically pure after distillation; whereas the distilled bromide was contaminated with bromoform (2-3%), which was removed by preparative gas liquid chromatography.

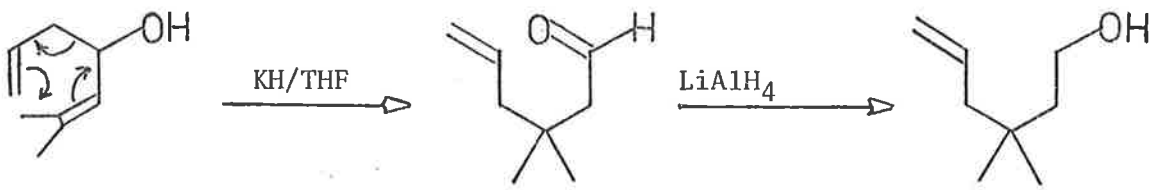
The preparation of 4,4-dimethyl-6-bromohex-1-ene was investigated at some length, because of the need for efficient preparation of summetrically substituted 4,4-dialkyl-6-bromohex-1-enes. During earlier studies of 3-propylhex-5-en-1-yl[57] and 3-allylhex-5-en-1-yl[47] radicals no simple, efficient synthesis of the bromo-precursors was available, and lengthy synthetic schemes had to be employed. The synthetic problem of monoalkyl substitution at C3 on the hex-5-en-1-ol system has been simply overcome in this work with the preparation of 4-methyl-6-bromohex-1-ene, the precursor for 3-methylhex-5-en-1-yl radical. Synthesis of 4,4-dimethyl-6-bromohex-1-ene was attempted by the sequence outlined in scheme 11.

Scheme 11

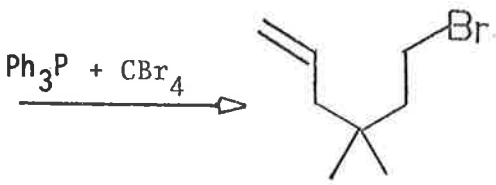
Synthesis of 4,4-dimethyl-6-bromohex-1-ene.



(30) (31)



(32) (33) (42)



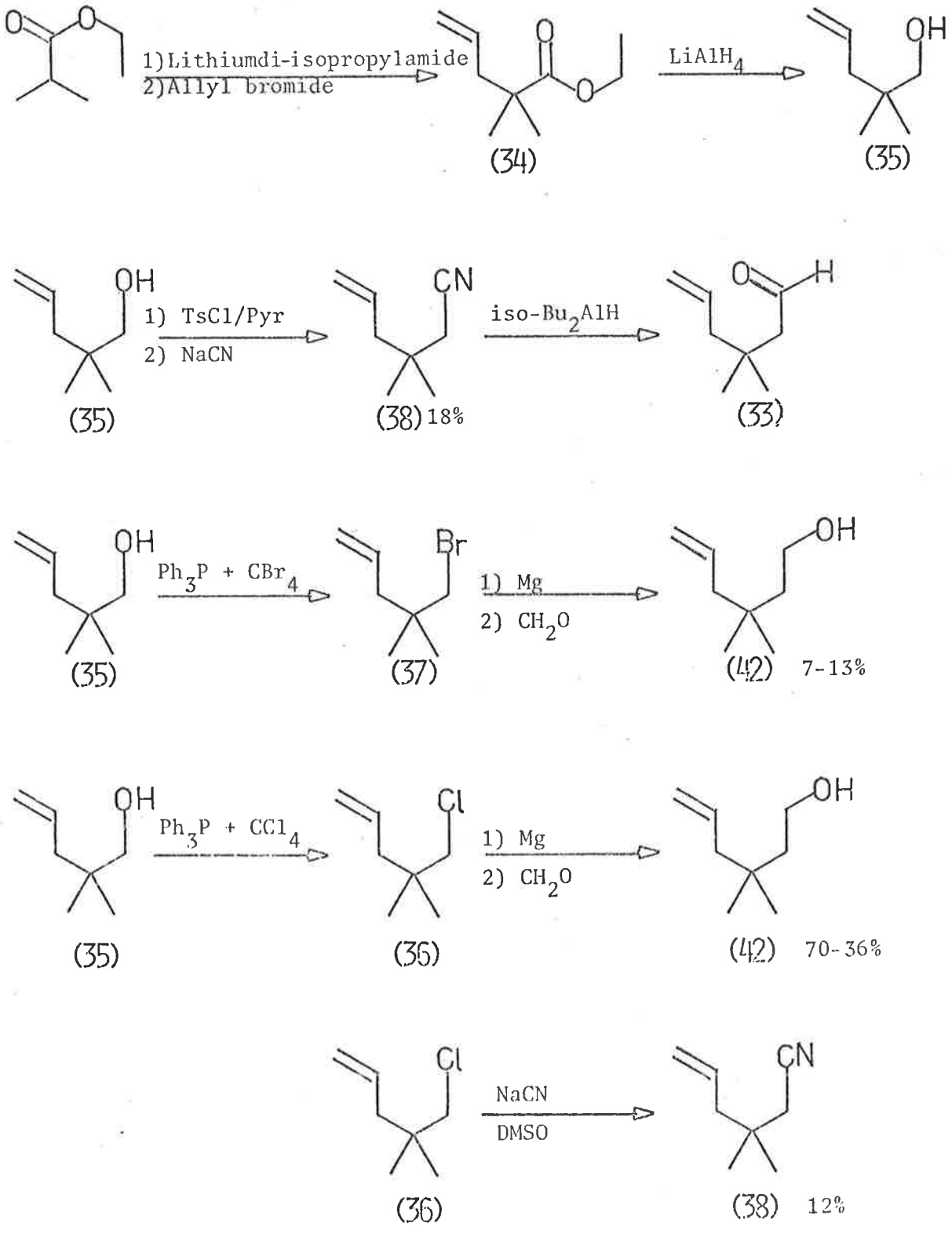
(43)

2-Methyl-2,6-heptadien-4-ol was thus prepared. Reduction of dimethylacrylic acid with $LiAlH_4$ proceeded well without the reduction of the double bond. Likewise a good yield of 3-methylbut-2-en-1-al was obtained by oxidation of 3-methylbut-2-en-1-ol with pyridinium chlorochromate. Attempted oxy-Cope rearrangement of 2-methyl-2,6-heptadien-4-ol did not take place as expected[67]. The reaction was followed by g.l.c. analysis. At room temperature no reaction was detectable after 30 hours. At the reflux temperature of the THF solution slow formation of 3,3-dimethylhex-5-en-1-al, and decrease in the concentration of the starting dienol was noted. After 26 hours the concentration of the product aldehyde reached its maximum, which corresponded to 8% of the initial concentration of the starting material. By this time the concentration of 2-methyl-2,6-heptadien-4-ol had decreased by 14%. Beyond this time the concentration of the product did not increase, while the concentration of the starting material continued to decrease and the solution progressively grew dark-red. After 116 hours of refluxing all the starting material was gone, and the concentration of the product began to decrease. The reaction was stopped, and worked up. 3,3-Dimethylhex-5-en-1-al was obtained in 5% yield. The reaction was repeated using ionophores - crown ether, and hexamethylphosphoramide, but this had no effect on the course of the reaction. A control reaction consisting of 2-methyl-2,6-heptadien-4-ol dissolved in THF (without potassium hydride) was refluxed for 150 hours; no reaction occurred, there was no discolouration, and no decrease in concentration of the dienol. This indicated that the starting material in the attempted oxy-Cope rearrangement was stable under the reaction condition, and that decomposition of the product 3,3-dimethylhex-5-en-1-al was taking place. The rate of decomposition or polymerisation was effectively competing with the rate of rearrangement. Decomposition of the initially formed alkoxide was another possibility.

The next attempt to prepare 4,4-dimethyl-6-bromohex-1-ene was by the synthetic route in scheme 12.

Scheme 12

Synthesis of 4,4-dimethyl-6-bromohex-1-ene.

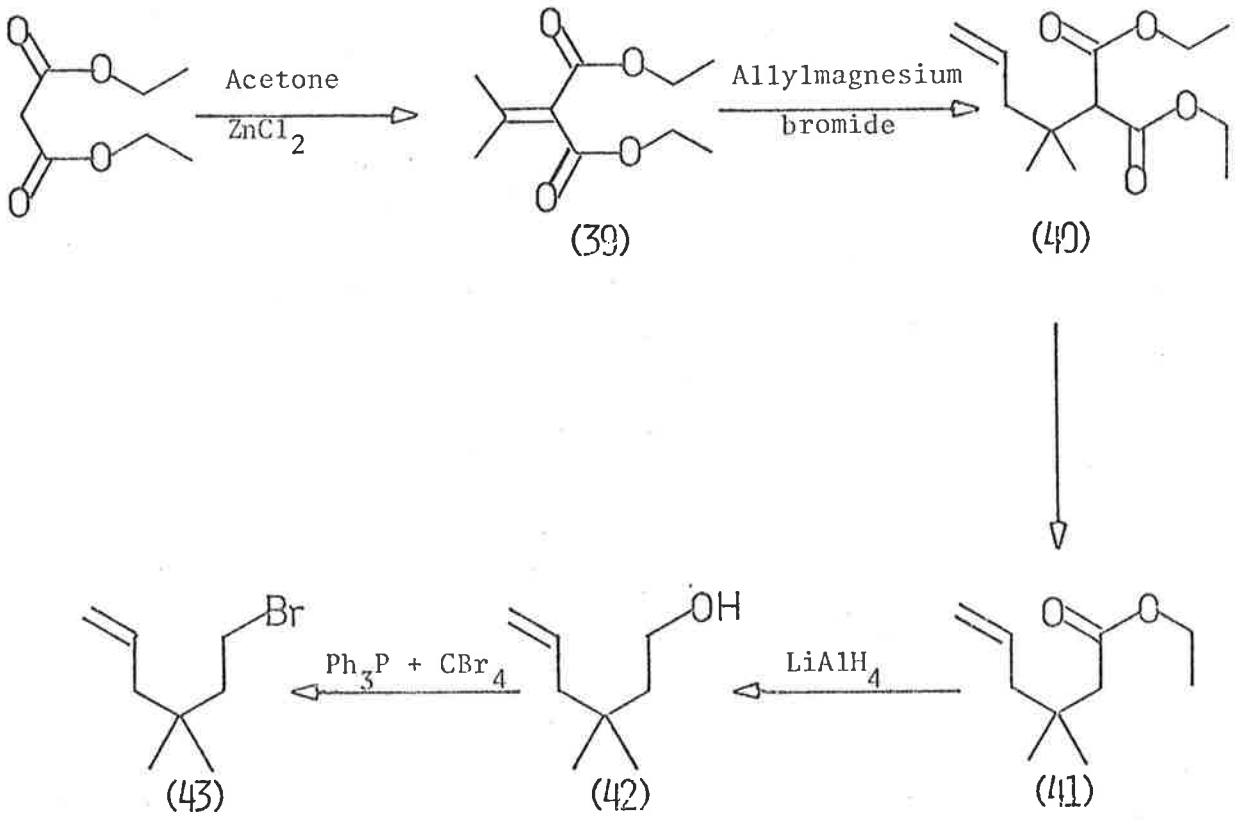


Synthetic routes outlined in scheme 12 were thoroughly investigated, but although the required 4,4-dimethyl-6-bromohex-1-ene could be prepared by the methods outlined, poor yields of 3,3-dimethylhex-5-en-1-ol from Grignard reactions, and the low yield of 3,3-dimethylhex-5-enonitrile made this scheme unacceptable for general use.

4,4-Dimethyl-6-bromohex-1-ene was finally prepared as shown in scheme 13.

Scheme 13

Synthesis of 4,4-dimethyl-6-bromohex-1-ene.



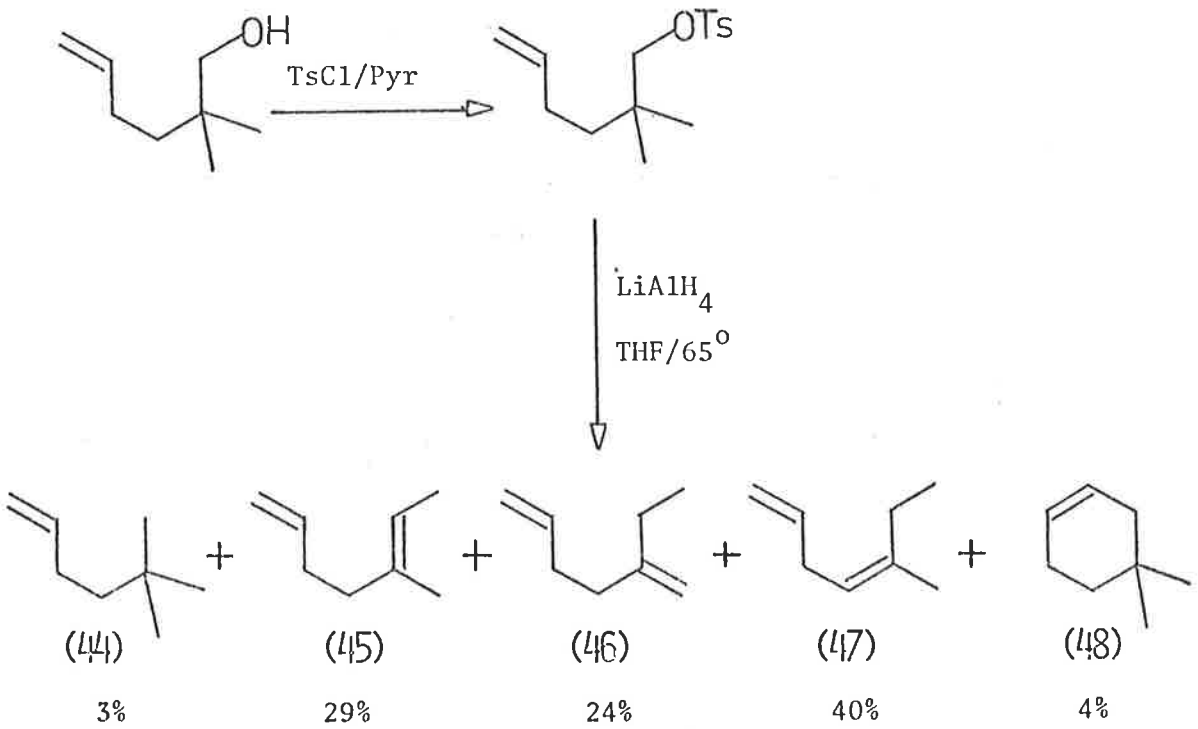
All reactions proceeded cleanly and in good yields.

By analogy to hex-5-en-1-yl, 2-methylhex-5-en-1-yl, and 3-methylhex-5-en-1-yl radicals the mechanism of irreversible rearrangement of 2,2-dimethylhex-5-en-1-yl and 3,3-dimethylhex-5-1-yl radicals was postulated in schemes 19 and 20.

Products predicted from these reactions are 5,5-dimethylhex-1-ene, 4,4-dimethylhex-1-ene, 1,1,3-trimethylcyclopentane, and 1,1-dimethylcyclohexane. For product identification and analytical purposes these hydrocarbons were synthesised as outlined in schemes 14, 15, 16, 17, and 18.

Scheme 14

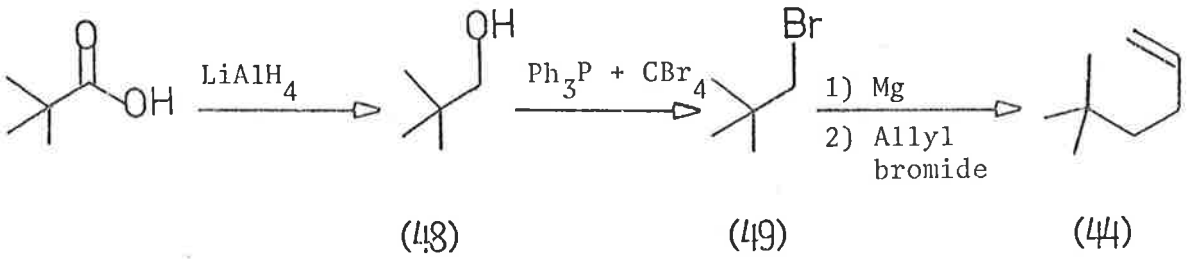
Synthesis of 5,5-dimethylhex-1-ene.



Reduction of the tosylate from 2,2-dimethylhex-5-en-1-ol with $LiAlH_4$ in ether at the reflux, or in THF at room temperature did not proceed. After 15 hours quantitative amounts of tosylate were recovered in each case. Reduction of this neopentyl tosylate did occur after refluxing with $LiAlH_4$ in THF for 17 hours, but only a trace of 5,5-dimethylhex-1-ene was present in the mixture of five products. Relative concentrations of the products were determined on the basis of their g.l.c. peak areas. The two minor products 2,2-dimethylhex-1-ene, and 4,4-dimethylcyclohexene were not isolated. Later on their structures were inferred from their retention times on gas chromotographic columns by comparison with those of authentic samples prepared as outlined in schemes 15 and 18. The three major hydrocarbons were isolated by preparative g.l.c. Their structures were inferred from N.M.R. spectra, and the molecular ions of their mass spectra.

Scheme 15

Synthesis of 5,5-dimethylhex-1-ene.



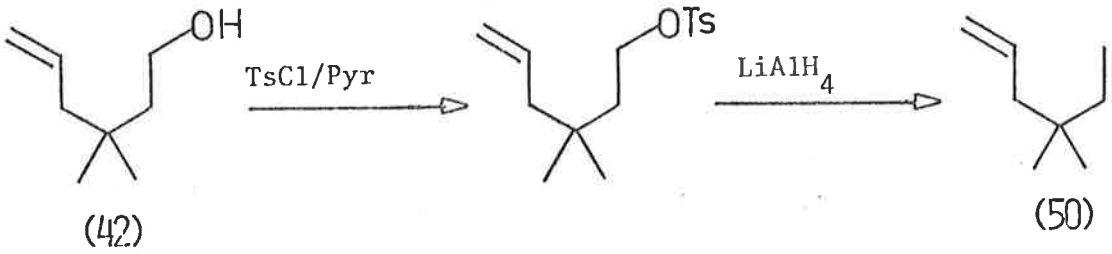
(48) (49) (44)

Slow addition of neopentylmagnesium bromide to allyl bromide in refluxing THF, resulted in efficient coupling of the Grignard reagent and allyl bromide.

4,4-Dimethylhex-1-ene was prepared as shown in scheme 16.

Scheme 16

Synthesis of 4,4-dimethylhex-1-ene.



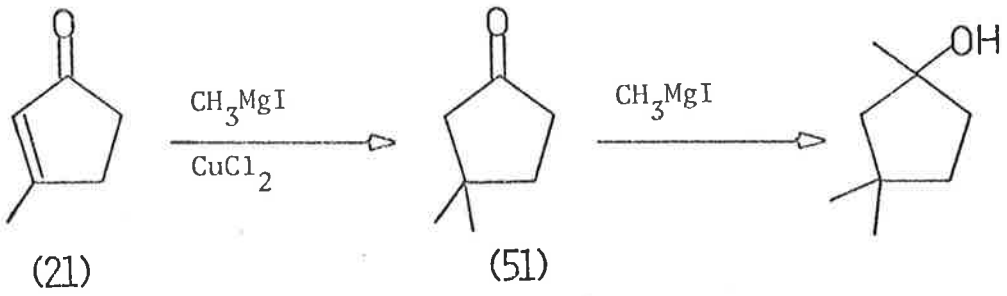
(42) (50)

Displacement of the tosyl group by a hydride in THF took place at room temperature, and no rearrangements were observed.

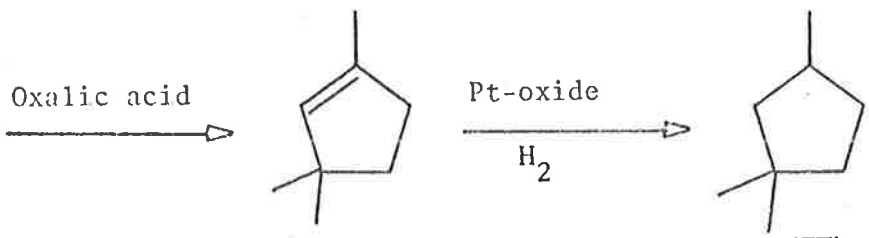
1,1,3-Trimethylcyclopentane, the reference compound for identifying the products of 1,5-cyclisation from both radicals, was prepared as outlined in scheme 17.

Scheme 17

Synthesis of 1,1,3-trimethylcyclopentane.



(21) (51)



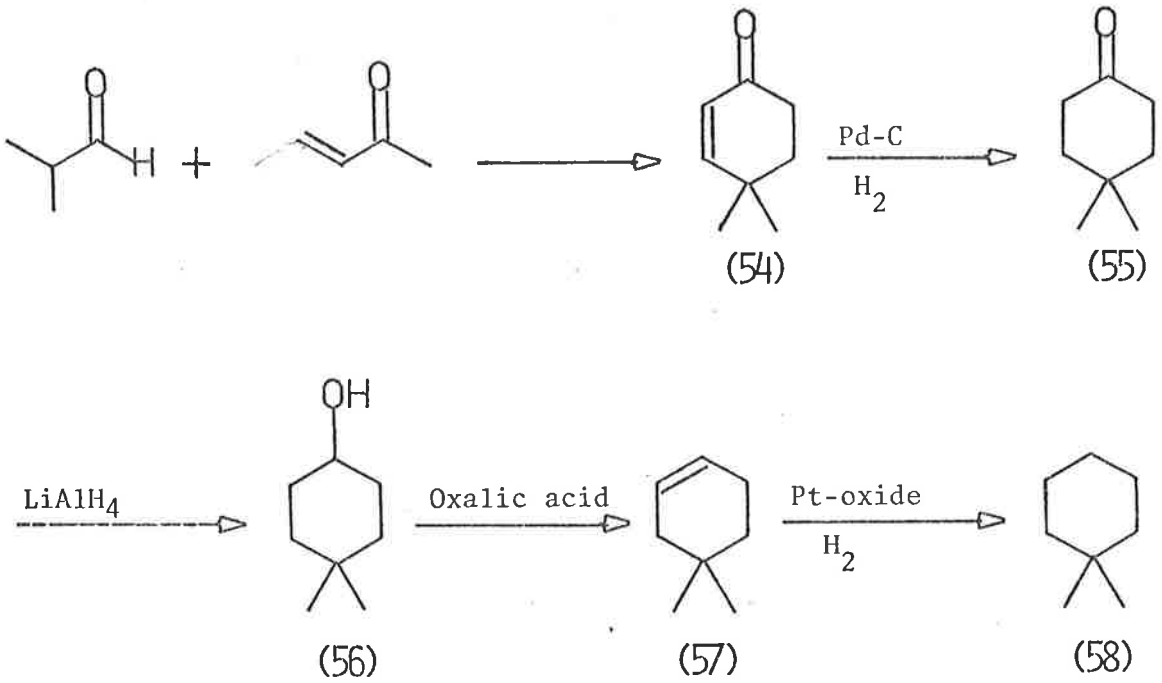
(52) (53)

All reactions proceeded in yields greater than 65%.

The last reference hydrocarbon was prepared by the synthetic sequence in scheme 18.

Scheme 18

Synthesis of 1,1-dimethylcyclohexane.



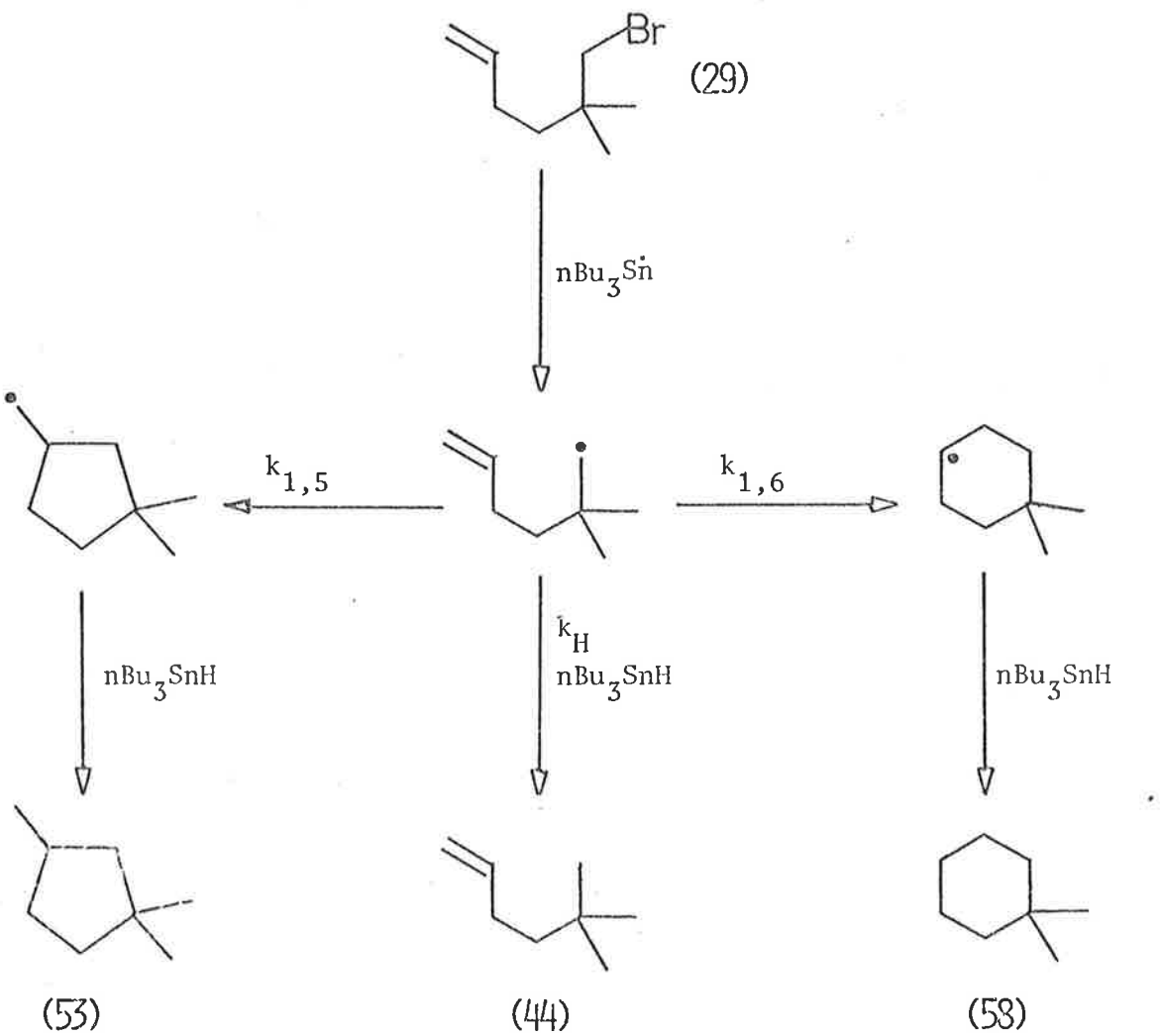
The yields from all reactions were in excess of 70%. Together with 5,5-dimethylhex-1-ene (Scheme 15) 4,4-dimethylcyclohexene (Scheme 18) was used for identifying the minor products from the synthetic sequence in scheme 14.

REDUCTION - RESULTS and DISCUSSION

The reduction mechanisms of 5,5-dimethyl-6-bromohex-1-ene, and 4,4-dimethyl-6-bromohex-1-ene were expected to be similar to those observed for 6-bromohex-1-ene, 5-methyl-6-bromohex-1-ene, and 4-methyl-6-bromohex-1-ene. These are outlined in scheme 19 and 20.

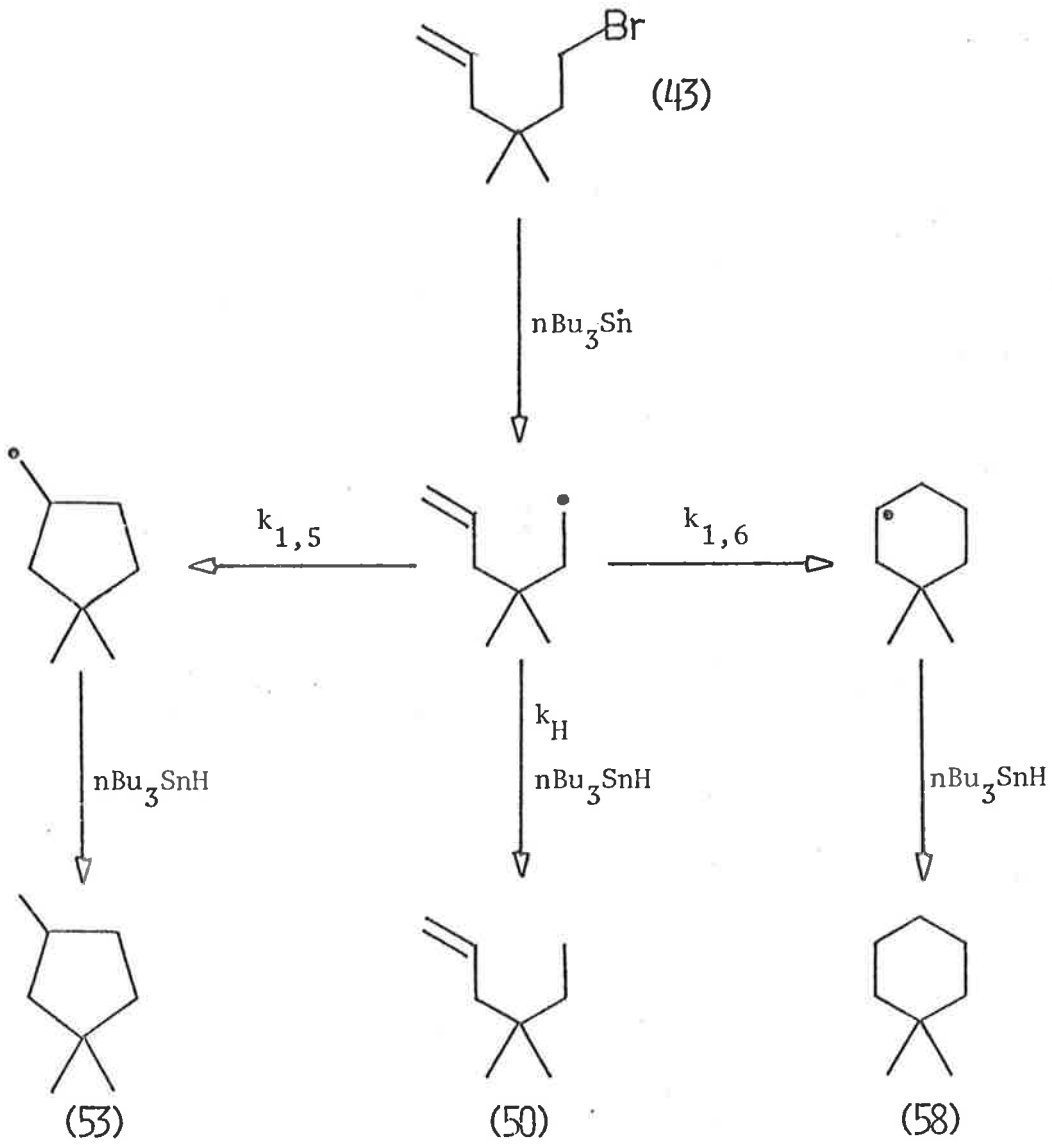
Scheme 19

Reduction of 5,5-dimethyl-6-bromohex-1-ene with nBu_3SnH.



Scheme 20

Reduction of 4,4-dimethyl-6-bromohex-1-ene with nBu_3SnH.



Reductions of 5,5-dimethyl-6-bromohex-1-ene, and 4,4-dimethyl-6-bromohex-1-ene were carried out at the temperatures and tri-n-butyltin hydride concentrations shown in tables 14 and 15. Reductions of both bromides were conducted in benzene. Except in the reduction of 5,5-dimethyl-6-bromohex-1-ene at 55°, in each reaction the bromide was used in an excess of 20%. Besides the acyclic olefin formed from each radical by hydrogen atom abstraction from tri-n-butyltin hydride, both radicals gave 1,1,3-trimethylcyclopentane - the product from irreversible 1,5-intramolecular cyclisation. All reactions proceeded in yields of 80% or greater. No 1,1-dimethylcyclohexane from either radical was detectable by gas chromatographic analysis. In both cases the references compound, 1,1-dimethy cyclohexane, showed a clear g.l.c. peak separation. Distributions of the products from the two sets of reductions are listed in tables 14 and 15.

Table 14 Distribution of products in the reduction of 5,5-dimethyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	Relative Yield %		Total Yield %
		(44)	(53)	
30	.200	5.9	94.1	80
30	1.000	22.8	77.2	83
30	1.395	30.0	70.0	86
40	1.239	24.5	75.7	83
40	1.395	26.7	73.3	85
55*	In. 1.860			
	F. .610	37.6	62.4	91
80	.500	9.6	90.4	90
80	1.000	16.9	83.1	90

* Initial $[nBu_3SnH]$ = 1.860 M, Final $[nBu_3SnH]$ = .610 M.

Table 15 Distribution of products in the reduction of 4,4-dimethyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	Relative Yield %		Total Yield %
		(50)	(53)	
40	.4822	9.1	90.9	82
40	.8348	14.2	85.8	88
40	1.4611	21.8	78.2	89
60	.4806	7.9	92.1	86
60	.8318	12.6	87.4	90
60	1.4609	19.6	80.4	92
80	.4821	7.1	92.9	85
80	.8326	11.6	88.4	91
80	1.4635	17.5	82.5	93
100	.4834	6.3	93.7	87
100	.8331	10.5	89.5	94
100	1.4618	16.5	83.5	96

In the reduction of 4,4-dimethyl-6-bromohex-1-ene the concentrations of tri-n-butyltin hydride were kept near constant at all temperatures. In this way the change in the extent of cyclisation as a function of stannane concentration at each temperature, and as a function of temperature at each concentration of stannane is readily demonstrated (Table 15).

The rate constants calculated from the data in tables 14 and 15 are listed in tables 16 and 17.

Table 16 Values of k_c/k_H for the reduction of 5,5-dimethyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	k_c/k_H l/mole	Mean k_c/k_H l/mole	St. Dev. %
30	.200	1.57		
30	1.000			
30	1.395	1.5072	1.5194	.70
40	1.239	1.7383		
40	1.395	1.7234	1.7234	.60
55*	In. 1.860			
	F. .610	1.9823	1.9823	
80	.500	2.2796		
80	1.000	2.3130	2.2963	1.03

* Initial $[nBu_3SnH]$ = 1.8600 mol/l, Final $[nBu_3SnH]$ = .6100 mol/l.

Table 17 Values of k_c/k_H for the reduction of 4,4-dimethyl-6-bromohex-1-ene with nBu_3SnH.

Temp. °C	$[nBu_3SnH]$ mol/l	k_c/k_H l/mole	Mean k_c/k_H l/mole	St. Dev. %
40	.4822	2.337		
40	.48348	2.4066		
40	1.4611	2.4125	2.3843	1.8
60	.4806	2.7177		
60	.8218	2.7609		
60	1.4609	2.7866	2.7551	1.3
80	.4821	3.0993		
80	.8326	3.0461		
80	1.4635	3.2269	3.1241	3.0
100	.4834	3.5373		
100	.8331	3.4392		
100	1.4618	3.4926	3.4897	1.4

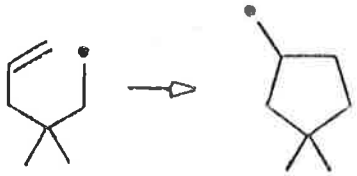
Considerable enhancement in the rate of intramolecular 1,5-cyclisation is observed. This is the consequence of *gem*-dimethyl substitution at C2 and C3 of the hex-5-en-1-yl system. For comparison relative rate constants are listed in table 18.

Table 18 $\Sigma k_c/k_H$ values at 80° for alkyl substituted hex-5-en-1-yl radicals relative to unsubstituted hex-5-en-1-yl radical.

Radical	$\Sigma k_c/k_H$ l/mole
Hex-5-en-1-yl	1.0
2-Methylhex-5-en-1-yl	2.57
3-Methylhex-5-en-1-yl	3.30
2,2-Dimethylhex-5-en-1-yl	10.11
3,3-Dimethylhex-5-en-1-yl	13.76

Energies of activation are listed in table 19.

Table 19 Energies of activation for the cyclisation of 2,2-dimethylhex-5-en-1-yl and 3,3-dimethylhex-5-en-1-yl radicals relative to hydrogen atom abstraction.

REACTION	$\Delta\Delta S^{\#}$ cal/mole/°K	$\Delta\Delta H^{\#}$ kcal/mole
	6.6 ± .2	1.7 ± .1
	6.4 ± .2	1.5 ± .1

Where $\Delta\Delta S^{\#} = \Delta S_c^{\#} - \Delta S_H^{\#}$, and $\Delta\Delta H^{\#} = \Delta H_c^{\#} - \Delta H_H^{\#}$

It is evident from table 19 that the observed rate enhancement of intramolecular cyclisation is driven by the enthalpy of activation. Like the monomethyl substitution at C2 or C3 positions, gem-dimethyl substitution at these carbons has no significant effect on the entropy of activation. Decrease in the enthalpy of activation is a function of the position and extent of methyl substitution as regards carbons 2 and 3 of the hex-5-en-1-yl system.

CONCLUSIONS

(1) Intramolecular cyclisation if 2,2-dimethylhex-5-en-1-yl and 3,3-dimethylhex-5-en-1-yl radicals is irreversible.

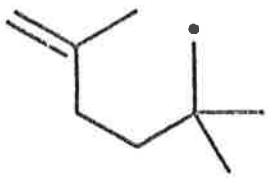
(2) Neither radical undergoes, 1,6-cyclisation under the experimental conditions of this work.

(3) 2,2-Dimethylhex-5-en-1-yl radical has the rate of intramolecular 1,5-cyclisation 10 times greater than the unsubstituted hex-5-en-1-yl radical.

(4) 3,3-Dimethylhex-5-en-1-yl radical undergoes 1,5-cyclisation 13.5 times as fast as its unsubstituted analogue, hex-5-en-1-yl radical.

(5) Entropy of activation for the cyclisation process of either radical is not significantly different from that of hex-5-en-1-yl radical.

(6) Decrease in the enthalpy of activation is a consequence of gem-dimethyl substitution and the sole cause of the increase in the rate of 1,5-cyclisation. This effect of dimethyl substitution is greater at C3 than at C2.



2,2,5-TRIMETHYLHEX-5-EN-1-YL RADICAL

Observations from studies of the kinetics of the radicals thus far investigated in this work offer little or no information as to the causes of their exclusive and almost exclusive 1,5-intramolecular cyclisation.

No evidence has emerged to confirm or deny either Beckwith's[25,35] explanation of stereoelectronic control, or Julia's[34,37] explanation of non-bonded interactions.

If we, for reasons stated earlier (page 14-15), reject the explanation that 1,5-cyclisation of the hex-5-en-1-yl radical is an entropy driven process, then Beckwith's and Julia's hypotheses are the only two models left for rationalising this fact. Beckwith's explanation is rather appealing; if there is to be a reaction the electronic orbitals involved must meet certain geometrical requirements, and the better is the geometrical positioning of these orbitals the lower is the energy of activation and the faster will the reaction take place. Yet it is not possible to put measurements into Beckwith's reasoning. Under what conditions is the hypothesis of stereoelectronic control refutable? Julia's hypothesis is easier to deal with, even though the magnitudes of through space interactions between the pseudo-axial proton at C2 and the *syn*-proton at C6 cannot be measured.

In an earlier work[35] it was noted that regioselectivity of intramolecular cyclisation of hex-5-en-1-yl radical was changed by a methyl substituent at C5. Unlike unsubstituted hex-5-en-1-yl radical, which undergoes almost exclusive 1,5-cyclisation, **5-methylhex-5-en-1-yl radical** underwent 1,6-cyclisation 50% faster than it did 1,5-cyclisation. Kinetic measurements showed that, relative to the unsubstituted hex-5-en-1-yl radical, the rate of 1,5-intramolecular cyclisation of **5-methylhex-5-en-1-yl** radical was greatly reduced (about 30 times), and that the rate of 1,6-cyclisation was about doubled. This increase in 1,6-cyclisation may have been illusory, because the rate of 1,6-cyclisation of the hex-5-en-1-yl

radical is difficult to measure. Due to the large decrease in the rate of 1,5-cyclisation of the 5-methylhex-5-en-1-yl radical, the rate of formation of 1-methylcyclohexyl radical could effectively compete with the rate of formation of the 1-methylcyclopentyl carbinyl radical.

By analogy to the 5-methylhex-5-en-1-yl radical, the 2,2,5-trimethylhex-5-en-1-yl radical would have a low rate of intramolecular 1,5-cyclisation. But unlike the 5-methylhex-5-en-1-yl radical, the 2,2,5-trimethylhex-5-en-1-yl radical would carry methyl groups at C2, which are considerably bulkier than hydrogens, and must have a greater radius of through space interactions with the *syn*-proton at C6. If Julia's hypothesis were true, no intramolecular 1,6-cyclisation of 2,2,5-trimethylhex-5-en-1-yl radical would occur. And if 1,6-cyclisation did take place at the same, or a greater rate, as that observed with hex-5-en-1-yl and 5-methylhex-5-en-1-yl radicals, then the explanation that 1,6-intramolecular cyclisation of the hex-5-en-1-yl radical is barred by non-bonded interactions between the protons at carbons 2 and 6 must be false. Study of 2,2,5-trimethylhex-5-en-1-yl radical was undertaken with the main aim of testing Julia's hypothesis of non-bonded interactions.

Synthesis

The preparation of 2,5,5-trimethyl-6-bromohex-1-ene, the precursor for the 2,2,5-trimethylhex-5-en-1-yl radical, presented synthetic difficulties at the bromination step of 2,2,5-trimethylhex-5-en-1-ol.

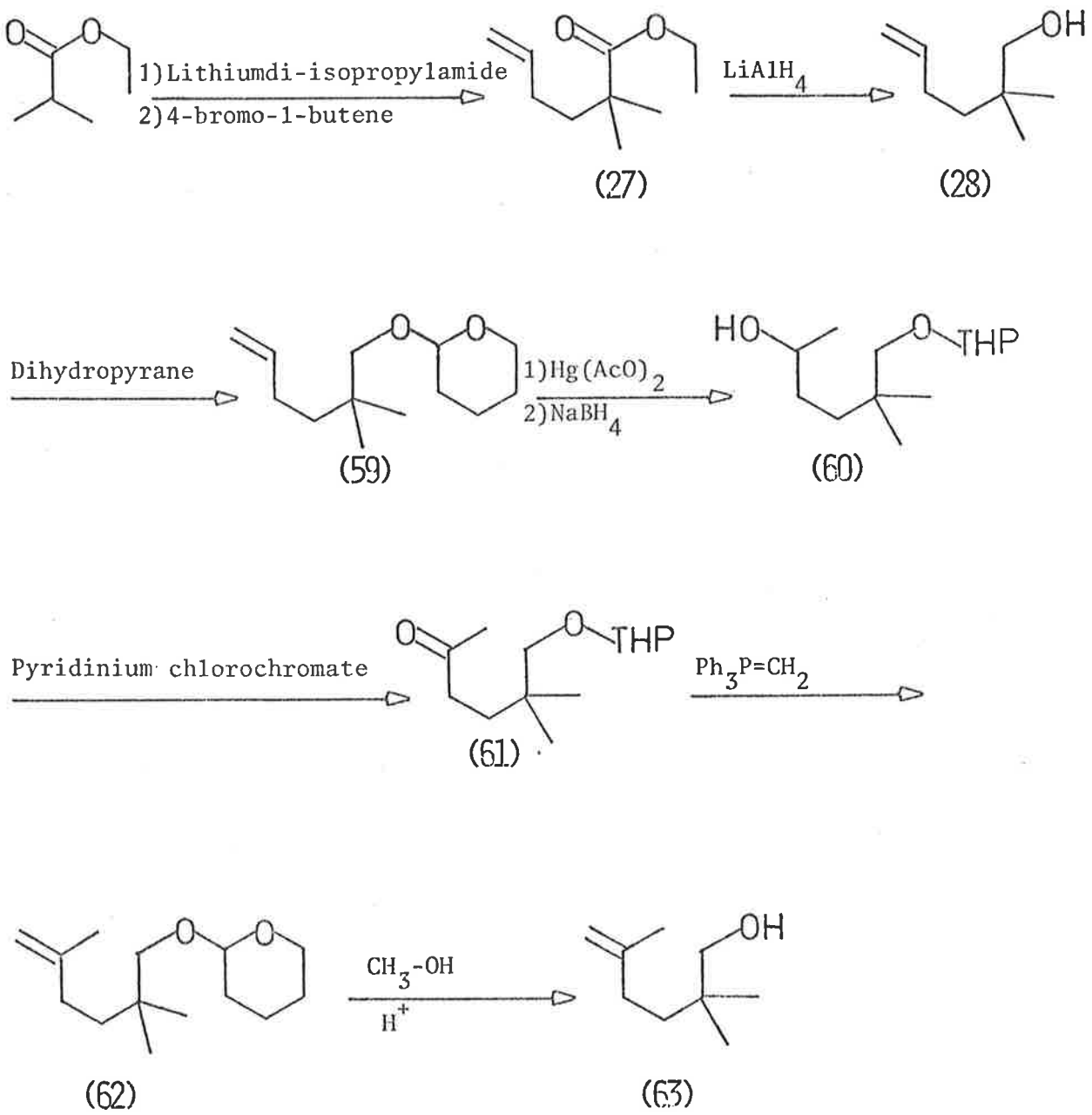
Synthetic methods employed earlier in the bromination of 3-methylbut-3-en-1-ol, and 2,2-dimethylhex-5-en-1-ol, which gave yields of the corresponding bromides in excess of 70% without detectable isomerisation of the double bond, either produced intractable polymeric products, or low yields of isomerised 2,5,5-trimethyl-6-bromohex-2-ene as the main product. Since the steric hindrance by the methyl groups makes the tosylates of

neopentyl alcohols inert to SN_2 displacements, no bromination of 2,2,5-trimethylhex-5-en-1-ol was attempted through its tosylate. This lack of reactivity of the neopentyl system was noted in the course of present work when it was found difficult to brominate the tosylate of 2,2,-dimethyl-hex-5-en-1-ol, or to displace the tosyl group by a hydride ion from $LiAlH_4$. When 2,2,5-trimethylhex-5-en-1-ol was added to triphenylphosphine and carbon tetrabromide in dichloromethane, bromination did take place, and was accompanied by a shift of the double bond from C1-C2 to C2-C3. The yield of the isomeric mixture was below 40%.

Prior to bromination the starting material, 2,2,5-trimethylhex-5-en-1-ol, was prepared by synthetic sequences in scheme 21 and scheme 22.

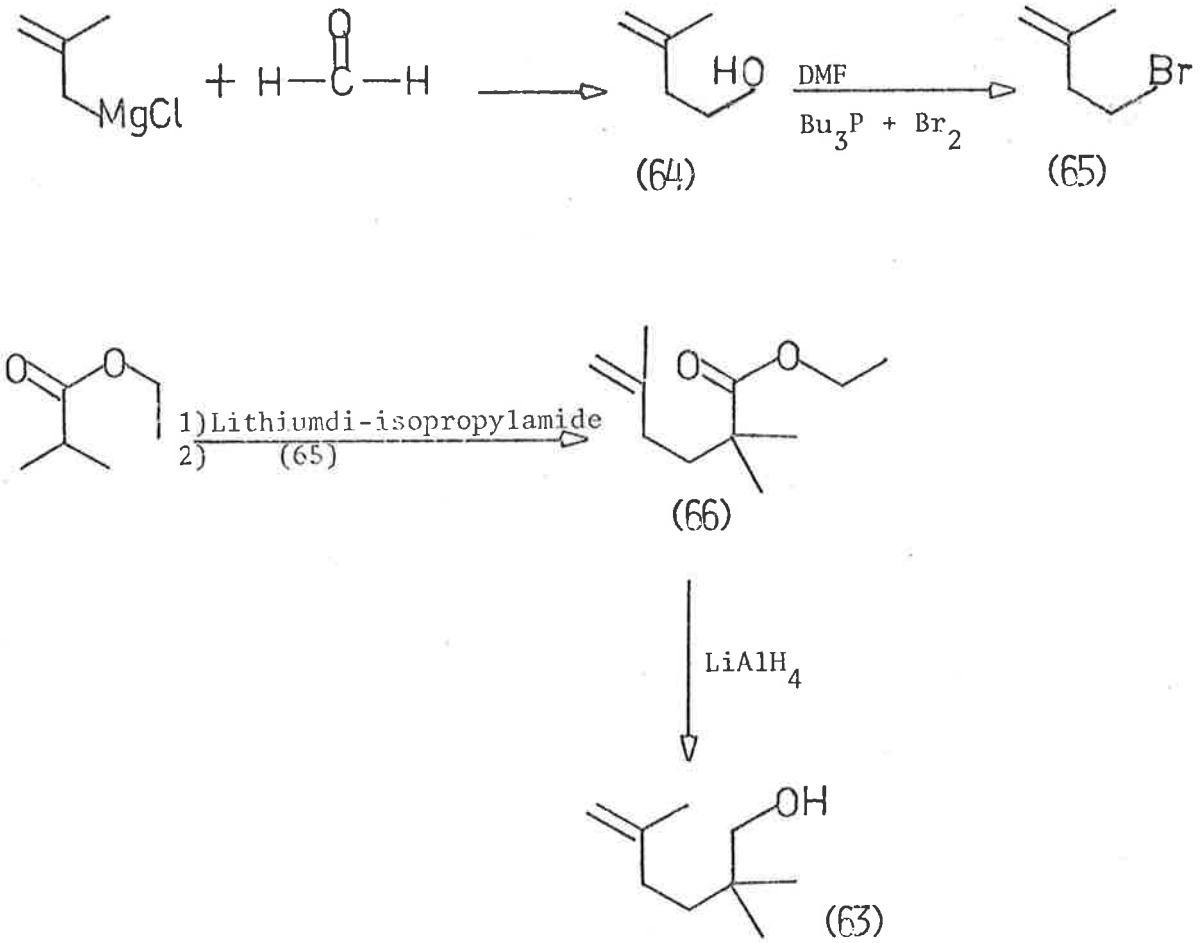
Scheme 21

Synthesis of 2,2,5-trimethylhex-5-en-1-ol.



Scheme 22

Synthesis of 2,2,5-trimethylhex-5-en-1-ol.



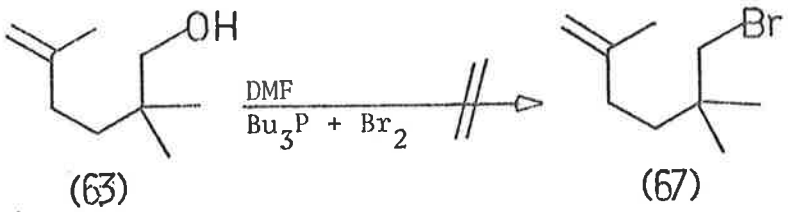
All reactions, except the Grignard reaction in the first step of scheme 22, proceeded with reproducible yields in excess of 75%. The yield of 3-methylbut-3-en-1-ol from 2-methylpropenemagnesium chloride, and gaseous formaldehyde fluctuated between 30% and 75%.

Bromination of 2,2,5-trimethylhex-5-en-1-ol was undertaken by the synthetic sequences in schemes 23 and 24. Because difficulties were encountered at this point, controls were set up in order to test the reaction conditions. All the reagents, and all the solvents were freshly purified and dried, and air and moisture were carefully excluded from the

reaction vessels.

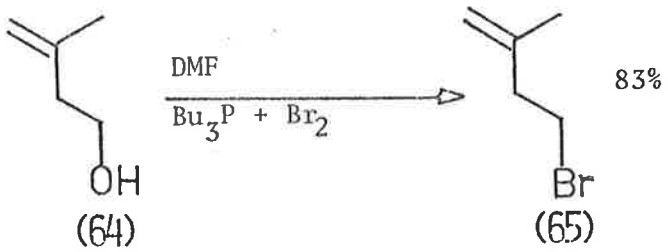
Scheme 23

Synthesis of 2,5,5-trimethyl-6-bromohex-1-ene.

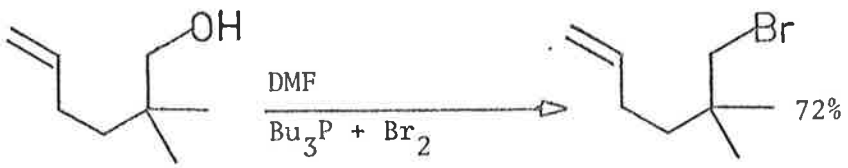


(63) (67)

Controls



(64) (65)



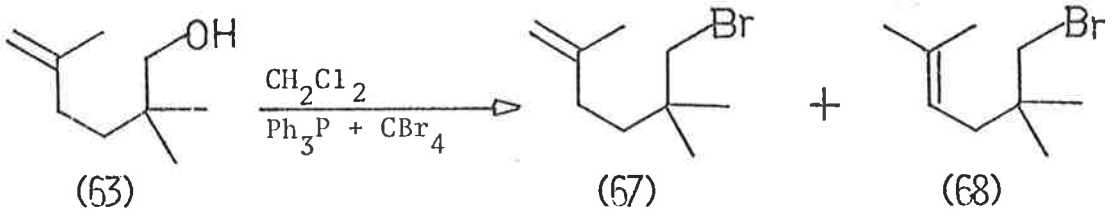
(28) (29)

An exothermic reaction ensued upon addition of 2,2,5-trimethylhex-5-en-1-ol to tributylphosphine in DMF, which had been treated with bromine. Gas chromatographic analysis showed a rapid disappearance of the starting

alcohol, but no products. No products could be recovered when the reaction was worked up. Viscous residue, which could not be distilled at 150°/.01 mm, indicated that the reaction was terminated by polymer formation. Control reactions with 3-methylbut-3-en-1-ol, and 2,2-dimethylhex-5-en-1-ol, gave the corresponding bromides in 83% and 72% yields respectively.

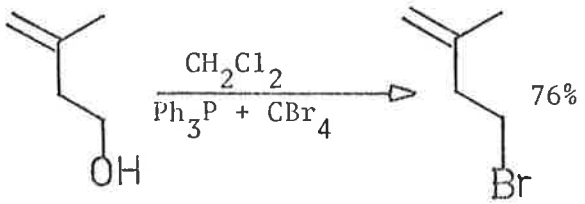
Scheme 24

Synthesis of 2,5,5-trimethyl-6-bromohex-1-ene.

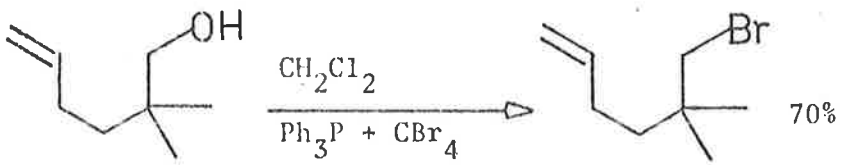


(63) (67) (68)

Controls



(64) (65)

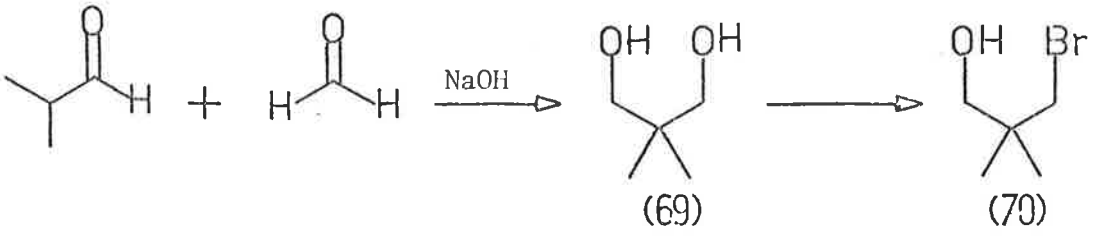


(28) (29)

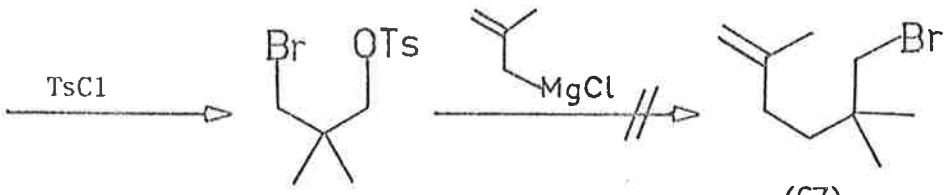
Reaction of 2,2,5-trimethylhex-5-en-1-ol with triphenylphosphine and carbon tetrabromide in dichloromethane produced a mixture of distilled 2,5,5-trimethyl-6-bromohex-1-ene (67), and 2,5,5-trimethyl-6-bromohex-2-ene (68), with the overall yield of 43%. Again control brominations of 3-methylbut-3-en-1-ol and 2,2-dimethylhex-5-en-1-ol alcohols produced distilled bromides in 76% and 70% yields. There was no evidence of double bond isomerisation in either control. At this point a new attempt to prepare 2,5,5-trimethyl-6-bromohex-1-ene was made by the synthetic sequence in scheme 25.

Scheme 25

Synthesis of 2,5,5-trimethyl-6-bromohex-1-ene.



(69) (70)



(67)

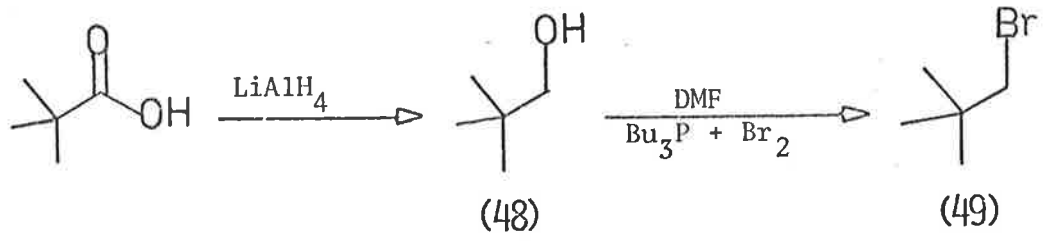
Even though in the course of this study it was observed that the tosylate of 2,2-dimethylhex-5-en-1-ol could not be brominated with LiBr, nor the tosyl group displaced by a hydride from $LiAlH_4$ under forcing conditions, synthesis of (67) by the above sequence was tried on the basis of reports[70] that the coupling of tosylates with Grignard reagents is more facile than the coupling of the corresponding bromides. The coupling of the tosylate of 3-bromomethane-3-methylpropan-1-ol to 2-methylpropenemagnesium chloride was tried more out of interest than belief that tosyl displacement could take place in such a hindered neopentyl system. No coupling occurred.

In the end 2,5,5-trimethyl-6-bromohex-1-ene, prepared by a series of bromination reactions (Scheme 24), was separated from 2,5,5-trimethyl-6-bromohex-2-ene by preparative gas liquid chromatography. The mean yield of pure 2,5,5-trimethyl-6-bromohex-1-ene thus obtained was 12-15%.

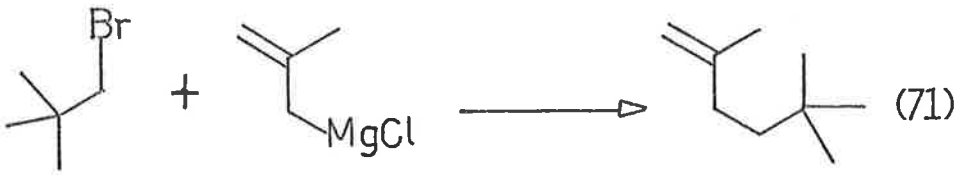
The reference compounds 2,5,5-trimethylhex-1-ene, 1,1,3,3-tetramethylcyclopentane, and 1,1,4-trimethylcyclohexane were prepared by synthetic sequences in schemes 26, 27, and 28. These hydrocarbons represent the products from the reduction of 2,5,5-trimethyl-6-bromohex-1-ene with tri-n-butyltin hydride, which are predicted by the postulated mechanism of reduction in scheme 29.

Scheme 26

Synthesis of 2,5,5-trimethylhex-1-ene.



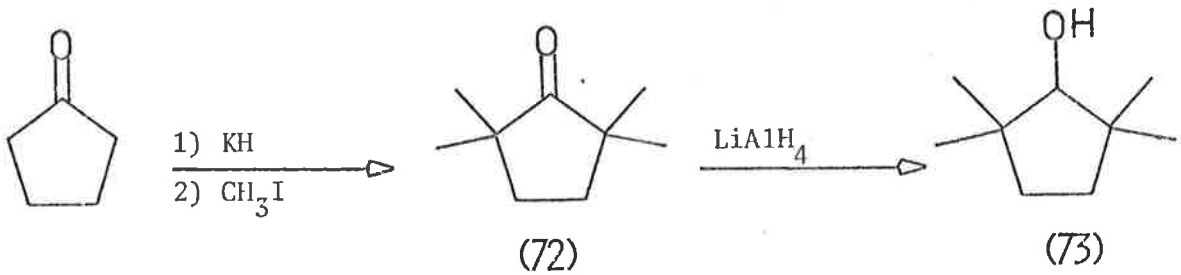
(48) (49)



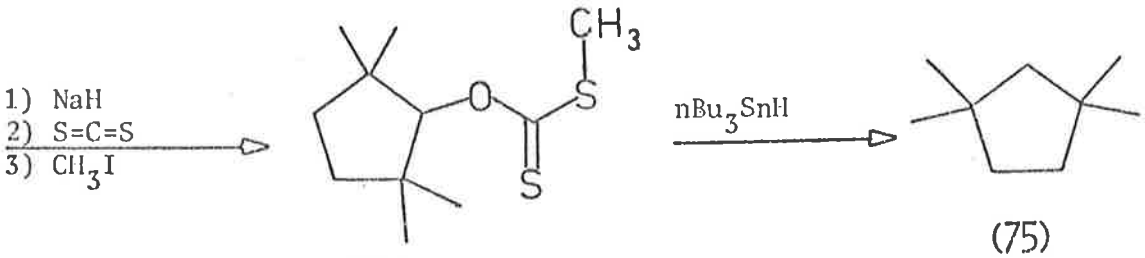
(71)

Scheme 27

Synthesis of 1,1,3,3-tetramethylcyclopentane.



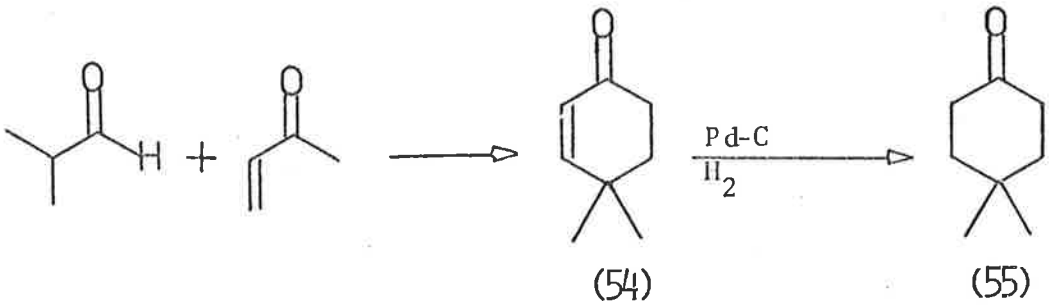
(72) (73)



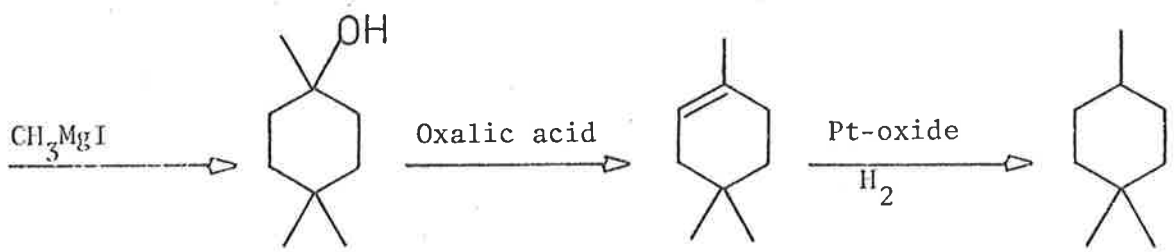
(74) (75)

Scheme 28

Synthesis of 1,1,4-trimethylcyclohexane.



(54) (55)



(76) (77)

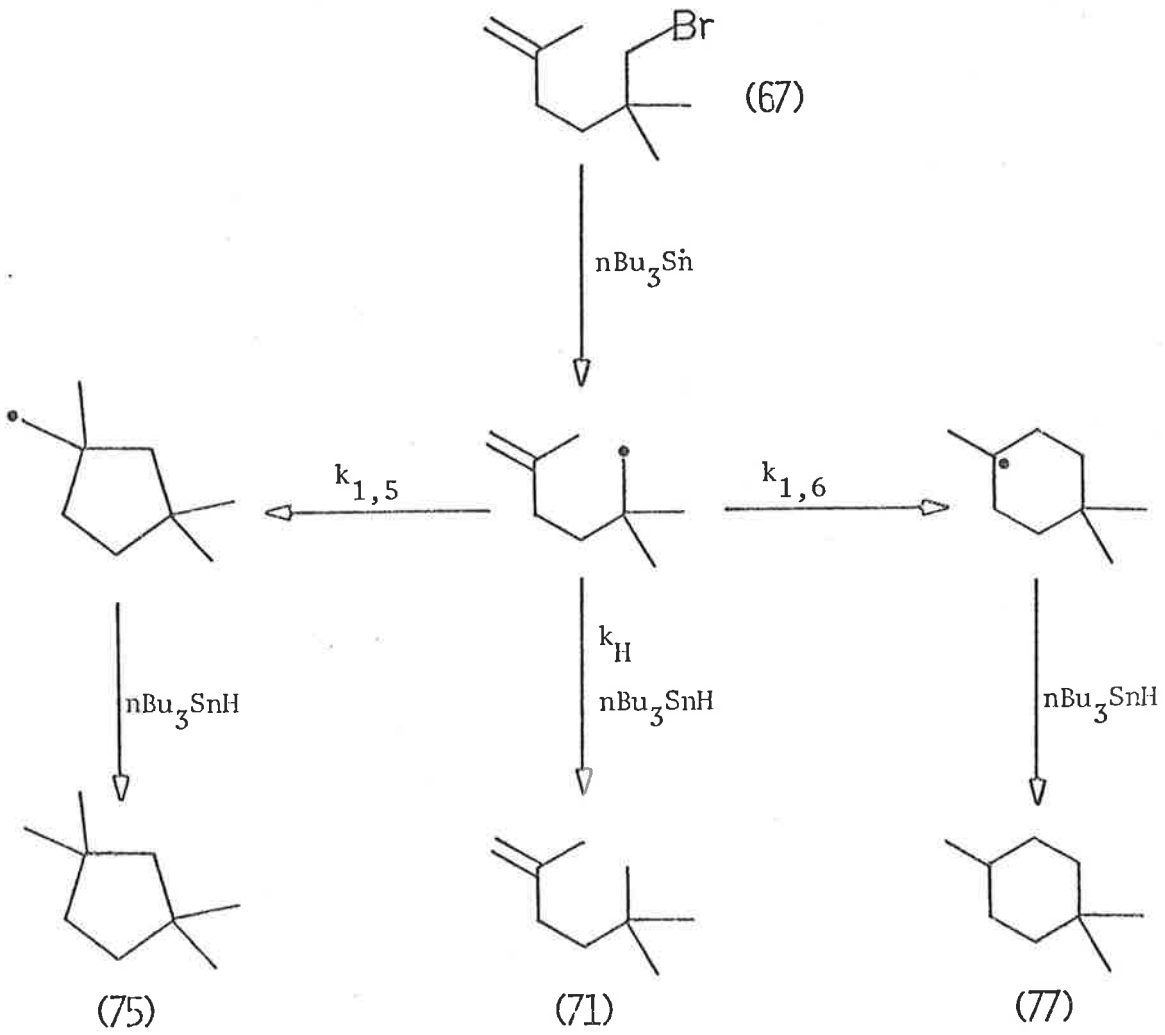
All the reactions outlined in schemes 26, 27, and 28 proceeded cleanly with no yield in any one step lower than 50%.

REDUCTION - RESULTS AND DISCUSSION

By analogy to earlier observations in this work the reduction of 2,5,5-trimethyl-6-bromohex-1-ene with tri-n-butyltinhydride was predicted to follow the mechanism outlined in scheme 29.

Scheme 29

Outline of the mechanism for the reduction of 2,2,5-trimethyl-6-bromohex-1-ene with nBu_3SnH.



2,5,5-Trimethyl-6-bromohex-1-ene was reduced at 55°, 60°, 80°, and 100° using bromide concentrations of .0139 M, .0278 M, and .0555 M. In all reactions tri-n-butyltin hydride was present in excess, at concentrations listed in table 20. Reductions were duplicated at 100° with tri-n-butyltin deuteride at concentrations also listed in table 20. This set of reductions differed from those of the preceeding bromides in that, through shortage of 2,5,5-trimethyl-6-bromohex-1-ene, excess stannane was employed in all reactions. With this method both the bromide and the stannane concentrations

had to be determined with high accuracy. Hence the probability of concentrations-related experimental errors was doubled. Nevertheless this did not impair the reliability of observations with respect to the extent of the relative rates of *exo* and *endo* cyclisations, although the values of the rates of total rearrangements at any one temperature may vary by a degree proprotional to the added probability of error (1-2.5%). Relative and overall yields of products are listed in table 20.

Table 20 Distribution of products from the reduction of 2,5,5-trimethyl-6-bromohex-1-ene with nBu_3SnH, and nBu_3SnD.

Temp. °C	$[nBu_3SnH]$ mol/l	[67] mol/l	Relative Yields % (71)	(75)	(77)	Total Yield %
55	.0378	.0139	35.2	45.6	19.2	88
55	.1511	.0555	67.6	22.5	9.9	89
60	.0378	.0139	32.8	32.8	20.4	90
60	.1511	.0555	65.8	23.8	10.4	90
80	.0378	.0139	25.0	51.3	23.7	90
80	.1511	.0555	56.5	29.7	13.8	91
100	.0378	.0139	18.9	55.4	25.8	93
100	.1511	.0555	48.7	34.8	16.5	95
100	.0378*	.0139	13.1	58.9	28.9	90
100	.0756*	.0278	22.8	52.7	24.5	92

* nBu_3SnD was used.

Distribution of the products was very different from **that** observed with earlier radicals. Whereas with all other radicals thus far examined in this work the extent of intramolecular 1,6-cyclisation was just measurable or non-existent; now one third of the cyclised product was formed by 1,6-addition. The mean ratios of 1,1,3,3-tetramethylcyclopentane to 1,1,4-trimethylcyclohexane were 2.320 at 55^0, 2.301 at 60^0, 2.160 at 80^0, and 2.125 at 100^0.

However, relative yields of products from these intramolecular rearrangements tell nothing about the absolute rates of their formation. Nevertheless, the results do show that even without the knowledge of the rate constants, 1,6-cyclisation is occurring to a greater extent than would be possible if non-bonded interaction of the type proposed by Julia existed.

Rate constants, k_c/k_H and k_c/k_D, were calculated from the data in table 20 and are listed in table 21. The deuterium isotope effect at 100^o was 1.6.

Table 21 Values of k_c/k_H and k_c/k_D for the reduction of 2,2,5-trimethyl-6-bromohex-1-ene with nBu_3SnH, and nBu_3SnD.

Temp. ^oC	$[nBu_3SnH]$ mol/l	[67] mol/l	$\Sigma k_c/k_H$ l/mole	$k_{c_{1,5}}/k_H$ l/mole	$k_{c_{1,6}}/k_H$ l/mole	Mean $\Sigma k_c/k_H$ l/mole	St. Dev %
55	.0378	.0139	.0565	.0398	.0167		
55	.1511	.0555	.0584	.0405	.0179	.0574	2.3
60	.0378	.0139	.0629	.0438	.0191		
60	.1511	.0555	.0633	.0441	.0192	.0631	.5
80	.0378	.0139	.0921	.0630	.0291		
80	.1511	.0555	.0940	.0642	.0298	.0931	1.4
100	.0378	.0139	.1320	.0901	.0419		
100	.1511	.0555	.1287	.0872	.0415	.1304	1.8
Temp. ^oC	$[nBu_3SnD]$ mol/l	[67] mol/l	$\Sigma k_c/k_D$ l/mol	$k_{c_{1,5}}/k_D$ l/mole	$k_{c_{1,6}}/k_D$ l/mol	Mean $\Sigma k_c/k_D$ l/mol	St. Dev %
100	.0378	.0139	.2000	.1355	.0645		
100	.0756	.0278	.2000	.1355	.0645	.2000	0.1

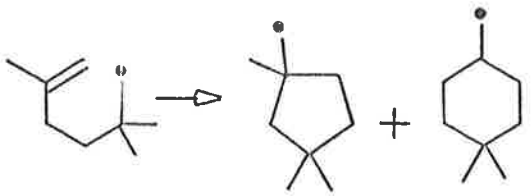
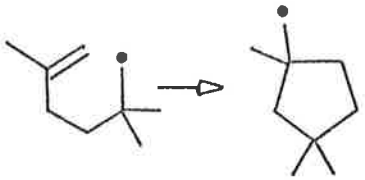
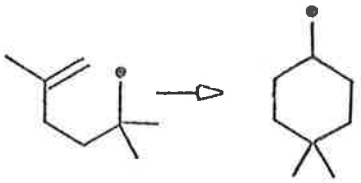
At 80° the k_c/k_H value for the 1,5-cyclisation of unsubstituted hex-5-en-1-yl radical was .2270 l/mole. The mean rate constant, k_c/k_H, for 1,6-cyclisation was .008 l/mol. An earlier estimate of $k_{c_{1,6}}/k_H$ for intramolecular 1,6-cyclisation of the hex-5-en-1-yl radical was ≈ .005 l/mol[41]. Results in table 21 show that the rate constant, k_c/k_H for intramolecular 1,6-cyclisation of 2,2,5-trimethylhex-5-en-1-yl radical at 80° is .0294 l/mole. That is 1,6-cyclisation is 4-6 times faster than the 1,6-intramolecular cyclisation of the hex-5-en-1-yl radical. A better comparison may be made between the rate constants, $k_{c_{1,6}}/k_H$, of 5-methylhex-5-en-1-yl and 2,2,5-trimethylhex-5-en-1-yl radicals. At 80° the $k_{c_{1,6}}/k_H$ value of the former radical was .012 l/mole, while the value of $k_{c_{1,6}}/k_H$ of the latter radical was .0294 l/mole.

These observations are inconsistent with Julia's hypothesis of non-bonded interactions[34,37] (page 15). Thus dimethyl substitution at C2 of the 5-methylhex-5-en-1-yl radical increases the rate of 1,6-intramolecular cyclisation by about 2.5 times, whereas the non-bonded interactions hypothesis predicts the opposite outcome from such gem-dimethyl substitution. At first it appeared[71] that to some extent 1,6-cyclisation was barred by non-bonded interactions between the gem-dimethyl groups and the C6 *syn*-hydrogen of the 2,2,-dimethylhex-5-en-1-yl radical, because this time no rate enhancement of 1,6-cyclisation was observed, while the rate of 1,5-cyclisation increased ten times. On the other hand no 1,6-cyclisation rate enhancement occurred in the 3,3,-dimethylhex-5-1-yl radical, where the rate of 1,5-cyclisation was increased thirteen times relative to the rate of the unsubstituted hex-5-en-1-yl radical. Though the cause of the differential effect of the *gem*-dimethyl substitution on the rates of 1,5- and 1,6- cyclisations is not known, lack of 1,6-cyclisation of the 3,3-dimethylhex-5-en-1-yl radical implies that such

effects are not attributable to through-space repulsions between substituents at C2 and C6.

Energies of activation, calculated from the rate constants in table 21, are listed in table 22.

Table 22 Energies of activation for intramolecular cyclisation of 2,2,5-trimethylhex-5-en-1-yl radical relative to hydrogen atom abstraction from nBu_3SnH.

REACTION	$\Delta\Delta S^{\#}$ cal/mole/^{o}K	$\Delta\Delta H^{\#}$ kcal/mole
	7.8 ± .2	4.4 ± .1
	6.6 ± .3	4.3 ± .1
	6.5 ± .3	4.8 ± .1

Where $\Delta\Delta S^{\#} = \Delta S^{\#}_{C} - \Delta S^{\#}_{H}$, and $\Delta\Delta H^{\#} = \Delta H^{\#}_{C} - \Delta H^{\#}_{H}$

This is the first hex-5-en-1-yl radical investigated in this work where estimation of the energy of activation for both *exo*- and *endo*-cyclisations was possible. It is evident that for both directions of the ring closure the rates are controlled by the enthalpies of activation. It is not possible, even partially, to attribute the relative rates of *exo*- and *endo*-cyclisations to the differences of their entropies of activation.

It appears as a general phenomenon that methyl substitutions of the hex-5-en-1-yl system change the rates of intramolecular cyclisation by their effects on the enthalpies of activation for the cyclisation of these reactive intermediates. It is possible that bulky alkyl substituents, like a tertiary-butyl at C3, could restrict the internal rotation, and enhance the rate of intramolecular cyclisation by increasing the populations of cyclic rotomers, but there is no evidence that such rotational restrictions are caused by methyl substituents. In all the radicals examined in this work methyl substitution increased the rates of intramolecular cyclisation by a destabilising effect of its gauche interactions in the acyclic systems. Decrease in rate occurs where the methyl group sterically hinders formation of a cyclic structure as in the case of C5 substitution.

Comparison of the kinetics of 5-methylhex-5-en-1-yl, 2,2-dimethylhex-5-en-1-yl, and 2,2,5-trimethylhex-5-en-1-yl radicals shows that methyl substitution at C5 of the 2,2-dimethylhex-5-en-1-yl radical decreases its rate of *exo*-cyclisation to one thirty-sixth at 80^{o}, and one forty-ninth at 55^{o}. At 80^{o} the rate of *exo* (1,5-cyclisation) is increased by 8 times when 5-methylhex-5-en-1-yl radical bears *gem*-dimethyl substituents at C2, while the rate of 1,6-cyclisation is increased 2.5 times (Table 23).

Table 23 Values of k_c/k_H at 80^{o} for 5-methylhex-5-en-1-yl, 2,2-dimethylhex-5-en-1-yl, and 2,2,5-trimethyhex-5-en-1-yl radicals.

Radical	$k_{c_{1,5}}/k_H$	$k_{c_{1,6}}/k_H$
5-methylhex-5-en-1-yl[35]	.008	.012
2,2,5-trimethylhex-5-en-1-yl	.064	.029
2,2-dimethylhex-5-en-1-yl	2.295	.000

Conclusions

1. 2,2,5-Trimethylhex-5-en-1-yl radical cyclises irreversibly.

2. The rate of 1,6-cyclisation relative to the rate of 1,5-cyclisation increases with temperature by 1-3% per $10^{o}C$.

3. The ratio of $k_{c_{1,5}}/k_H$ to $k_{c_{1,6}}/k_H$ is 2.32 at 55^{o}, 2.30 at 60^{o}, 2.16 at 80^{o}, and 2.13 at 100^{o}.

4. Methylsubstitution at C5 reduces the rate 1,5-cyclisation of 2,2-dimethylhex-5-en-1-yl radical by 36 times at 80^{o} and by 49 times at 55^{o}.

5. At 80^{o} gem-dimethyl substitution increases the rate of 1,5-cyclisation of the 5-methylhex-5-en-1-yl radical 8 times, and the rate of 1,6-cyclisation 2.5 times.

6. Relative to unsubstituted hex-5-en-1-yl radical at 80^{o} the rate of 1,5-cyclisation of 2,2,5-trimethylhex-5-en-1-yl radical is reduced 3.6 times, while its rate of 1,6-cyclisation is increased by 4-6 times. At 80^{o} the ratio of the overall rates of rearrangement of hex-5-en-1-yl radical to 2,2,5-trimethylhex-5-en-1-yl radical is 2.4:1.

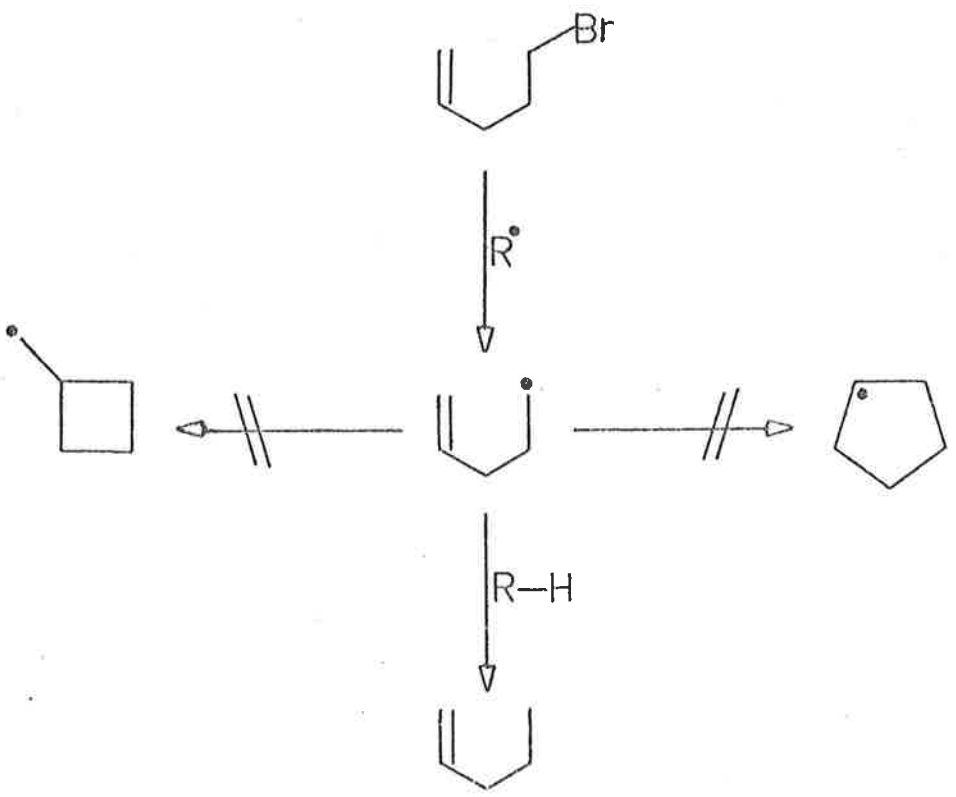
7. The effect of methyl substituents on the kinetics of the 2,2,5-trimethylhex-5-en-1-yl radical is due to changes in the enthalpy of activation.

8. Kinetics of intramolecular 1,6-cyclisation of 2,2,5-trimethylhex-5-en-1-yl radical are in contradiction with Julia's hypothesis of non-bonded interactions.

2,2-DIMETHYLPENT-4-EN-1-YL AND

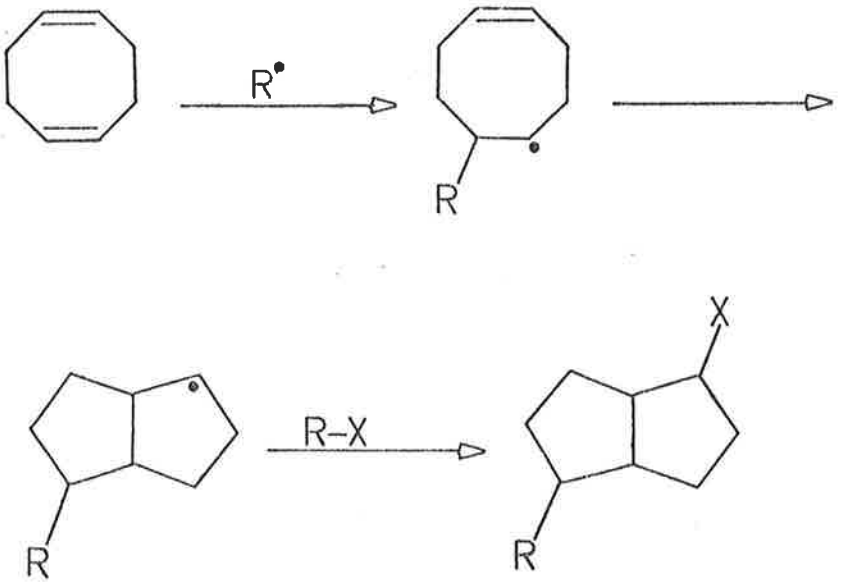
3,3-DIMETHYLPENT-4-EN-1-YL RADICALS

The pent-4-en-1-yl radical does not undergo intramolecular cyclisation under conditions in which the hex-5-en-1-yl radical undergoes a nearly quantitative cyclisation. If the pent-4-en-1-yl radical were to cyclise in solution then on thermodynamic grounds one would expect the formation of the cyclopentyl radical by *endo*-cyclisation. Cyclisation to cyclopentyl radicals is more exothermic by 18 kcal/mole than is cyclisation to cyclobutylmethyl radicals[25]. Nevertheless cyclisation of the pent-4-en-1-yl radical to methylcyclobutane is predicted by Baldwin's rules for ring closure[72]; that is 1,4-cyclisation being 4-*exo*-trigonal is allowed, while 1,5-cyclisation being 5-*endo*-trigonal is disallowed on the basis of "stereochemical requirements of the transition states"[72]. At any rate the pent-4-en-1-yl radical does not cyclise in solution at all. No cyclic products were observed in the reaction of pent-4-ene-1-thiol with triethyl phosphite[2]. Neither were cyclic products formed from the thermolysis of bis-5-hexenoylperoxide[73].

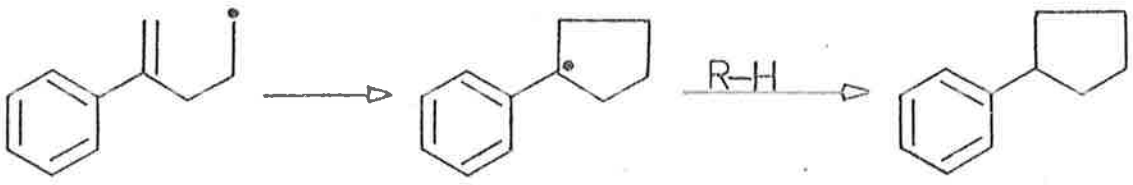


Very slow rates of cyclisations of substituted pent-4-en-1-yl radicals as compared to similar hex-5-en-1-yl radicals were reported by Julia[74], and Brace[75].

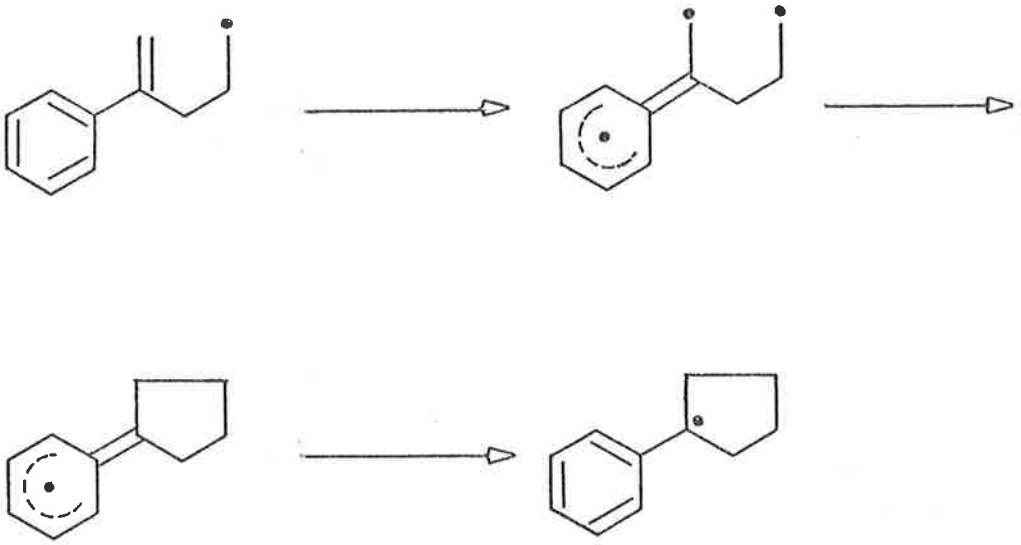
Significant yields of cyclised products from pent-4-en-1-yl radicals are obtained only from molecules whose structures are compatible with conformational requirements of the transition states. Thus transannular 1,5-addition of radicals from 1,5-cyclo-octadienes proceeds readily[76,77].



Intramolecular 1,5-cyclisation was observed[78,79] with molecules, which contained suitable electronic properties for the enhancement of 1,5-addition.

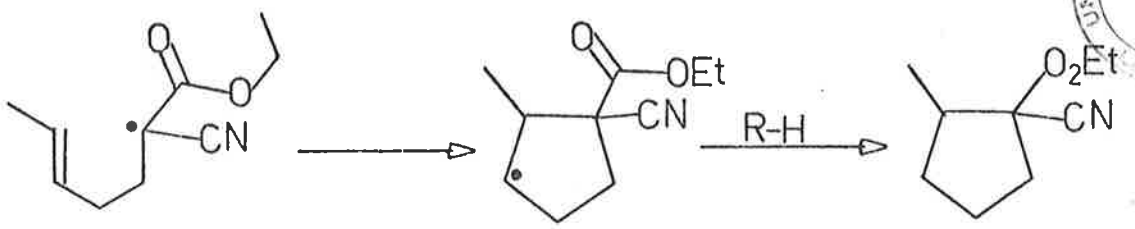


However it is possible that the reaction illustrated above does not involve 1,5 free radical addition to a double bond, but an intramolecular 1,5 diradical coupling process which resembles the biradical self-propagated polymerisation of styrene.



The extent of irreversible intramolecular addition of any given radical depends on the rate of its intramolecular addition, and on its life time in the reaction environment. Under the conditions of alkyl halide reduction with tri-n-butyltin hydride or tri-n-butyltin deuteride the lifetime of pent-4-en-1-yl radical can be prolonged by reducing the frequency of its intermolecular reactions with tri-n-butyltin hydride, and the cyclisation rate increased with higher temperatures. A limit to reagent concentrations (approx .0025 M) is reached below which detection of 5-10% (.000125-.000250 M) of cyclised products is beyond the resolution of the analytical equipment available during this work.

It was reported[1] that 1,5-cyclisation did take place when acyclic pent-4-en-1-yl radical was stabilized by suitable substituents, which gave it a longer lifetime.



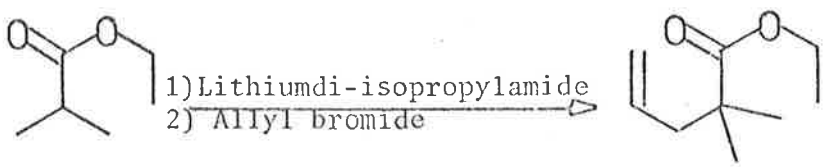
It has been observed in the present work that *gem*-dimethyl substitution of the hex-5-en-1-yl radical at C2, and C3 increased the rate of intramolecular cyclisation by 10 and 13 times respectively. Since the extent of intramolecular cyclisation depends on both the reaction rate and the lifetime of the free radical, and since it appeared reasonable to expect that *gem*-dimethyl substitution at C2, and C3 would increase the rate of 1,5-*endo*-cyclisation, it was decided to investigate intramolecular reactivities of 2,2-dimethylpent-4-en-1-yl and 3,3-dimethylpent-4-en-1-yl radicals.

SYNTHESIS

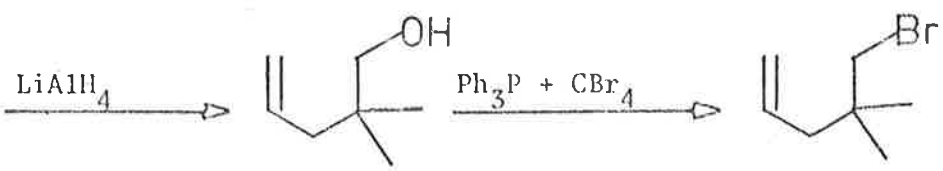
4,4-Dimethyl-5-bromopent-1-ene and, 3,3-dimethyl-5-bromopent-1-ene, which are the precursors for the 2,2-dimethylpent-4-en-1-yl and 3,3-dimethylpent-4-en-1-yl radicals, were prepared by the synthetic sequences outlined in schemes 30 and 31.

Scheme 30

Synthesis of 4,4-dimethyl-5-bromopent-1-ene.



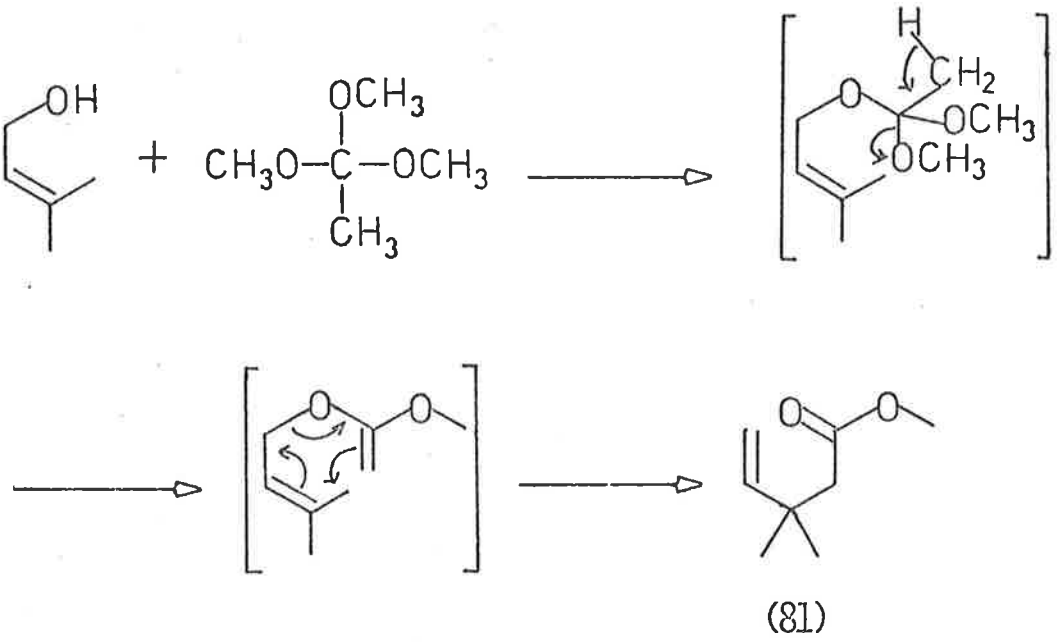
(78)



(79) (80)

Scheme 31

Synthesis of 3,3-dimethyl-5-bromopent-1-ene.



All reactions proceeded in yields between 65% and 85%.

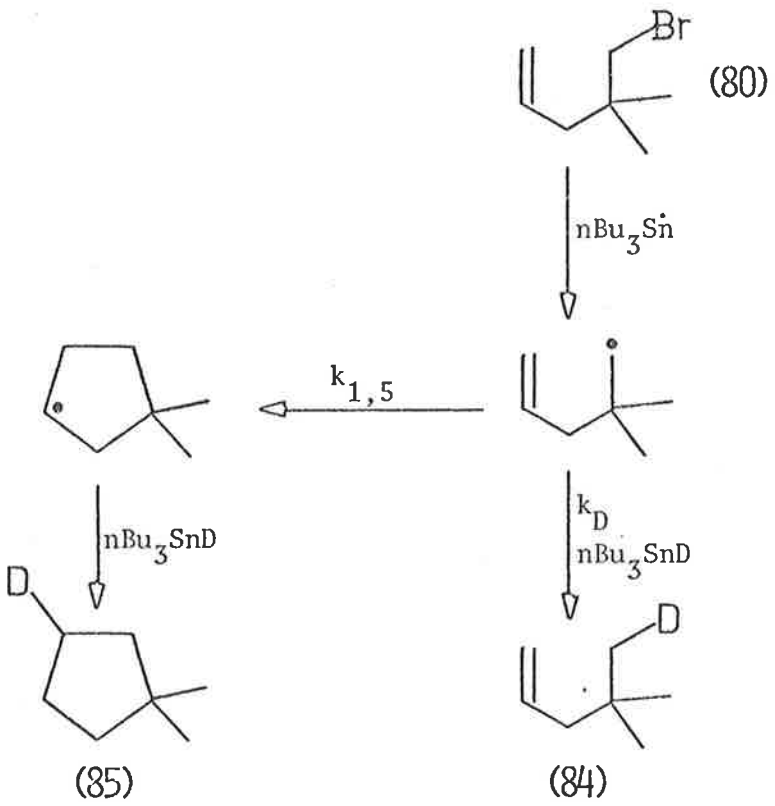
Of the reference hydrocarbons (84, 85, and 86), which are required for identifying the products from the reactions outlined in schemes 32 and 33, 1,1-dimethylcyclopentane was available from earlier work[55]. The two acyclic products 4,4-dimethylpent-1-ene, and 3,3-dimethylpent-1-ene were identified by bromination.

REDUCTION - RESULTS and DISCUSSION

The likely reaction mechanisms of 1,5-cyclisation are outlined in schemes 32 and 33.

Scheme 32

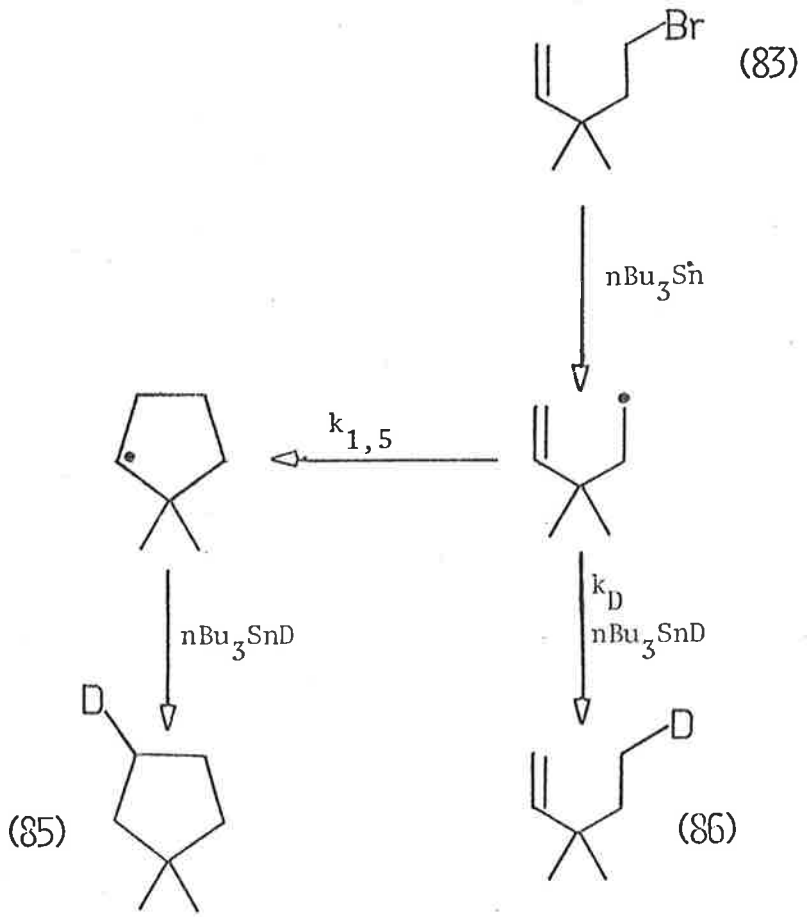
Reduction of 4,4-dimethyl-5-bromopent-1-ene with nBu_3SnD.



No formation of the 3,3-dimethylcyclobutylcarbinyl radical was expected.

Scheme 33

Reduction of 3,3-dimethyl-5-bromopent-1-ene with nBu_3SnD.



Again no *exo*-cyclisation, which would give the 2,2-dimethylcyclobutylcarbinyl radical, was predicted. In order to maximise the conditions for intramolecular cyclisation low concentrations of tri-n-butyltin deuteride were employed and higher than usual reaction temperatures were resorted to. Reductions were carried out using standard methods. In each reaction the bromide was present in excess of 20%. G.l.c. product analysis varied from the usual procedures in that olefin products were identified by brominating a sample from each reaction mixture and thus identifying the peaks of olefinic compounds. When a sample of the reaction mixture is treated with bromine until orange colour appears

the olefinic hydrocarbons are converted to dibromides, which have longer retention times than the corresponding olefinic hydrocarbons. Dibromides from olefinic hydrocarbons were not eluted from g.l.c. columns under the conditions of analysis.

Reaction temperatures, reagent concentrations, and the yields of products are shown in tables 24 and 25. In all reactions tri-n-butylin deuteride was used in order to reduce the rates of intermolecular reactions - deuterium atom abstraction is 2-2.7 times slower than hydrogen atom abstraction.

Table 24 Distribution of products in the reduction of 4,4-dimethyl-5-bromopent-1-ene with nBu_3SnD.

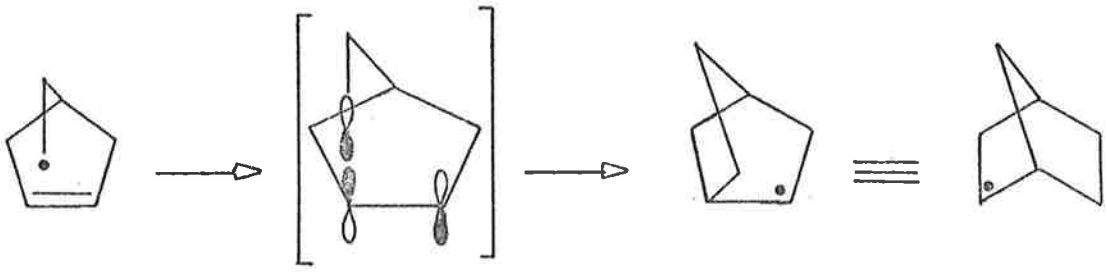
Temp ^oC	$[nBu_3SnD]$ mol/l	Yield of (84), %
60	.0100	80
60	.0050	85
60	.0100	85
60	.0250	88
80	.0025	82
80	.0050	86
80	.0100	85
80	.0250	89
100	.0025	92
100	.0050	90
100	.0100	90
130	.0025	84
130	.0050	93
130	.0100	95
130	.0250	95
160	.0025	76
160	.0050	78
160	.0100	80
160	.0250	77

Table 25 Distribution of products in the reduction of 3,3-dimethyl-5-bromopent-1-ene with nBu_3SnD.

Temp °C	$[nBu_3SnD]$ mol/l	Yield of (86), %
60	.0025	79
60	.0050	83
60	.0100	84
60	.0250	87
80	.0025	80
80	.0050	85
80	.0100	88
80	.0250	85
100	.0025	82
100	.0050	83
100	.0100	82
100	.0250	86
130	.0025	90
130	.0050	90
130	.0100	89
130	.0250	89
160	.0025	79
160	.0050	80
160	.0100	84
160	.0250	78

In spite of low concentration and the isotope effect of tri-n-butyltin deuteride, *gem*-dimethyl substitutions could not bring about intramolecular cyclisation of pent-4-en-1-yl radicals even at 160°. This time the Dreiding models showed without dispute why intramolecular 1,5-cyclisation of pent-4-en-1-yl is not possible. There is no conformation in which the free radical centre can vertically approach the π orbitals of the double bond within the distance at which intramolecular reaction can take place. The ease of formation of a five-membered ring, when the transition state for cyclisation can attain the correct geometry, was illustrated by the

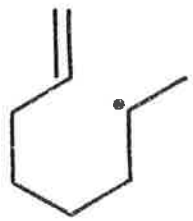
cyclisation of the 2-(Δ^3-cyclopentenyl)ethyl radical[80]. Formation of 2-norbornyl radical in the reductive cyclisation of 2-(Δ^3-cyclopentenyl) ethyl bromide[80] showed the importance of structural geometry in intramolecular cyclisation.



This observation gives support to Beckwith's hypothesis of stereoelectronic control[25,35], which in its essence considers the geometry of the transition states of the cyclising radicals. 2-Norbornyl radical possesses a strain energy somewhere between that of norbornene (17.55 kcal/mole) and norbornane (27.2 kcal/mole)[59,80,81], yet when the essential geometry of the transition state is possible 1,5-cyclisation of the pent-4-en-1-yl system takes place with relative ease[80].

CONCLUSIONS

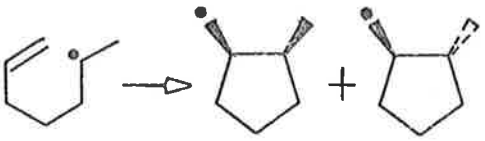
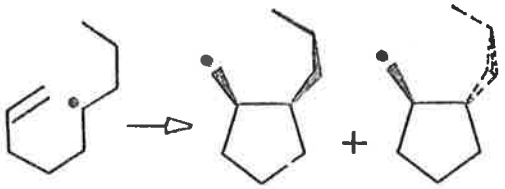
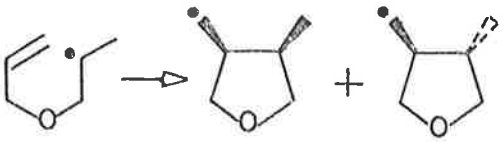
1. 2,2-Dimethylpent-4-en-1-yl, and 3,3-dimethylpent-4-en-1-yl radicals in solution do not undergo intramolecular cyclisation under the reaction conditions employed in this work.
2. The absence of intramolecular cyclisation is attributed to the conformational geometries of the acyclic pent-4-en-1-yl radicals, none of which permit the formation of the transition state essential for cyclisation.



OCT-7-ENE-2-YL RADICAL

In 1967 Brace[82] observed that intramolecular cyclisation of the hept-6-en-2-yl radical led to predominance of the *cis* isomer of the cyclic product. In a later work Beckwith and co-workers[83] investigated intramolecular cyclisations of several 1-alkylhex-5-en-1-yl radicals and found that all gave predominantly *cis*-1,2-dialkylcyclopentane isomers (Table 26).

Table 26 Cyclisation of hept-6-en-2-yl and related radicals at 65°[73].

REACTION	*cis*:*trans* ratio	k_c/k_H
	2.3	.26
	2.3	.30
	2.3	3.00

Transition state complexes in these intramolecular cyclisations must be formed early in the reaction and bear little resemblance to products, because thermodynamic considerations imply *trans*-cyclisation.

However for some systems *cis*-cyclisation is predictable from considerations of orbital symmetry[84]. The extent of orbital symmetry application to such reactions, and the geometry of the electron orbitals in the transition states were examined by Hoffmann[85] and co-workers[84,86].

It could be asked whether prevalent formation of *cis*-1,2-dialkyl cyclopentanes is the property characteristic of the transition states of 1-alkylhex-5-en-1-yl radicals undergoing 1,5-intramolecular cyclisation. Is such a transition state related to structurally restricted stereoelectronic geometry which may be the main causal factor of 1,5-cyclisation of the hex-5-en-1-yl radical? A six-membered cyclic transition state of the hept-6-en-1-yl radical is not subject to restrictions of conformational strain, which are believed[25,35] to bar 1,6-cyclisation of hex-5-en-1-yl radicals. If a definite stereoelectronic geometry must exist in the transition state for intramolecular cyclisation, then, in a heptenyl system, the compromise between *exo* and *endo* cyclic transition states will not reflect the corresponding conformational strain differences. Intramolecular cyclisation of hept-6-en-1-yl radicals would not be expected to be under stereoelectronic control. Neither of the two possible cyclic structures involves the conformational strain thought to be associated with the six-membered cyclic structures of the hex-5-en-1-yl radical.

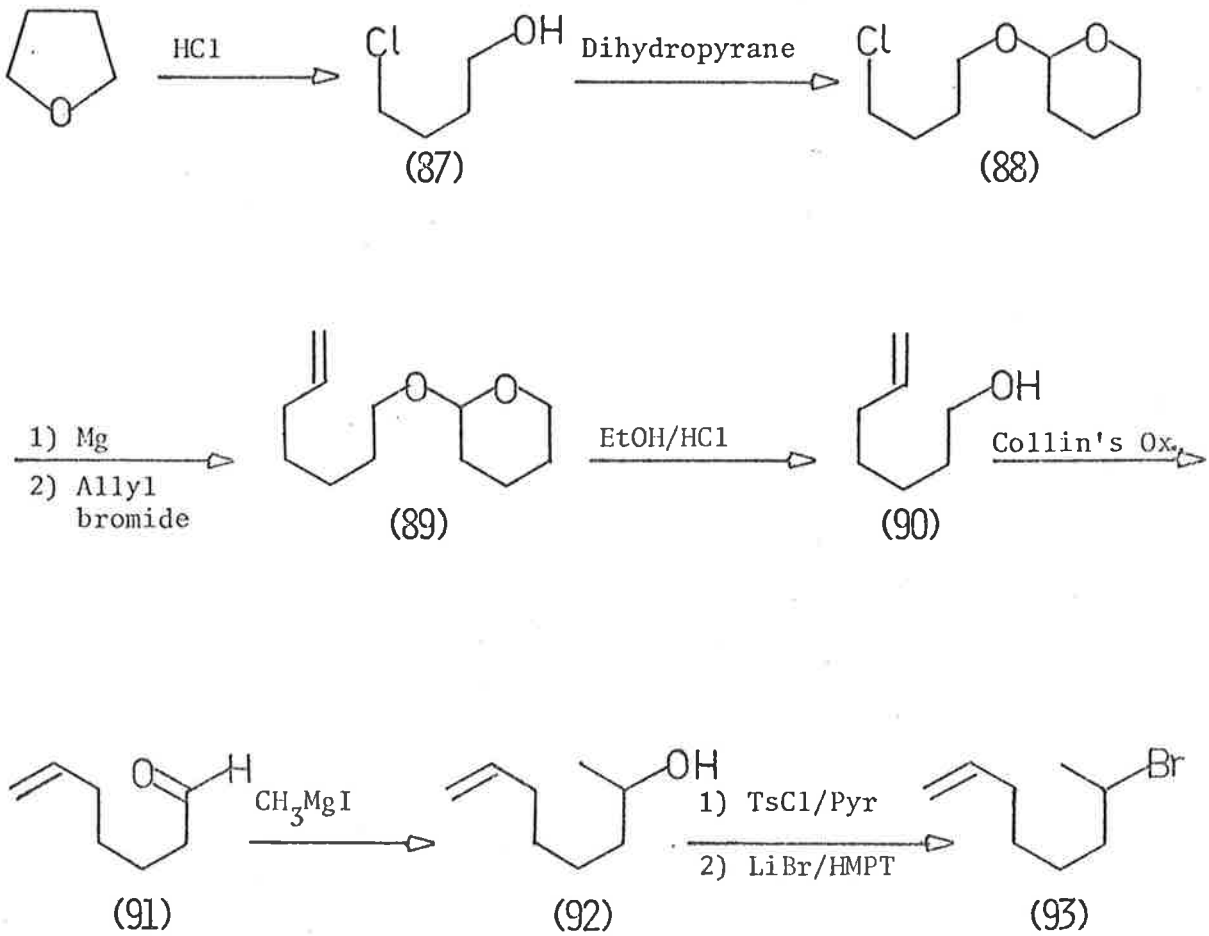
Study of the oct-7-en-2-yl (1-methylhept-6-en-1-yl) radical was chosen in order to investigate its kinetics of intramolecular cyclisation, and to determine the ratio of *cis*:*trans* isomers of 1,2-dimethylcyclohexane, which were expected to form by 1,6-cyclisation. 1,6-Cyclisation was predictable on the basis of earlier work[41], and by the prevalent *exo*-cyclisations of the radicals studied thus far in this work. Intramolecular free radical addition to the nearer carbon of the unsaturated bond (*exo*-cyclisation) is predictable for the hex-5-en-1-yl and hept-6-en-1-yl radicals by application of Baldwin's rules for ring closure[72]. Baldwin's rules are based on empirical generalisations, and rationalised by application of vector analysis methods to the stereochemistry of enone reductions[87]. In their essence the rules for ring closure, as adumbrated by Baldwin[72], follow the reasoning on which Beckwith based his hypothesis of stereoelectroni control[25,35].

SYNTHESIS

7-Bromo-oct-1-ene, the precursor for the oct-7-en-2-yl radical, was prepared by the synthetic sequence in scheme 34 .

Scheme 34

Synthesis of 7-bromo-oct-1-ene.



All reaction steps proceeded in yields greater than 76%.

Possible products from the reduction of 7-bromo-oct-1-ene, as predicted in scheme 35, are *cis* and *trans*-1,2-dimethylcyclohexane, methylcycloheptane, oct-1-ene and oct-2-ene. Oct-1-ene, oct-2-ene, and methylcycloheptane were available as commercial reagents.

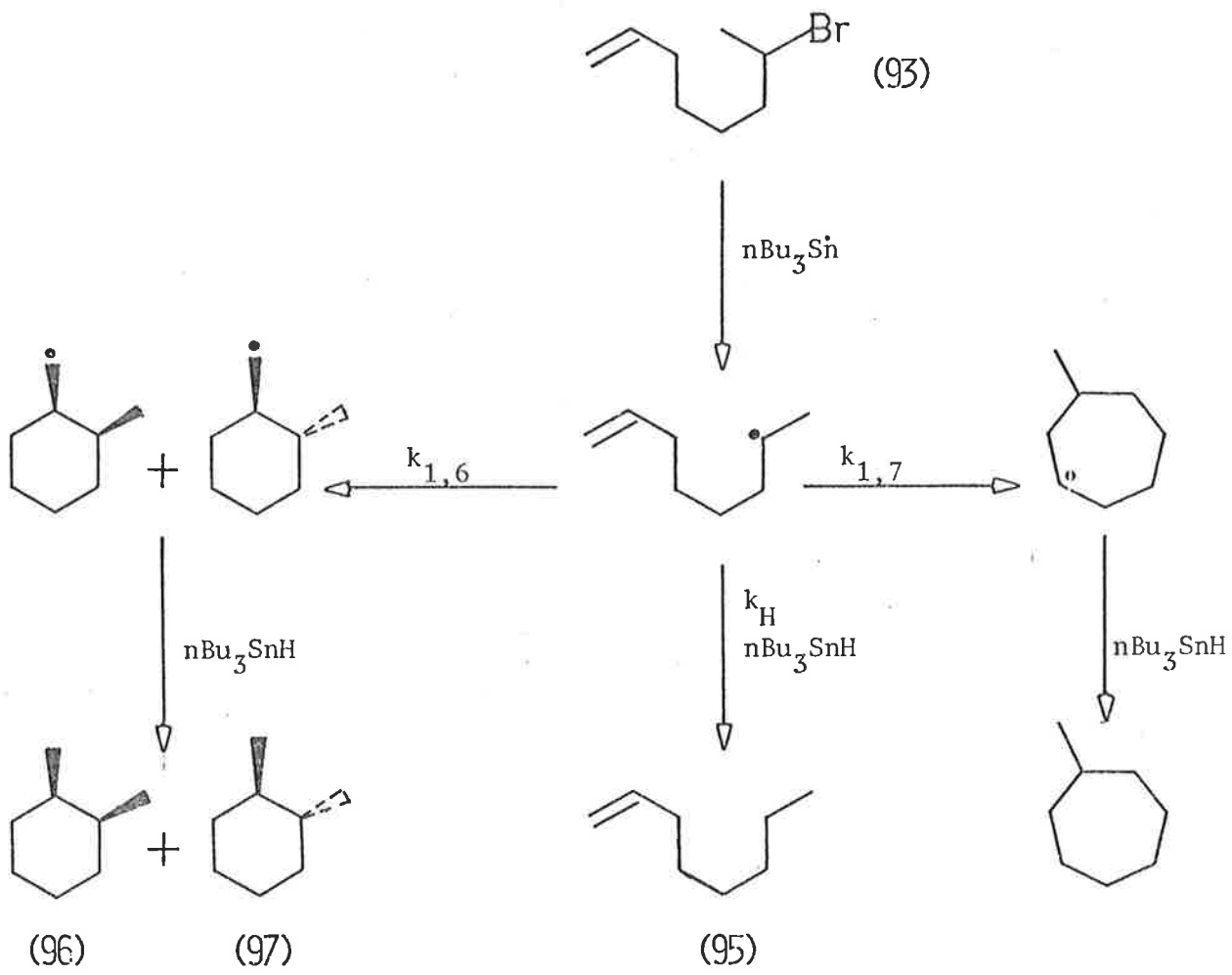
Both isomers of 1,2-dimethylcyclohexane were isolated from the reduction mixture by preparative gas liquid chromatography, and identified by their ^{13}C n.m.r. spectra and refractive indices.

REDUCTION - RESULTS and DISCUSSION

7-Bromo-oct-1-ene was reduced with tri-n-butyltin hydride by standard methods. The course of the reaction was predictable from the mechanism outlined in scheme 35. Reductions were carried out at the temperatures and the tin hydride concentrations listed in table 27.

Scheme 35

Reduction of 7-bromo-oct-1-ene with nBu_3SnH.



Products from the reductions are listed in table 27. No methylcycloheptene was formed in the reduction of 7-bromo-oct-1-ene. Hence the oct-7-en-2-yl radical does not undergo *endo*-cyclisation under the reaction conditions employed here. The small amount of oct-2-ene (≈1%) must have been formed by 1,5-hydrogen shift.

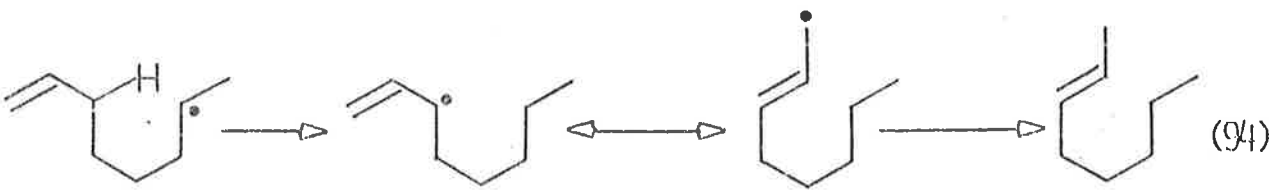


Table 27 Product distribution in the reduction of 7-bromo-oct-1-ene with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/l	Relative Yields %			Total Yield %
		(95)	(96)	(97)	
60	.0104	36.8	44.6	18.6	89
60	.0163	46.5	38.1	15.4	89
60	.0324	61.4	27.6	11.1	92
80	.0163	37.8	43.1	19.1	90
80	.0238	45.9	37.8	16.3	92
80	.0466	59.9	27.9	12.2	94
100	.0238	37.3	43.2	19.5	91
100	.0682	60.4	27.4	12.2	96

At 60° no oct-2-ene was detectable in the products. At 80° the yield of oct-2-ene was .8%, and 1.0% at 100°.

Distribution of other products (Table 27) follows the usual pattern of irreversible *exo*-cyclisation of alkenyl radicals. *Cis*-1,2-dimethylcyclohexane was formed in excess over *trans*-1,2-dimethylcyclohexane. The ratio of *cis*:*trans* isomers varied with the reaction temperature. At 60° the *cis*:*trans* isomer ratio was 2.45, at 80° 2.29, and at 100° 2.23.

Relative rate constants, $\Sigma k_c/k_H$, were calculated from the data in table 27. These are listed in table 28. The calculated rate constants include the rates of 1,5-hydrogen shift, and are in error to the extent of 1-2%, as estimated from the relative yield of oct-2-ene (≈1%).

Table 28 Values of k_c/k_H for the reduction of 7-bromo-oct-1-ene with nBu_3SnH.

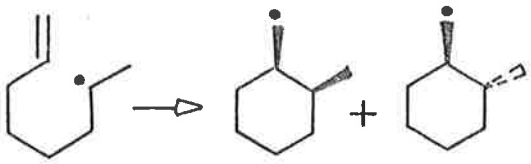
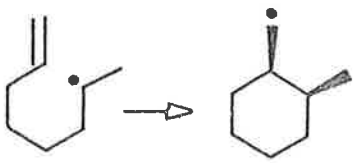
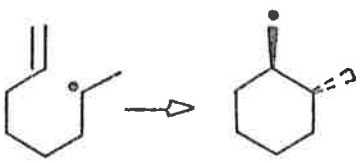
Temp °C	$[nBu_3SnH]$ mol/l	$\Sigma k_c/k_H$ l/mole	$k_{c_{1,6\text{-}cis}}/k_H$ l/mole	$k_{c_{1,6\text{-}trans}}/k_H$ l/mole	Mean $\Sigma k_{c/H}$ l/mole	St. Dev. %
60	.0104	.0077	.0054	.0023		
60	.0163	.0076	.0054	.0022		
60	.0324	.0075	.0054	.0021		
					.0076	1.4
80	.0163	.0115	.0080	.0035		
80	.0238	.0115	.0080	.0035		
80	.0466	.0116	.0081	.0035		
					.0115	.7
100	.0238	.0172	.0119	.0053		
100	.0342	.0167	.0115	.0052		
100	.0682	.0166	.0115	.0051		
					.0168	2.0

1,6-Cyclisation of 1-methylhept-6-en-1-yl (oct-7-en-2-yl) radical is about 1.5 times faster than 1,6-cyclisation of the hex-5-en-1-yl radical - the ratio of the mean rate constants at 80° is .0115 : .008. Compared to earlier estimated $k_{c_{1,6}}/k_H$ for the hex-5-en-1-yl radical (≈.005 l/mole)[41] 1,6-cyclisation of the methylhept-6-en-1-yl radical is 2.3 times faster. The fact that this radical undergoes 1,6-cyclisation faster than the hex-5-en-1-yl radical may be indicative of some conformational strain in

the transition state of the hex-5-en-1-yl radical undergoing 1,6-cyclisation. The rate of 1,6-cyclisation of the 1-methylhept-6-en-1-yl radical is about 50% faster than the corresponding rate of the hept-6-en-1-yl radical[41].

Activation parameters for the cyclisation of 1-methylhept-6-en-1-yl radical relative to hydrogen atom abstraction from tri-n-butyltin hydride are listed in table 29.

Table 29 Energies of activation for cyclisation of the oct-7-en-2-yl radical relative to hydrogen atom abstraction from nBu_3SnH.

REACTION	$\Delta\Delta S^{\#}$ cal/mole/^{o}K	$\Delta\Delta H^{\#}$ kcal/mole
	5.0 ± .2	4.9 ± .1
	3.8 ± .3	4.7 ± .1
	3.8 ± .3	5.3 ± .1

Where $\Delta\Delta S^{\#} = \Delta S^{\#}_{C} - \Delta S^{\#}_{H}$, and $\Delta\Delta H^{\#} = \Delta H^{\#}_{C} - \Delta H^{\#}_{H}$

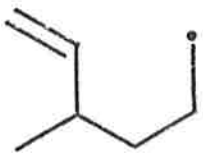
CONCLUSIONS

1. The oct-7-en-2-yl radical cyclises irreversibly.

2. 1,6-Cyclisation gives predominatly *cis*-1,2-dimethylcyclohexane. The ratio of *cis*:*trans* isomers varies from 2.45 at 60^{o} to 2.23 at 100^{o}.

3. The *cis* cyclisation has a lower enthalpy of activation by .6 kcal/mole.

4. Prevalent formation of *cis*-1,2-dimethylcycloalkanes from 1-methylalkenyl radicals by *exo*-cyclisation appears to be a general consequence of methyl substitution at the free radical centre, not a property confined to 1-methylhex-5-en-1-yl radicals.



4-METHYLHEX-5-EN-1-YL RADICAL.

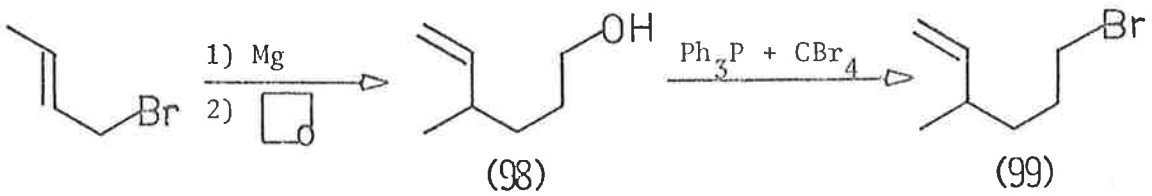
Having found that C1 methyl substitution of the hept-6-en-1-yl system leads predominantly to *cis*-1,2-dimethylcycloalkane by *exo*-cyclisation, and knowing from earlier work[41] that C1 methyl substitution of the hex-5-en-1-yl radicals gave very similar results, it appeared desirable to investigate the stereochemistry of the 1,2-dimethylcycloalkane formed from the 4-methylhex-5-en-1-yl radical by *exo*-cyclisation. With this radical the methyl substituent would not be attached to the free spin bearing carbon. The information concerning the stereochemistry of 1,2-dimethylcyclopentane would be useful in establishing whether 1,2-*cis*-cyclisation was restricted to alkyl substitution at the free radical centre.

SYNTHESIS

3-Methyl-6-bromohex-1-ene, the precursor for the 4-methylhex-5-en-1-yl radical, was prepared by the two step synthesis outlined in scheme 36.

Scheme 36

Synthesis of 3-methyl-6-bromohex-1-ene.



(98) (99)

This short and easy synthetic route produced the required products in yields of 88% and 83%. Only a trace (1-2%) of hept-5-en-1-ol was formed. After bromination trace amounts of 7-bromohept-2-ene were removed by preparative g.l.c. The reference compounds 3-methylhex-1-ene, and 1,2-dimethylcyclo-

pentane were prepared as outlined in schemes 37 and 38. Methylcyclohexane was available as a commercial reagent.

Scheme 37

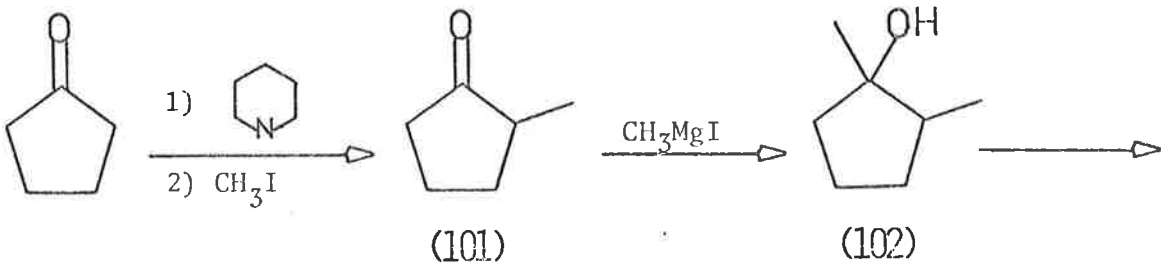
Synthesis of 3-methylhex-1-ene.

(100)

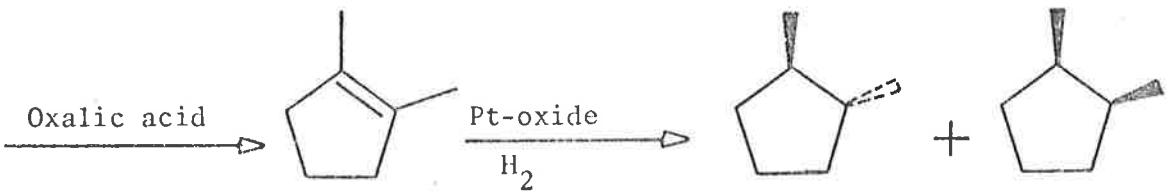
The distilled hydrocarbon was pure by g.l.c. analysis.

Scheme 38

Synthesis of 1,2-dimethylcyclopentane.



(101) (102)



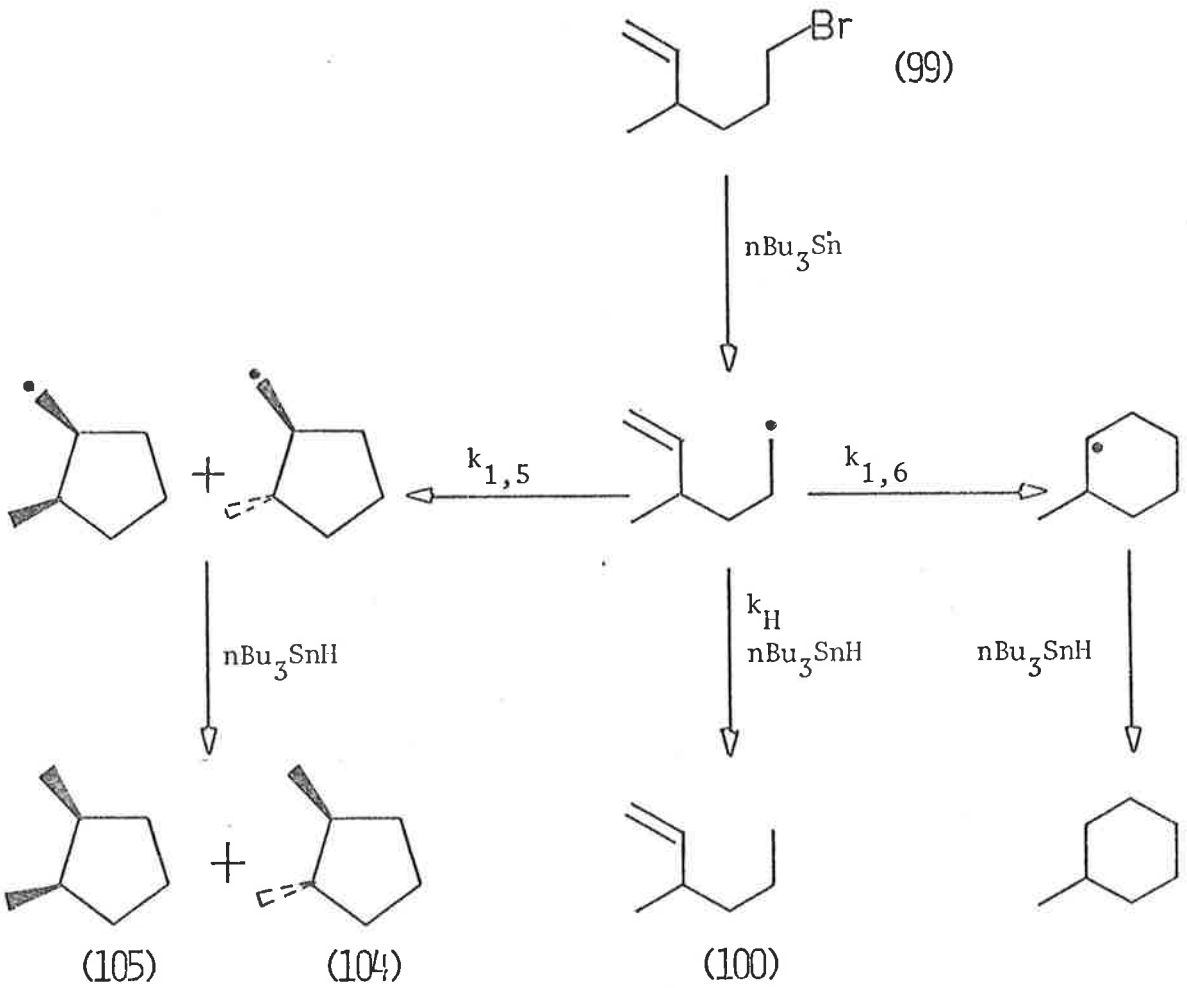
(103) (104) (105)

The ^{13}C n.m.r. spectrum of 1,2-dimethylcyclopentane showed that the *cis* isomer was in about threefold excess.

REDUCTIONS - RESULTS and DISCUSSIONS

The mechanism of reduction is postulated in scheme 39.

Scheme 39



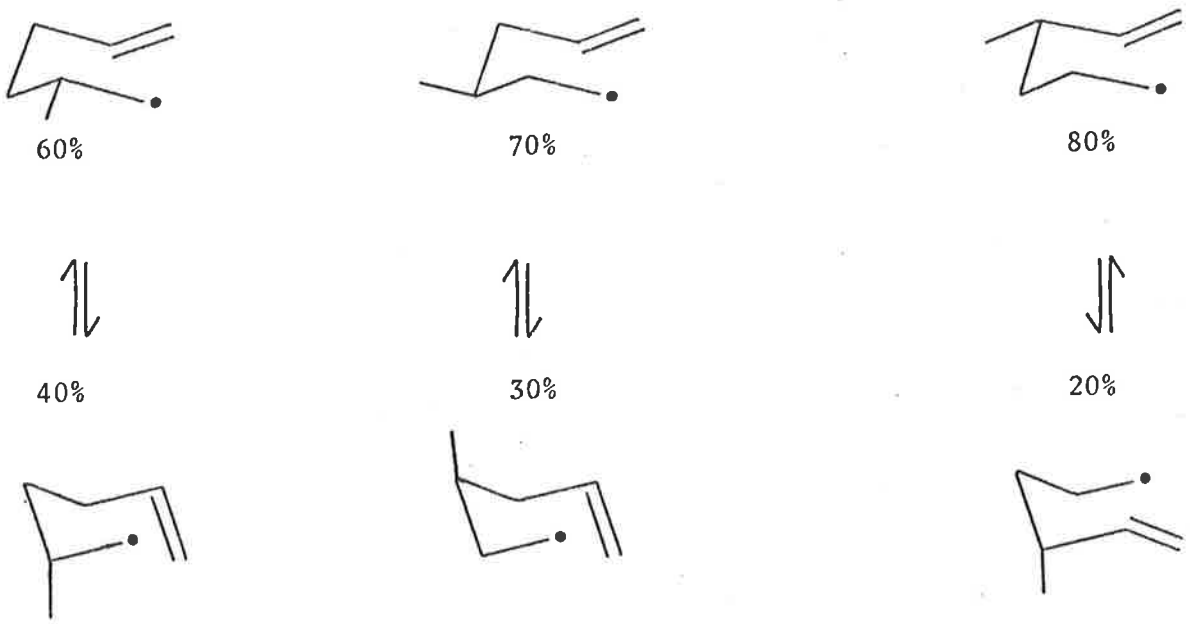
3-Methyl-6-bromohex-1-ene was reduced with tri-n-butyltin-hydride by standard methods at 60°, 80°, and 100° and the tin hydride concentrations as listed in table 30. The products were identified and quantitatively analysed by standard methods of g.l.c. analysis. Only trace amounts (2-3%)

of methylcyclohexane were formed. At any one temperature the relative yields of cyclic products showed inverse dependence on the concentration of tri-n-butyltin hydride.

Table 30 Ditribution of products in the reduction of 3-methyl-6-bromohex-1-ene with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mol/l	Relative yields & (100)	(104)	(105)	Total Yield %
60	.1749	20.4	63.6	16.0	90
60	.3149	30.8	55.3	13.8	92
60	.5557	42.1	46.4	11.5	96
80	.0829	8.8	71.3	19.9	91
80	.1476	14.3	67.4	18.3	94
80	.2738	23.3	60.3	16.4	95
100	.1718	13.4	67.1	19.5	93
100	.3149	21.6	60.7	17.7	95
100	.5557	31.5	52.6	15.9	96

The ratio of *trans* to *cis*-1,2-dimethylcyclopentane was 4.00 at 60°, 3.65 at 80°, and 3.39 at 100°. There can be little doubt about the prevalent equatorial orientation of the 4-methyl substituent in the cyclising 4-methylhex-5-en-1-yl radical. Differentiation of equatorial and axial methyl orientations in 2-methyl-, 3-methyl-, and 4-methylhex-5-en-1-yl radicals implies a ring conformation other than that of a puckered cyclopentane ring during the cyclic transition state. It must be an envelope-like or a half-chair like structure where axial and equatorial orientations are distinct. The cyclic conformations must exist at equilibrium just prior to the irreversible formation of the transition state for cyclisation as outlined below.

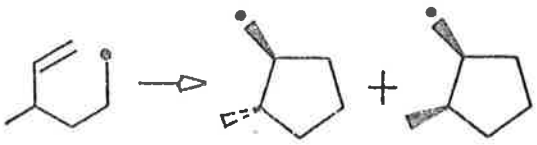
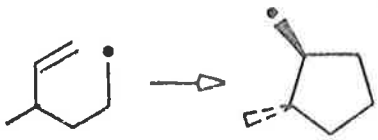


The prevalence of equatorial methyl substituent increases from 60% to 70% then to 80% as the position of substitution changes from C2 to C3 and C4. With respect to C2, C3 and C4 the extent of equatorial orientation of the methyl substituent is inversely related to the distance of the substituted carbon from the double bond. The underlying causes of this distribution of stereoisomers must be attributed to non-bonded interactions exerted by the axial methyl group. The true nature of such interactions is speculative. The rate constants, k_c/k_H, were calculated from the data in table 30 and are listed in table 31. The corresponding activation parameters are listed in table 32.

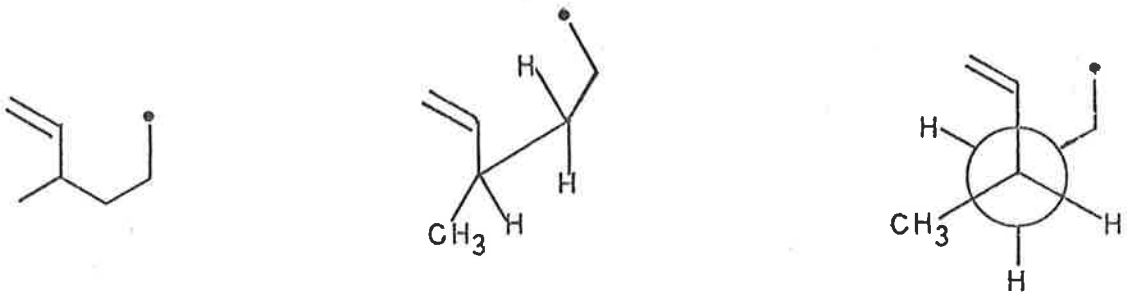
Table 31 Values of k_c/k_H for the reduction of 3-methyl-6-bromohex-1-ene with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/l	$\Sigma k_c/k_H$ l/mole	$k_{c\,1,5\text{-}trans}/k_H$	$k_{c\,1,5\text{-}cis}/k_H$	Mean $\Sigma k_c/k_H$ l/mole
60	.1749	.3165	.2529	.0636	
60	.3149	.3126	.2501	.0625	
60	.5557	.3186	.2554	.0632	.3159
80	.0829	.4140	.3238	.0902	
80	.1476	.4192	.3299	.0893	
80	.2738	.4118	.3237	.0881	.4150
100	.1718	.5283	.4095	.1188	
100	.3149	.5286	.4093	.1193	
100	.5557	.5337	.4096	.1241	.5302

Table 32 Energies of activation for the cyclisation of 4-methylhex-5-en-1-yl radical relative to hydrogen atom abstraction from nBu_3SnH.

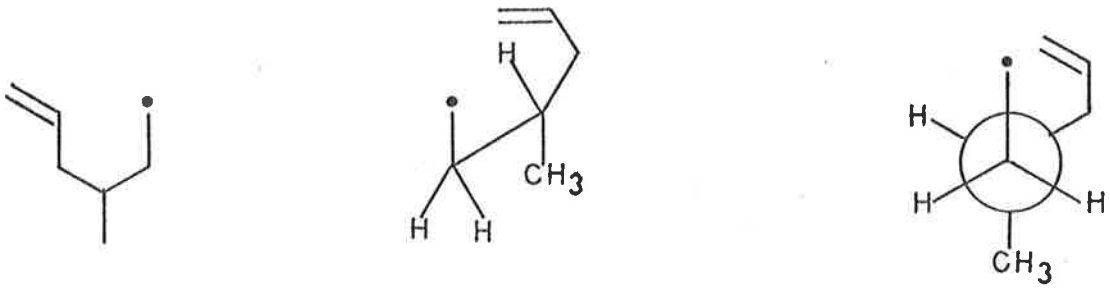
REACTION	$\Delta\Delta S^{\#}$ cal/mole/°K	$\Delta\Delta H^{\#}$ kcal/mole
	7.3 ± .2	3.2 ± .1
	6.2 ± .2	2.9 ± .1
	6.5 ± .2	4.0 ± .1

The first point to note is that the rates of cyclisation of the 4-methyl-hex-5-en-1-yl radical are lower than those of the 2-methylhex-5-en-1-yl radical which in turn are lower than the rates of cyclisation of the 3-methylhex-5-en-1-yl radical. A pattern has emerged which shows that - with respect to C2, C3, and C4 - the rates of intramolecular cyclisation of methyl substituted hex-5-en-1-yl radical increase parallel with the increase of gauche interactions. This applies to both monomethyl and dimethyl substitution. The extent of gauche interactions is shown below.



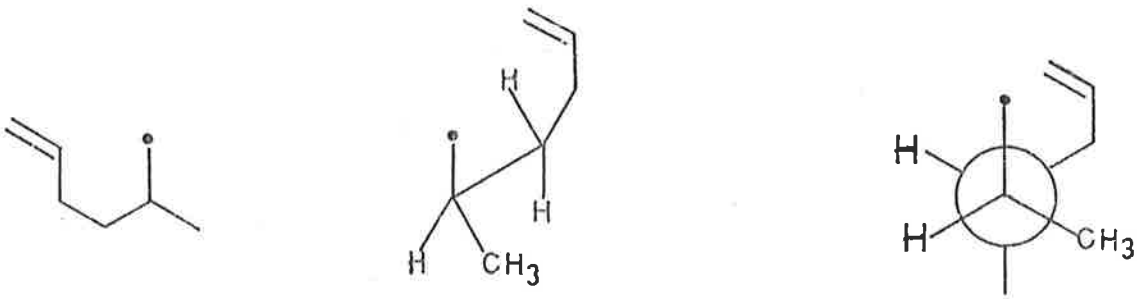
Gauche interactions of the methyl group at C4 with substituents at C3 (two hydrogens and $-CH_2-\dot{C}H_2$).

Gauche interactions of the methyl group at C4 with substituents at C5 (one hydrogen and a methylene group).

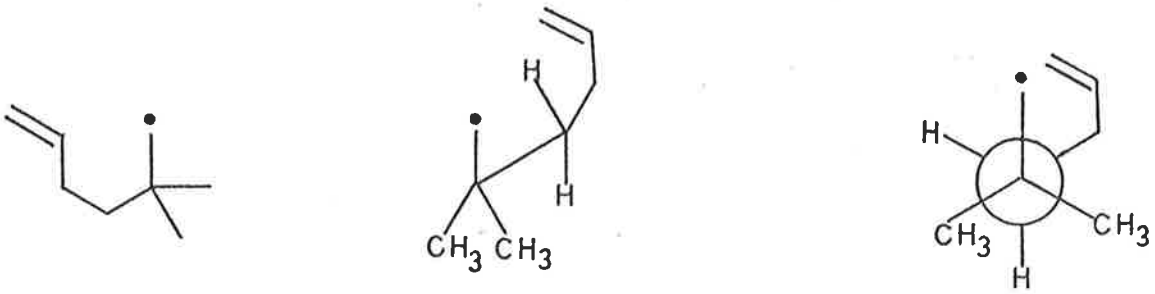


Gauche interactions of the methyl group at C3 with substituents at C2 (two hydrogens and a $-\dot{C}H_2$ group).

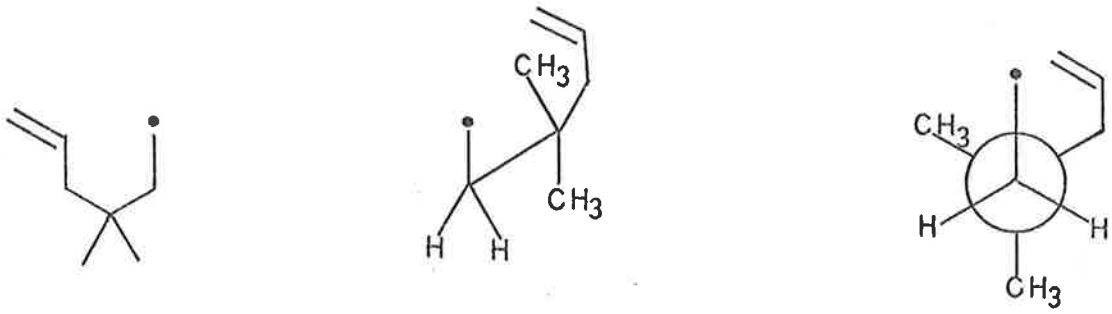
Gauche interactions of the methyl group at C3 with substituents at C4 (two hydrogens and a vinyl group).



Gauche interactions of the methyl group at C2 with substituents at C3 (two hydrogens and an allyl group).



Gauche interactions of the two methyl groups at C2 with substituents at C3 (two hydrogens and an allyl group).



Gauche interactions of the two methyl groups at C3 with substituents at C2 (two hydrogens and a -$\dot{C}H_2$ group).

Gauche interactions of the two methyl groups at C3 with substituents at C4 (two hydrogens and a vinyl group).

It is evident that methyl induced gauche interactions decrease in the order C3 > C2 > C4. As a net result the enthalpy of activation for cyclisation increases with the extent of gauche interactions at C2, C3, and C4 (Table 33).

Table 33 Relative rates of cyclisation of hex-5-en-1-yl radicals at 80°.

Radical	$\Sigma k_c/k_H$ l/mole	$\Delta\Delta^{\#}$ cal/mol/°K	$\Delta\Delta^{\#}$ kcal/mole
hex-5-en-1-yl	1.00	6.1	3.50
4-methylhex-5-en-1-yl	1.83	7.3	3.20
2-methylhex-5-en-1-yl	2.57	6.3	2.62
3-methylhex-5-en-1-yl	3.44	6.4	2.46
2,2-dimethylhex-5-en-1-yl	10.12	6.6	1.74
3,3-dimethylhex-5-en-1-yl	13.76	6.4	1.47

$\Delta\Delta S^{\#} = \Delta S^{\#}_c - \Delta S^{\#}_H$, $\Delta\Delta H^{\#} = \Delta H^{\#}_c - \Delta H^{\#}_H$

The lowering of the enthalpy of activation by *gem*-dimethyl substitution may be considered to be due to the Thorpe-Ingold effect[88,89]. In terms of the Thorpe-Ingold effect *gem*-dialkyl substituents enhance the cyclisation of small rings by relieving the steric compression between substituents attached to the same carbon. This explanation is probably true for small rings where the internal angle is so small (e.g. cyclopropane - 60°) as to lead to significant spreading apart of the external angle. In cyclopentane, cyclohexane, and larger rings bond angles on all carbons deviate little, if at all, from tetrahedral angles. The Thorpe-Ingold effect cannot be evoked to explain the lowering of the enthalpies of activation in monomethyl substituted hex-5-en-1-yl radicals studied here.

The consequence of monomethyl and *gem*-dimethyl substitution at C2, C3, and C4 pertaining to rates of cyclisation of the hex-5-en-1-yl system

is best explained in terms of extra gauche interactions[90,91]. The "*gem*-dialkyl effect" explanation as advanced by Allinger and Zalkow[91] allows for the effects of both monomethyl and *gem*-dimethyl substitutions. That alkyl substituents affect mainly the enthalpy of activation was also observed in carbonium ion cyclisations[92]. Gauche interactions in the ground state are partly relieved upon formation of the cyclic transition state. The gauche interactions raise the free energy of the *gem*-dimethylhex-5-en-1-yl radical relative to that of the cyclic transition state; hence the ring closure is more exothermic than the ring closure of the unsubstituted hex-5-en-1-yl radical. Such *gem*-dimethyl substitution has little effect on the entropy of activation. The observed change in the enthalpy of activation of about 1.3 kcal/mole corresponds closely[93] to two extra gauche interactions in the reactant radical.

CONCLUSIONS

1. Causes of the prevalent formation of *cis*-1,2-dimethylcyclopentanes from 1-methylhex-5-en-1-yl radicals, and *cis*-1,2-dimethylcyclohexane from the 1-methylhept-6-en-1-yl radical are different from those operating in the formation of 1,2-dimethylcyclopentane from the 4-methylhex-5-en-1-yl radical.

2. 4-Methylhex-5-en-1-yl radical cyclises irreversibly.

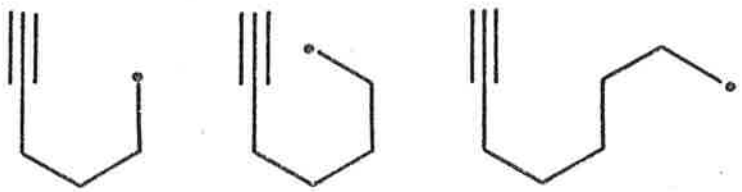
3. *Exo*-1,5-cyclisation amounts to 98% of the total cyclisation. Only trace amounts of methylcyclohexane are formed (≈2%).

4. The ratio of *trans* to *cis* 1,2-dimethylcyclopentane, which is the product of 1,5-cyclisation, is 4.00 at 60^{o}, 3.65 at 80^{o}, and 3.40 at 100^{o}.

5. 4-Methylhex-5-en-1-yl radical cyclises about two times as fast as the unsubstituted hex-5-en-1-yl radical.

6. The increase in the rate of cyclisation is brought about by the substituent-induced lowering of the enthalpy of activation.

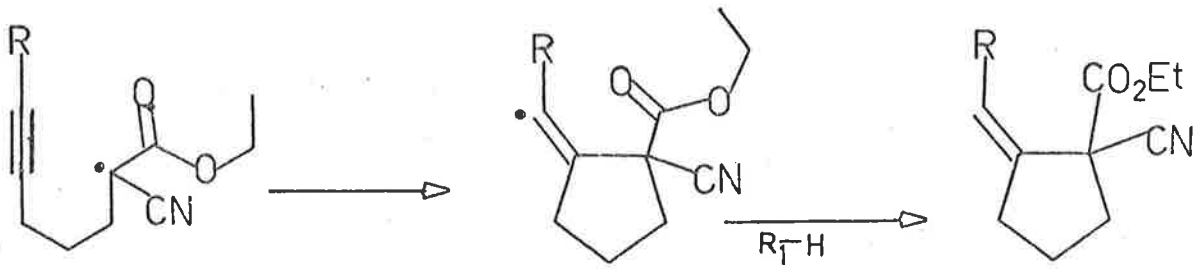
7. The enhancements of the rates of cyclisation of hex-5-en-1-yl radicals by methyl substituents at C2, C3, or C4 is attributed to gauche interactions of the methyl groups.



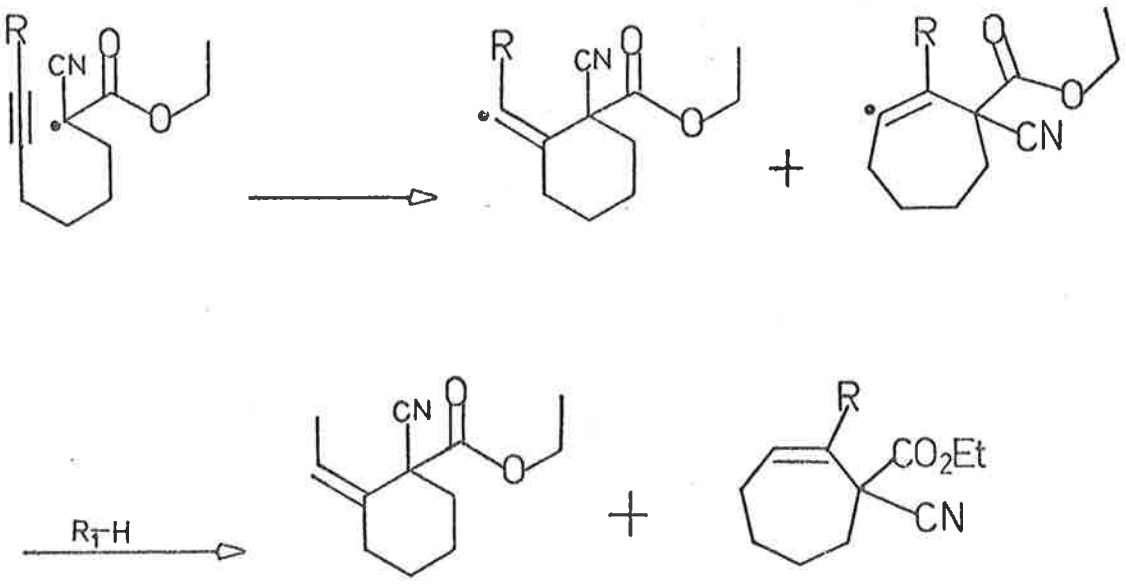
HEX-5-YN-1-YL, HEPT-6-YN-1-YL,

AND OCT-7-YN-1-YL RADICALS.

Relative to alkenyl radicals research into intramolecular additions of alkynyl radicals has been sparse. Compared to homologous alkenyl radicals the alkynyl radicals would be expected to have lower rates of intramolecular addition, because the acetylenic bonds are less reactive than olefinic bonds. Also unlike olefinic systems the geometric arrangement the triple bond imposes greater restrictions to cyclic conformations, which could partially or completely control the direction of cyclisation. In contrast to their olefinic homologous hex-5-yn-1-yl radicals, which carry free spin stabilising substituents at the free radical centre (C1), undergo exclusive 1,5-intramolecular cyclisation[94,95].

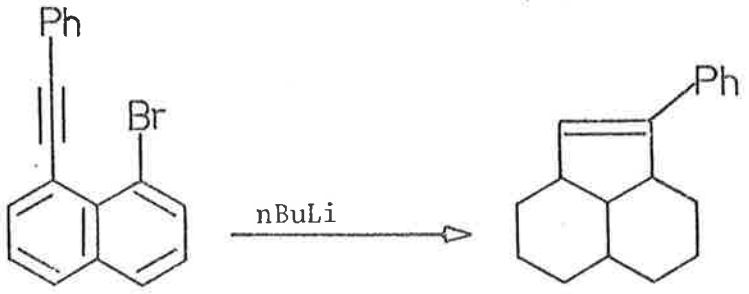


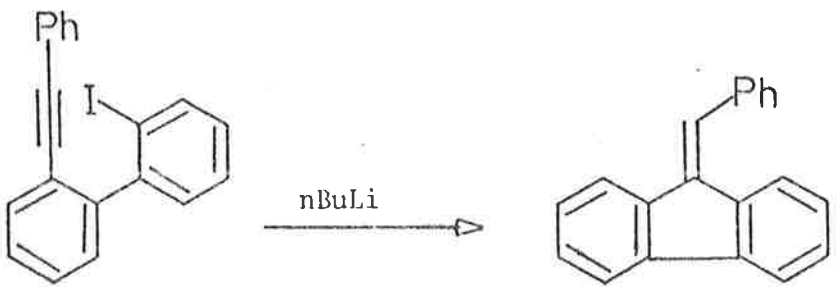
This must be the consequence of the conformational barrier, inherent in the molecular structure of hex-5-yn-1-yl radicals, which bars close approach of the free radical centre at C1 and the *endo* carbon (C6) to within the distance required for intramolecular addition. The homologous hept-6-yn-1-yl radicals, where structural restraint to cyclic conformations is less severe, underdo both *exo*- and *endo*-cyclisations[94,95].



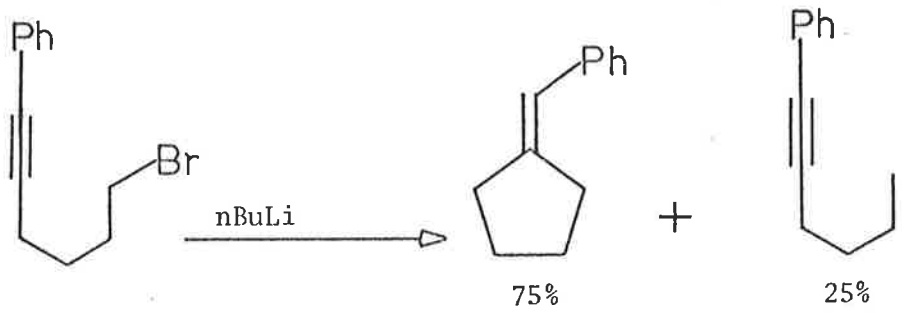
The above process may be under thermodynamic control.

Another early report involving alkynyl free radical cyclisation came from Kandil and Dessy[96]. They reported isolation of cyclic products from the reactions of n-butyl-lithium with substituted naphthalenes and biphenyls, which gave acenaphthylene, and fluorene derivatives.



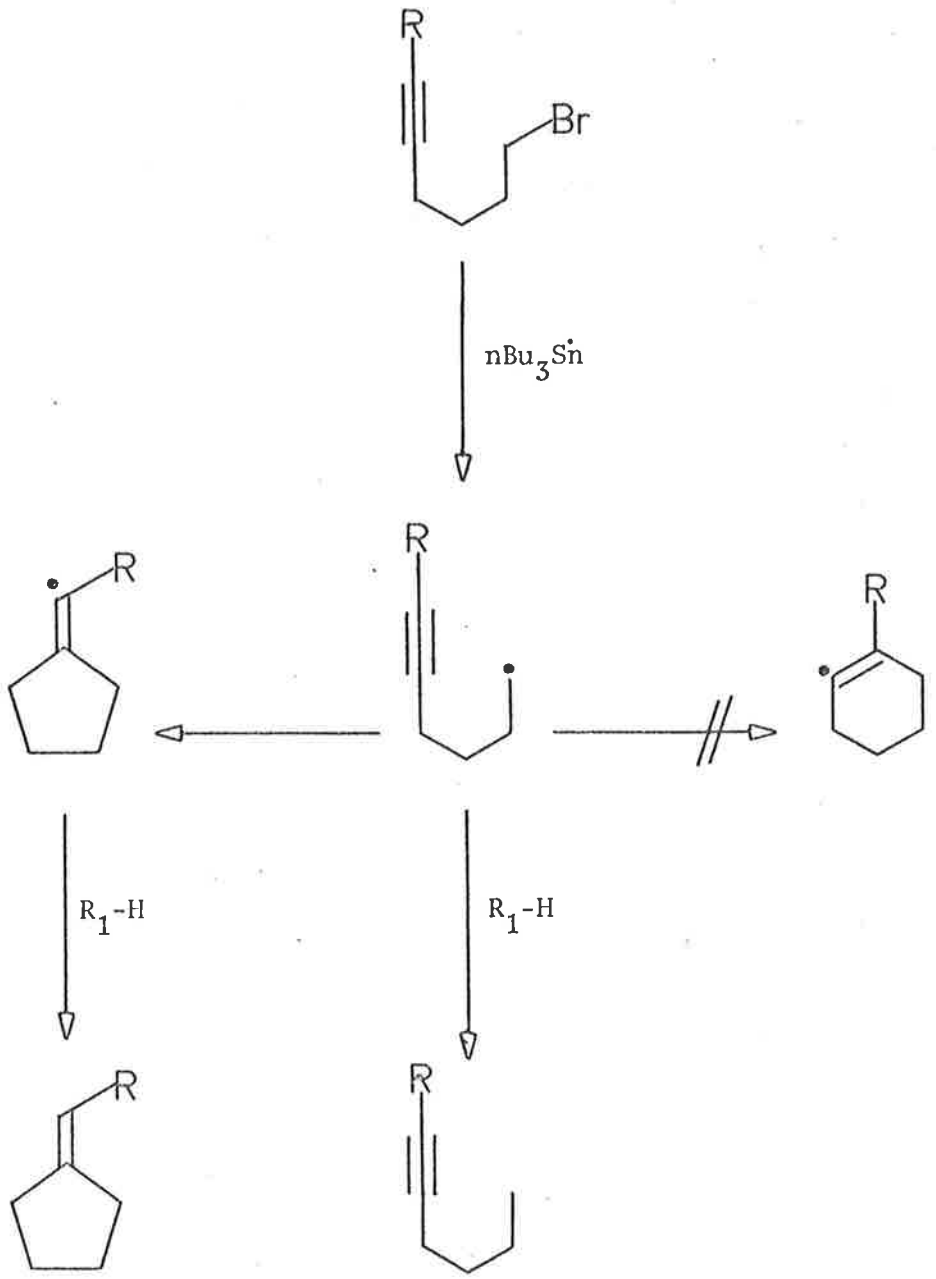


They conjectured that the intramolecular reactivity of the acetylenic bond was due to its close proximity to the reactive carbon in the locked conformation. They also thought that these reactions involved carbanionic intermediates. That such steric coercion is not necessary for the cyclisation of acetylenes was later demonstrated by Ward[97] with the cyclisation of 6-bromo-1-phenylhex-1-yne in the reaction with n-butyl-lithium.



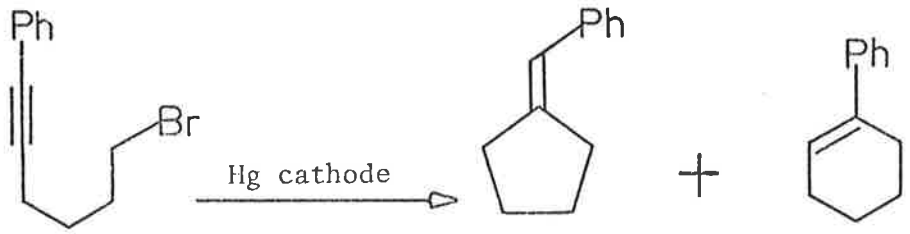
Ward pointed out that his observations were consistent with a free radical mechanism, which in turn was consistent with the proposal of Bryce-Smith[98] that the products of the reaction of n-butyl bromide with n-butyl-lithium in benzene were best explained as free radical reactions. In a subsequent report Ward and Lawler[99] confirmed the existence of free radical intermediates by showing that the reaction of n-butyl bromide and n-butyl-lithium exhibited chemically induced dynamic nuclear polarisations (CIDNP).

Series of straight chain acetylenic radicals were generated by Crandall and Keyton[100] from the corresponding bromides with tri-n-butyltin hydride. They had followed the reduction process which was well established to involve a free radical chain mechanism[101], and knew that they were dealing with alkynyl free radical intermediates.

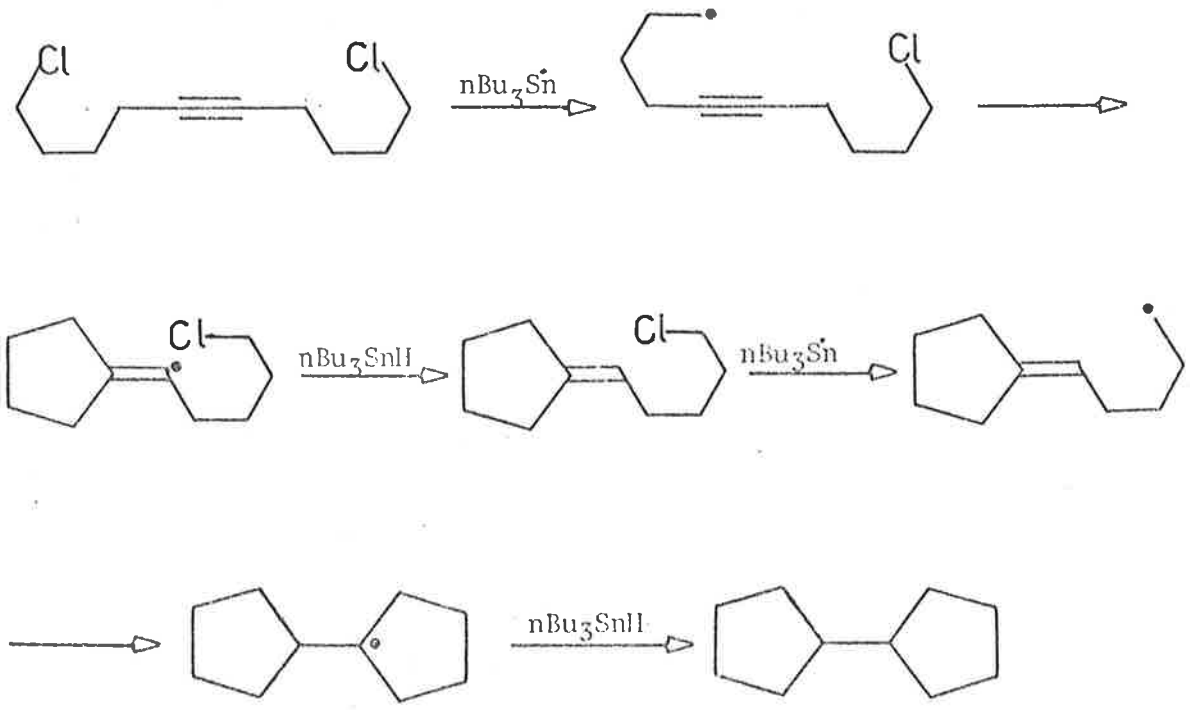


No *endo*-cyclisation was observed. Quantitative yields of cyclic products (ylidenecyclopentanes) were obtained when the R substitution was either a phenyl or an alkyl group. In order to maximise the yields of cyclic products it was necessary to work with low concentrations of tri-n-butyltin hydride, which implied that the observed free radical cyclisations were irreversible. Partial cyclisation of the hept-6-yn-1-yl radical was observed when the R group was a phenyl, and no cyclisation when the R group was an alkyl group or hydrogen.

Electrochemical reduction of 6-chloro-1-phenylhex-1-yne and 6-bromo-1-phenylhex-1-yne at a mercury cathode in DMF resulted in both *exo*- and *endo*-cyclisations of the free radical intermediate[102,103].



This was attributed[96] to reduction of the carbon-bromine bond, followed by stepwise reduction of the phenyl-activated carbon-carbon-triple bond. The workers reported difficulties in controlling the reaction conditions[102]. The relative yields of methylenecyclopentane and cyclohexene derivatives were not reproducible. In 1975 selective 1,5-cyclisation illustrated below was observed[104].



In the reduction of 1,10-dichlorodec-5-yne with tri-n-butyltin hydride only *exo*-cyclisation was observed.[104]

Thus far intramolecular cyclisations of only hex-5-yn-1-yl radicals were reported. Kinetic data of such intramolecular cyclisations are not available. Intramolecular cyclisation of the hept-6-yn-1-yl radical was reported to occur only when the acetylenic bond was activated by a phenyl substituent.[100]

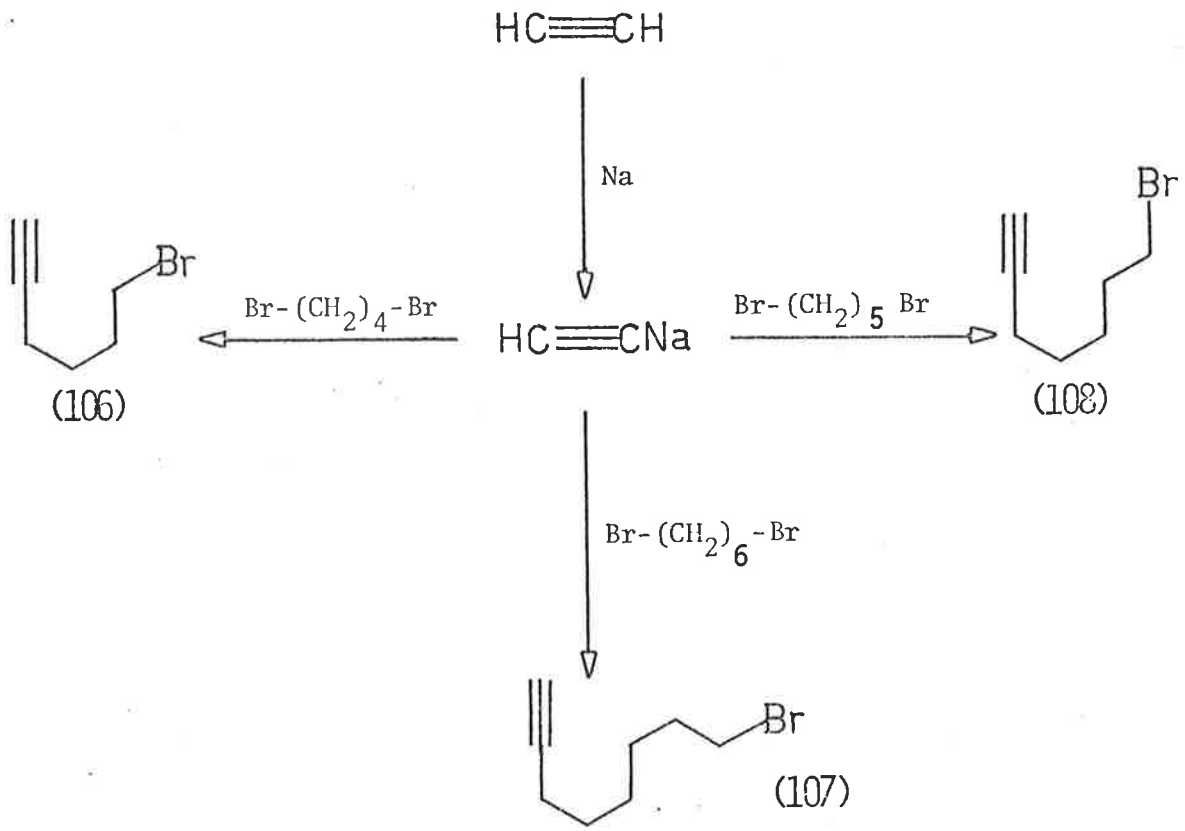
The present work includes investigations of hex-5-yn-1-yl, hept-6-yn-1-yl, and oct-7-yn-1-yl radicals under the reduction conditions employed in the studies of alkenyl radicals.

SYNTHESIS

6-Bromohex-1-yne, 7-bromohept-1-yne, and 8-bromo-oct-1-yne were prepared by simple one step syntheses outlined in scheme 40.

Scheme 40

Synthesis of 6-bromohex-1-yne, 7-bromohept-1-yne, and 8-bromo-oct-1-yne.

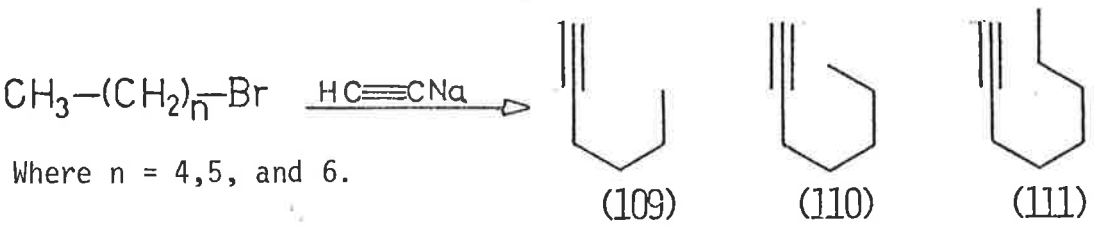


A large excess, 5 equivalents, of dibromoalkanes was employed in order to minimise addition of acetylide anions at both ends. The unreacted dibromoalkanes were recovered by fractional distillation. The yields of bromoalkynes were 80-85%. Less than 5% of dialkynes were recovered on distillation.

The acyclic reference alkynes were prepared as outlined in scheme 41.

Scheme 41

Synthesis of hex-1-yne, hept-1-yne, and oct-1-yne.

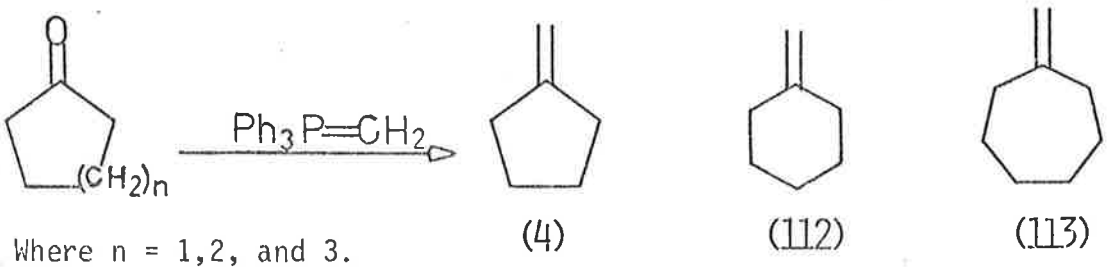


Where n = 4,5, and 6.

The three methylene cycloalkanes - methylenecyclopentane, methylenecyclohexane, and methylenecycloheptane - were prepared via the Wittig reaction on the corresponding ketones (Scheme 42).

Scheme 42

Synthesis of methylenecyclopentane, methylenecyclohexane, and methylenecycloheptane.



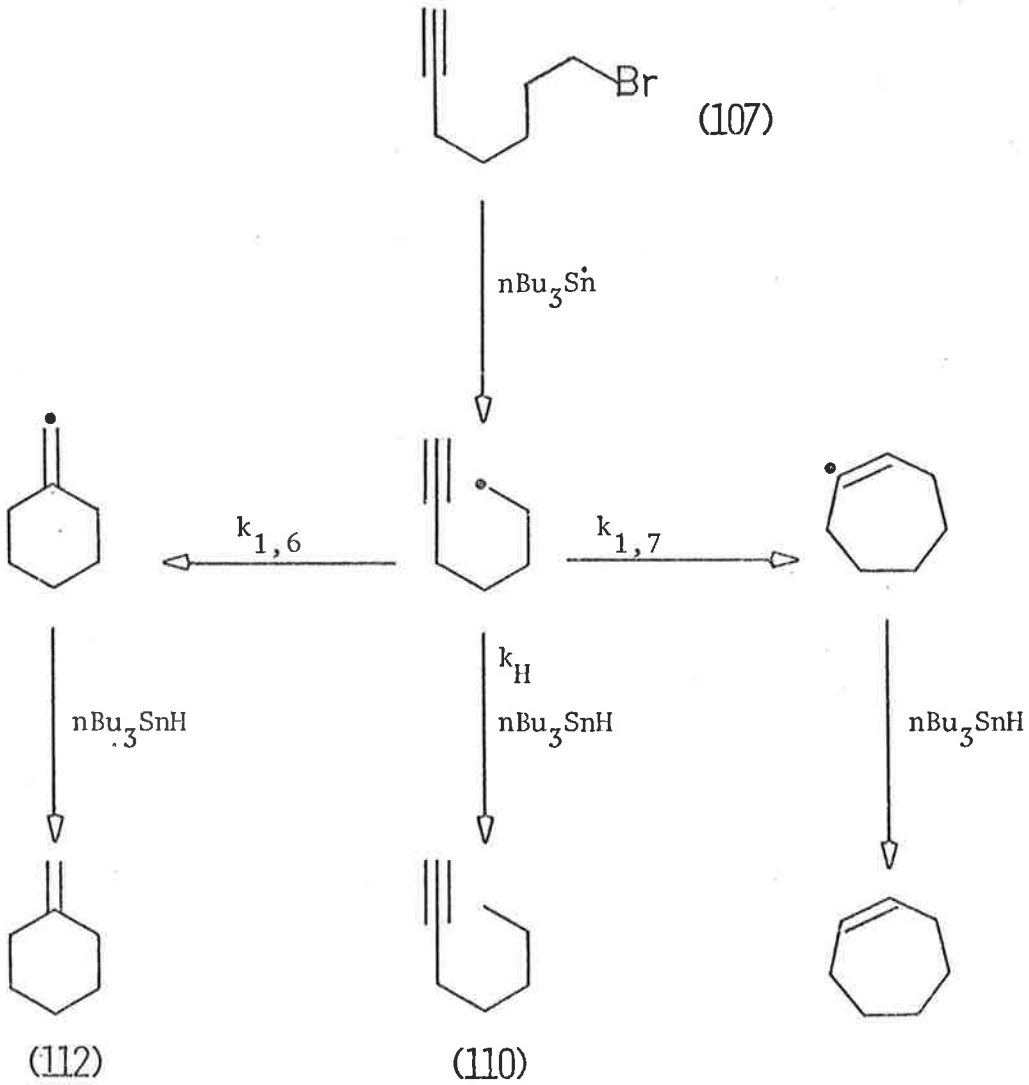
Where n = 1,2, and 3.

All yields were low - 30-40%.

The cyclic alkenes (cyclohexene, cycloheptene, and cyclo-octene) were available as commercial products.

Scheme 44

Reduction of 7-bromohept-1-yne with nBu_3SnH.

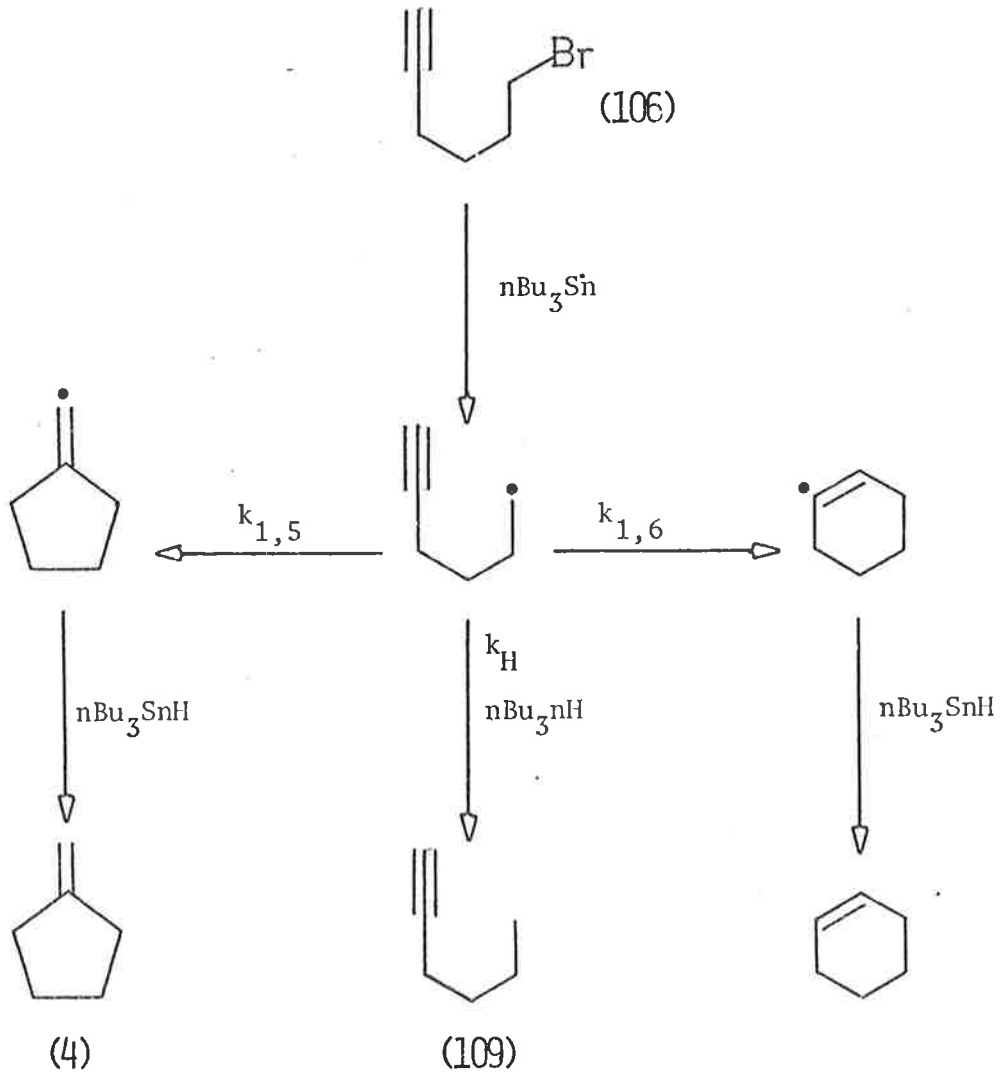


REDUCTION - RESULTS and DISCUSSION

Reductions were carried out by standard methods. The likely courses of the reactions are outlined in schemes, 43, 44, and 45.

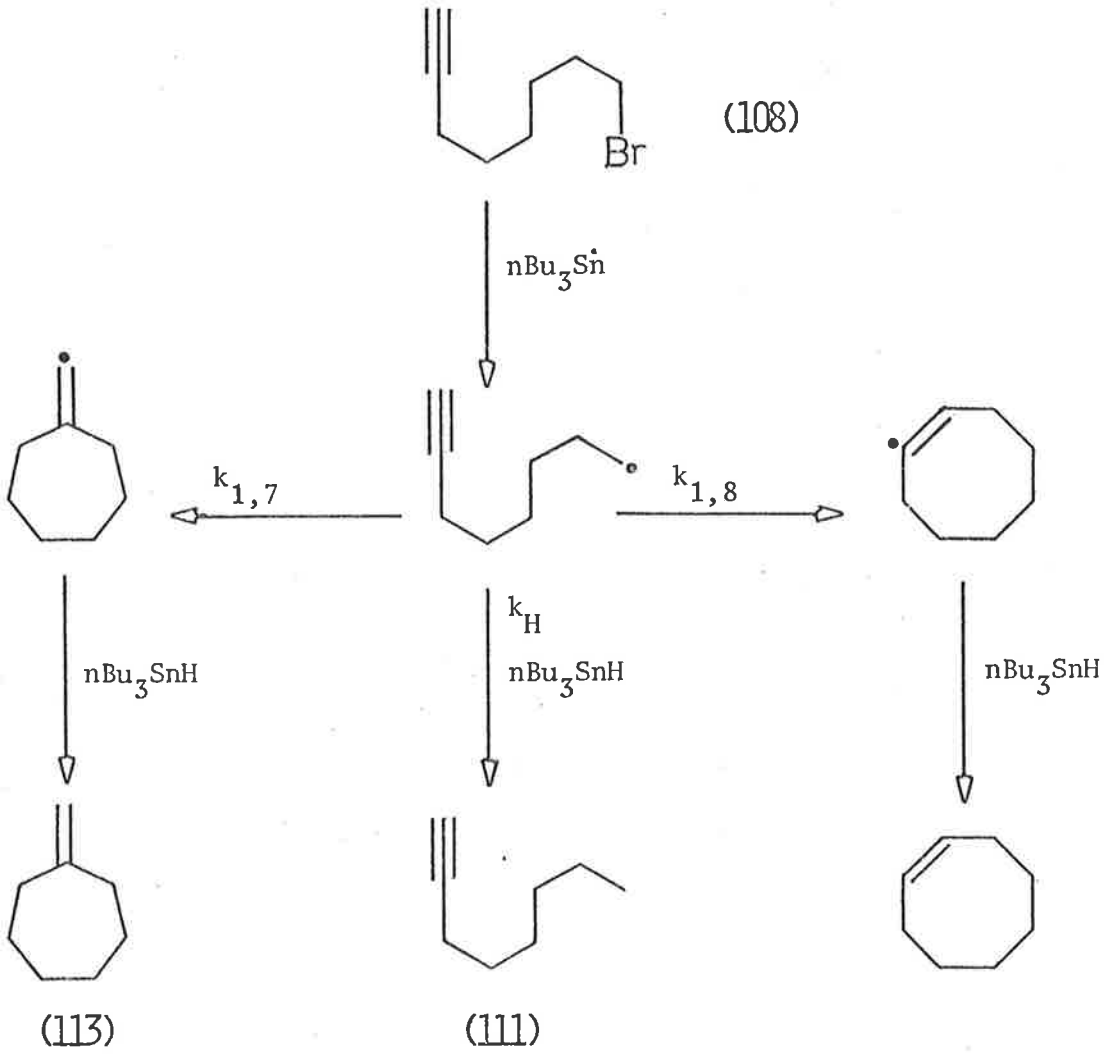
Scheme 43

Reduction of 6-bromohex-1-yne with nBu_3SnH.



Scheme 45

Reduction of 8-bromo-oct-1-yne with nBu_3SnH.



In all reactions the solvent was benzene, and the bromides were used in 20% excess. Reaction temperatures and the concentrations of tri-n-butyltin hydride were as listed in tables 34, 35, 36, and 37. At 80^{o} 7-bromohept-1-yne was also reduced with tri-n-butyltin deuteride.

Table 34 Distribution of products in the reduction of 6-bromohex-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/l	Relative % Yields		Total Yields %
		(109)	(4)	
40	.1500	73.9	26.1	91
40	.3000	83.1	16.9	94
40	.6000	89.7	10.3	95
60	.1500	66.5	33.5	92
60	.3000	77.8	22.2	92
60	.6000	86.0	14.0	93
80	.0750	42.2	57.8	94
80	.1500	57.4	42.6	95
80	.3000	70.5	29.5	96
80	.6000	80.8	19.2	95
100	.3000	68.0	32.0	95
100	.6000	79.0	21.0	95

No cyclohexene was formed from the hex-5-yn-1-yl radical. Relative yields of hex-1-yne and methylene cyclopentane depended on the concentration of tri-n-butyltin hydride in a way which implied irreversible cyclisation.

Table 35 Distribution of products in the reduction of 7-bromohept-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/l	Relative Yields %		Total Yields %
		(110)	(112)	
60	.0481	89.6	10.4	93
60	.0814	92.9	7.1	93
60	.1412	95.4	4.6	93
60	.2488	96.9	3.1	90
80	.1007	91.7	8.3	94
80	.1701	94.4	5.6	95
80	.3501	97.0	3.0	92
80	.5549	97.7	2.3	92
80	.7955	98.3	1.7	90
94	.0397	78.3	21.7	96
94	.0850	87.3	12.7	96
94	.1491	91.7	8.3	93
94	.2166	93.7	6.3	92
94	.2405	94.1	5.9	95

Table 36 Distribution of products in the reduction of 7-bromohept-1-yne with nBu_3SnD.

Temp °C	$[nBu_3SnD]$ mole/l	Relative Yield %		Total Yields %
		(110)	(112)	
80	.0189	63.7	36.3	92
80	.0429	77.7	22.3	94
80	.0829	85.4	14.6	95
80	.1574	90.6	9.4	95
80	.2907	94.4	5.6	93

Again there was no evidence of *endo*-cyclisation. No cycloheptene could be detected in the products. Contrary to an earlier report[100] the hept-6-yn-1-yl radical, which carries no electron donating substituent at C7, does undergo 1,6-cyclisation. Since the cyclisation is irreversible a simple calculation (page 29) will show that high yields of methylene cyclohexane can be obtained at higher reaction temperatures and low concentrations of the tri-n-butyltin hydride, say, 100° and .005M.

Table 37 Distribution of products in the reduction of 8-bromo-oct-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/l	Relative Yield %		Total Yield %
		(111)	(113)	
60	.0076	95.5	4.5	92
81	.0076	93.4	6.6	92
81	.0126	95.4	4.6	94
100	.0076	89.3	10.7	93
100	.0126	92.7	7.3	95

That intramolecular cyclisation of the oct-7-yn-1-yl radical is very slow is evident from the low yields of methylenecycloheptane even at rather low concentrations of tri-n-butyltin hydride (Table 37).

In order to obtain meaningful results it was necessary to carry out many reactions (30-40 reductions) at each temperature and each tri-n-butyltin hydride concentration. The relative yields in table 37 are the mean values from all the reductions at each concentration. The standard deviation of any one mean relative yield was lower than 3.1% (two failed test). No cyclo-octene was found in the products, hence the oct-7-yn-1-yl

radical does not undergo *endo*-cyclisation. It could be argued that relatively low yields of cyclo-octane were not detectable by the methods of product analysis.

The relative yield of the cyclised product was inversely related to the concentration of tri-n-butyltin hydride, which implied irreversible cyclisation.

The rate constants, k_c/k_H, for intramolecular cyclisation of hex-5-yn-1-yl, hept-6-yn-1-yl, and oct-7-yn-1-yl radicals are listed in tables 38, 39, 40, and 41.

Table 38 Values of k_c/k_H in the reduction of 6-bromohex-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mol/l	$k_{c_{1,5}}/k_H$ l/mole	Mean $k_{c_{1,5}}/k_H$ l/mole	St.Dev. %
40	.1500	.0173		
40	.3000	.0175		
40	.6000	.0173	.0174	.8
60	.1500	.0265		
60	.3000	.0265		
60	.6000	.0266	.0265	.2
80	.0750	.0428		
80	.1500	.0420		
80	.3000	.0422		
80	.6000	.0425	.0424	.8
94	.3000	.0488		
94	.6000	.0486	.0487	.3

Table 39 Values of k_c/k_H in the reduction of 7-bromohept-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mol/l	$k_{c_{1,6}}/k_H$ l/mole	Mean $k_{c_{1,6}}/k_H$ l/mole	St.Dev. %
60	.0481	.0014		
60	.0814	.0014		
60	.1412	.0014		
60	.2488	.0015	.0014	4.2
80	.1007	.0022		
80	.1701	.0022		
80	.3501	.0021		
80	.5548	.0023		
80	.7955	.0024	.0022	5.2
94	.0397	.0034		
94	.0850	.0033		
94	.1491	.0032		
94	.2166	.0033		
94	.2405	.0033	.0033	2.0

Table 40 Values of k_c/k_H in the reduction of 7-bromohept-1-yne with nBu_3SnD.

Temp °C	$[nBu_3SnD]$ mol/l	$k_{c_{1,6}}/k_D$ l/mole	Mean $k_{c_{1,6}}/k_D$ l/mole	St.Dev. %
80	.0189	.0039		
80	.0429	.0038		
80	.0829	.0039		
80	.1574	.0040		
80	.2906	.0037	.0039	2.8

Table 41 Values of k_c/k_H in the reduction of 8-bromo-oct-1-yne with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mol/l	$k_{c_{1,7}}/k_H$ l/mole	Mean $k_{c_{1,7}}/k_H$ l/mole	St.Dev. %
60	.0076	.00008	.00008	1.8
81	.0076	.00012		
81	.0126	.00013	.00012	2.4
100	.0076	.00023		
100	.0126	.00023	.00023	2.2

None of the three radicals underwent *endo*-cyclisation to form the corresponding cycloalkene. In each case free radical addition to the nearer acetylenic carbon took place to produce the corresponding methylenecycloalkane. The rates of cyclisation decrease with the chain length. The rate of 1,6-cyclisation of the hept-6-yn-1-yl radical is 19 times slower than the rate of 1,5-cyclisation of the hex-5-yn-1-yl radical; and the rate of 1,7-cyclisation of the oct-7-yn-1-yl radical is 18 times slower than the rate of 1,6-cyclisation of the hept-6-yn-1-yl radical. Each additional carbon in the chain length lowers the the rate of intramolecular cyclisation by 18-19 times. It is clear that intramolecular cyclisation of the hex-5-yn-1-yl radical offers good prospects for introduction of exocyclic methylene groups during synthesis. The hex-5-yn-1-yl radical undergoes intramolecular cyclisation 5 times slower than the hex-5-en-1-yl radical. Although still considerably slower (19 times) hept-6-yn-1-yl radical undergoes 1,6-cyclisation at a rate which could be used in the synthesis of complex molecules containing

methylenecyclohexane groups in their structures. For technical reasons it was not possible to determine the rates of 1,5-hydrogen atom transfer in the hept-6-yn-1-yl radical. Hence the rate constants for the cyclisation of this radical (Table 39) are in fact the ratios of k_c to k_H plus $K_{1,5\text{-hydrogen}}$. That the errors thus introduced into the calculated values of $k_{c_{1,6}}/k_H$ are very small is indicated by two factors:

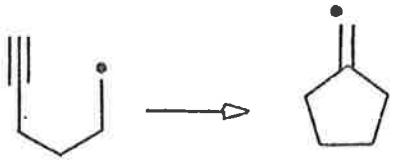
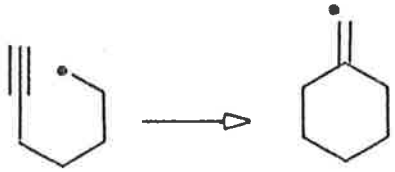
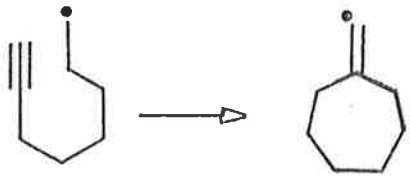
(1) The calculated rate constants, where it was assumed that no 1,5-hydrogen shift had occurred, do not show significant variation with changes in the concentration of the hydrogen atom donor (nBu_3SnH) at the same temperature (Table 39).

(2) The extent of 1,5-hydrogen atom transfer in the oct-7-en-2-yl radical (page 114) was so low as to have no significant effect on the rates of cyclisation of this radical; yet such transfer involved the formation of an allyl radical, which has the relative rate of formation by hydrogen atom abstraction 8 times greater than the analogous propargyl radical[58,105].

Intramolecular cyclisation of the oct-7-yn-1-yl radical is so slow (Table 41) as to be of little synthetic utility. Determination of the rates of cyclisation of this radical presented considerable difficulties, because the rate of hydrogen atom abstraction is much faster than the rate of intramolecular cyclisation. Nevertheless the oct-7-yn-1-yl radical does undergo intramolecular cyclisation. The cyclisation is irreversible.

Activation parameters were calculated from the rate constants in tables 38, 29, and 41 by standard methods (page 30). These are listed in table 42.

Table 42 Energies of activation for the cyclisation of hex-5-yn-1-yl, hept-6-yn-1-yl, and oct-7-yn-1-yl radicals relative to hydrogen atom abstraction from nBu_3SnH.

REACTION	$\Delta\Delta S^{\#}$ cal/mole/^{o}K	$\Delta\Delta H^{\#}$ kcal/mole
	6.7 ± .2	4.6 ± .1
	4.6 ± .2	5.9 ± .1
	2.4 ± .2	7.1 ± .1

Where $\Delta\Delta S^{\#} = \Delta S^{\#}_{C} - \Delta S^{\#}_{H}$, and $\Delta\Delta H^{\#} = \Delta H^{\#}_{C} - \Delta H^{\#}_{H}$

The calculated energies of activation show that with increase in the chain length both the entropy and the enthalpy of activation become less favourable for cyclisation. The entropy of activation for the cyclisation of the hex-5-yn-1-yl radical is similar to that of the hex-5-en-1-yl radical; hence the five-fold reduction in the rate of cyclisation is due to higher enthalpy of activation.

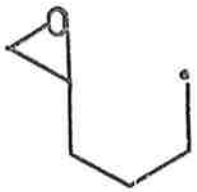
CONCLUSIONS

1. Hex-5-yn-1-yl, hept-6-yn-1-yl, and oct-7-yn-1-yl radicals undergo irreversible intramolecular *exo*-cyclisation to form methylene cycloalkane derivatives.

2. The rates of intramolecular cyclisation decrease by 18-19 times as the chain length increases by one carbon.

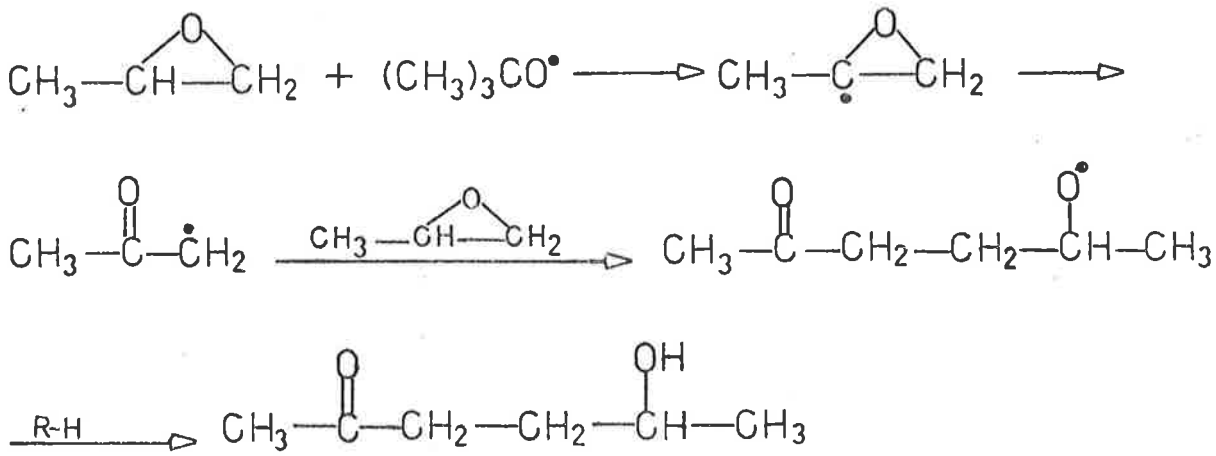
3. The hex-5-yn-1-yl radical undergoes 1,5-cyclisation 5 times slower than the hex-5-en-1-yl radical. This decrease in the rate of cyclisation is due to higher enthalpy of activation.

4. The oct-7-yn-1-yl radical cyclises 18 times slower than the hept-6-yn-1-yl radical, which in turn cyclises 19 times slower than the hex-5-yn-1-yl radical. The calculated activation parameters show that these differences in the rates of cyclisation are due to changes in both the entropy and the enthalpy of activation.



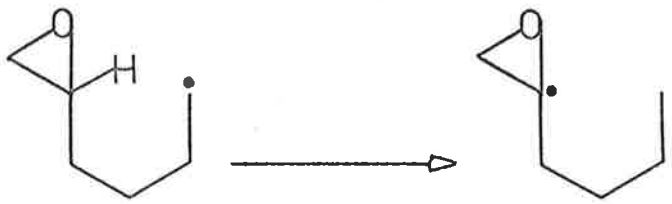
5,6-EPOXYHEXAN-1-YL RADICAL

Early work in the free radical chemistry of epoxides showed that the radical formed from propylene oxide by hydrogen atom abstraction isomerised to a keto-radical which attacked the epoxide ring by intermolecular addition[106].



Although under the reaction conditions of these experiments the yield of 5-hydroxy-2-hexanone was very low (2%), it appeared to us that under more favourable reaction conditions addition of the alkyl radical to the expoxide ring might be increased considerably. By comparison to the hex-5-en-1-yl radical, where the effective double bond concentration for intramolecular addition is ≈ 40 M[59], the 5,6-epoxyhexan-1-yl radical offered conditions where interaction of the free radical centre with the epoxide ring was high relative to all intermolecular reactions. In the reduction of 1,2-epoxy-6-bromohexane with tri-n-butyltin hydride the reaction conditions could be further adjusted to favour intramolecular free radical addition to the epoxy ring by employing low concentrations of tri-n-butyltin hydride and relatively high reaction temperatures (100-150^{o}).

A drawback to this project was the risk of the competing 1-5-hydrogen atom transfer reaction[107,108].



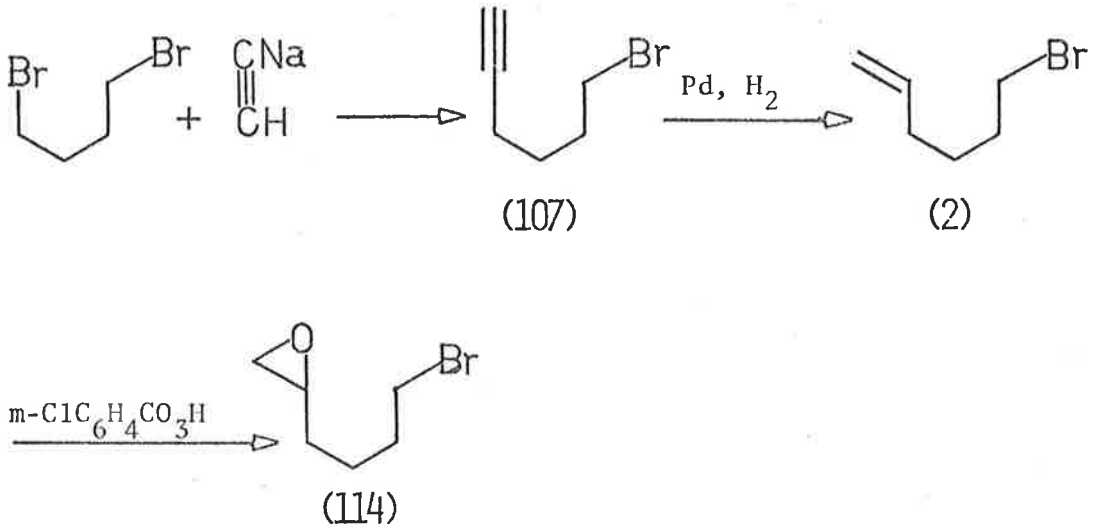
At the best 1,5-hydrogen atom shift would complicate the kinetics of intramolecular addition of the 5,6-epoxyhexan-1-yl radical. At its worst this competing intramolecular reaction could be so fast as to preclude the free radical addition to the epoxy group. Our interest lay not so much in the kinetics of intramolecular cyclisation of the 5,6-epoxyhexan-1-yl radical as in the direction of the ring closure — that is whether *exo*- or *endo*-cyclisation would take place.

SYNTEHSIS

1,2-Epoxy-6-bromohexane was prepared by the reaction sequence outlined in scheme 46.

Scheme 46

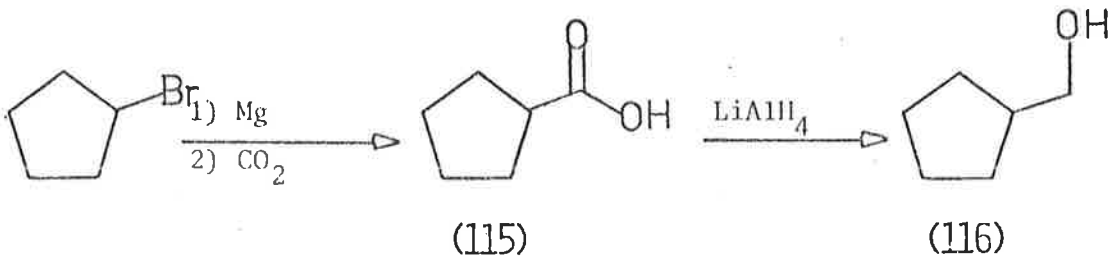
Synthesis of 1,2-epoxy-6-bromohexane.



The yield from each reaction was in excess of 75%. The reference compound 1,2-epoxyhexane was prepared by the epoxidation of 1-hexene, cyclohexanol was commercially available, and methanol cyclopentane was prepared as outlined in scheme 47.

Scheme 47

Synthesis of methanol cyclopentane.

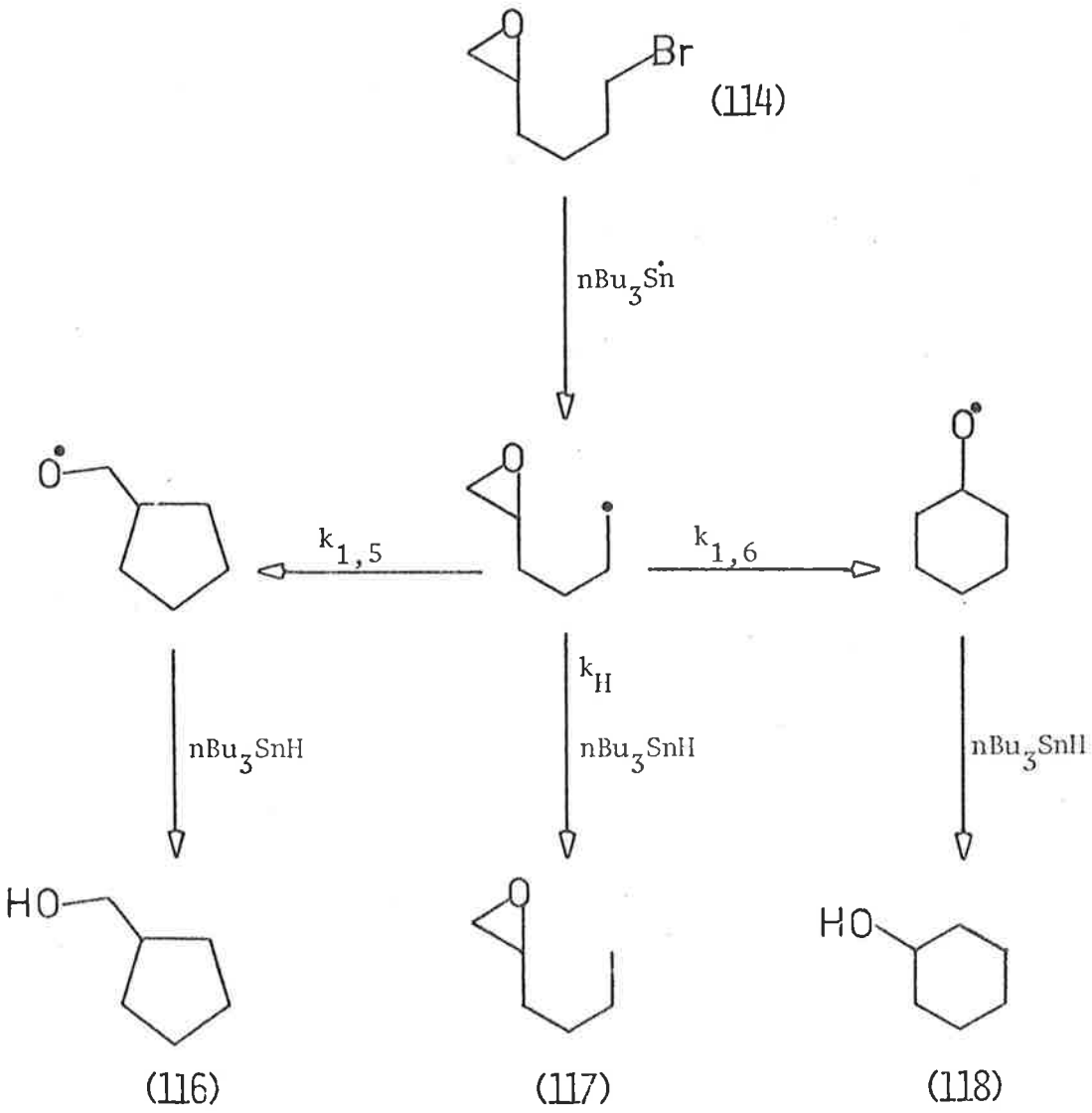


REDUCTION - RESULTS and DISCUSSION

1,2-Epoxy-6-bromohexane was reduced with tri-n-butyltin hydride at temperatures between 60° and 160° (Table 43). The likely products from the reduction are postulated in scheme 48.

Scheme 48

Reduction of 1,2-epoxy-6-bromohexane with nBu_3SnH.



At all temperatures the reaction mixtures were incubated for 48 hours. G.l.c. analysis revealed no cyclic products (Table 43).

Table 43 Distribution of products in the reduction of 1,2-epoxy-6-bromohexane with nBu_3SnH.

Temp °C	$[nBu_3SnH]$ mole/ℓ	Yield (117) %
60	.0025	90
60	.0050	90
60	.0125	91
60	.0250	92
80	.0025	91
80	.0050	90
80	.0125	92
80	.0250	93
100	.0025	88
100	.0050	90
100	.0125	90
100	.0250	93
120	.0025	85
120	.0050	86
120	.0125	85
120	.0250	87
140	.0025	83
140	.0050	84
140	.0125	82
140	.0250	84
160	.0025	77
160	.0050	79
160	.0125	80
160	.0250	80

For technical reasons it was not possible to determine the rate of 1,5-hydrogen transfer. No 2-hexanone was detectable in the products.

Hence to whatever extent 1,5-hydrogen transfer did take place it did not lead to subsequent cleavage of the epoxy ring, which would have resulted in the formation of 2-hexanone.

CONCLUSION

The 5,6-epoxyhexan-1-yl radical in solution does not undergo intramolecular cyclisation under the reaction conditions employed in this study.

AFTERWARD

Alkynyl Radicals

Prior to this work no intramolecular cyclisations of unsubstututed hept-6-yn-1-yl and oct-7-yn-1-yl radicals were reported. It is now known that hex-5-yn-1-yl, hept-6-yn-1-yl, and oct-7-yn-1-yn radicals all undergo intramolecular *exo*-cyclisation, albeit the last one so slowly as to be of little synthetic use under the reaction conditions employed in this work. No doubt the extent of 1,7-intramolecular cyclisation of the oct-7-yn-1-yl radical could be increased in the presence of a poorer hydrogen atom donor than tri-n-butyltin hydride.

Having measured the kinetics and determined the magnitudes of activation parameters of intramolecular *exo*-cyclisation of the hept-6-yn-1-yl radical, it was not technically possible to assess the rate of intramolecular 1,5-hydrogen atom transfer. When an ^{2}H n.m.r. spectrometer becomes available, reduction of 7-bromohept-1-yne with tri-n-butyltin deuteride will give products in which the distribution of the deuterium label will be clearly shown.

5,6-Epoxyhexan-1-yl Radical

How reactive are the ring bonds of 1,2-epoxides towards radicals? The present work on the 5,6-epoxyhexan-1-yl radical has demonstrated complete lack of reactivity of the carbon-oxygen bonds with the free radical carbon. This inertness of the 1,2-epoxy ring to free radical attack may have been due to the fact that the 1,5-hydrogen transfer reaction was much faster than the ring opening. Again for technical reasons the extent of 1,5-hydrogen transfer could not be determined. Further studies of a 5,6-epoxyhexan-1-yl radical without the hydrogen at C5 should be undertaken in order to examine the intramolecular reactivity of the epoxide ring with the free spin carbon without the interference of 1,5-hydrogen transfer reaction.

Hex-5-en-1-yl Radicals

The present work has established that methyl substitution of the hex-5-en-1-yl radical at either C2, C3, or C4 increases the rate of intramolecular cyclisation parallel with the extent of substituent induced gauche interactions in the acyclic radical. This knowledge may be of considerable use in general organic synthesis and in industrial cyclopolymerisation where selective control of rates of free radical cyclisation is desirable.

On the basis of present observations it may be expected that more extensive methyl substitutions of the hex-5-en-1-yl systems at C2, C3, and C4 would result mainly in the change of the enthalpy of activation for cyclisation with much smaller changes in the entropy of activation. In such systems the rates of intramolecular cyclisation would be controlled by the enthalpy of activation. However substitution of the same carbons by branched alkanes might control the rates of cyclisation principally through the entropy of activation. Through severe gauche interactions isopropyl and especially tertiary butyl groups could bar the random distribution of rotomer populations by restricting internal rotations and holding the hexenyl radical in a bent, ring-like conformation. The probability of intramolecular free radical interaction with the double bond would be greatly increased, and considerable changes in the entropy of activation would be noted.

Examinations of 2-methyl-, 3-methyl-, and 4-methylhex-5-en-1-yl radicals have revealed stereoselective ring closures which are consistent with a chair-like conformation in the transition state with the methyl substituents in pseudoequatorial orientations. The observation that the stereochemical outcome of 1,5-ring closure in hex-5-en-1-yl radicals is controlled by conformational effects in a chair-like transition state

may be of wide generality and hold true for related hetero-atom centred radicals. Because the extent of stereoselectivity is related to the conformational preference of the substituent it should be more pronounced with bulky groups. This prediction is supported by the observation that 1,5-cyclisation of the 3-methylhex-5-en-1-yl radical to 1,3-dimethylcyclopentane resulted in the *cis* to *trans* isomer ratio of 2.6, whereas 1,5-cyclisation of the 3-propylhex-5-en-1-yl radical[57] under similar conditions produced *cis* and *trans*-1-methyl-3-propylcyclopentane in the *cis* to *trans* ratio of 4.8.

Further studies of the hex-5-en-1-yl systems should involve more extensive than hitherto undertaken substitutions by methyl groups, and substitutions by branched alkanes at carbons 2, 3, and 4.

Stereoelectronic Control

Studies of the direction of ring closure of the 2,2,5-trimethylhex-5-en-1-yl radical have shown that non-bonded interactions between hydrogens at C2 and C6 could not be the cause of the selective 1,5-cyclisation of the hex-5-en-1-yl radical. Having thus disproved the hypothesis of stereochemical control, we are left with the hypothesis of stereoelectronic control as the only explanation for the initially unexpected 1,5-cyclo-addition of the hex-5-en-1-yl radical. Based on the assumption that electronic orbitals involved in a reaction process must meet definite geometrical requirements, and supported by calculations of the geometric probability factors[159] the hypothesis of stereoelectronic control is the best explanation for the regiospecific intramolecular addition of the hex-5-en-1-yl systems.

EXPERIMENTAL SECTION

METHODS OF REDUCTION

Compounds

Only bromo compounds were used for generating radicals by reaction with tri-n-butyltin hydride and occasionally tri-n-butyltin deuteride. The following bromocompounds were prepared and reduced in the course of this work:

1) 6-Bromohex-1-ene
2) 5-Methyl-6-bromohex-1-ene
3) 4-Methy-6-bromohex-1-ene
4) 3-Methyl-6-bromohex-1-ene
5) 5,5-Dimethyl-6-bromohex-1-ene
6) 4,4-Dimethyl-6-bromohex-1-ene
7) 5,5,2-Trimethyl-6-bromohex-1-ene
8) 4,4-Dimethyl-5-bromopent-1-ene
9) 3,3-Dimethyl-5-bromopent-1-ene
10) 7-Bromo-oct-1-ene
11) 6-Bromohex-1-yne
12) 7-Bromohept-1-yne
13) 8-Bromo-oct-1-yne
14) 6-Bromo-1,2-epoxyhexane

Solvent

Without exception benzene was used as the solvent. Analytical grade reagent was purified by repeated partial freezing until no trace of impurities was detectable by analytical gas liquid chromatography at a greater than the maximum resolution employed during product analysis.

In order to remove oxygen, purified benzene was frozen in liquid nitrogen and evacuated to 0.1 mm Hg for ten minutes. The evacuated

flask was shut off from the vacuum pump, and the frozen benzene left to melt to liquid, then frozen again and evacuated for ten minutes. This deoxygenation process was repeated five times, after which the reduced pressure inside the flask was equalised to atmospheric pressure with high purity nitrogen. The flask was sealed with a rubber seal under nitrogen, and the solvent withdrawn with a syringe when required. The syringes were always flushed with nitrogen and the withdrawn volume of benzene replaced by high purity nitrogen. Immediately upon withdrawal of the solvent the syringe puncture and the nitrogen inlet puncture on the seal were covered over with silicon grease; this cover had to be intact prior to the next withdrawal of the solvent.

Reaction conditions

The temperature of the reaction environment, and concentrations of reactants were the only factors which were varied during reactions. In general reaction temperatures were in the range of 60-100^{o}, but temperatures as low as 30^{o}, and high as 160^{o} were employed. Because most of the work involved investigations of kinetic changes as a function of changes in the structures of the reactive intermediates, it was considered essential to maintain identical reaction conditions throughout all the reductions. In the preparation of the reaction samples of particular importance were the exclusion of oxygen, the purities of the solvent and the reagents, and the accuracy of the reagent concentrations.

Temperature

Each compound was reduced at 3-4 temperatures; the most common reaction temperatures were 40^{o}, 60^{o}, 80^{o} and 100^{o}, but 30^{o}, 55^{o}, 120^{o}, 130^{o}, 140^{o}, 150^{o}, and 160^{o} were employed for specific purposes. A thermostat controlled 20 litre silicone oil bath was used for temperatures between 30^{o}

to 100°. Temperature fluctuations of this bath did not exceed ·1°C. For temperatures over 100° a small thermostat oil bath (.5-1.5 litre) was used; variations of its preset temperatures were plus-minus 1°C. Reductions at temperatures over 100° were done for non-kinetic purposes and 1° fluctuations were of no consequence.

Reagent concentrations

Effective reagent concentrations are by far the most important single factor in this type of work. Errors of 2-3% are likely to give unacceptably erroneous results. Errors in concentrations are difficult to detect. If the bromide being reduced is present in, say, 20% excess over the concentration of stannane then small fluctuations in its concentration have no effect on the results, and the problem of concentration accuracy is confined to a single reagent. For this reason bromides were used in excess in most reactions. Prior to reduction it was assured that all bromides were analytically pure, homogenous by g.l.c. analysis, dry, and deoxygenated. Tri-n-butyltin hydride and tri-n-butyltin deuteride were prepared as described under "Synthetic Methods" and stored under nitrogen.

Two methods of measuring required amounts of stannane were examined:

1. The required amount of stannane was weighed under nitrogen. Accuracy of weighing was within 1.0×10^{-5} gm with the standard deviation of .2-.5% (two tailed test). The response of the balance varied with weight and the weighing time.
2. The required amount of stannane was measured volumetrically. The mean specific gravity of tri-n-butyltin hydride was determined by weighing 10 x 100 µl, 15 x 50 µl, 15 x 10 µl, and 15 x 5 µl volumes to within 1.0×10^{-5} g at 18-21° and found to be 1.0996 g/ml with a standard deviation of .1-.3%

(two tailed test). The specific gravity of tri-n-butyltin deuteride, determined by a similar method, was found to be 1.1039 g/ml.

Method (1) requires longer time and there is a considerable likelihood of contaiminating the sample with air oxygen. Method (2) is at least 100 times faster, and the possibility of contaminating the sample with oxygen is negligible. At similar concentrations and temperatures yields of products from 10 identical reaction mixtures prepared by method (1) varied by 4-17%; those prepared by method (2) varied by 1-5%. In both cases the fluctuations were inversely related to concentration. The tests were carried out by reducing 6-bromohex-1-ene with tri-n-butyltin hydride at 80^{o} at concentrations of 1.00 M, .500 M, .10 M, .01 M, and .005 M. The yield variations are recorded in table 44.

Table 44 Variation in hydrocarbon yields where stannane concentrations were measured by weight, and volume, expressed as standard deviation from the mean (two tailed test).

$[nBu_3SnH]$	1.00M	.500M	.100M	.010M	.005M
Weight	4.2%	5.3%	8.4%	12.5%	17.0%
Volume	.9%	1.4%	2.0%	3.6%	5.2%

Ten samples were prepared by each method at each concentration. 6-Bromohex-1-ene was used in an excess of 20%. Fluctuations in yields corresponded to concentration deviations of tri-n-butyltin hydride.

Unless otherwise stated all reaction mixtures during this study were prepared by method (2). Volumetric measurements are no less accurate than

weighing, and have the advantage of improved efficiency of preparation of the reaction mixtures. The risk of contaminating the reaction mixtures with oxygen is greatly reduced.

Preparation of reaction mixtures

Ampoules used for reductions were 3-15 ml volume when 75% full. They were of heavy pyrex walls, and with necks for attaching a wire. In a typical reduction clean glass ampoules (5-20 at each concentration) were wired and tagged, flushed with nitrogen, and stoppered. Under a blanket of nitrogen a trace of azobisisobutyronitrile (AIBN) was added to each ampoule. Likewise under nitrogen the required amount of solvent was added with a volumetric syringe to all ampoules. Next the bromide (1.2 equivalents), the density of which had already been determined, was added with a volumetric syringe to each ampoule under nitrogen, and the ampoule immediately stoppered. With the appropriate size volumetric syringe, tri-n-butyltin hydride was then added under nitrogen. Each ampoule was immediately frozen in liquid nitrogen with a continuous stream of high purity nitrogen above its opening to exclude air, then sealed by melting the open end and drawing out. The sealed ampoules were weighted with prepared lead strips and suspended in a pre-equilibrated constant temperature oil bath. Unless otherwise noted all ampoules were incubated for 48 hours.

In general at each temperature the reaction mixtures were prepared in 2-4 different concentrations. The number of reactions at each concentration varied from 5-20. In the study of oct-7-yn-1-yl radical no less than 30 reactions were run at each concentration at the same temperature. At a given temperature the rate of free radical rearrangement is independent of concentration. Reductions at more than a single concentration are needed for checking the accuracy of the obtained rate

constants.

An arbitrary standard employed in this work was that at a given temperature the standard deviation of the mean value of the rate constant determined from reactions of identical reagent concentration had to be below 1.1%, and the standard deviation at the mean rate constant at the same temperature determined over a range of concentrations had to be below 3%.

It was found by trial and error that within these limits entropies of activation, determined over 3-4 temperatures, did not vary by more than 1.0 cal/mole/^{o}K; and the enthalpies of activation did not vary by more than .2 kcal/mole.

Controls

Controls were run for each set of reagent concentrations at each temperature. The following controls were used regularly:

(1) Solvent only

(2) Solvent, and AIBN

(3) Solvent, bromide, and AIBN

(4) Solvent, stannane, and AIBN

(5) Solvent, bromide, stannane.

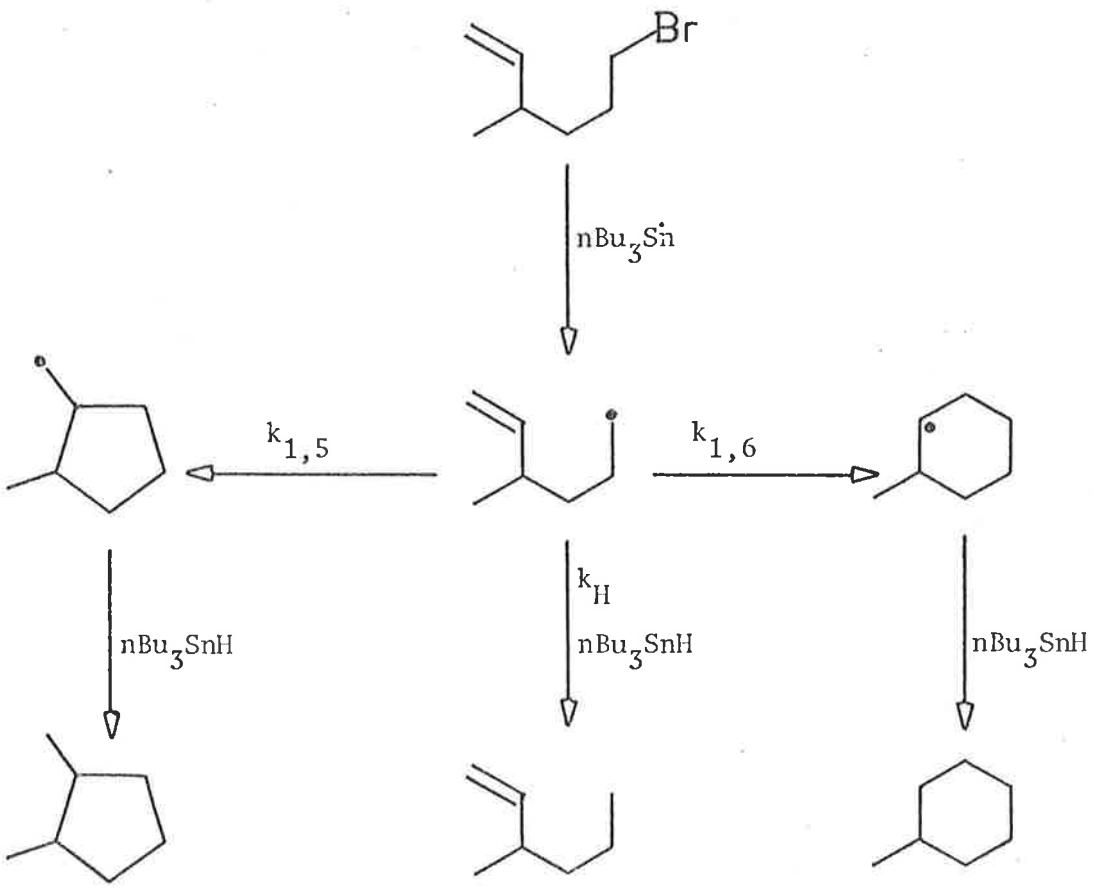
Only a single sample of each control was employed. Control (1) was no more than a check on solvent purity. As a rule the solvent contained no impurities. Control (2) showed that AIBN did not react with the solvent to produce products detectable by the methods of analysis. Control (3) was a check on whether any products, detectable by g.l.c. analysis, were formed by the reaction of AIBN and the bromide. None were found.

Control (4) identified products formed in the reaction of stannane with AIBN. A single small peak of short retention time, detectable

on all g.l.c. columns, was invariably present. It never interfered with analysis. Control (5) constituted a test for the necessity of the free radical initiator (AIBN) in the reaction mixture. Absence of AIBN made no difference to relative or overall yields of the products. Nevertheless AIBN was used with all reactions for uniformity, and because by the time the control showed that AIBN was not required those reactions for which the control was used had been completed.

METHODS OF ANALYSIS

On the basis of the established free radical mechanism, which is involved in the reduction of 6-bromohex-1-ene with tri-n-butyltin hydride, it is possible to predict the products from similar reductions of analogous compounds. For example reduction of 3-methyl-6-bromohex-1-ene is expected to follow the mechanisms outlined below:



All analytical work was done by gas liquid chromatography. For identification purposes reference compounds were prepared by unambiguous synthetic routes.

After preparation the purity of the reference compounds was checked by their boiling points, spectral data, and gas liquid chromatographic (g.l.c) analysis. For every reference compound it was found that the g.l.c. peak area was linearly related to concentration. This was determined by preparing a 2.5M solution of each reference and diluting it stepwise down to .00025M, then loading a series of comparable volumes onto g.l.c. columns and comparing the peak area. These standard solutions had two functions:

1) Checking whether the gas liquid chromatograph responded linearly to variations in concentration.
2) Determining the overall reaction yields by comparing the peak areas of the standard solutions of the reference hydrocarbons, or to the linear plot of reference concentrations versus peak area.

Hence internal standards could be eliminated from the reaction mixtures - thus simplifying analysis.

It was further found that cyclic and acyclic hydrocarbon products from any one radical had similar response ratios within the resolution limits of the gas chromatograph. The preparation of reference compounds and their g.l.c. analysis may in the end prove superfluous. The free radical under investigation may not rearrange at all; only a single product from intermolecular hydrogen atom abstraction may be present in the reaction mixture. Such was the case with 2,2-dimethylpent-4-en-1-yl and 3,3-dimethylpent-4-en-1-yl radicals. Accordingly when it was suspected that no cyclisation of 2,2-dimethylpent-4-en-1-yl and 3,3-dimethylpent-4-en-1-yl might take place, the reaction mixtures were analysed by g.l.c. without recourse to references. The g.l.c. trace showed a single sharp peak followed by the solvent peak. When a sample of the reaction mixture was treated with bromine until the solution just turned orange, the peak representing the products disappeared completely from the g.l.c. trace,

and only the solvent peak remained. This showed that the only product was an alkene and no cyclisation had taken place. Overlap of the solvent peak with that of the possible cyclic product was ruled out on the basis of g.l.c. conditions and the separation properties of pent-1-ene, 1,1-dimethylcyclopentane and benzene. Later the use of a reference hydrocarbon, 1,1-dimethylcyclopentane, showed that no cyclisation took place at all. Bromination of a sample from the reaction mixture will identify the g.l.c. peaks from olefinic and acetylenic compounds.

When, during the initial analysis of products from the reduction of 5,5-dimethyl-6-bromohex-1-ene, every column - tested under diverse conditions - gave only a single peak well separated from the solvent, bromination of the sample still gave a single g.l.c. peak but now reduced in area and intensity. Subsequent calibration of reference compounds showed that 5,5-dimethylhex-1-ene and 1,1,3-trimethylcyclopentane could not be separated on any single column available. This was achieved by coupling two columns in series.

The following gas liquid chromatographs were used for quantitative analysis:

Perkin-Elmer, model 990, which was equipped with a disc integrator.

Pye-Unicam, model 104.

Both instruments had flame ionisation detectors. The carrier gas was nitrogen or helium. Relative peak areas were determined by disc integration, triangulation, and by cutting out each peak above the base line and weighing the paper on a micro-balance, which was sensitive to 1×10^{-5} gm. Best accuracy was possible by paper weight, followed by integration, followed by triangulation which was rarely used. The following g.l.c. columns were employed:

Gas Liquid Chromatography Columns

Column	Length meters	Int. Diam. mm	Structure	Liquid phase	Solid Support	Mesh Angst.
A	4.6	2.1	s.steel	5% Apiezon M	Varaport 30	100-120
B	4.6	2.1	s.steel	5% Carbowax 20M	Varaport 30	100-120
C	6.1	3.2	s.steel	20% Carbowax 20M	Varaport 30	100-120
D	6.3	3.2	s.steel	2.5% FFAP	Varaport 30	100-120
E	6.7	8.0	glass	14% Carbowax 20M-TPA	Chromosorb A	40-60
F	3.0	7.0	glass	20% Carbowax 20M-TPA	Chromosorb A	40-60
G	3.3	3.2	s.steel	5% PDEAS	Varaport 30	100-120
H	3.0	3.2	s.steel	3% NPGS-XE60 1:1	Varaport 30	80-100
I	70.0	0.5	glass	Carbowax 20M	Surface coated	Hollow
J	70.0	0.5	glass	Squalene	Surface coated	Hollow
K	100.0	0.5	s.steel	Apiezon L	Surface coated	Hollow
L	70.0	0.5	glass	FFAP	Surface coated	Hollow
M	6.0	8.0	glass	20% OV17	Chromosorb W	60-80
N	6.0	7.0	glass	20% FFAP	Chromosorb A	40-60
O	6.0	8.0	glass	30% QF1:NPGS 2:1	Chromosorb A	40-60
P	3.0	7.0	glass	10% SE30	Varaport 30	80-100

Gas liquid chromatographic conditions, which were employed during quantitative analysis of products from the investigated radicals, are summarised in table 45.

Table 45 G.l.c. conditions for product analysis

Radical	Column	Temp ^{o}C	Carrier gas ml/min
Hex-5-en-1-yl	C	70	N_2, 60
2-Methylhex-5-en-1-yl	C-A*	110	N_2, 65
	E	70	N_2, 25
	L	20	He, 2
3-Methylhex-5-en-1-yl	C-A*	110	N_2, 65
	M	100	N_2, 80
	L	20	He, 2
4-Methylhex-5-en-1-yl	J	65	He, 2.5
2,2-Dimethylhex-5-en-1-yl	B-A*	70	N_2, 35
3,3-Dimethylhex-5-en-1-yl	K	75	N_2, 3
2,2,5-Trimethylhex-5-en-1-yl	C	120	N_2, 60
2,2-Dimethylpent-4-en-1-yl	C-A*	70	N_2, 20
3,3-Dimethylpent-4-en-1-yl	C-A*	70	N_2, 20
1-Methylhept-6-en-1-yl	I or K	60	N_2, 3-4
4-Methylhex-5-en-1-yl	J	30	He, 3.5
Hex-5-yn-1-yl	C	100	N_2, 55
Hept-6-yn-1-yl	C	110	N_2, 50
Oct-7-yn-1-yl	L	110	N_2, 5
5,6-Epoxyhexan-1-yl	D	85-115	N_2, 50-70

* Columns in line

SYNTHETIC METHODS

General Notes

Light petroleum refers to the fraction of b.p. 30-40°.

Infrared spectra (I.R.) were recorded on an Unicam SP200 or a JASCO IRA-1 spectrophotometer; positions of bands are in cm^{-1}.

^{1}H n.m.r. spectra (N.M.R.) were recorded in deuteriochloroform (containing tetramethyl silane as an internal standard) with a Varian T60 spectrometer operative at 60 MHz. The chemical shifts are in δ ppm relative to TMS. Spectral data are reported in the following order : shift, multiplicity, integral, coupling constant.

^{13}C n.m.r. spectra were recorded in deuteriochloroform with a Bruker HX90-E spectrometer fitted with a Nicolet B-NC12 Fourier system and a Bruker B-SV3PM pulse unit. Chemical shifts are in δ ppm relative to TMS.

Mass spectra (M.s.) were determined with a Perkin-Elmer-Hitachi RMU-6D instrument operating at 70 eV.

Microanalysis were carried out by the Australian Microanalytical Service, Melbourne.

Tri-n-butyltin hydride and Tri-n-butyltin deuteride (1)

Anhydrous ether (50 ml) was added to $LiAlH_4$ or $LiAlD_4$ (0.005 mole) and cooled to 0^o.

Tri-n-butyltin chloride (6 g, .018 moles) was added in ether (10 ml). The mixture was stirred for 30 mins at 0^oC, then for 3 hours at room temperature, and again cooled to 0^oC. Deoxygenated water (10 ml) was added dropwise. The mixture was transferred to a separating funnel and more deoxygenated water (90 ml), and ether (50 ml) were added. The ether portion was washed with deoxygenated brine (2 x 50 ml), dried over $MgSO_4$, and the ether removed on a rotatory evaporator under nitrogen. The crude product was distilled under reduced pressure on a vacuum jacketted 30 cm x 1.3 cm glass column filled with glass helices. nBu_3SnH (4.5 g, .015 mole) was distilled at $80^o/.3$ mm, and the oil bath temperature of 160^o.

Yield 80%.

nBu_3SnD was distilled at $90^o/.7$ mm, oil bath temperature 130^o-140^o.

Yield 78% (4.1 g, .014 mole). On the same distillation setup with the bath temperature 150^o-160^o, nBu_3SnCl distilled at 115-$119^o/.7$ mm.

It was verified subsequently that very efficient separation of nBu_3SnD (.6 g) from nBu_3SnCl (6.0 g) is possible on the same distillation apparatus with the oil bath temperature of 130-140^o, and the pressure of .7 mm.

I.R. nBu_3SnH 1820 cm^{-1} strong band, nBu_3SnD 1300 cm^{-1} strong band $d_{18\text{-}21^o}$: nBu_3SnH = 1.0996 g/ml, nBu_3SnD = 1.1039 g/ml.

CAUTION: *Both tributyltinhydride and tributyltindeuteride are highly toxic*[109]. *Contact with skin caused extensive ulceration and cell damage. This occurred in spite of immediate washing with soap and water.*

6-Bromohex-1-ene (2)

6-Bromohex-1-ene was prepared by partial hydrogenation of 6-bromohex-1-yne. 6-Bromohex-1-yne (8.5 g, .05 mole) was dissolved in ethyl acetate (100 ml). 10% Palladium on carbon (.5 g) was added, and the flask connected to a graduated hydrogen cylinder at atmospheric pressure. When, after 7.5 hours of stirring, 1.2 equivalents of hydrogen was taken up the catalyst was removed by filtration through a pad of celite. The solution was washed with 5% sodium carbonate (2 x 25 ml), dried over magnesium sulphate, and the solvent removed by fractional distillation.

6-Bromohex-1-ene (5.2 g, .03 mole) was obtained by distillation of the crude product under reduced pressure. Prior to use in kinetic experiments 6-bromohex-1-ene was further purified by preparative g.l.c. (F, 110°, N_2 80 ml/min).

Yield 64% after distillation.

B.p. 60°/23 mm, literature[110] b.p. = 47-51°/16 mm.

I.R. 915, 1650

N.M.R. 1.3 - 2.5 (m, 6H), 3.4 (t, 2H, J=7Hz),
4.8 - 5.2 (m, 2H), 5.5 - 6.2 (m, 1H)

Methylenecyclopentane (4)

Triphenylmethylphosphonium iodide was prepared by addition of methyl iodide (.12 mole) to triphenylphosphine (.1 mole) in benzene (25 ml). The mixture was left stirring overnight, then filtered, and the crystals placed under reduced pressure (.5 mm Hg) over phosphorous pentoxide for 5 hours. A quantitative yield (39.4 g, .097 mole) of clean, white, crystalline triphenymethylphosphonium iodide was thus obtained, all of which was added in portions to potassium tertiary butoxide (11.2 g, .1 mole) in anhydrous DMSO (200 ml). Cyclopentanone (8.57 ml, .097 mole)

was added with a syringe over 10 min. The mixture was left stirring under nitrogen for 28 hours, then heated to 90-100° for 3 hours, and left to cool back to room temperature. Decalin (50 ml) was added. The mixture was filtered, and washed with 5% sodium carbonate (3 x 50 ml), then with brine (2 x 50 ml). The solution was dried over magnesium sulphate, and the methylenecyclopentane (2.9 g, .035 mole) was recovered by fractional distillation. The product was pure by g.l.c. analysis (A, 45-70°, N_2 50-60 ml/min).

Yield 36%.

B.p. 77°, literature[111] b.p. = 77-78°.

I.R. 1650, 3010

N.M.R. 1.6 (m, 4H), 2.2 (m, 4H), 4.8 (s, 2H)

M.s. Mol. ion at 82 (Mw = 82).

Methylcyclopentane (5)

Methylenecyclopentane (1.64 g, .02 mole) was hydrogenated over platinum oxide (.03 g) in acetic acid (3.0 ml) at atmospheric pressure. After 4.5 hours 1.08 equivalents of hydrogen were taken up. The catalyst was removed by filtration. Water (3.0 ml) was added, and the hydrocarbon layer separated, and dried over 3A molecular sieves.

Microdistillation at atmospheric pressure gave methylcyclopentane (1.3 g, .015 mole) - pure by g.l.c. analysis (C, 70°, N_2 60 ml/min).

Yield 75%.

B.p. 71-72°, literature[112] b.p. = 72°.

M.s. Molecular ion at 84, (Mw = 84).

Methyl diethylmalonate (7)

Ethanol (150 ml) was distilled from sodium ethoxide into the reaction flask under nitrogen. Sodium (4.6 g, 0.20 mole) was added in

pieces at a rate to maintain a steady reflux. After all the sodium had reacted diethylmalonate (32 g, 0.20 mole) was added dropwise. Half way through addition the mixture set solid and stopped the magnetic stirrer. The reaction flask was heated by immersing into a hot water bath (80^{o}) and the mixture quickly dissolved. The stirring was continued using the hot water bath until the remainder of diethylmalonate was added. A dry-ice ethanol condenser was set up on top of the double surface, water cooled condenser. Methyl bromide gas (20 g, 0.21 mole) was passed from a cylinder into a stream of nitrogen, and thence through a potassium hydroxide packed column (50 x 2 cm) connected to a glass tube (5 mm inside diameter), which was immersed into the reaction mixture to just above the magnetic stirring bar. Methylbromide was added over thirty minutes at a rate which maintained a slow reflux. Periodically the cylinder was disconnected and weighed. Sodium bromide precipitated as a white solid. At the end of the reaction the solution remained clear and slightly alkaline. After addition of methyl bromide the mixture was refluxed for 30 min., then cooled and neutralised with acetic acid. Sodium bromide was separated by suction filtration. Ethanol (140 ml) was removed by distillation at atmospheric pressure. Sodium bromide was dissolved in water (60 ml) to which conc. hydrochloric acid (1.0 ml) was added, and the solution combined with the cooled distillation residue. The organic layer was separated, and the aqueous layer extracted with ether (3 x 20 ml). The ether extracts were added to the crude ester, and the solution shaken with calcium chloride and immediately filtered. Ether was removed on a rototary evaporator and the ester shaken for one minute with sodium hydroxide (1.0 g) in water (3.0 ml). The aqueous layer was separated, and the ester washed with dilute hydrochloric acid (2 x 5 ml) and dried over calcium chloride.

Methyl diethylmalonate (31.6 g, 0.18 mole) was obtained by distillation under reduced pressure.

Yield	91%
B.p.	68^{o}/3 mm, literature[113] b.p. = 96^{o}/16 mm
I.R.	1765-1775
N.M.R.	1.2 (t, 6H, J=7Hz), 1.3 (d, 3H, J=7Hz), 3.4 (q, 1H, J=7Hz), 4.2 (q, 4H, J=7Hz).

Diethyl 1-methylpent-4-ene-1,1-dicarboxylate (8)

Sodium (2.3 g, 0.1 mol) was added to dry ethanol (100 ml) under nitrogen. Methyl diethylmalonate (14.4 g, 0.1 mol) was added through a dropping funnel after the reaction with sodium was complete. The mixture was refluxed for 20 hours, then 4-bromobut-1-ene (13.5 g, 10.2 ml, 0.1 mole) was added dropwise. There was immediate precipitation of sodium bromide. After the addition of 4-bromobut-1-ene was complete the mixture was stirred under reflux for one hour, cooled, and acetic acid (3 ml) was added. Most of the ethanol (90 ml) was distilled off while stirring, then water (30 ml) was added, and the mixture stirred until all the sodium bromide was dissolved. The organic layer was separated, and the aqueous portion extracted with ether (3 x 25 ml). Combined organic portions were washed with brine (3 x 25 ml), and dried over magnesium sulphate. Ether was removed by fractional distillation, and the product (17.6 g, .077 mole) distilled under reduced pressure.

Yield	77%
B.p.	90^{o}/1.5 mm.
I.R.	915, 1650, 1750, 3070
N.M.R.	1.2 (t, 6H, J=7Hz), 1.4 (s, 3H), 2.0 (m, 4H), 4.2 (q, 4H, J=7Hz), 4.8-5.3 (m, 1H)

Analysis for $C_{12}H_{20}O_4$: calculated C = 63.14, H = 8.83 ;
found C = 62.73, H = 8.50.

Ethyl 2-methylhex-5-en-1-oate (9)

Diethyl 2-methylpent-4-ene-1,1-dicarboxylate (11.4 g, 0.05 mole) was dissolved in dimethyl sulfoxide (100 ml) to which lithium chloride (4.2 g, 0.1 mole) and water (0.9 ml, 0.5 mole) were already added. The solution was refluxed overnight, then cooled, and poured into cold brine (200 ml). The products were extracted with pentane (4 x 30 ml), and dried over magnesium sulphate. The solvent was removed by fractional distillation, and products - ethyl 2-methylhex-5-en-1-oate (4.5 g, 0.029 mole), 2-methylhex-5-en-1-oic acid (1.3 g, 0.01 mole) - were obtained by slow fractional micro-distillation under reduced pressure.

Yield of ester 58% ; b.p. 103^{o}/90 mm.

Yield of acid 20% ; b.p. 48^{o}/.3 mm, literature[114] b.p. = 108^{o}/12 mm.

Ester : I.R. 915, 1650, 1750, 3060.

N.M.R. 1.2 (t, 3H, J=8Hz), 1.25 (s, 3H), 1.4-2.5 (m, 5H), 4.2 (q, 2H, J=8Hz), 4.8-5.2 (m, 2H), 5.4-6.1 (m, 1H).

Acid : I.R. 915, 1650, 1720

N.M.R. 1.25 (d, 3H, J=8Hz), 1.4-2.8 (m, 5H), 4.8-5.3 (m, 1H), 11.8 (s, 1H).

Ester : Analysis for $C_9H_{16}O_2$: calculated C = 69.19, H = 10.32 ;
found C = 69.59, H = 10.05.

2-Methylhex-5-en-1-ol (10)

Ethyl 2-methylhex-5-en-1-oate (3.12 g, .02 mole) in ether (5 ml) was added to a stirred suspension of lithium aluminium hydride (.5 g, .013 mole) in ether (10 ml) at a rate to maintain a steady reflux. After

addition the mixture was stirred under nitrogen for 3 hours. Sodium hydroxide solution (15%) was added very slowly until clean, white granular salts precipitated. The ethersolution was decanted, and the residue washed with more ether (2 x 5 ml), which was combined with the first portion. After drying with anhydrous potassium carbonate ether was removed by slow fractional distillation, and the product (2.05 g, .018 mol) obtained by distillation under reduced pressure.

Yield 90%

B.p. 79^{o}/22 mm, literature[115] b.p. = 68^{o}/12 mm, & 166-168^{o}/736 mm.

I.R. 915, 1650, 3060, 3320

N.M.R. 1.0 (d, 3H, J=7Hz), 1.1-1.8 (m, 3H), 1.9 (s, 1H, D_2O exchange), 1.9-2.3 (m, 2H), 3.5 (d, 2H, J=7Hz), 4.9 (s, 1H), 5.0-5.3 (m, 1H), 5.4-6.2 (m, 1H).

5-Methyl-6-bromohex-1-ene (11)

2-Methylhex-5-en-1-ol (2.0 g, .0175 mole), and triphenylphosphine (4.72 g, .018 mole) were dissolved in methylene chloride (10 ml) under nitrogen. Carbon tetrabromide (6.64 g, .020 mole) was added slowly in portions. The reaction is highly exothermic. After addition the mixture was left stirring overnight. The reaction flask was connected to a distillation apparatus fitted with a dry ice ethanol condenser. Solvent and the products were separated from the reaction mixture by distillation under reduced pressure. The solvent was subsequently removed by fractional distillation, and the bromide (2.66 g, .015 mole) recovered by distillation under reduced pressure. The bromide was further purified by preparative g.l.c. (F, 120^{o}, N_2 120 ml/min).

Yield 86%

B.p. 62^{o}/25 mm

I.R. 915, 1650, 3060

N.M.R. 1.0 (d, 3H, J=7.5Hz), 1.3-2.3 (m, 5H), 3.4 (d, 2H, J=6Hz), 4.8-5.3 (m, 2H), 5.5-6.2 (m, 1H).

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12; found: C = 47.37, H = 7.22, Br = 44.80.

Pent-4-en-2-ol (12)

Allyl bromide (24.2 g, .20 mole) in ether (500 ml) was added dropwise to magnesium turnings (14.4 g, .60 mole) in ether (200 ml) at 0-5°. After addition the reaction mixture was brought to reflux for 15 min., then again cooled to 0-5°. Acetaldehyde (17.0 ml, .3 mole) was added dropwise over 30 min. The mixture was warmed to room temperature and the stirring continued for another 30 min. A saturated solution of ammonium chloride was added very slowly drop by drop, with the stirrer going, until white, granular, magnesium salts precipitated and the ether solution became clear. The clear solution was decanted, and the ether removed by fractional distillation. Pent-4-en-2-ol (15.6 g, .18 mole) was obtained by distillation under reduced pressure.

Yield 91%

B.p. 63°/20 mm, literature[116] b.p. 57°/11 mm

I.R. 915, 1650, 3050, 3330

N.M.R. 1.2 (d, 3H, J=8Hz), 2.1-2.4 (m, 2H), 2.5 (s, 1H, D_2O exchange), 3.7-4.1 (m, 1H) 4.9-5.1 (m, 1H), 5.1-5.3 (s, 1H), 5.5-6.3 (m, 1H).

4-Bromopent-1-ene (13)

Pent-4-en-2-ol (8.6 g, .10 mole) with pyridine (2.0 ml) was added dropwise over 1 hour to phosphorus tribromide (3.5 ml, .037 mole) in ether (25 ml) at 0°C.

Stirring was continued at 0° for 10 hours, then the mixture let

warm to room temperature and stirred for further 6 hours. The solvent and the product were distilled off using dry ice ethanol condenser, and the distillate was washed with saturated sodium carbonate (3 x 10 ml) then brine (3 x 10 ml). After drying over magnesium sulphate the solvent was removed by fractional distillation at atmospheric pressure, and the product (10.5 g, .07 mole) recovered by distillation under reduced pressure. After three hours standing on the bench under nitrogen the product began to develop a pink colour. This has been regularly noted with bromides and chlorides prepared from alcohols with phosphorus tribromide and phosphorous pentachloride. The bromide was loaded on a florisil column (30 cm x 1.5 cm) and eluted with light petroleum ether. Subsequent removal of the solvent and distillation gave 4-bromopent-1-ene (10.0 g, .067 mole) which no longer discoloured on standing. This bromide is a lachrymator.

Yield	67%
B.p.	62^{o}/120 mm, literature[117] b.p. 116.5^{o}/756 mm
I.R.	960, 1650, 3060
N.M.R.	1.7 (d, 3H, J=7Hz), 2.2-2.4 (m, 2H), 4.0-4.4 (m, 1H), 4.8-5.3 (m, 2H), 5.6-6.3 (m, 1H).

Diethyl 2-methylpent-4-ene-1,1-dicarboxylate (14)

Diethyl malonate (16.0 g, .10 mole) was added to dry N,N-dimethylformamide (100 ml) under nitrogen. Sodium hydride (2.4 g, .10 mole) was added slowly in small portions without exposure to air. Hydrogen evolution was immediate and rapid. After all sodium hydride was added the mixture was stirred until no further hydrogen evolved.

4-Bromopent-1-ene (14.9 g, .10 mole) was added with a syringe over 15 min. The mixture was left stirring for 3 hours, then transferred to a separatory funnel. Water (200 ml) was added, and the product

extracted with ether (3 x 60 ml). Combined organic fractions were washed with dilute HCl (1 x 100 ml), and brine (1 x 100 ml), then dried over magnesium sulphate. Ether was removed on a rotatory evaporator. The product, pent-1-ene-4-(diethyl malonate) (16.6 g, .073 mole) was distilled under reduced pressure.

Yield 73%

B.p. 76^{o}/.4 mm

I.R. 920, 1650, 1750, 3040

N.M.R. 1.0 (t, 6H, J=7Hz), 1.3 (d, 3H, J=8Hz),1.9-2.5 (m, 3H), 3.3 (d, 1H, J=8Hz), 4.2 (q, 4H, J=7Hz), 4.8-5.3 (m, 2H). 5.4-6.2 (m, 1H).

Analysis for $C_{12}H_{20}O_4$: calculated C = 63.14, H = 8.83; found C = 63.18, H = 8.76

M.s. Mol. ion at 228, Mw = 228.

Ethyl 3-methylhex-5-en-1-oate (15)

Diethyl 2-methylpent-4-ene-1,1-dicarboxylate (11.4 g, .05 mole) was added to a suspension of lithium chloride (4.2 g, .10 mole) and water (.9 ml, .05 mole) in dimethylsulphoxide (100 ml). The mixture was refluxed for 12 hours, then cooled, and poured into ice cold brine (200 ml). The product was extracted with pentane (4 x 30 ml), then back extracted with 10% sodium hydroxide (1 x 30 ml) in order to separate any 3-methylhex-5-en-1-oic acid. The sodium hydroxide solution was acidified by dropwise addition of dilute HCl, then extracted with ether (3 x 20 ml). Both ether solutions were dried over magnesium sulphate and filtered. Ether was removed by fractional distillation, and ethyl 3-methylhex-5-en-1-oate (6.55 g, .042 mole) distilled under reduced pressure. No 3-methylhex-5-en-1-oic acid was formed in this reaction.

Yield 84%

B.p. $100^{o}/78$ mm

I.R. 915, 1650, 1745, 3060

N.M.R. 1.0, (s, 3H), 1.2 (t, 3H, J=8Hz), 2.0-2.4 (m, 5H), 4.1 (q, 2H, J=7Hz), 4.8-5.3 (m, 2H), 5.4-6.2 (m, 1H)

Analysis for $C_9H_{16}O_3$: calculated C = 69.19, H = 10.32; found C 68.99, H = 10.00.

3-Methylhex-5-en-1-ol (16)

Ethyl 3-methylhex-5-en-1-oate (62 g, .04 mol) was added with a syringe to a suspension of lithium aluminium hydride (1.5 g, .04 mol) in anhydrous ether (50 ml) at a rate which maintained a steady reflux. The mixture was left stirring overnight, then 10% sodium hydroxide solution was added dropwise at a rate of about 20 drops/min. When white granular salts completely precipitated out of solution addition of sodium hydroxide was stopped. The ether solution was decanted, and the residue washed with more ether (2 x 25 ml). After drying over anhydrous potassium carbonate, ether was removed by fractional distillation. 3-Methylhex-5-en-1-ol (4.0 g, .035 mole) was distilled under reduced pressure.

Yield 88%

B.p. $77^{o}/18$ mm, literature[115] b.p. $73\text{-}74^{o}/12$ mm

I.R. 920, 1650, 3050, 3320

N.M.R. 1.0 (d, 3H, J=6Hz), 1.2-2.2 (m, 5H), 1.6 (s, 1H, D_2O exchange), 3.7 (t, 2H, J=7Hz), 4.8-5.0 (m, 1H), 5.0-5.3 (m, 1H), 5.4-6.2 (m, 1H).

4-Methyl-6-bromohex-1-ene (17)

This bromide was prepared from 3-methylhex-5-en-1-ol by bromination with carbon tetrabromide and triphenylphosphine using the procedure

described for the prearation of 5-methyl-6-bromohex-1-ene (11).

Traces of bromoform were removed by preparative g.l.c. (F, 120°, N_2 60 ml/min).

Yield 89%

I.R. 915, 1650, 3030

N.M.R. .9 (d, 3H, J=7Hz), 1.3-2.3 (m, 5H), 3.5 (t, 2H, J=8Hz), 4.8-5.0 (m, 1H) 5.0-5.3 (m, 1H), 5.4-6.2 (m, 1H).

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12; found C = 47.36, H = 7.25, Br = 45.10.

1,5-Heptadien-4-ol (18)

Allyl bromide (24.2 g, .20 mole) in ether (500 ml) was added over 3 hours to magnesium turnings (14.4 g, .60 mole) in ether (200 ml) at -5°. After addition the reaction mixture was refluxed for 15 min then cooled to -5°. Freshly dried and distilled crotonaldehyde (20.5 ml, .25 mole) was added with a syringe while maintaining the temperature below 0°. The cooling bath was removed, and the mixture left stirring for 2.5 hours.

Saturated ammonium chloride solution was added dropwise until white magnesium salts precipitated and the point was reached when the cloudy solution turned clear, and no further. Ether was decanted and separated from the crude product by fractional distillation. 1,5-Heptadien-4-ol (18.2 g, .16 mole) was distilled under reduced pressure. The product was homogeneous by g.l.c. analysis (D, 110°, N_2 40 ml/min).

Yield 81%

B.p. 63°/17 mm, literature[118] b.p. = 151-152°/760 mm.

I.R. 920, 1650, 3050, 3340.

N.M.R. 1.7 (d, 3H, J=6Hz), 2.0 (s, 1H, D_2O exchange),

2.2-2.5 (m, 2H). 4.0-4.3 (m, 1H), 4.9-5.1 (m, 1H),
5.1-5.3 (m, 1H). 5.5-6.2 (m, 3H).

5-Methylhex-1-ene (19)

Isobutylmagnesium bromide was prepared from 1-bromo-2-methylpropane (6.85 g, .05 mole) and magnesium (2.4 g, .10 mole) in THF (50 ml). This Grignard reagent was decanted into a dropping funnel under nitrogen, and added dropwise to a refluxing solution of allyl bromide (6.05 g, .05 mole) in THF (50 ml). After addition the mixture was stirred for a further 2 hours under reflux, then 2 hours more at room temperature. Saturated ammonium chloride solution (100 ml) was added. The solution was decanted into a separatory funnel, and extracted with purified pentane (3 x 30 ml). The combined pentane fractions were washed with water (6 x 50 ml), and dried over magnesium sulphate.

Pentane was separated by slow fractional distillation using a 30 cm x 12 mm vacuum-jacketted glass column filled with glass helices, followed by distillation of 5-methylhex-5-ene (3.74 g, .038 mole), which was pure by analytical g.l.c. (C 70-90°, N_2 30-50 ml/min)

Yield 76%

B.p. 85°, literature[112] b.p. = 85.3°

I.R. 915, 1650, 3020

N.M.R. .9 (d, 6H, J=7Hz), 1.0-2.1 (m, 5H), 4.8 (s, 1H),
4.9-5.1 (m, 1H), 5.4-6.1 (m, 1H).

4-Methylhex-1-ene (20)

This hydrocarbon was prepared from 2-bromobutane and allyl bromide on the same scale and by the same procedure as the 5-methylhex-1-ene.

Yield 74%

B.p. 86°, literature[112] b.p. = 86.7°

I.R. 915, 1650, 3040

N.M.R. .7-1.1 (m, 5H), 1.1-1.7 (m, 4H), 1.7-2.2 (m, 2H), 4.8-5.0 (m, 1H), 5.0-5.2 (m, 1H), 5.4-6.2 (m, 1H)

3-Methylcyclopent-2-en-1-one (21)

2,5-Hexanone (11.5 g, .10 mole) was added quickly to .25M solution of sodium hydroxide (100 ml) under reflux. The mixture was refluxed for further 15 min, cooled rapidly in an ice bath, saturated with NaCl, and extracted with ether (4 x 25 ml). Combined ether extracts were washed with brine (3 x 5 ml), and dried over 4A molecular sieves. Ether was removed on a rotatory evaporator, and the product (4.42 g, .046 mole) distilled under reduced pressure.

Yield 46%

B.p. 75^{o}/16 mm, literature[119] b.p. = $74\text{-}76^{o}$/16 mm

I.R. 1630, 1720

N.M.R. 2.2 (s, 3H), 2.3-2.8 (m, 4H), 6.0 (s, 1H)

3-Methylcyclopentanone (22)

3-Methylcyclopent-2-en-1-one (3.85 g, .04 mole) was dissolved in acetic acid (25 ml) to which 10% palladium on carbon (.15g) was added. The mixture was stirred and connected to hydrogen at atmospheric pressure. The uptake of hydrogen was very rapid; after 2.5 min. 1.01 equivalent of hydrogen was taken up. The mixture was filtered through a pad of celite. Ether (100 ml) was added, and the acetic acid extracted with water (3 x 20 ml). Combined water extracts were back extracted with ether (2 x 15 ml). Ether solution was shaken with saturated hydrogen sodium carbonate (1 x 50 ml), then washed with brine (2 x 50 ml).

After drying over magnesium sulphate, ether was removed by fractional distillation, and the product (3.53 g, .036 mole) was distilled

under reduced pressure.

Yield	90%
B.p.	64^{o}/42 mm, literature[120] b.p. = 143-144.5^{o}/756-764 mm.
I.R.	1750
N.M.R.	1.2 (d, 3H, J=7Hz), 1.4-2.4 (m, 7H)

1,3-Dimethylcyclopentanol (23)

The Grignard reagent was prepared in ether (25 ml) from methyl iodide (2.2 ml, .035 mole) and magnesium (1.0 g, .03 mole). 3-Methylcyclopentanone (3.0 g, .03 mole) in ether (5 ml) was added with a syringe. The mixture was stirred for 1.5 hours, and a saturated solution of ammonium chloride was added dropwise until white magnesium salts precipitated and the solution turned from cloudy to clear. The ether solution was decanted, and the residue washed with anhydrous ether (2 x 15 ml). Ether was separated by fractional distillation. 1,3-Dimethylcyclopentanol (2.74 g, .024 mole) was distilled under reduced pressure.

Yield	80%
B.p.	82^{o}/13 mm
I.R.	3350
N.M.R.	1.1 (d, 3H, J=6Hz), 1.3 (s, 3H), 1.4-2.0 (m, 7H), 2.1 (s, 1H, D_2O exchange)

The n.m.r. spectral data are essentially identical with those reported in the literature[121].

1,3-Dimethylcyclopentene (24)

1,3-Dimethylcyclopentanol (2.51 g, .022 mole) was added to anhydrous oxalic acid (3.6 g, .04 mole), which was freshly prepared by dehydration of dihydro-oxalic acid (5.65 g, .045 mole) at 100^{o} for

3 hours. The mixture was heated in an oil bath (130-160°) until the product distilled at atmospheric pressure. 1,3-Dimethylcyclopentene (1.93 g, .02 mole) thus obtained was pure by g.l.c. analysis (C, 50-75°, N_2 50 ml/min).

Yield	91%
B.p.	91-93°, literature[122] b.p. 91.5-92.5°
I.R.	1450, 3025
N.M.R.	1.0 (d, 3H, J=7Hz), 1.7 (s, 3H), 1.8-2.8 (m, 5H), 5.3 (s, 1H).

1,3-Dimethylcyclopentane (25)

1,3-Dimethylcyclo[illegible] (1.73 g, .018 mole) was hydrogenated at atmospheric pressure in acetic acid (5 ml) over platinum oxide (.05 g). The mixture was stirred for 4 hours until 1.01 equivalent of hydrogen was consumed, then spun in a centrifuge to precipitate the catalyst. The solution was decanted, and added to water (5 ml). The hydrocarbon layer was separated, washed with 5% sodium carbonate (1 x 1 ml), and dried over 4A molecular sieves. 1,3-Dimethylcyclopentane (1.02 g , .01 mole) was obtained by microdistillation at atmospheric pressure.

Yield	56%
B.p.	91°, literature[112] b.p. = 91°
^{1}H N.M.R.	1.0 (d, 6H, J=6Hz), 1.2-2.2 (m, 8H)
^{13}C N.M.R.	44.82 (*cis* C_2), 43.00 (*trans* C_2), 35.22 (*cis* C_1 + *trans* C_4), 34.13 (*cis* C_4), 33.40 (*trans* C_1), 21.62 (*trans* CH_3), 21.26 (*cis* CH_3).
Literature[123] ^{13}C N.M.R.	45.10 (*cis* C_2), 43.20 (*trans* C_2), 35.5 (*cis* C_1), 35.30 (*trans* C_4), 34.40 (*cis* C_4), 33.60 (*trans* C_1), 21.5 (*trans* CH_3), 21.20 (*cis* CH_3).

The mean *cis:trans* intensity ratio of the resolved peaks was 7.6 : 1. The product was pure by g.l.c. analysis (L, 30-60°, N_2 3 ml/min). The *cis* and *trans* isomers were separated and identified by subsequent g.l.c. analysis (L, 20°, He 2 ml/min), where *cis*-1,3-dimethylcyclopentane had shorter retention time by 58 seconds. The ratio of the *cis:trans* g.l.c. peak areas was 8.5 : 1.

Ethyl 2,2-Dimethylhex-5-en-1-oate (27)

Di-isopropylamine (14 ml, .1 mole) was added to THF (100 ml) at ice bath temperature. The mixture was let stir for 30 minutes to equilibrate the temperature of the solution with that of the ice bath. nButyl-Li in hexane 1.8M (.1 mole) was added dropwise with a syringe. The mixture was cooled to -78° and let stir for 40 mins, then **ethyl isobutyrate** (11.5 g, .1 mole) was added dropwise. The mixture was stirred for 30 mins then 4-bromobutene (13.5 g, .1 mole) in HMPT (20 ml) was added dropwise.

Stirring was continued for 1 hour at dry ice ethanol bath temp., then no more dry ice was added and the mixture was left overnight. Water (200 ml) was added and the product together with diisopropylamine was extracted with 30-40° pet. ether. Di-isopropylamine was recovered using 5% HCl. After drying with magnesium sulphate, and the removal of solvent, the required ester (14 g, .082 mole) was obtained by distillation under reduced pressure. The product was pure by g.l.c. analysis (A, 120°, N_2 45 ml/min).

Yield	82%
B.p.	28°/.02 mm
I.R.	1720, 1640
N.M.R.	.8-1.5 (m, 8H), 1.5-2.1 (m, 5H), 4.1 (q, 2H, J=8Hz), 5.0-5.4 (m, 2H), 5.3-6.1 (m, 1H).

M.S. Molecular ion at 170, Mw = 170

Analysis for $C_{10}H_{18}O_2$: calculated C = 70.55, H = 10.66;
found C = 70.20, H = 10.33.

2,2-Dimethylhex-5-en-1-ol (28)

Ethyl 2,2-dimethylhex-5-en-1-oate (12.0 g, .070 mole) in ether (10 ml) was added to a suspension of $LiAlH_4$ (2.7 g, .071 mole) in ether (90 ml) at a rate to maintain a slow reflux, and left stirring under nitrogen for 13 hours. Sodium hydroxide solution (10%) was added dropwise very slowly until white granular salts precipitated. The ether solution was decanted, and the residue washed with more ether (50 ml). After drying over anhydrous potassium carbonate, the solvent was removed by fractional distillation and the crude product distilled under reduced pressure. 2,2-Dimethylhex-5-en-1-ol (7.17 g, .056 mole) was pure by g.l.c. analysis (A, 120°, N_2 50 ml/min).

Yield 80%

B.p. 41°/.5 mm, literature[124] b.p. = 98°/45 mm.

I.R. 915, 1640, 3100, 3300

N.M.R. .9 (s, 6H), 1.2-1.4 (m, 2H), 1.8-2.3 (m, 2H), 3.2 (s, 1H, D_2O exchange), 3.3 (s, 2H), 5.0-5.4 (m, 2H), 5.5-6.2 (m, 1H).

Analysis for $C_8H_{18}O$: calculated C = 74.94, H = 12.58;
found C = 74.73, H = 12.25.

5,5-Dimethyl-6-bromohex-1-ene (29)

In a typical reaction 2,2-dimethylhex-5-en-1-ol (2.6 g, .02 mole) and triphenylphosphine (6.0 g, .023 mole) were stirred in dichloromethane (20 ml) under nitrogen. Carbon tetrabromide (7.0 m, 021 mole) was added as a solid in portions over 20 min. The mixture was left stirring

overnight. The solvent, and the products, were recovered by fractional distillation.

The required product, 5,5-dimethyl-6-bromohex-1-ene (2.1 g) was contaminated with a trace of bromoform, which was separated by preparative gas chromatography (F, 110°, N_2 65 ml/min).

Yield 56% distilled product, 30% after prep. g.l.c.

B.p. 59°/.5 mm

I.R. 915, 1640, 3100

N.M.R. 1.0 (s, 6H), 1.3-1.7 (m, 2H), 1.8-2.3 (m, 2H), 3.3 (s, 2H), 5.0-5.4 (m, 2H), 5.4-6.2 (m, 1H).

Analysis for $C_8H_{15}Br$: calculated C = 50.28, H = 7.91, Br = 41.81; found C = 50.30, H = 7.81, Br = 41.70.

3-Methylbut-2-en-1-ol (30)

3-Methyl-2-butenoic acid (10 g, 0.1 mole) in ether (50 ml) was added to a suspension of $LiAlH_4$ (3.8 g, 0.1 mole) in ether (150 ml) at a rate to maintain a steady reflux. The mixture was refluxed for 46 hours, then cooled in an ice bath, and sodium hydroxide (15%)was added very slowly until white granular salts precipitated. The ether layer was decanted, the resiude washed with ether (2 x 20 ml), and the combined ether solutions dried over anhydrous potassium carbonate. Ether was separated by fractional distillation and 3-methylbut-2-en-1-ol (6.5 g, .075 mole) was recovered by distillation under reduced pressure.

Yield 75%

B.p. 54-55°/25 mm, literature[125] b.p. = 45-55°/25 mm.

N.M.R. 1.7 (s, 3H), 1.8 (s, 3H), 3.8 (s, 1H, D_2O exchange), 4.0 (d, 2H, J=8Hz), 5.4 (t, 1H, J=7Hz).

3-Methylbut-2-en-1-al (31)

3-Methylbut-2-en-1-ol (6.02 g, .07 mole) was oxidised with pyridinium chlorochromate (22.6 g, .105 mole) in anhydrous methylene chloride (200 ml) by literature[126] methods. The reaction is highly exothermic and the alcohol must be added slowly and be dissolved in methylene chloride (.10 mole in 20-30 ml). The aldehyde (4.2 g, .05 mole) was pure g.l.c. analysis (D, 100°, N_2, 50-65 ml/min).

Yield	71%
B.p.	44°/23 mm, literature[127] b.p. = 132-133°/730 mm
I.R.	1640, 1670-1700
N.M.R.	2.0 (s, 3H), 2.2 (s, 3H), 5.9 (d, 1H, J=8Hz), 10.0 (d, 1H, J=8Hz).

2-Methyl-2,6-heptadien-4-ol (32)

Allyl bromide (13.2 ml, .15 mole) in ether (120 ml) was added dropwise over two hours to magnesium (4.8 g, .2 mole) in ether (400 ml). After addition the mixture was refluxed for 30 min. 3-Methylbut-2-en-1-al (8.4 g, .10 mole) in ether (100 ml) was added at a rate which maintained a steady reflux. Subsequently the mixture was stirred under reflux for 16 hours, then cooled, and saturated ammonium chloride was added very slowly until white magnesium salts precipitated and left a clear solution.

Ether was decanted and the residual salts washed with more ether (2 x 100 ml). The solvent was removed by fractional distillation, and the crude product separated by slow fractional distillation under reduced pressure. The starting aldehyde (.6 g, .007 mole, 7%) was recovered in the first fraction. The distillation was followed by g.l.c. analysis (D, 110°, N_2 60-65 ml/min).

2-Methyl-2,6-heptadien-4-ol (10.0 g, .08 mole) was distilled over two fractions. The first fraction (1.5 g) was contaminated by a trace

(.5-1.0%) of an unidentified byproduct.

Yield	80%
B.p.	74^{o}/20 mm
I.R.	1640, 1670, 3070, 3350
N.M.R.	1.7 (s, 6H), 1.9 (s, 1H, D_2O exchange), 2.3 (t, 2H, J=7Hz), 4.2-4.7 (m, 1H), 5.0-5.4 (m, 3H), 5.5-6.2 (m, 1H).
Analysis for $C_8H_{14}O$:	calculated C = 76.14, H = 11.18; found C = 76.16, H = 11.03.

3,3-Dimethylhex-5-en-1-al (33)

(A) 2-Methyl-2,6-heptadien-4-ol (6.3 g, .05 mole) was added to a suspension of potassium hydride (2.2 g, .055 mole) in THF (50 ml). The reaction was followed by g.l.c. analysis (D, 100^{o}, N_2 50 ml/min). The mixture was stirred for 30 hours at room temperature, and no product formation could be detected. Thence the mixture was refluxed, and slow formation of a single product was noted. After 26 hours the concentration of the product was about 8% of the initial concentration of the starting dienol, the concentration of which by this time had decreased by 14%. Beyond this time the concentration of the product increased no further, while that of the reactant was continuously decreasing. The solution grew dark-red progressively. After 116 hours of refluxing all the dienol had disappeared; and the concentration of the product, which up to then was approximately constant, began to decrease. The solution was very dark with a tinge of red. It was cooled and water (100 ml) was slowly added. The product was extracted with ethyl acetate (5 x 25 ml), washed with brine (3 x 5 ml), and dried over 4A molecular sieves. The bulk of the solvent was removed by slow fractional distillation. 3,3-Dimethyhex-5-en-1-al (.32 g, .0025 mole) was obtained by microdistillation under reduced pressure.

Yield	5%
B.p.	74^{o}/50 mm
I.R.	920, 1650, 1730, 3020
N.M.R.	1.0 (s, 6H), 2.1 (d, 2H, J=8Hz), 2.3 (s, 2H), 4.8-5.3 (m, 2H), 5.5-6.3 (m, 1H), 10.1 (s, 1H).

Analysis for $C_8H_{14}O$: calculated C = 76.14, H = 11.18;
found C = 75.72, H = 10.94.

(B) 3,3-Dimethylhex-5-enylnitrile (1.23 g, .01 mole) was dissolved in dry hexane (30 ml) and cooled to -78^{o}. Di-isobutylaluminium hydride (1.7 g, .012 mole) in hexane (10 ml) was added over 30 min. The cooling bath was removed and the mixture left to warm to room temperature, and stirred for another six hours. Saturated solution of ammonium chloride (50 ml) was added dropwise. The hexane layer was separated, and the aqueous solution extracted with ether (3 x 20 ml). Combined extracts were washed with saturated sodium carbonate (2 x 50 ml), then water (1 x 50 ml) and brine (1 x 50 ml), and dried over 4A molecular sieves. The solvent was removed by fractional distillation, and 3,3-dimethylhex-5-en-1-al (.91 g, .007 mole) obtained by microdistillation under reduced pressure.

Boiling point and spectral data were identical with those of the same compound prepared by method A above.

Caution: 3,3-dimethylhex-5-en-1-al is a strong lachrymator, and a potent irritant to the mucous membranes.

Ethyl 2,2-dimethylpent-4-en-1-oate (34)

This ester was prepared on the same scales and by the same method as the ethyl 2,2-dimethylhex-5-en-1-oate except that in place 4-bromobut-1-ene allyl bromide was reacted with the anion of ethyl isobutyrate. Di-isopropylamine recovery was 90%. Ethyl 2,2-dimethylpent-4-en-1-oate

(12.5 g, .08 mole) was obtained by distillation under reduced pressure as a pure compound - g.l.c. analysis (D, 70°, N_2 30 40 ml/min).

Yield 80%

B.p. 61°/17 mm, 57°/10 mm

I.R. 910, 1640, 1760, 3010

N.M.R. 1.1 (s, 6H), 1.2 (t, 3H, J=8Hz), 2.3 (d, 2H, J=7Hz), 4.1 (q, 2H, J=8Hz), 4.8-5.2 (m, 2H), 5.4-6.1 (m, 1H).

Analysis for $C_9H_{16}O_2$: calculated C = 69.19, H = 10.32
found C = 69.19, H = 10.58.

2,2-Dimethylpent-4-en-1-ol (35)

Dissolved in ether (100 ml) ethyl 2,2-dimethylpent-4-en-1-oate (10.95 g, .07 mole) was added slowly to a suspension of lithium aluminium hydride (2.7 g, .07 mole) in ether (200 ml). The reaction wasinstantaneous and highly exothermic. The product salts are insoluble in ether and form a polymer like mass. Sodium hydroxide solution (10%) was added slowly, and the grey insoluble mass slowly broke up and released the stirrer. When clean, white salts precipitated the clear solution was decanted, and the residual salts washed with ether (2 x 50 ml). After drying over anhydrous potassium carbonate, the solvent was separated by fractional distillation. 2,2-Dimethyl-pent-4-en-1-ol (6.62 g, .058 mole) was distilled under reduced pressure. The compound was pure by g.l.c. analysis (D, 100°, N_2 40 ml/min).

Yield 83%

B.p. 62°/15 mm

I.R. 910, 1640, 3015, 33000

N.M.R. .9 (s, 6H), 2.0 (d, 2H, J=7Hz), 2.3 (s, 1H, D_2O exchange), 3.4 (s, 2H), 4.8-5.3 (m, 2H), 5.5-6.2 (m, 1H).

Analysis for $C_7H_{14}O$: calculated C = 73.63, H = 12.36

found C = 73.08, H = 12.33.

4,4-Dimethyl-5-chloropent-1-ene (36)

Triphenylphosphine (13.1 g, .05 mole) was added to carbon tetrachloride (100 ml, dried and freshly distilled). The mixture was stirred under nitrogen for 30 minutes, then 2,2-dimethylpent-4-en-1-ol (5.7 g, .05 mole) was added. The clear solution was refluxed for 5 hours, and cooled to room temperature. Pentane (500 ml) was added. Triphenylphosphine oxide was separated by filtration, and the solvent removed by fractional distillation. The crude product, which was mixed with a residue of triphenylphosphine oxide, was dissolved in pentane (15 ml) and filtered. After removal of pentane by slow fractional distillation, 4,4-dimethyl-5-chloropent-1-ene (5.8 g, .044 mole) was distilled under reduced pressure.

Yield 88%. B.p. 65^{o}/37 mm, 42^{o}/15 mm.

I.R. 920, 1650, 3030

N.M.R. .9 (s, 6H), 2.1 (d, 2H, J=8Hz), 3.3 (s, 2H), 4.8-5.3 (m, 1H).

Analysis for $C_7H_{13}Cl$: calculated C = 63.39, H = 9.88, Cl = 26.73;

found C = 63.17, H = 9.81, Cl = 26.65.

4,4,-Dimethyl-5-bromopent-1-ene (37)

Tri-n-butylphosphine (12.5 ml, .05 mole) was dissolved in dimethyl formamide (100 ml) and stirred under nitrogen. Bromine (8.0 g, .05 mole) was added dropwise (15 drops/min) while keeping the temperature below 40^{o}. The solution developed a purple colour. 2,2-Dimethylpent-4-en-1-ol (5.7 g, .05 mole) was added slowly with a syringe. The mixture was stirred for 2 hours, then distilled under reduced pressure using a dry ice ethanol condenser. The distillate was collected up to 75^{o}/2 mm, which consisted of DMF and the product. This was transferred into a separatory

funnel, and water (100 ml) was added. The product separated as the bottom layer. The aqueous phase was further extracted with light petroleum (3 x 20 ml), and the extract combined with the crude bromide. The bromide solution was washed with 10% sodium carbonate (2 x 30 ml), then with brine (1 x 50 ml), and dried over 4A molecular sieves.

4,4-Dimethyl-5-bromopent-1-ene (6.4 g, .036 mole) was distilled under reduced pressure.

Yield 72%. B.p. 57^{o}/18 mm.

N.M.R. 1.0 (s, 6H), 2.1 (d, 2H, J=7Hz), 3.3 (s, 3H), 4.8-5.3 (m, 2H), 5.4-6.2 (m, 1H).

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12; found C = 47.42, H = 7.46, Br = 45.25.

3,3-Dimethylhex-5-enyl nitrile (38)

(A) Following literature[128] procedures dry sodium cyanide (3.5 g, .071 mole) was added to DMSO (20 ml). The thick slurry was stirred and heated to 90^{o}. 4,4-Dimethyl-5-chloropent-1-ene (6.5 g, .05 mole) was added slowly with a syringe. The reaction was followed by g.l.c. (D, 70^{o}, N_2 50 ml/min), and stirred at 90^{o} until all the chloride had disappeared, then cooled and poured into cold water (100 ml). By this time the reaction mixture was a strongly coloured dark-purple. The product was extracted with ether (5 x 20 ml), washed with brine (3 x 50 ml), and the solution dried over calcium chloride. Ether was separated by fractional distillation, and the product, 3,3-dimethylhex-5-enyl carbonitrile (.74 g, .006 moles) obtained by microdistillation under reduced pressure.

Yield 12%. B.p. 60^{o}/10 mm.

I.R. 920, 1650, 2220, 3030.

N.M.R. 1.0 (s, 6H), 2.1 (d, 2H, J=8Hz), 2.3 (s, 2H), 4.9-5.1 (m, 1H), 5.2 (s, 1H), 5.4-6.2 (m, 1H).

Analysis for $C_8H_{13}N$: calculated C = 77.99, H = 10.64, N = 11.37;
found C = 78.23, H = 10.28, N = 11.64.

(B) 2,2-Dimethylpent-4-en-1-ol (5.7 = .05 mole) was converted to its tosylate and added to N-methylpyrolidone (50 ml) under nitrogen. Sodium cyanide (7.5 g, .15 mole) was added as a solid. The mixture was stirred at room temperature for 48 hours. Water (100 ml) was added and the nitrile extracted with light petroleum (5 x 20 ml). The solution was washed with brine (2 x 50 ml) and dried over 4A molecular sieves. The solvent was removed by fractional distillation. 3,3-Dimethylhex-5-enyl-nitrile (1.10 g, .009 mole) was distilled under reduced pressure. The starting tosylate (63%) was recovered.

Yield 18%

Boiling point and spectral data were identical with those of the same compound obtained in method (A) above.

Diethyl isopropylidenemalonate (39)

This compound was prepared by literature[129] methods on a .10 mole scale. Yield 90%

B.p. 80°/1 mm, literature[129] b.p. 110-115°/9-10 mm.

I.R. 920, 1650, 1740

N.M.R. 1.3 (t, 6H, J=7Hz), 7.0 (s, 6H), 4.3 (q, 4H, J=7Hz).

Diethyl 2,2-dimethylpent-4-ene-1,1-dicarboxylate (40)

Allyl bromide (9.7 g, .08 mole) in ether (100 ml) was added to magnesium turnings (5.8 g, .24 mole) in ether (50 ml) at 0° over one hour. After addition the mixture was refluxed for 30 min, and cooled at -45°. Cuprous chloride, (8.0 g, .08 mole) was added, and the mixture stirred for 10 mins.

Diethyl isopropylidenemalonate (16.0 g, .08 mole) in ether (50 ml) was added dropwise over 30 min. The mixture was stirred for one hour at -35°, then the cooling bath was removed, and the stirring continued for another hour. Anhydrous ether (100 ml) was added and the solution decanted from unreacted magnesium turnings into another flask equipped with a stirrer and a condenser. Magnesium residue was washed with anhydrous ether (2 x 30 ml and the ether solutions combined. Saturated solution of ammonium chloride was added dropwise very slowly until white granular magnesium salts precipitated and left a clear solution. The solution was decanted and the residue washed with more ether (2 x 20 ml). The solvent was separated by fractional distillation. 1-Pentene-4-methyl-4-(diethyl malonate) (14.8 g, .061 mole) was distilled under reduced pressure.

Yield 76%. B.p. 91°/.5 mm.

N.M.R. 1.2 (s, 6H), 1.3 (t, 6H, J=8Hz), 2.3 (q, 4H, J=7Hz), 3.3 (s, 1H), 4.2 (q, 4H, J=7Hz), 4.8-5.2 (m, 2H), 5.5-6.2 (m, 1H).

Analysis for $C_{13}H_{22}O_4$: calculated C = 64.44, H = 9.15; found C = 64.76, H = 8.94.

Ethyl 3,3-dimethylhex-5-en-1-oate (41)

Diethyl 2,2-dimethylpent-4-ene-1,1-dicarboxylate was decarboxylated in DMSO in the presence of lithium chloride at 160° by the method described for the preparation by ethyl 3-methylhex-5-en-1-oate.

Yield 86%. B.p. 87°/20 mm.

I.R. 920, 1640, 1745, 3020.

N.M.R. 1.0 (s, 6H), 1.2 (t, 3H, J=8Hz), 2.1 (d, 2H, J=8Hz) 2.3 (s, 2H), 4.1 (q, 2H, J=8Hz) 4.8-5.0 (m, 1H), 5.2 (s, 1H), 5.5-6.2 (m, 1H).

Analysis for $C_{10}H_{18}O_2$: calculated C = 70.55, H = 10.66;
found C = 70.29, H = 10.83.

3,3-Dimethylhex-5-en-1-ol (42)

Ethyl 3,3-dimethylhex-5-en-1-oate (4.25 g, .025 mole) was reduced with $LiAlH_4$ in ether by methods identical to those described for the reduction of ethyl 3-methylhex-5-en-1-oate (15). The above alcohol (2.8 g, .022 mole) was distilled under reduced pressure.

Yield 88%

B.p. 81^{o}/13 mm

I.R. 915, 1645, 3015, 3280

N.M.R. .9 (s, 6H), 1.5 (t, 2H, J=8Hz), 2.0 (d, 2H, J=7Hz), 2.5 (s, 1H, D_2O exchange), 3.7 (t, 2H, J=8Hz), 4.7-5.0 (m, 1H), 5.2 (s, 1H), 5.5-6.3 (m, 1H).

Analysis for $C_{18}H_{16}O$: calculated C = 74.94, H = 12.58;
found C = 74.90, H = 12.77.

4,4-Dimethyl-6-bromohex-1-ene (43)

3,3-Dimethylhex-5-en-1-ol (2.6 g, .02 mole) was converted to 4,4-dimethyl-6-bromohex-1-ene by reaction with carbon tetrabromide and triphenylphosphine in dichloromethane using the methods described for the preparation of 5-methyl-6-bromohex-1-ene (11). The product (3.7 g, .019 mole)was contaminated with bromoform (1.2-1.6%).

Subsequent purification by preparative g.l.c. (O, 150^{o}, N_2 40-65 ml/min; or P, 130^{o}, N_2 45 ml/min), produced pure 4,4-diemthyl-6-bromohex-1-ene (2.9 g, .015 mole).

Yield 75%

B.p. 88^{o}/35 mm

I.R. 920, 1645, 3010

N.M.R. .9 (s, 6H), 1.7 (t, 2H, J=8Hz), 2.0 (d, 2H, J=7Hz), 3.5 (t, 2H, J=8Hz), 4.8-5.1 (m, 1H), 5.2 (s, 1H), 5.5-5.3 (m, 1H).

Analysis for $C_8H_{15}Br$: calculated C = 50.28, H = 7.91, Br = 41.81; found C = 50.11, H = 7.85, Br = 41.90.

5,5-Dimethylhex-1-ene (44)

Neat neopentyl bromide (15.1 g, .10 mole) was added with a syringe to magnesium (4.8 g, .20 mole) in THF (100 ml) at a rate which maintained a slow reflux. The mixture was refluxed for a further 1.5 hours, then cooled, and the solution of neopentylmagnesium bromide transferred into a dropping funnel under nitrogen. Thus prepared, the Grignard reagent was added dropwise to allyl bromide (15.15 g, .125 mole) in THF (100 ml) under reflux. After addition of neopentylmagnesium bromide the mixture was refluxed for two hours, then cooled, and saturated ammonium chloride (50 ml) added slowly, followed by water (150 ml). The solution was filtered and extracted with purified pentane (5 x 30 ml). The pentane solutions were combined and washed with water (3 x 50 ml), then dried over magnesium sulphate. The solvent was separated by slow fractional distillation on a 30 cm x 12 mm vacuum jacketed glass column filled with glass helices, and the product (8.0 g, .07 mole) distilled at atmospheric pressure. 5,5-Dimethyhex-1-ene thus obtained was pure by g.l.c. analysis (C, 100°, N_2 40 65 ml/min).

Yield 70%

B.p. 100°, literature[112] b.p. = 102.5°.

I.R. 915, 1645, 3015

N.M.R. 1.0 (s, 9H), 1.1-2.2 (m, 4H), 4.7-5.2 (m, 2H), 5.4-6.2 (m, 1H).

3-Methyl-2,6-heptadiene (45), *2-Ethyl-1,6-hexadiene* (46), *and 3-Methyl-3,6-heptadiene* (47)

2,2-Dimethylhex-5-en-1-ol (2.6 g, .02 mole) was converted to its tosylate in a quantitative yield (5.54 g, .019 mole). The product (5.5 g) was dissolved in THF (50 ml) and added to a suspension of $LiAlH_4$ (.76 g, .02 mole) in THF (50 ml). The mixture was refluxed for 15 hours. The reaction was followed by g.l.c. (C, 100, N_2 60 ml/min), and worked up by slow addition of dilute sodium hydroxide solution. The clear solution was decanted, and the residual solid washed with pentane (2 x 50 ml). The organic extracts were combined, and THF extracted with water (10 x 50 ml). The solution was dried over magnesium sulphate and fractionally distilled at atmospheric pressure. G.l.c. analysis (I, 40-80°, N_2 2 ml/min) showed 5 peaks.

5,5-Dimethylhex-1-ene (3%), and 4,4-dimethylcyclohexene (4%) were identified later by spiking with authentic samples, but could not be isolated. 3-Methyl-2,6-heptadiene (29%), 2-ethyl-1,6-hexadiene (24%), and 3-methyl-3,6-heptadiene (40%) were separated by preparative g.l.c. (E, 100, N_2 75 ml/min). The above yields in brackets refer to relative peak areas during g.l.c. analysis of the distilled mixture. The overall yield before prep. g.l.c. was 1.13 g, .01 mole (50%). The isolated products were identified by their n.m.r. spectra.

N.M.R. 3-methyl-2,6-heptadiene: 1.3-2.3 (m, 4H), 1.7 (s, 6H). 4.8-5.1 (m, 2H), 5.4-6.2 (m, 2H).

2-Ethyl-1,6-hexadiene: .9 (t, 3H, J=7Hz), 1.1-2.4 (m, 6H), 4.8-5.1 (m, 4H), 5.4-6.1 (m, 1H).

3-Methyl-3,6-heptadiene: .9 (t, 3H, J=7Hz), 1.0 (s, 3H), 1.3-2.3 (m, 4H), 4.8-5.1 (m, 2H), 5.4-6.1 (m, 2H).

M.s. Common molecular ion at 112, Mw = 112.

2,2-Dimethylpropan-1-ol (48)

Pivalic acid (10.2 g, .10 mole) was reduced with $LiAlH_4$ to give neopentyl alcohol (5.3 g, .06 mole) in 60% yield. At atmospheric pressure the alcohol distilled at 113-114° (lit.[130] b.p. = 110-111°/734 mm) and solidified into waxy-soft white crystals which melted at 51-53°.

2,2-Dimethyl-1-bromopropane (49)

2,2-Dimethylpropan-1-ol (4.4 g, .05 mole) was added to tributylposphine (12.2 g, .06 mole) dissolved in DMF (60 ml) and the stirred mixture treated with bromine (2.6 ml, .053 mole) over 20 mins. *(All brominations of this type are highly sensitive to water; reactions must be conducted under anhydrous conditions with freshly purified and carefully dried solvent and reagents.)* The reaction temperature was kept below 50° by occasional cooling. Twenty min. after addition of bromine all components with boiling points below 80° at 2.5 mm were distilled from the mixture. The distillate was diluted with water (300 ml), and the bottom layer of crude neopentyl bromide separated. The aqueous layer was extracted with light petroleum (2 x 50 ml), the extracts combined with the crude product, and dried over 3A molecular sieves. The solvent was separated by fractional distillation, and 2,2-dimethyl-1-bromopropane (8.1 g, .054 mole) was distilled under reduced pressure. The product was pure by g.l.c. analysis (D, 75-100°, N_2 50 ml/min).

Yield	89%
B.p.	53°/120 mm, literature[130] b.p. = 105°/732 mm.
N.M.R.	1.0 (s, 9H), 2.5 (s, 2H).

4,4-Dimethylhex-1-ene (50)

3,3-Dimethylhex-5-en-1-ol (2.56 g, .02 mole) was treated with p-toluenesulphonyl chloride (7.64 g, .04 mole) in dry pyridine (60 ml)

at 0-5°. The mixture was stirred under nitrogen for 12 hours at 5°, then water (.75 ml) was added slowly with a syringe, and the stirring continued for 10 min. The mixture was poured into cold water (300 ml) and extracted with ether (5 x 20 ml). Combined organic extracts were washed with cold HCl (100 ml) then with water (1 x 100 ml) and dried over 4A molecular sieves. Ether was removed under reduced pressure at 0-5°, and the crude product recrystallised from light petroleum at -76° to give a quantitative yield (5.5 g, .019 mole) of the required tosylate. The whole of the obtained tosylate was dissolved in ether (50 ml) and added dropwise to a suspension of $LiAlH_4$ (.76 g, .02 mole) in ether (50 ml). The mixture was stirred at 5° for 20 hours then 10% solution of sodium hydroxide (50 ml) was added very slowly. The organic layer was separated and washed with dilute HCl (50 ml) then with water (2 x 20 ml). The solution was dried over 3A molecular sieves and fractionally distilled at atmospheric pressure ti give 4,4-dimethylhex-1-ene (1.2 g, .011 mole), which was pure by g.l.c. analysis (C, 75-100°, N_2 60 ml/min).

Yield	54%
B.p.	107°, literature[112] b.p. = 107.2°
I.R.	920, 1645, 3010
N.M.R.	.9 (s, 6H), 1.0-2.1 (m, 7H), 4.8-5.2 (m, 2H)
	5.5-6.3 (m, 1H).

3,3-Dimethylcyclopentanone (51)

Methylmagnesium iodide (.03 mole) was prepared in ether (15 ml) from magnesium (.72 g, .03 mole), and methyl iodide (4.33 g, .03 mole). The solution was cooled to -35° and cuprous chloride (0.1 g, .001 mole) was added. Stirring was continued for 10 mins. 3-Methyl-2-cyclopenten-1-one (2.9 g, .03 mole) in ether (10 ml) was added dropwise over 13 min. The temperature of the reaction flask was maintained between -35° and -30°.

Twenty minutes after addition the cooling bath was removed, and the mixture let warm to room temperature over 30 min. Saturated ammonium chloride was added dropwise until the solution turned clear, and white magnesium salts precipitated. Ether solution was decanted, and the residue washed with more ether (2 x 5 ml). Combined ether fractions were dried over $MgSO_4$, and the solvent removed by fractional distillation. 3,3-Dimethylcyclopentanone (1.12 g, .01 was obtained by distillation under reduced pressure.

Yield	33%
B.p.	64^{o}/18 mm
I.R.	1730
N.M.R.	1.1 (s, 6H), 1.9 (s, 2H), 1.5-2.4 (m, 4H).

The I.R. and N.M.R. spectra were similar to those reported in literature [131].

1,3,3-Trimethylcyclopentene (52)

Magnesium turnings (.48 g, .02 mole) were dried in the reaction flask by flaming under a passing stream of nitrogen, then cooled before adding ether (5 ml). Methyl iodide (1.0 ml, .016 mole) was added with a syringe, at a rate to maintain a steady reflux. 3,3-Dimethylcyclopentanone (1.0 g, .0089 mole) was dissolved in ether (3 ml) and added to the Grignard reagent with a syringe. After addition the mixture was refluxed for 30 min, then saturated ammonium chloride was added with a syringe until the mixture became clear. The ether layer was decanted and the residue washed with anhydrous ether (3 ml). The solvent was removed by fractional distillation, and the crude product added to anhydrous oxalic acid (1.62 g, .018 mole) in a distillation apparatus. The mixture was heated in an oil bath at 130^{o}, and the product (0.8 g, .007 mole) distilled at atmospheric pressure as it was formed.

Yield 82% relative to 3,3-dimethylcyclopentanone.

B.p. 102-103°, literature[132] b.p. of 1,4,4-trimethylcyclopentene = 100-102°.

N.M.R. 1.0 (s, 6H), 1.3-2.1 (m. 7H), 5.3 (s, 1H).

1,1,3-Trimethylcyclopentane (53)

1,1,3-Trimethylcyclopentane was prepared by hydrogenation of 1,3,3-trimethylcyclopentene (.77 g, .007 mole) in acetic acid (3 ml) over platinum oxide (.02 g). The stoichiometric amount of hydrogen (1.01 eq) was taken up after 17 hours. The mixture was diluted with purified pentane (10 ml), filtered, and the acetic acid extracted with water (4 x 5 ml). The organic layer was further washed with saturated sodium hydrogen carbonate (1 x 5 ml), and brine (1 x 5 ml), and dried over 3A molecular sieves. Pentane was removed by slow fractional distillation, and 1,1,3-trimethylcyclopentane (.56 g, .005 mole) was recovered by distillation at atmospheric pressure. The product was pure by gas chromatographic analysis (B-A in line, 70°, N_2 35-60 ml/min).

Yield 71%

B.p. 106°/760, literature[133] b.p. = 105-106°/760.

N.M.R. .9 (d, 3H, J=6Hz), 1.0 (s, 6H), 1.2-1.8 (c.m. 7H).

4,4-Dimethyl-2-cyclohexen-1-one (54)

4,4-Dimethyl-2-cyclohexen-1-one was prepared by literature methods[134] on a .05 mole scale.

Yield 72%

B.p. 75°/15 mm. literature[134] b.p. = 73-74°/14 mm

I.R. 1680

N.M.R. 1.2 (s, 6H), 1.9 (t, 2H, J=6Hz), 2.4 (t, 2H, J=6Hz), 5.9 (d, 1H, J=10Hz), 6.7 (d, 1H, J=10Hz).

4,4-Dimethylcyclohexanone (55)

4,4,-Dimethyl-2-cyclohexen-1-one (3.72 g, .03 mole) was dissolved in acetic acid (20 ml) to which 10% of palladium on carbon (0.1 g) was added. The mixture was stirred under hydrogen at atmospheric pressure for eight hours, after which time 1.02 eq of hydrogen was taken up. The mixture was filtered through a pad of celite, and diluted with ether (100 ml). Acetic acid was extracted with water (3 x 20 ml), and the combined aqueous fractions back extracted with ether (2 x 15 ml). After additional washing with saturated sodium hydrogen carbonate (2 x 20 ml) followed by brine (1 x 40 ml), the organic portion was dried over $MgSO_4$, and the ether removed by fractional distillation. 4,4-Dimethylcyclohexanone (2.87 g, .023 mole) was obtained by distillation under reduced pressure using a dry ice ethanol condenser.

Yield	76%
B.p.	75^{o}/19 mm, m.p. 43-44^{o}; literature[135] b.p. = 78^{o}/23 mm m.p. = 43-44^{o}.
I.R.	1720
N.M.R.	1.1 (s, 6H), 1.9 (t, 4H, J=8Hz), 2.4 (t, 4H, J=8Hz).

4,4-Dimethylcyclohexanol (56)

2,2-Dimethylcyclohexanone (2.52 g, .02 mole) in ether (5 ml) was added dropwise to a suspension of $LiAlH_4$ (.4 g, .01 mole) in ether (10 ml). The mixture was left stirring for 35 hours at room temperature. 0.2M Sodium hydroxide (5 ml) was added slowly to destroy the excess $LiAlH_4$ and to precipitate lithium aluminium salts. The ether layer was decanted, the residue extracted with more ether (2 x 5 ml), and the combined ether solutions dried over $MgSO_4$. The solvent was removed on a rotatory evaporator and 4,4-dimethylcyclohexanol (2.3 g, .018 mole) recovered by distillation under reduced pressure.

Yield	90%
B.p.	70^{o}/6 mm, literature[136] b.p. = 186^{o}/760 mm
I.R.	3300
N.M.R.	0.9 (s, 6H), 1.4 (t, 4H, J=4Hz), 1.6 (t, 4H, J=5Hz), 2.2 (s, 1H, D_2O exchange), 3.6 (m, 1H).

4,4-Dimethylcyclohexene (57)

4,4-Dimethylcyclohexanol (2.05 g, 0.16 mole) was added with a syringe to anhydrous oxalic acid (2.9 g, .032 mole, 2 eq) in a distillation flask under nitrogen. The flask was immersed into an oil bath preheated to 150^{o}. The dehydration product began to distill immediately. When, after 35 min, no more product distilled over, the reaction was stopped and the product dried over several grains of 4A molecular sieves. Redistillation at atmospheric pressure gave 4,4-dimethylcyclohexene (1.3 g, .012 mole) - pure by gas chromatographic analysis (C, 100, N_2 50 ml/min).

Yield	74%
B.p.	117^{o}, literature[112] b.p. = 117^{o}.
N.M.R.	0.9 (s, 6H), 1.3 (t, 2H, J=6Hz), 1.6-2.2 (m, 4H), 5.4 (s, 2H).

1,1-Dimethylcyclohexane (58)

1,1-Dimethylcyclohexane was prepared by hydrogenation of 4,4-dimethylcyclohexene (1.1 g, .01 mole) in acetic acid (3 ml) over platinum oxide (.03 g) at atmospheric pressure. Hydrogen (1.05 eq) was taken up after 9 hours, and at this point the reaction was worked up. 1,1-Dimethylcyclohexane (.90, .008 mole) was obtained by micro-distillation at atmospheric pressure.

Yield 80%. B.p. 119°, literature[112] b.p. = 119.5°.

N.M.R. .9 (s, 6H), 1.0-1.5 (m, 10H).

2-(2,2-Dimethyhex-5-enyloxy)tetrahydropyran (59)

2,2-Dimethylhex-5-en-1-ol (14.2 g, .10 mole) was added dropwise to dihydropyrane (25 g, .3 mole) to which two drops of con. HCl had already been added. The mixture was kept below 60° by occasional cooling and stirred for two hours. The solution was shaken with sat. sodium carbonate (2 x 25 ml), dried over anhydrous $NaCO_3$, and distilled at reduced pressure to give the required tetrahydropyranyl ether (18.6g, .088 mole) - pure by g.l.c. analysis (D, 120°, N_2 50 ml/min).

Yield 88% B.p. 72°/.1 mm

N.M.R. 0.9 (s, 6H), 1.1-2.4 (m, 10H), 2.9-4.1 (m, 4H)
4.6 (s, 1H), 4.8-5.2 (m, 2H), 5.4-6.3 (m, 1H).

M.s. Molecular ion at 212 (MW = 212).

Analysis for $C_{13}H_{24}O_2$: calculated C = 73.54, H = 11.39;
found C = 73.53, H = 11.34.

Tetrahydro-2-(2,2-dimethyl-5-hydroxyhexyloxy)-pyran (60)

Water (70 ml) was added to mercuric acetate (22.5 g, .07 mole), followed by THF (70 ml). The mixture was stirred at room temperature, then 2-(2,2-dimethylhex-5-enyloxy)tetrahydropyan (15 g, .07 mole) was added dropwise. Stirring was continued and the disappearance of the starting pyranyl ether followed by g.l.c. (D, 120°, N_2 50 ml/min). After 15 min. the oxymercuration was complete. Now 70 ml of 3.0 M sodium hydroxide was added, followed by 70 ml of a solution of .5 M sodium borohydride in 3.0 M sodium hydroxide. The mixture was

stirred for 15 min., saturated with sodium chloride, and the mercury was allowed to settle. The upper layer of THF was separated, and dried with $MgSO_4$. The solvent was removed on a rotatory evaporator, and the product alcohol (14.5 g, .063 mole) recovered by distillation under reduced pressure.

Yield 90%

B.p. 109^{o}/.2 mm

I.R. -OH stretch at 3300 cm^{-1}, no olefinic absorption at 1640 cm^{-1}.

N.M.R. 0.9 (s, 6H), 1.2 (d, 3H, J=7Hz), 1.0-2.0 (m, 10H), 2.2 (s, 1H, D_2O exchange), 3.0-4.1 (m, 6H), 4.6 (s, 1H).

M.s. Molecular ion at 230 (MW = 230).

Analysis for $C_{13}H_{26}O_3$: calculated C = 67.79, H = 11.38 ; found C = 68.18, H = 11.72.

Tetrahydro-2-(2,2-dimethyl-5-oxohexyloxy)pyran (61)

This **tetrahydropyranyl** ether was prepared from tetrahydro-(2,2-dimethyl-5-hydroxyhexyloxy)pyran (19.5 g, .085 mole) by oxidation with pyridinium chlorochromate[126].

Yield 80%

B.p. 106^{o}/.2mm

I.R. Absence of -OH absorption at 3300 cm^{-1}, carbonyl stretch at 1720 cm^{-1}.

N.M.R. 1.0 (s, 6H), 1.4-1.9 (m, 8H), 2.3 (s, 3H), 2.4-2.8 (m, 2H), 3.4-4.0 (m, 4H), 4.7 (s, 1H).

M.s. Molecular ion at 228 (MW = 228).

Analysis for $C_{13}H_{24}O_3$: calculated C = 68.38, H = 10.59 ; found C = 68.56, H = 10.62.

Tetrahydro-2-(2,2,5-trimethylhex-5-enyloxy)pyran (62)

Tertiary potassium butoxide (10 g, .088 mole, 1.3 eq) was suspended in anhydrous benzene (200 ml). Triphenylphosphonium iodide (30.0 g, .082 mole, 1.2 eq) was added in portions. The reaction mixture was diluted with THF (200 ml), and the stirring continued for 10 mins. Tetrahydro-2-(2,2-dimethyl-5-oxohexyloxy)pyran (16.0 g, .068 mole, 1.0 eq) was added with a syringe, and the reaction mixture left overnight at room temp. Next day the mixture was heated to a gentle reflux (bath temp. 95°) and the stirring thus continued for 48 hours. The mixture was cooled, diluted with ether (300 ml), and filtered. The solution was washed with 5% sodium carbonate (3 x 300 ml) then with brine (2 x 300 ml). All solvent was removed by fractional distillation, and the crude product extracted with light petroleum ether (4 x 50 ml) from triphenylphosphine oxide. The combined extracts were dried over magnesium sulphate, the solvent removed by fractional distillation, and the product (12.4 g, .055 mole) recovered by distillation under reduced pressure.

Yield 78%

I.R. 915, 1640, 3020, no carbonyl stretch.

N.M.R. .9 (s, 6H), 1.3-2.4 (m, 10H), 1.75 (s, 3H), 3.0-3.5 (m, 2H), 3.3-4.1 (m, 2H), 4.6 (s, 1H), 4.7 (s, 2H).

M.s. Molecular ion at 226 (MW = 226)

Analysis for $C_{14}H_{26}O_2$: calculated C = 74.29, H = 11.58 ; found C = 74.59, H = 11.36.

2,2-5-Trimethylhex-5-en-1-ol (63)

(A) Tetrahydro-2-(2,2,5-trimethylhex-5-enyloxy)pyran (11.5 g, .05 mole) was added to methanol (100 ml), to which para-toluene sulphonic acid (.19 g, .001 mole) was already added. The mixture was stirred for two hours at room temp., then brine (100 ml) was added, and the product extracted with ethyl acetate (6 x 10 ml). The fractions were combined, washed with sat. sodium carbonate (50 ml) then water (2 x 25 ml), and dried over magnesium sulphate. The solvent was removed by fractional distillation, and 2,2,5-trimethylhex-5-en-1-ol was distilled under reduced pressure (5.2 g, .037 mole). This alcohol was pure by g.l.c. analysis (A, 120°-150°, N_2 50 ml/min; D, 120-150°, N_2 50-55 ml/min).

Yield 73%

B.p. 42°/1 mm.

I.R. 925, 1645, 3000, 3300

N.M.R. .9 (s, 6H), 1.8 (s, 3H), 1.2-2.3 (m, 4H), 2.8 (s, 1H, D_2O exchange), 3.4 (s, 2H), 4.8 (s, 2H).

Analysis for $C_9H_{18}O$: calculated C = 76.00, H = 12.76;
found C = 75.84, H = 12.42.

(B) Ethyl 2,2,5-trimethylhex-5-en-1-oate (9.2 g, .05 mole) was reduced with $LiAlH_4$ in ether by the method described for the reduction of 3-methylhex-5-en-1-oate. The distilled product was pure by g.l.c. analysis (A, 120-150°, N_2 50 ml/min; D, 120-150°, N_2 50-55 ml/min).

Yield 88%

B.p. and spectral data were identical with those of the product from (A).

3-Methylbut-3-en-1-ol (64)

3-Chloro-2-methylpropene (9.0 g, .10 mole) in ether (25 ml) was added to magnesium turnings (3.1 g, .13 mole) in ether (50 ml) at a rate which maintained a slow reflux. After addition the white suspension of the Grignard reagent, which is insoluble in ether, was refluxed for 30 min. Paraformaldehyde (9.0 g, .30 mole) was sublimed over 1.5 hours, and through a glass tube (1 cm internal diameter) carried by a stream of nitrogen to just above the surface of the reaction mixture. The stirring was continued for additional two hours at the reflux. The mixture was cooled and saturated ammonium chloride added dropwise until clear separation of magnesium salts occurred. The ether solution was decanted, and the precipitate washed with more ether (2 x 15 ml). The solvent was separated by fractional distillation, and 3-methylbut-3-en-1-ol (6.4 g, .74 mole) was distilled under reduced pressure. The product was pure by g.l.c. analysis (D, 100°, N_2 40 ml/min).

Yield	74%
B.p.	55°/25 mm, literature[137] b.p. = 130-135°.
I.R.	930, 1650, 1725, 3015, 3300.
N.M.R.	1.7 (s, 3H), 2.3 (t, 2H, J=7Hz), 2.9 (s, 1H, D_2O exchange), 3.6 (t, 2H, J=7Hz), 4.8 (s, 2H).

2-Methyl-4-bromobut-1-ene (65)

Bromine (1.4 ml, .027 mole) was added to freshly distilled tributylphosphine (6.1 g, .03 mole) dissolved in DMF (30 ml). 3-Methylbut-3-en-1-ol (2,2 g, .025 mole) was added dropwise with a syringe. At all times the temperature in the reaction mixture was kept below 50°. After 1 hour stirring the solvent and the product were distilled under reduced pressure using ethanol dry ice condenser. The distillate was transferred into a dropping funnel and water (100 ml) was added. The product bromide,

which separated as the bottom layer, was drawn off and the aqueous solution extracted with light petroleum (2 x 10 ml). Organic fractions were combined, washed with water (2 x 5 ml), and dried over 3A molecular sieves, then the solvent removed by fractional distillation. The crude product was distilled under reduced pressure. 2-Methy-4-bromobut-1-ene (3.4 g, .0225 mole) thus obtained was pure by g.l.c. analysis (D, 110°, N_2 40 ml/min).

Yield	90%
B.p.	68°/110 mm, literature[138] b.p. = 105-107°/760 mm
I.R.	930, 1650, 1725, 3015.
N.M.R.	1.8 (s, 3H), 2.6 (t, 2H, J=7Hz), 3.4 (t, 2H, J=7Hz), 4.8 (s, 2H).

Ethyl 2,2,5-trimethylhex-5-en-1-oate (66)

The above ester was prepared from ethyl isobutyrate (11.5 g, .10 mole) and 2-methyl-4-bromobut-1-ene (14.9 g, .10 mole) by the method employed in the synthesis of ethyl 2,2-dimethylhex-5-en-1-oate (27). The product was pure by g.l.c. analysis (A, 120°, N_2 50 ml/min).

Yield	85%
B.p.	37°/4 mm
N.M.R.	1.2 (s, 6H), 1.3 (t, 3H, J=7Hz), 1.5-2.0 (m, 4H), 1.8 (s, 3H), 4.2 (q, 2H, J=7Hz), 4.6 (s, 2H).
Analysis for $C_{11}H_{20}O_2$:	calculated C = 71.70, H = 10.94; found C = 71.49, H = 10.67.

2,5,5-Trimethyl-6-bromohex-1-ene (67) and *2,5,5-trimethyl-6-bromohex-2-ene* (68

Carbon tetrabromide (4.0, .012 mole) was added in portions to a solution of 2,2,5-trimethylhex-5-en-1-ol (1.5 g, .011 mole) and triphenylphosphine (3.4 g, .013 mole) in methylene chloride (10 ml). The reaction

generated heat and was maintained at 18-20° by cooling. The mixture was left stirring overnight under nitrogen, then pentane (10 ml) was added to precipitate the bulk of triphenylphosphine oxide. The solution was decanted, and the residue washed with pentane (2 x 5 ml). The solvent was removed by fractional distillation. Microdistillation under reduced pressure gave a mixture (.97 g, .005 mole) of 2,5,5-trimethyl-6-bromohex-1-ene and 2,5,5-trimethyl-6-bromohex-2-ene.

Yield 43%. Common b.p. 55°/.7 mm

The two isomers were separated by prep. g.l.c. (E, 120°, N_2 100 ml/min). The yield of pure 2,5,5-trimethyl-6-bromohex-1-ene (.27 g, .0013 mole) obtained was 12%.

I.R. 925, 1645, 3000.

N.M.R. 1.0 (s, 6H), 1.3-2.1 (m, 4H), 1.7 (s, 3H), 3.3 (s, 2H), 4.7 (s, 2H).

Analysis for $C_9H_{17}Br$:: calculated C = 52.70, H = 8.35, Br = 38.95 ; found C = 53.03, H = 8.25, Br = 38.60.

The yield of pure 2,5,5-trimethyl-6-bromohex-2-ene (.406 g, .002 mole) was 18%.

I.R. 1680.

N.M.R. 1.0 (s, 6H), 1.6 (s, 1H), 1.7 (s, 1H), 2.0 (d, 2H, J=9Hz), 3.3 (s, 2H), 5.0-5.3 (m, 1H).

M.s. Two molecular ions at 204 and 206 (Mw = 205).

2,2-Dimethylpropanediol (69)

This diol was prepared on a .15 mole scale by literature methods[139].

Yield 74%. M.p. 130°, literature[139] m.p. 129-131°.

N.M.R. 1.0 (s, 6H), 2.8 (s, 2H, D_2O exchange), 3.4 (s, 4H).

3-Bromo-2,2-dimethylpropan-1-ol (70)

Monobromination of 2,2-dimethylpropanediol was carried out by literature methods[140].

Yield 62%

B.p. 59-62°/4 mm. literature[140] b.p. = 76-80°/13 mm

N.M.R. 1.0 (s, 6H), 1.8 (s, 1H, D_2O exchange) 2.4 (s, 2H), 2.5 (s, 2H).

2,5,5-Trimethylhex-1-ene (71)

2,5,5-Trimethylhex-1-ene (1.5 g, .012 mole) was synthesised by addition of neopentylmagnesium bromide (.02 mole) in THF (5 ml) to 2-methyl-3-chloropropene (.02 mole) in THF (15 ml) by methods described for the preparation of 5,5-dimethylhex-1-ene.

Yield 60%

B.p. 108°/760

I.R. 875, 1650, 3000

N.M.R. .9 (s, 9H), 1.2-2.3 (m, 4H), 1.8 (s, 3H), 4.7 (s, 2H).

Analysis for C_9H_{18} : calculated C = 85.65, H = 14.37 ;
found C = 85.78, H = 14.13.

2,2,5,5-Tetramethylcyclopentanone (72)

Ketone (72) was prepared from cyclopentanone and methyl iodide by literature[141] methods.

Yield 85%

B.p. 47°/23 mm, literature b.p. = 47°/23 mm.

I.R. 1780

N.M.R. 0.8 (s, 12H), 1.6 (t, 4H, J=4Hz)

2,2,5,5-Tetramethylcyclopentanol (73)

2,2,5,5-Tetramethylcyclopentanone (4.0 g, .028 mole) in ether (10 ml) was added to a suspension of $LiAlH_4$ (0.53 g, .014 mole) in ether (20 ml). The mixture was stirred overnight at room temperature. Sodium hydroxide (.15M) was added dropwise until lithium salts precipitated as granular white solids. The clear solution was decanted, the residue washed with ether (2 x 5 ml), and the solution dried over $MgSO_4$. After removal of solvent by fractional distillation, 2,2,4,4-tetramethylcyclopentanol was distilled under reduced pressure (3.6 g, .025 mole).

Yield 90%

B.p. 53^o/15 mm

I.R. 3300

N.M.R. .9 (s, 12H), 1.7 (s, 1H, D_2O exchange), 1.5 (t, 4H, J=6Hz), 3.8 (s, 1H).

Analysis for $C_9H_{18}O$: calculated C = 76.00, H = 12.76;
found C = 76.13, H = 12.65.

Oxy-(2,2,5,5-tetramethylcyclopentyl)-S-methyl dithiocarbonate (74)

2,2,5,5-Tetramethylcyclopentanol (2.8 g, .02 mole) 50% sodium hydride dispersion in mineral oil (.02 mole), and imidazole (.40 g) were stirred and refluxed for 3 hours in THF (50 ml) under nitrogen. Carbon disulphide (6 ml) was added, and, after refluxing for 30 min. methyl iodide (6 ml) was added, and the refluxing continued for another 30 min. Acetic acid (6 ml) was now added, followed by water (20 ml). The product was extracted with dichloromethane (3 x 20 ml), and the combined extracts washed with 5% HCl (2 x 25 ml) then with saturated solution of sodium hydrogen carbonate (50 ml), followed by water (50 ml), and brine (50 ml). The extract was filtered through a short column (25 cm x 2 cm) of silica gel, then dried over $MgSO_4$, and the solvent removed on a rotatory

evaporator.

Yield 68%

B.p. $80^{o}/.2$ mm

1,1,3,3-Tetramethylcyclopentane (75)

2,2,4,4-Tetramethyl-1-oxycyclopentyl-S-methyl dithiocarbonate (74) (3.08 g, .014 mole) was dissolved in deoxygenated xylene (5 ml); and, over 30 min, added with a syringe to tributyl stannane (4.65 g, .016 mole) in deoxygenated xylene (10 ml) under reflux. The mixture was stirred and refluxed under nitrogen overnight. 1,1,3,3-Tetramethylcyclopentane (0.9 g, .007 mole) was obtained by fractional distillation.

Yield 52%

B.p. 118^{o}, literature[112] b.p. = 118, and[142] 118.5^{o}

N.M.R. 0.9 (s, 12H), 1.0-1.8 (m, 6H).

Regractive index, $n_D^{21} = 1.4128$, lit.[142] $n_D^{20} = 1.4125$.

1,4,4-Trimethylhex-1-ene (76)

4,4-Dimethylcyclohexanone (2.52 g, .02 mole) in ether (20 ml) was added to methylmagnesium iodide (1.25 eq) in ether (30 ml) which was prepared from methyl iodide (3.55 g, .025 mole) and magnesium turnings (.75 g, .03 mole). The mixture was stirred for two hours under reflux, and saturated ammonium chloride added dropwise until the point was reached when magnesium salts precipitated from the cloudy mixture leaving a clear solution. The salts were allowed to settle for 15 min, then the supernatant solution was decanted. The precipitate was washed with anhydrous ether (2 x 10 ml). The ether was removed under reduced pressure and the crude product added to anhydrous oxalic acid

(3.6 g, .04 mole), which was freshly prepared by dehydration of dihydro-oxalic acid (5.4 g, .04 mole) at 100° over 3 hours. The mixture was heated in an oil bath in a distilling apparatus at 160°. The product 1,4,4-trimethylhex-1-ene (1.4 g, .013 mole) was distilled at atmospheric pressure, and was pure by g.l.c. analysis (C, 120, N_2 65 ml/min).

Yield	62% relative to 4,4-dimethylcyclohexanone.
B.p.	138-140°, literature[143] b.p. = 140°.
N.M.R.	1.0 (s, 6H), 1.2-2.0 (m, 9H), 5.3 (s, 1H).

1,1,4-Trimethylcyclohexane (77)

1,4,4-Trimethylcyclohexene (1.4 g, .013 mole) was hydrogenated over platinum oxide (.03 g) in acetic acid (2.5 ml) at atmospheric pressure. After 24 hours 1.01 equivalents of hydrogen was taken up. The catalyst was precipated by centrifuging and the solution decanted. Water (3.0 ml) was added, and the hydrocarbon layer separated, and dried over 4-A molecular sieves. 1,1,4-Trimethylcyclohexane (1.2 g, .01 mole), obtained by microdistillation, was pure by g.l.c. analysis (C, 120°, N_2 60 ml/min).

Yield	77%.
B.p.	135°, literature[112,144] b.p. = 135°.
N.M.R.	.9 (s, 6H; plus d, 3H, J=6Hz), 1.0-1.7 (m, 9H).

Ethyl 2,2-Dimethylpent-4-en-1-oate (78)

The above ester was prepared from ethyl isobutyrate (.06 mole), and allyl bromide (1 equivalent) by the method described for preparation of ethyl dimethylhex-5-en-1-oate (27). The product was pure by g.l.c. analysis (D, 70°, N_2 43 ml/min).

Yield 73%.

B.p. 61°/17 mm.

I.R. 905, 1645, 1730, 3015.

N.M.R. 1.1 (s, 6H), 1.3 (t, 3H, J=8Hz).
2.3 (d, 2H, J=7Hz), 4.1 (q, 2H, J=8Hz),
4.8-5.0, (m, 1H), 5.0-5.2 (m, 1H), 5.4-6.1 (m, 1H).

M.s. Molecular ion at 156, Mw = 156.

Analysis for $C_9H_{16}O_2$: calculated C = 69.19, H = 10.32;
found C = 69.19, H = 10.58.

2,2-Dimethylpent-4-en-1-ol (79)

Ester (78) was reduced with $LiAlH_4$ on a .03 mole scale using standard methods. The distilled product was pure by g.l.c. analysis (D, 100°, N_2 58 ml/min).

Yield 80%.

B.p. 62°/15 mm.

N.M.R. .9 (s, 6H), 2.0 (d, 2H, J=7Hz), 2.7 (s, 1H, D_2O exchange) 3.3 (s, 2H), 4.8-5.0 (m, 1H), 5.0-5.2 (m, 1H), 5.3-6.2 (m, 1H).

Analysis for $C_7H_{14}O$: calculated C = 73.63, H = 12.36;
found C = 73.08, H = 12.33.

4,4-Dimethyl-5-bromopent-1-ene (80)

Alcohol (79) was brominated by the method described for preparation of the bromide (29) using triphenylphosphine and carbon tetrabromide on a .02 mole scale. G.l.c. analysis D, 100°, N_2 60 ml/min) showed no starting alcohol in the distilled product which was contaminated with bromoform (2.7%). Pure 4,4-dimethyl-5-bromopent-1-ene was obtained by preparative g.l.c. (E, 130°, N_2 120 ml/min).

Yield after distillation 68%.

N.M.R. 1.0 (s, 6H), 2.1 (d, 2H), J=8Hz, 3.3 (s, 2H), 4.8-5.0 (m, 1H), 1.2 (s, 1H), 5.4-6.1 (m, 1H).

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12; found C = 47.42, H = 7.46, Br = 45.20.

Methyl 3,3-dimethylpent-4-en-1-oate (81)

A mixture of 3-methylbut-2-en-1-ol (8.5 g, .10 mole), trimethyl orthoacetate (12 g, .10 mole) and n-propionic acid (4.5 g, .06 mole) was stirred in a distillation apparatus, and slowly heated (≈ 1°/min) to 145°. During this time methanol was distilled as the reaction progressed. The temperature of the reaction mixture was maintained at 143-145° until 1.85 equivalents (7.5 ml) of methanol was distilled (3.2 hours).

The mixture was cooled, and washed with dilute hydrogen sodium carbonate (3 x 50 ml), and the product extracted with ether (3 x 50 ml). After drying over magnesium sulphate, the solvent was distilled on a fractionating column, and the product (11.5 g, .081 mole) distilled under reduced pressure. G.l.c. analysis showed no impurities D, 70°, N_2 45-60 ml/min).

Yield 81%.

B.p. 59°/33 mm.

I.R. 910, 1640, 1740, 3010.

N.M.R. 1.1 (s, 6H), 2.3 (s, 2H), 3.7 (s, 3H), 4.8-5.2 (m, 2H), 5.7-6.3 (m, 1H).

M.s. Molecular ion at 142, Mw = 142.

Analysis for $C_8H_{14}O_2$: calculated C = 67.57, H = 9.92; found C = 67.62, H = 9.81.

3,3-Dimethylpent-4-en-1-ol (82)

Methyl 3,3-dimethylpent-4-en-1-oate (7.1 g, .05 mole) in ether (50 ml) was added to a suspension of $LiAlH_4$ (1.9 g, .05 mole) in ether (50 ml). The reaction was instantaneous. The product salts were insoluble in ether, and the reaction mixture formed a polymer-like mass. Saturated ammonium chloride was added slowly until the solidified mixture broke up with the precipitation of white salts from a clean ether solution. The ether solution was decanted and the residual solids washed with more ether (2 x 25 ml).

The solvent was separated by fractional distillation, and the product (4.62 g, .041 mole) distilled under reduced pressure. No impurities were detected by g.l.c. analysis (D, 100°, N_2 55 ml/min).

Yield 82%.

B.p. 72°/19 mm.

I.R. 910, 1640, 3020, 3270.

N.M.R. 1.0 (s, 6H), 1.5 (t, 2H, J=8Hz), 2.4 (s, 1H, D_2O exchange), 3.5 (t, 2H, J=H8Hz), 4.7-4.9 (m, 1H), 4.9-5.1 (m, 1H), 5.6-6.1 (m, 1H).

Analysis for $C_7H_{14}O$: calculated C = 73.63, H = 12.36;
found C = 73.49, H = 12.28.

3,3-Dimethyl-5-bromopent-1-ene (83)

Bromine (4.8 g, .03 mole) was added slowly to a stirred solution of tributylphosphine (6.06, g, .03 mole) in DMF (25 ml). The rate of addition had to be so slow as to bar the development of an orange colour in the solution. Temperature of the reaction mixture was kept at 0-5°. After addition the mixture was stirred for 30 minutes, then 3,3-dimethylpent-4-en-1-ol (3.42 g, .03 mole) was added dropwise. The cooling bath was removed and the mixture

stirred for two hours. Still under nitrogen the reaction flask was connected to a distillation apparatus; the solvent and the products were distilled until no more material came over at 60°/15 mm. The distillate was poured into a separatory funnel with water (50 ml), and the crude bromide drawn off as the bottom layer. The product was dried over 4-A molecular sieves then distilled under reduced pressure. The bromide (4.2 g, .024 mole) was pure by g.l.c. analysis (D, 90°, N_2 45-60 ml/min).

Yield 79%.

B.p. 56-57°/18 mm.

I.R. 910, 1640, 3020.

N.M.R. 1.0 (s, 6H), 2.9 (t, 2H, J=8Hz), 3.4 (t, 2H, J=8Hz), 4.8-5.0 (m, 1H), 5.1 (s, 1H), 5.6-6.1 (m, 1H).

M.s. Molecular ions at 176 and 178, Mw = 177.

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12;
found C = 47.29, H = 7.46, Br = 45.10.

4-Chlorobutan-1-ol (87)

Gaseous hydrochloric acid was bubbled through anhydrous tetrahydrofurane (162 ml, 2.0 moles) under nitrogen. The reaction was followed by thin layer chromatography. After 45 minutes the reaction mixture was washed with water (3 x 150 ml), then with saturated potassium carbonate, and dried over magnesium sulphate. The product (186 g, 1.72 moles) was distilled under reduced pressure. No impurities were detectable by g.l.c. analysis (A, 60°, N_2 45 ml/min).

Yield 86%.

B.p. 62°/2 mm, literature[145] b.p. = 81-82°/14 mm.

I.R. 3300.

N.M.R. 1.6-2.0 (m, 4H), 3.4-3.8 (m, 4H), 4.4 (s, 1H, D_2O exchange).

Tetrahydro-2-(4-chloro-1-oxybutyl)pyran (88)

4-Chlorobutan-1-ol (160.5 g, 1.5 moles) was added dropwise to dihydropyrane (135 g, 1.6 moles) to which concentrated hydrochloric acid (.25 ml) had already been added. The mixture was kept at 50-55° by occasional cooling, and stirred for 2.5 hours. The solution was placed in a separating funnel and washed with saturated sodium carbonate (2 x 200 ml). After drying over anhydrous sodium carbonate, tetrahydropyranyl ether (238 g, 1.24 moles) was distilled under reduced pressure. The product was pure by g.l.c. analysis (A, 150°, N_2 80 ml/min).

Yield 83%.

B.p. 77°/1.7 mm.

N.M.R. 1.3-1.9 (m, 10H), 3.3-3.9 (m, 6H), 4.6 (s, 1H).

Analysis for $C_9H_{17}O_2Cl$: calculated C = 56.10, H = 8.89;
found C = 56.31, H = 9.03.

Tetrahydro-2-(hept-6-enyl-1-oxy)pyran (89)

Tetrahydro-2-(4-chloro-1-oxybutyl)pyran (9.7 g, .05 mole) in THF (30 ml) was added to magnesium turnings (1.4 g, .06 mole) in THF (50 ml). The reaction proceeded well. The Grignard reagent thus prepared was transferred into a dropping funnel under nitrogen, and dropwise added to allyl bromide (6.0 g, = .05 mole) in THF (50 ml). The reaction generated heat, and the addition rate was adjusted to maintain a slow reflux. Two hours after addition the stirrer was stopped, and the reaction mixture left overnight under nitrogen.

Water (300 ml) was added, the product was extracted with light petroleum (4 x 50 ml), washed with water (3 x 50 ml), and dried over anhydrous potassium carbonate. The required tetrahydropyranyl ether (7.5 g, .04 mole) was distilled under reduced pressure. G.l.c. analysis showed no impurities (A, 150°, N_2 80 ml/min).

Yield 80%.

B.p. 64°/.2 mm.

I.R. 915, 1640, 3020.

N.M.R. 1.2-2.4 (m, 14H), 3.1-3.9 (m, 4H), 4.6 (s, 1H), 4.8-5.3 (m, 2H), 5.5-6.2 (m, 1H).

M.s. Molecular ion at 198, Mw = 198.

Analysis for $C_{12}H_{22}O_2$: calculated C = 72.68, H = 11.18; found C = 72.46, H = 11.09.

Hept-6-en-1-ol (90)

Tetrahydro-2-(hept-6-enyl-1-oxy)pyran (7 g, .035 mole) was added to 2N hydrochloric acid (50 ml) and ethanol (50 ml), and stirred for one hour. The mixture was saturated with sodium chloride, and extracted with ethyl acetate (5 x 20 ml). The combined extracts were washed with water (2 x 20 ml) and dried over 4-A molecular sieves (removal of water and traces of ethanol). G.l.c. analysis showed no ethanol impurity in the crude product which was distilled under reduced pressure (3.4 g, 0.3 mole).

Yield 86%.

B.p. 50°/1.5 mm, literature[146] b.p. 76°/12 mm.

I.R. 915, 1640, 3020, 3250.

N.M.R. 1.2-1.8 (m, 6H), 1.8-2.4 (m, 2H), 3.5 (s, 1H, D_2O exchange) 3.6 (t, 2H, J=7Hz), 4.9-5.3 (m, 2H), 5.5-6.3 (m, 1H).

Hept-6-en-1-al (91)

Chromium trioxide (2.5 g, .025 mole) was added to a stirred solution of pyridine (4 g, .05 mole) and methylene chloride (65 ml). The dark-red solution was stirred for 15 minutes, under nitrogen. Hept-6-en-ol (2.85 g, .025 mole) in methylene chloride (10 ml) was added in one portion. The mixture was stirred for 20 minutes, and the solution decanted from the black tarry solid.

The residue was washed with ether (2 x 50 ml). The combined organic solutions were washed with 5% sodium hydroxide (3 x 50 ml), 5% hydrochloric acid (1 x 50 ml), 5% hydrogensodium carbonate (1 x 50 ml), and brine (1 x 50 ml). The solution was dried over magnesium sulphate, and the solvent removed by fractional distillation. Hept-6-en-1-al (2.0 g, .018 mole) was distilled under reduced pressure. No impurities were detectable by g.l.c. analysis (A, 100°, N_2 50 ml/min).

Yield	72%.
B.p.	52°/20 mm, literature[147] b.p. = 89-90°/80 mm.
I.R.	910, 1640, 1720, 3020.
N.M.R.	1.3-2.0 (m, 4H), 2.0-2.7 (m, 4H), 4.8-5.2 (m, 2H), 5.4-6.2 (m, 1H), 9.8 (s, 1H).

Oct-7-en-2-ol (92)

Hept-6-en-1-al (1.9 g, .017 mole) in ether (5 ml) was added to methylmagnesium iodide (2 equivalents) in ether 20 ml, and stirred for 30 minutes. A cold solution of saturated ammonium chloride was added dropwise until white granular magnesium salts precipitated and left a clear solution. The solution was decanted, and the residue washed with ether 2 x 5 ml.

The solvent was removed by fractional distillation, and the

alcohol (2.1 g, .016 mole) distilled under reduced pressure.

Yield 94%.

B.p. 54°/1.3 mm.

I.R. 910, 1640, 3010, 3300.

N.M.R. 1.1 (d, 2H, J=7Hz), 1.2-1.5 (m, 6H), 1.8 (s, 1H, D_2O exchange), 1.8-2.3 (m, 2H), 3.3-3.9 (m, 1H), 4.8-5.2 (m, 2H), 5.5-6.1 (m, 1H).

Analysis for $C_8H_{16}O$: calculated C = 74.94, H = 12.58; found C = 74.72, H = 12.18.

7-Bromo-oct-1-ene (93)

Oct-7-en-2-ol (1.92 g, .015 mole) was converted to its tosylate by literature[148] methods using p-toluenesulfonyl bromide (7.2 g, .03 mole) in pyridine (15 ml). The recrystallised tosylate (3.1 g, .012 mole) was added to LiBr (2.1 g, .024 mole) in HMPT (60 ml). The reaction was stirred at room temperature overnight, then water (120 ml) was added, and the bromide extracted with light petroleum (3 x 25 ml). After drying over magnesium sulphate, the solvent was removed by fractional distillation. 7-Bromo-oct-1-ene (2.5 g, .013 mole) was distilled under reduced pressure, and was pure by g.l.c. analysis (H, 120°, N_2 50 ml/min).

Yield 87%.

B.p. 65°/6 mm.

I.R. 910, 1640, 3010.

N.M.R. 1.3-2.3 (m, 8H), 1.7 (d, 3H, J=7Hz), 4.0-4.4 (m, 1H), 4.8-5.3 (m, 2H), 5.5-6.2 (m, 1H).

Analysis for $C_8H_{15}Br$: calculated C = 50.28, H = 7.91; found C = 50.22, H = 7.99.

1,2-Dimethylcyclohexane cis (96), *and trans* (97)

Under anhydrous and oxygen free conditions 7-bromo-oct-1-ene (.48 g, .0025 mole) was added to decalin (50 ml) to prepare a .05 M solution. Tri-n-butyltin hydride (.73 g, .0025 mole) was added. The solution was sealed under nitrogen in a glass ampoule, and incubated at 100° for 48 hours. The ampoule was cooled, opened, and the contents added to an aqueous solution of .15 m potassium fluoride in order to convert the soluble tri-n-butyltin bromide to the insoluble tri-n-butyltin fluoride[149]. The organic portion was separated and washed with brine (1 x 25 ml), then dried over 4-A molecular sieves. The solution was distilled at atmospheric pressure until g.l.c. analysis (C, 95°, N_2 55 ml/min) showed no 1,2-dimethylcyclohexane. From the collected distillate (7.5 ml) the *cis* and *trans* stereoisomers of 1,2-dimethylcyclohexane were separated by preparative g.l.c. (M, 100-120°, N_2 55-75 ml/min) as pure compounds. The *cis* isomer had a longer retention time of 3-8 minutes - depending on the column temperature and the flow rate of the carrier gas.

Ref. Index: *cis* n_D^{21} = 1.4347, literature[112] n_D^{20} = 1.4360;

trans n_D^{21} = 1.4268, literature[112] n_D^{20} = 1.4270.

^{13}C N.M.R. δ ppm: *cis* 34.8 (C_1, C_2), 3.19 (C_3, C_6), 24.1 (C_4, C_5), 16.0 (CH_3).

trans 39.9 (C_1, C_2), 36.2 (C_3, C_6), 27.2 (C_4, C_5), 20.5 (CH_3).

Lit.[130] δ ppm: *cis* 35.0 (C_1, C_2), 32.1 (C_3, C_6), 24.3 (C_4, C_5), 16.3 (CH_3).

trans 40.1 (C_1, C_2), 36.6 (C_3, C_6), 27.4 (C_4, C_5), 20.8 (CH_3).

4-Methylhex-5-en-1-ol (98)

4-Bromobut-2-ene (6.75 g, .05 mole) in ether (30 ml) was added to magnesium (3.6 g, .15 mole) in ether (30 ml) at a rate which maintained a slow reflux. After addition the mixture was stirred until its temperature dropped to room temperature (50 min). Trimethylene oxide (5.8 g, .10 mole) in ether (20 ml) was added dropwise. White precipitate began to form, which stuck to excess magnesium turnings and several times stopped the magnetic stirrer. When the addition of the epoxide was finished the precipitate was uniformly distributed in the reaction mixture and did not obstract the stirring bar. The mixture was stirred for an additional 16 hours after which time no precipitate was left. The clear ether solution was decanted into another flask fitted with a condenser, and the magnesium residue washed with anhydrous ether (50 ml) which was combined with the decanted solution. Saturated cold ammonium chloride was added slowly (≈ 45 drops/min) until white granular magnesium salts precipitated from the clear solution, which was then filtered and the ether removed by fractional distillation. 4-Methylhex-5-en-1-ol (5.0 g, .044 mole) was distilled under reduced pressure. G.l.c. analysis (N, 100-130°, N_2 45 ml/min; P, 80-100°, N_2 40-60 ml/min) showed a single impurity with the relative peak area of 2.3% - possibly hept-5-en-1-ol.

Yield	88%.
B.p.	81°/20 mm, literature[115] b.p. = 68°/12mm.
I.R.	915, 1650, 3010, 3280.
N.M.R.	1.0 (d, 3H, J=7Hz), 1.2-1.8 (m, 4H), 1.9-2.4 (m, 1H), 2.3 (s, 1H, D_2O exchange), 3.6 (t, 2H, J=7Hz), 4.7-4.9 (m, 1H), 4.9-5.2 (m, 1H), 5.4-6.1 (m, 1H).

3-Methyl-6-bromohex-1-ene (99)

4-Methylhex-5-en-1-ol (4.56 g, .04 mole) was added to a solution of triphenylphosphine (10.5 g, .04 mole) in dichlorome - thane (50 ml). Solid carbon tetrabromide (13.6 g, .041 mole) was added under nitrogen. The mixture was left stirring for 3 hours. The bulk of the solvent (45 ml) was distilled off and the product extracted with n-heptane (4 x 25 ml). The solution was filtered and the solvent separated by fractional distillation. The bromide (5.86 g, .033 mole) was distilled by slow fractional distillation under reduced pressure. G.l.c. analysis (D, 100°, N_2 45 ml/min) showed a bromoform impurity (≈ 2.5%) which is a common contaminant in this type of bromination. Another single impurity with the relative g.l.c. peak area of 2.2% was present - possibly 7-bromohept-2-ene. Pure 3-methyl-6-bromohex-1-ene was easily separated by preparative g.l.c. (P, 90-110°, N_2 50 ml/min).

Yield after distillation 83%.

B.p. 79°/50 mm.

I.R. 915, 1650, 3010.

N.M.R. 1.0 (d, 3H, J=7Hz), 1.2-2.3 (m, 5H), 3.4 (t, 2H, J=7Hz), 4.7-4.9 (m, 1H), 4.9-5.1 (m, 1H), 5.4-6.1 (m, 1H).

M.s. Molecular ions at 176 and 178, Mw = 177.

Analysis for $C_7H_{13}Br$: calculated C = 47.48, H = 7.40, Br = 45.12;
found C = 47.80, H = 7.11, Br = 45.20.

3-Methylhex-1-ene (100)

3-Bromopentane (7.5 g, .05 mole) in THF (50 ml) was treated with vinyl lithium (1 equivalent) in THF (1.2 M). The

mixture was extracted with decalin (2 x 25 ml). The organic portion was dried over 4-A molecular sieves and distilled at atmospheric pressure. The product 3.2 g, .033 mole) was contaminated by two impurities, which were separated by preparative g.l.c. (N, 90°, N_2 50 ml/min).

The yield of pure product was 2.1 g, .02 mole, 43%.

B.p. 84°, literature[112] b.p. = 83.9°.

I.R. 915, 1650, 3010.

N.M.R. (m, 6H), 1.1-2.1 (m, 5H), 4.7-4.9 (m, 1H), 4.9-5.1 (m, 1H), 5.4-6.1 (m, 1H).

2-Methylcyclopentanone (101)

The morpholine enamine of cyclopentanone was prepared by literature[151] methods from cyclopentanone (8.4 g, .10 mole) and morpholine (13.1 g, .15 mole) in toluene (50 ml). 1-Morpholine-1-cyclopentene (13.9 g, .09 mole) was distilled under reduced pressure. Yield 90%. B.p. 98°/8 mm, literature[152, 153] b.p. = 97°/7.5 mm and 105-109°/13 mm. Following a literature procedure[154] the whole of the product was added to a solution of one equivalent of ethylmagnesium bromide in dry THF, and refluxed under nitrogen until one equivalent of ethane gas was formed. Methyl iodide was added, and the mixture refluxed for 18 hours. The reaction was worked up[154], and the crude product distilled under reduced pressure. 2-Methylcyclopentanone (6.4 g, .065 mole) thus obtained was pure by g.l.c. analysis (D, 90°, N_2 60 ml/min).

Yield 72%.

B.p. 46°/20 mm, literature[155] b.p. = 44°/18 mm.

I.R. 1720.

N.M.R. 1.0 (d, 3H, J=7Hz), 1.2-2.6 (m, 7H).

1,2-Dimethylcyclopentanol (102)

2-Methylcylopentanone (5.9 g, .06 mole) in ether (25 ml) was added to methylmagnesium iodide (1.2 equivalents) in ether (25 ml). The mixture was stirred for 2 hours under reflux. Saturated ammonium chloride was added dropwise until clear ether solution separated from the white precipitate of magnesium salts. The ether solution was decanted and the residue washed with anhydrous ether (2 x 15 ml). The solvent was separated by fractional distillation, and the product distilled under reduced pressure (6.4 g, .056 mole).

Yield 93%.

B.p. 63°/8 mm.

I.R. 3300, no carbonyl absorption.

N.M.R. 1.0 (d, 3H, J=7Hz), 1.1 (s, 3H), 1.2-2.7 (m, 7H), 2.3 (s, 1H, D_2O exchange).

Analysis for $C_7H_{14}O$: calculated C = 73.63, H = 12.36;
found C = 73.48, H = 12.43.

1,2-Dimethylcyclopentene (103)

1,2-Dimethylcyclopentanol (5.7 g, .05 mole) was added to anhydrous oxalic acid (9.0 g, .10 mole) under nitrogen. The mixture was heated slowly (≈ 2°/min) until 1,2-dimethylcyclopentene began distilling at atmospheric pressure, then held constant (both temperature 120°) until the distillation ceased. The product was stored over 4-A molecular sieves overnight, then distilled at atmospheric pressure. 1,2-Dimethylcyclopentene (4.1 g, .043 mole) thus prepared was pure by g.l.c. analysis (C, 75-90°, N_2 40-50 ml/min).

Yield 84%.

B.p. 106°, literature[112] b.p. = 105.8°.

1,2-Dimethylcyclopentene (trans, 104), cis, 105)

1,2-Dimethylcyclopentene (4.1 g, .043 mole) was hydrogenated in acetic acid (10 ml) over palladium on carbon at atmospheric pressure. The reduction was fast, and appeared to proceed at the rate of hydrogen diffusion. When one equivalent of hydrogen was taken up the mixture was centrifuged and the clear solution decanted into a separatory funnel. Water (20 ml) was added, and the product extracted with purified decalin (3 x 5 ml). The organic portion was washed with saturated potassium carbonate (10 ml), and dried over 4-A molecular sieves. 1,2-Dimethylcyclopentene (3.4 g, .035 mole) was fractionally distilled at atmospheric pressure. No impurities were detectable by g.l.c. analysis (C, 70°, H_2 50 ml/min; J, 40-60°, He 2-4 ml/min). The *cis* and *trans* isomers were easily separable. The ratio of *cis* to *trans* 1,2-Dimethylcyclopentene was 4.2:1. The g.l.c. peaks were identified by the ^{13}C n.m.r. spectrum of the isomer mixture, which showed that peaks with chemical shifts corresponding to *cis*-1,2-dimethylcyclopentene were four times as intense as the peaks of the *trans* isomer.

Yield 81%.

B.p. 95-99°, literature[112] b.p. = 99.5°.

^{13}C N.M.R. shifts, in δ ppm.

	Isomer	C_1	C_3	C_4	CH_3
Observed	*cis*	37.3	33.0	23.3	15.2
Literature[68]	*cis*	37.7	33.3	23.3	15.2
Observed	*trans*	42.6	34.9	23.3	18.8
Literature[68]	*trans*	42.8	35.1	23.4	18.8

6-Bromohex-1-yne (106)

A two litre, three neck round bottom flask was fitted with a 500 ml, three neck, pressure equalising dropping funnel. On top of the dropping funnel was fitted a dry ice-ethanol condenser, which had a gas inlet at the base and a neck for a drying tube at the top. Nitrogen was connected to the flask, with which the apparatus was flushed and closed atop the condenser with a drying tube. Ammonia cylinder was connected to the bottom of the condenser. Anhydrous ether (500 ml) was added to the reaction flask, followed by 1,4-dibromobutane (.75 mole). The mixture was cooled to - 76°, then ammonia (≈ 500 ml) was distilled through the dropping funnel and into the ether solution. More ammonia (400 ml) was distilled into the dropping funnel.

Acetylene cylinder was now connected to the dropping funnel and acetylene bubbled into ammonia through a glass tube (5 mm inside diameter) which reached to within 1 cm near the bottom of the dropping funnel. Sodium wire (.25 mole) was added through the third neck of the dropping funnel at a rate which avoided formation of blue colour. Addition was stopped as soon as the blue colour began to appear, and resumed upon disappearance of blue

colour. When all the sodium was added to form acetylide anions with acetylene, the ammonia solution of acetylide ions was added dropwise to the magnetically stirred solution of dibromobutane. After addition the mixture was stirred for two hours, ammonia was evaporated, and water (500 ml) was added. The ether portion was separated, and the aqueous portion extracted with ether (2 x 100 ml). The combined ether extracts were washed with dillute HCl (2 x 200 ml), then with brine (2 x 200 ml), and dried over magnesium sulphate. The solvent was removed by fractional distillation. 6-Bromohex-1-yne (34.2 g, .21 mole) was separated from the excess starting material, and 1,7-dioctyne (1.8 g, .017 mole 6.8%) by fractional distillation under reduced pressure. The product was pure by g.l.c. analysis (A, 100°, N_2 50 ml/min).

Yield 84%.

B.p. 53°/6 mm.

I.R. 2000, 3250.

N.M.R. 1.6-2.4 (m, 7H), 3.4 (t, 2H, J=7Hz).

Analysis for C_6H_9Br: calculated C = 44.75, H = 5.63;
found C = 45.05, H = 5.36.

7-Bromohept-1-yne (107)

This bromide was prepared on a .15 mole scale from 1,5-dibromopentane and acetylide ions by the method described for preparation of 6-bromohex-1-yne (106).

Yield 78%.

B.p. 74°/13 mm.

I.R. 2080, 3210.

N.M.R. 1.3-2.5 (m, 9H), 3.4 (t, 2H, J=7Hz).

M.s. Molecular ions at 174 and 176, Mw = 175.

Analysis for $C_7H_{11}Br$: calculated C = 48.02, H = 6.33, Br = 45.64;
found C = 48.07, H = 6.38, Br = 45.61.

8-Bromo-oct-1-yne (108)

Preparation from 1,6-dibromohexane by the method employed in the synthesis of 6-bromohex-1-yne (106) on a .20 mole scale.

Yield 70%.

B.p. 60°/1.3 mm.

I.R. 2030, 3210.

N.M.R. 1.3-2.5 (m, 11H), 3.5 (t, 2H, J=7Hz).

M.s. Molecular ions at 188 and 190, Mw = 189.

Analysis for $C_8H_{13}Br$: calculated C = 50.81, H = 6.93, Br = 42.26;
found C = 51.15, H = 7.06, Br = 42.40.

Hex-1-yne (109)

Hept-1-yne (110)

Oct-1-yne (111)

These three alkynes were prepared from sodium acetylide and the corresponding 1-bromoalkanes by the method described for the synthesis of 6-bromohex-1-yne (106). 1.2 Equivalents of sodium acetylide was reacted with .05 mole of each bromide. The yields were quantitative.

Hex-1-yne:

B.p. 71°, literature[112] b.p. = 71.33°.

I.R. 2050, 3220.

N.M.R. 1.0 (t, 3H, J=7Hz), 1.2-1.9 (m, 6H, 2.3 (s, 1H).

Hept-1-yne:

B.p. 99°, literature[112] b.p. = 99.74°.

I.R. 2040, 3210.

N.M.R. 1.0 (t, 3H, J=7Hz), 1.2-1.8 (m, 8H), 2.3 (s, 1H).

Oct-1-yne:

B.p. 126°, literature[112] b.p. = 126.20°.

I.R. 2070, 3230.

N.M.R. 1.0 (t, 3H, J=7Hz), 1.2-1.9 (m, 10H), 2.3 (s, 1H).

Methylenecyclohexane (112)

Methylenecycloheptane (113)

Endocyclic methylene groups were introduced via the Wittig reaction of cyclohexanone and cycloheptanone with triphenylmethylphosphonium iodide on a .05 mole scale. The method described for the synthesis of methylenecyclopentane (4) was employed. The yields of distilled products were 30-40%.

Methylenecyclohexane:

B.p. 106°, literature[156] b.p. = 99-101°/740 mm.

I.R. 1650, 3000.

N.M.R. 1.6 (m, 6H), 2.2 (m, 4H), 4.7 (s, 2H).

Methylenecycloheptane:

B.p. 138°, literature[157] b.p. = 136-138°.

I.R. 1640.

N.M.R. 1.6 (m, 8H), 2.2 (m, 4H), 4.8 (s, 2H).

1,2-Epoxy-6-bromohexane (114)

m-Chloroperbenzoic acid (10.4 g, .06 mole) was dissolved in methylene chloride (150 ml). 6-Bromohex-1-ene (8.2 g, .05 mole) was added with a syringe over ten minutes. The mixture was stirred at 25° for one hour, then neutralised with 10% sodium sulphite. The organic portion was washed with 5% **sodium hydrogen** carbonate (3 x 50 ml), then with brine (2 x 50 ml). The solvent was removed by fractional distillation, and 1,2-epoxy-6-bromohexane (5.8 g, .03 mole) was distilled under reduced pressure. No impurities were detectable by g.l.c. analysis (D, 80°, N_2 50 ml/min; A, 135, N_2 55 ml/min).

Yield 60%.

B.p. 52°/.5 mm.

N.M.R. 1.3-2.2 (m, 6H), 2.2-2.4 (m, 1H), 2.7 (d, 2H, J=6Hz), 3.5 (t, 2H, J=7Hz).

M.s. Molecular ions at 178 and 180, Mw = 179.

Analysis for $C_6H_{11}Br$: calculated C = 40.25, H = 6.19, Br = 44.62;
found C = 40.43, H = 6.08, Br = 44.80.

Cyclopentylcarboxylic acid (115)

Carried by a steam of dry nitrogen carbon dioxide was passed through a tube (50 cm x 1.5 cm inside diameter) of blue silica gel crystals and bubbled into a solution of cyclopentylmagnesium bromide (.05 mole) in ether (150 ml). After four equivalents of carbon dioxide (9 g, dry ice) had been bubbled into the solution the mixture was worked up with dilute sulphuric acid. The organic portion was washed with brine (2 x 50 ml), and the product extracted with 5% sodium hydroxide (2 x 50 ml). The aqueous extract was

acidified with con. HCl, and the product extracted with ether (3 x 50 ml). The ether solution was dried over 4-A molecular sieves, and the solvent removed by fractional distillation. Cyclopentylcarboxylic acid (5.1 g, .045 mole) was distilled under reduced pressure.

Yield	90%.
B.p.	83°/1 mm, literature[158] b.p. = 215.5-216°.
I.R.	1710.
N.M.R.	1.4-2.2 (m, 8H), 2.5-3.0 (m, 1H), 11.9 (s, 1H).

Cyclopentylcarbinol (116)

Cyclopentylcarboxylic acid (4.6 g, .04 mole) was added slowly to a suspension of $LiAlH_4$ (1.5 g, .04 mole) in ether (100 ml). After addition the mixture was stirred for 3 hours, then dillute sodium hydroxide was added until white granular salts precipitated from the clear solution. The ether solution was decanted and the residue washed with more ether (2 x 15 m). After drying over 4-A molecular sieves the solvent was removed by fractional distillation, and the product (3.2 g, .032 mole) distilled under reduced pressure. No impurities were detectable by g.l.c analysis.

Yield	80%.
B.p.	64°/1.5 mm, literature[158] b.p. = 163.5°.
I.R.	3280.
N.M.R.	1.2-2.2 (m, 9H), 2.7 (s, 1H, D_2O exchange), 3.5 (d, 2H, J=7Hz).

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