The Regio- and Stereo- Chemistry of Some Alkenyl Radical Cyclizations

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by

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DECLARATION

The work described in this thesis is original and has not previously been submitted for a degree or diploma in any other University or College, and, to the best of my knowledge, does not contain material previously published or presented by another person, except where due reference is made in the text.

Carl H. Schiesser
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Any list of individuals, who have helped make my stay at the Research School of Chemistry fruitful and rewarding, must out of necessity be incomplete. I owe a great deal of thanks to many colleagues whose names do not appear here. A few individuals deserve special mention.

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"The time has come," the Walrus said,
"To talk of many things:
Of shoes- and ships- and sealing-wax-
   Of cabbages- and kings-
And why the sea is boiling hot-
   And whether pigs have wings."

Lewis Carroll, *The Walrus and the Carpenter.*
# TABLE OF CONTENTS

Declaration ............................................. i
Acknowledgements ..................................... ii
Abstract ................................................. vi

INTRODUCTION ......................................... 1

CHAPTER 1  
Development of the MM2/MNDO Method ............. 13

CHAPTER 2  
Application of the MM2/MNDO Method ............... 29  
i) ω-Alkenyl Radicals ....................................... 29  
ii) Alkenylaryl and Related Radicals ................. 33  
iii) Stereochemistry ........................................ 36  
iv) Application to Regio- and Stereo- Chemical Problems ................. 39

CHAPTER 3  
The Effect of Radical Geometry on the Rate and Stereochemistry of Ring Closure .... 46  
i) Conformational Acceleration- The Methylene cyclooctyl Radical .................. 46  
ii) The Effect of Olefin Geometry- E- and Z- isomerism ....................... 55

CHAPTER 4  
The Effect of Substitution at Position 1 in the Cyclization of Alkenyl Radicals ...... 66  
i) The Effect of Substituent in Non-Polar Solvent .................................. 66  
ii) The Effect of Solvent on the Cyclization of Substituted Hexenyl Radicals ......... 76  
iii) The Preparation of Radical Precursors and Product Standards ................. 82

EXPERIMENTAL ............................................ 102  
General .................................................. 103  
Compound Index ......................................... 105  
The Synthesis of Radical Precursors and Product Standards ......................... 108  
Kinetic Studies Using Tri- n- butyltin Hydride ..................................... 155
APPENDIX A
Kinetic Studies of the Reaction of the Radical Precursors with Tri-n-butyltin Hydride

a) Mathematical Considerations ...

b) Experimental Data ...

APPENDIX B
On the Analysis of Errors ...

NOTES AND REFERENCES ...

Table of Contents...

Page.

APPENDIX A
Kinetic Studies of the Reaction of the Radical Precursors with Tri-n-butyltin Hydride

a) Mathematical Considerations...

b) Experimental Data...

APPENDIX B
On the Analysis of Errors...

NOTES AND REFERENCES...

Page...
ABSTRACT

Free-radical cyclization methods have shown an increase in popularity with synthetic chemists over the last few years. This is mainly due to our increased knowledge of the regio- and stereochemical outcome of these reactions, and, in part, because the method offers an easy point of entry into some unusual and complex ring systems.

While the regio-preferences in the cyclization of alkenyl radicals have generally been explained in terms of steric factors operating in the exo and endo transition states, few hypotheses concerning the stereo-preferences, especially of 1-substituted alkenyl systems, have been suggested. Among these few are explanations incorporating polar transition states and secondary-orbital overlap in the required cis transition structures, leading to a favouring of the cis mode of ring closure.

This thesis presents experimental and theoretical discussions directed toward an understanding of the factors responsible for the regio- and stereochemistry of these cyclization reactions.

In the Introduction it will become apparent that previous theoretical work, using semi-empirical molecular orbital techniques, such as MINDO/3, was unable to model correctly these reactions. Chapter 1 details the development of a theoretical method specifically designed to model the ring closure of alkenyl radicals. It will be shown that the combination of molecular mechanics (MM2) and molecular orbital (MNDO) techniques can reproduce the outcome of these cyclization reactions with considerable success. The success of the technique also reinforces the view that steric factors are mostly responsible for directing these reactions.

In Chapter 2, the MM2/MNDO method is applied to a large number of systems. It will be shown that the method provides excellent qualitative and good quantitative agreement with available experimental data. The method also provides a useful tool for predicting the outcome of these reactions.

Chapters 3 and 4 deal with experimental considerations. In Chapter 3, which discusses the importance of radical geometry on the rate and stereochemistry of cyclization, it will be shown that favourable conformational effects, such as those found in the 6-methylene cyclodecyl radical, have an enormous effect on the rate of cyclization. It will also be shown that geometrical isomerism, such as found in E-
and Z- isomeric alkenyl radicals, has little effect on the rate or stereochemistry of ring closure.

Chapter 4 is devoted to a study of the stereochemistry of the cyclization of 1-substituted alkenyl radicals. It will become clear that while steric effects are important in these reactions, the stereochemistry is also affected by other factors. These factors tend to disfavour the trans mode of cyclization over the cis. Also discussed is the effect of solvent polarity, which has a large influence on the observed stereochemistry in some cases.
INTRODUCTION

Early this century Hey and Waters reported that hydrogen bromide adds in both Markovnikov and anti-Markovnikov senses to olefins\(^1\), depending upon whether or not the olefin has been exposed to air for prolonged periods. Although they suspected that the anti-Markovnikov process was radical in nature, they could not account for the observed reversal of regiochemistry.

\[
\begin{align*}
\text{CH}_3\text{CH}=\text{CH}_2 + \text{HBr} & \quad \rightarrow \quad \text{CH}_3\text{CHCH}_3 \quad \text{(Markovnikov)} \\
\text{CH}_3\text{CH}=\text{CH}_2 + \text{HBr} \quad \text{air} & \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \quad \text{(anti-Markovnikov)}
\end{align*}
\]

A few years later Mayo and Walling proposed that hydrogen bromide initially reacts with oxygen present in the olefin to produce atomic bromine which can react with the olefin by a chain process leading to the observed products\(^2\). They also developed the concept of radical stability (ie. tertiary > secondary > primary) to account for the regiochemistry observed in the radical process.

\[
\begin{align*}
\text{CH}_2=\text{CHR} + \text{CCl}_4 & \quad \rightarrow \quad \text{CCl}_3\text{CH}_2\text{CHR} \\
\text{CH}_2=\text{CHR} + \text{CHCl}_3 & \quad \rightarrow \quad \text{CCl}_3\text{CH}_2\text{CH}_2\text{R}
\end{align*}
\]

A short time later, Kharasch and co-workers published the first observation of a free-radical chain process leading to a 1:1 adduct rather than polymerization\(^3\). The regiochemistry could now be explained in terms of the concept developed by Mayo and Walling.

Since these early days many free-radical addition processes have been observed\(^4,5,6,7\) including additions to alkynes\(^8\), conjugated dienes\(^9\), heteroatomic systems\(^10\) and others\(^11\). These studies have shown that while the concept of radical stability is important, many other factors affect the outcome of these reactions and
that effects such as steric, polar and electronic need to be considered along with the concept of intrinsic reactivity\textsuperscript{12}.

About ten years ago Tedder and Walton, in review articles\textsuperscript{13}, stated that "no simple property could be used to determine the orientation of free-radical additions." They depend on "the complex interplay of polar, steric and bond strength terms." In 1982 Tedder proposed five rules governing radical addition reactions\textsuperscript{14}. In summary they were:

i) Radicals prefer to add at the unsubstituted end of a monosubstituted olefin. This is attributed to steric compression and is usually the dominant factor.

ii) Conjugation, at the remote end of the olefin, enhances the rate of addition. This is attributed to a lowering of the energy of the interacting LUMO orbital.

iii) Polarity is an important factor. Neutral or electron rich radicals, such as methyl, tend to be nucleophilic, whereas electron deficient radicals such as trifluoromethyl, are electrophilic. Additions of electrophilic radicals are retarded by electron withdrawing substituents on the olefin while these substituents enhance the additions of nucleophilic radicals.

iv) The regiochemistry of additions to polysubstituted olefins is primarily controlled by steric effects. If the steric effects are mutually opposed, then radical polarity is often the controlling factor.

v) Even when the regiochemistry is qualitatively controlled by steric factors, the magnitude of the effect can still be influenced by polar factors.

Recently Giese has formulated several rules\textsuperscript{15a}, which, while being fundamentally similar to those of Tedder, stress the difference between the effects of \(\alpha\) and \(\beta\) olefinic substituents. Essentially, Giese maintains that the \(\alpha\) substituent exerts both polar and steric effects while the \(\beta\) substituent exerts only polar effects on the rate of addition.

Despite this, it is still nevertheless difficult to predict the outcome of radical addition reactions. It is clear that the naïve approach, the view that these reactions follow the most exothermic path to afford the most stable product radical, is of limited use. As these reactions are believed to have early transition states\textsuperscript{15a,16} and as they are mostly irreversible, the stability of the product radical is largely
unimportant. The reactions are under kinetic rather than thermodynamic control, thus factors affecting the transition states leading to the various product radicals are the more important\textsuperscript{17}.

Predicting the outcome of these reactions is a formidable task that has challenged theoreticians for many years. It is not surprising, with recent advances in computer technology, that the last decade has provided a wealth of theoretical data aimed at our understanding of these radical addition processes, as well as attempting to predict the course of yet unknown reactions.

While the early work was of a semi-empirical nature employing computer methods such as MINDO/2\textsuperscript{18} and MINDO/3\textsuperscript{19}, the vast majority are \textit{ab initio} calculations. The restrictions placed on \textit{ab initio} calculations by computer hardware have necessitated the examination of "small" addition processes. Thus, there are many examples of the addition of atomic hydrogen to substituted olefins\textsuperscript{15b,20} and acetylenes\textsuperscript{20a,f,21} which, while being good systems for studying electronic effects in these additions, are clearly poor for studying steric effects. Fewer cases exist of other attacking species. Among these are examples of the addition of methyl\textsuperscript{20g,22} as well as vinyl\textsuperscript{20g}, phenyl\textsuperscript{23} and other\textsuperscript{20g} radicals to alkenes and alkynes. Even fewer works address the problem of stereochemistry\textsuperscript{24} or the effect of substituents\textsuperscript{25}.

Calculations of this type have been criticized for being inconsistent. An example of this is illustrated by Arnaud and co-workers\textsuperscript{22a,26} who state that "different techniques give contradictory predictions on the early or late character of the transition state" and go on to say that "there is no clear explanation for the variation of the relative reactivity of ethylenic and acetylenic substrates." Another criticism is directed toward the calculated activation energies for these reactions, which vary depending on the method used and are often significantly different from those observed experimentally\textsuperscript{19}.

The contribution to our understanding of these radical addition processes from theoretical studies cannot be denied. In many cases theory has supported experimental findings. For example, the calculations of Dewar and Olivella\textsuperscript{19} and Houk and co-workers\textsuperscript{20g} suggest that steric factors control the attack of methyl radical on alkylethylenes, which is in agreement with the rules proposed by Tedder\textsuperscript{14}. Furthermore, it is now generally agreed that the transition states involved in these reactions occur early along the reaction path\textsuperscript{27}.
More readily studied radical addition processes are those that occur by an intramolecular addition leading to cyclic products. These cyclization reactions occur under conditions in which the intermolecular process would not, due to the proximity of the attacking radicals to the double- or triple-bond. The most studied of these cyclizations is that of the 5-hexenyl radical (1) which cyclizes to give the cyclopentylmethyl (2) and cyclohexyl (3) radical with the former dominating by a factor of almost 100 at room temperature 17.28.29 (Scheme 1).

![Scheme 1](image)

Similar results were obtained with the 5-hexynyl (4) 30, the allenyl (5) 31 and the cyanoalkyl radical (6) 17.32. It is the regiochemical preference observed in these cyclizations which has prompted numerous elegant syntheses incorporating radical cyclization reactions. These include the cyclization of 2-(Δ3-cyclopentenyl)ethyl radical (7) to give norbornane 33 as well as the cyclization of the ω-alkynyl radical (8) leading to the highly functionalized 5-membered carbocycle (9) 34 (Scheme 2).

![Scheme 2](image)
Clive and co-workers have reported the synthesis of γ-lactones involving radical cyclizations\textsuperscript{35} while Curran, Chen and Kim have employed a novel radical cyclization involving iodine atom transfer as the chain propagating step\textsuperscript{36}, to give substituted cyclopentylidene iodides (Scheme 3). The method is dependent upon the reactivity difference between vinyl and alkyl radicals and iodides.

Porter and co-workers have shown that the free-radical cyclization methodology can not only be used to generate smaller rings, but can also be incorporated into the syntheses of macrocyclic systems\textsuperscript{37}. An example of this is the cyclization to give cyclooctadecanone (10) (Scheme 4).
Many examples of radical cyclization processes as key steps in the syntheses of natural products have appeared in the literature. Hart and co-workers have employed radical cyclizations as key steps in the syntheses of various pyrrolizidine alkaloids. An example is the cyclization of the alkynyl radical (11) in the synthesis of heliotridine and hastanecine (Scheme 5).

\[ \text{SiMe}_3 \quad \text{OAc} \quad \quad \rightarrow \quad \quad \text{Me}_3\text{Si} \quad \text{OAc} \]

Scheme 5

Curran and Rakiewicz have incorporated a tandem radical cyclization into the syntheses of linearly fused (triquinnane) cyclopentanoids (Scheme 6), while Winkler and Sridar have employed a transannular approach to the same system (Scheme 7).
Bakuzis and co-workers have devised a total synthesis of sativene (12) and copacamphene (13) using free-radical cyclization steps as depicted in Scheme 8.

\[ \text{Scheme 8} \]

Bachi et al. have incorporated the radical cyclization methodology in the construction of the 1-oxacepham and 1-oxahomocepham systems while Stork and Baine have demonstrated the usefulness of vinyl radical cyclizations in the synthesis of seychellene (14) (Scheme 9).

\[ \text{Scheme 9} \]

Porter and co-workers have incorporated the cyclization of the hydroperoxy radical (15) in their studies of prostaglandin model systems (Scheme 10) while Corey et al. have used radical methodology directed toward 8-epi-prostaglandin $F_{2\alpha}$.

\[ \text{Scheme 10} \]
Other radical cyclizations in synthesis have appeared in the literature. Over the last few years this methodology has become increasingly popular in syntheses requiring convenient methods for generating cyclic systems. This has largely come about as a result of our better understanding of free-radical cyclization processes. Work of people such as Julia, Beckwith, Ingold, Walling and others has largely dispelled the belief that radical reactions proceed with little or no control.

It is not surprising that earlier work in this area, guided by little more than the concept of radical stability, could offer no explanation for the observed regiochemistry. Thus, Lamb and co-workers, in their report on the decomposition of 6-heptenoyl peroxide to give primarily methylcyclopentane (2), were puzzled at the abundance of the thermodynamically less stable product. They state that: "It is difficult to justify the large yield of methylcyclopentane" and go on to say that "it is known that cyclohexane is slightly more stable than methylcyclopentane" and that "cyclohexaneformyl peroxide decomposes 34 times as rapidly in carbon tetrachloride at 70° as cyclopentylacetyl peroxide, again an indication that the cyclohexyl radical is more stable than the cyclopentylmethyl radical." Indeed it is well established that the cyclohexyl radical is more stable than the cyclopentylmethyl case. Then why does the 5-hexenyl radical cyclize predominantly in the exo (1,5-cyclization) mode?

If, as is the case with the acyclic radical additions, the transition states involved lie early along the reaction path, then, as previously discussed, the product stability is mostly unimportant, provided that the reaction is irreversible. The reactions are then under kinetic control and the stabilities of the various transition states leading to cyclization are the more important.
Julia has argued along these lines and has proposed that the endo (1,6-cyclization) transition structure (17) is destabilized by an unfavourable non-bonded interaction between the pseudo-axial hydrogen at C-2 and the syn hydrogen at C-6 which does not occur in the exo structure (16)\textsuperscript{51}.

Beckwith has also considered the transition structures involved in these cyclizations. He argues that "the strain engendered in accommodating the mandatory disposition of reactive centres within the transition complex for 1,6-ring closure outweighs those steric and thermochemical factors expected to favour the formation of the more stable possible product."\textsuperscript{17,52} He goes on to state that "inspection of models and statistical calculations reveal that the required disposition of (reacting) centres can be much more readily accommodated in the transition complex for 1,5-ring closure of 5-hexenyl than in that for 1,6-ring closure."

Factors controlling the stereochemical outcome of these cyclizations appear to be more subtle. Cyclization of the hept-6-en-2-yl (18) proceeds almost exclusively in the exo mode to give primarily cis-1,2-dimethylcyclopentane\textsuperscript{53} (Scheme 11).
Beckwith and co-workers\textsuperscript{17,53} have suggested that this is due to favourable secondary orbital overlap in the transition structure leading to the cis product (19a) which does not appear in the trans case. An alternative explanation rests on the premise that "the preferred cis cyclization reflects a favourable electrostatic interaction in a dipolar transition state"\textsuperscript{17} (19b).

A limited number of theoretical approaches to these cyclization reactions have appeared in the literature. The systems in question are clearly too large to examine with \textit{ab initio} methods, thus only semi-empirical studies of these reactions have been reported. Bischof has examined the cyclization of \(\omega\)-alkenyl radicals using the unrestricted Hartree-Fock (UHF) version of MINDO/3\textsuperscript{54,55}. The method gives activation energies considerably larger than those observed experimentally and fails to account for the degree of regioselectivity observed in the 5-hexenyl and 6-heptenyl\textsuperscript{56} systems. Bischof himself admits that "the calculated activation parameters quantitatively compare poorly with experimental findings"\textsuperscript{54b} and goes on to suggest that the hexenyl reactions are essentially entropically controlled, which is an hypothesis that has previously been put forward\textsuperscript{57}. Thus, Bischof's calculations suggest that there is no difference in the energies of activation (16.5 kcal mol\(^{-1}\) in each case) and a difference of 3.4 cal K\(^{-1}\) mol\(^{-1}\) in the entropies of activation for the exo and endo modes of cyclization of the 5-hexenyl radical. While the difference in the activation entropies compares favourably with the experimental value\textsuperscript{56} of 2.6 cal K\(^{-1}\) mol\(^{-1}\), it alone is clearly insufficient to account for the observed regioselectivity. Bischof's calculated data suggest a temperature independent exo/endo ratio of 5 which compares poorly with the observed ratio of 56 at 26° and over 100 at 80°. The suggestion that the reaction is essentially entropically controlled, from calculated data that agree poorly with experimental findings, is a clear indication of the inability of the method to reliably predict the thermochemical consequences of the reactions in question. It is also interesting to note that while the hexenyl system is predicted to be entropically controlled, Bischof's calculations suggest that the heptenyl system is under enthalpic control.

Recently Canadell and Igual have examined both the regio- and stereochemistry of the cyclization of some substituted 5-hexenyl radicals using
MINDO/3\textsuperscript{58}. They too explain the gross regiochemical control on entropic factors and fail to account for the observed preferential trans cyclization of 2-methylhex-5-enyl radical\textsuperscript{59}.

The semi-empirical methods have met with limited success in this area. More recently Poblet and co-workers have investigated the cyclization of alkenylsilyl radicals using MINDO/3\textsuperscript{60}. In accordance with experimental observations\textsuperscript{61}, they find that dimethylpent-4- enylsilyl (20) and but-3- enylsilylmethyl (21) radicals cyclize with strong endo preference, however, their activation energies are quantitatively overestimated.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure.png}
\end{center}

In the paper by Canadell and co-workers\textsuperscript{58}, the cyclization of 5-methylhex-5-enyl radical, in accordance with experimental observations\textsuperscript{62}, is reported to cyclize preferentially endo.

Following the suggestion that these radical cyclizations are indeed controlled mainly by steric factors, it would seem appropriate to use a theoretical method designed to evaluate strain energies. Allinger's MM2 version\textsuperscript{63} of the force-field approach\textsuperscript{64} is such a method. There have been few attempts to use this method to obtain transition state energies. Noteable exceptions include the calculations of the energies of the transition structures for solvolysis reactions\textsuperscript{65}, borohydride reduction of ketones\textsuperscript{66} and others\textsuperscript{67}. One of the more sophisticated approaches has been that of Houk and co-workers who have combined force-field and \textit{ab initio} calculations to predict the selectivity in the hydroboration of olefins\textsuperscript{68}. Their method involves the determination of \textit{ab initio} (3-21G) transition structures for the hydroboration of smaller olefins, such as ethylene and propylene, with reagents such as borane. The transition structure dimensions are then used in larger model systems and strain energies determined, with the assumption that substitution has little or no effect on the transition state geometry.
The current work, reported here, is aimed toward a better understanding of the factors affecting both the regio- and stereo-chemistry of free-radical cyclization reactions. This has been achieved in two ways. Firstly from a theoretical approach. It is clear that most theoretical approaches have had little success in this area. The development of a theoretical method designed with these cyclization reactions in mind was necessary.

Chapters 1 and 2 of this work describe the development and application of such a method. The method, which involves the combinations of force-field and molecular-orbital techniques, while being fundamentally similar to, but developed independently of, the method of Houk et al. has been successful at reproducing experimental observations and useful in the design of syntheses based on free-radical cyclization methodology. Its use in the resolution of regio- and stereo-chemical problems will be discussed.

Secondly, from an experimental approach. Chapters 3 and 4 of this work are directed toward the study of the cyclization of 1-substituted hexenyl type radicals. The preparation of the required radical precursors as well as their decomposition and subsequent rearrangement will be discussed in detail.

These radicals cyclize almost exclusively in the exo mode to give the cis- and trans- disubstituted products. The cis/trans ratio is dependent upon the substituents and, in some cases, on the nature of the solvent. The factors affecting the stereochemical outcome of these reactions are more subtle than those affecting the regiochemistry. Combinations of theoretical and experimental studies of these rearrangements have been invaluable in the development of our understanding of the important factors involved in directing the cyclization of alkenyl radicals.
CHAPTER 1

Development of the MM2/MNDO Method.

Molecular Mechanics may be thought of as modelling molecules as if the atoms contained were "joined by mutually independent springs, restoring natural values of bond lengths and angles." The method assumes a "Hooke's Law" relationship for bond length and angle functions:

\[ V_r = \frac{k_r}{2}(r - r_0)^2 \] \hspace{1cm} ... 1.1

\[ V_\theta = \frac{k_\theta}{2}(\theta - \theta_0)^2 \] \hspace{1cm} ... 1.2

where \( V_r \) and \( V_\theta \) are the bond length and angle potentials, \( k_r \) and \( k_\theta \) are the required force constants while \( r \) and \( \theta \) represent the bond length and angle respectively (the subscript "o" denotes "equilibrium").

The torsional potential is modelled by a trigonometric relationship:

\[ V_\omega = \frac{V_1}{2}(1 + \cos \omega) + \frac{V_2}{2}(1 - \cos 2\omega) + \frac{V_3}{2}(1 + \cos 3\omega) \] \hspace{1cm} ... 1.3

where \( V_1, V_2 \) and \( V_3 \) are the torsional parameters which define the torsional potential \( V_\omega \) for the dihedral angle \( \omega \).

The total potential \( V \) is the sum of these individual potentials over all degrees of freedom and also includes a Van der Waals term which is approximated by a specific Buckingham Potential:\n
\[ V_{VDW} = 2.90 \times 10^5 \varepsilon \, e^{-12.5d/d_0} - 2.25 \varepsilon \left( \frac{d_0}{d} \right)^6 \] \hspace{1cm} ... 1.4

where \( d \) is the interatomic distance.
Thus:

\[ \mathbf{V} = \sum \mathbf{V}_r + \sum \mathbf{V}_\theta + \sum \mathbf{V}_\phi + \sum \mathbf{V}_{\text{VDW}} \]  

The constants \( r_0 \), \( \theta_0 \), \( V_1 \), \( V_2 \), \( V_3 \), \( \varepsilon \) and \( d_0 \) for each molecular mode define the Force Field. The Force Field is fully parameterized\(^{64}\). Differing Force Fields lead to differing Molecular Mechanics methods\(^{64}\).

For this work, strain energies were calculated using Allinger’s Molecular Mechanics (MM2) program\(^{63}\) with 1977 Force Field\(^{63,64}\). Structures were optimized using a Newton-Raphson minimization technique\(^{64}\).

The form of equation 1.1 and the MM2 definition of bonding\(^{63}\) do not allow the method to determine transition states in bond forming/breaking reactions.

Cyclization of the hexenyl radical (1) is clearly a reaction of the bond forming/breaking type. The _exo_ and _endo_ transition structures (16, 17) can therefore not be found using MM2 calculations.
MM2 can, however, determine the strain energy of these transition structures if the reacting centres (1,5,6) are fixed at the correct geometry for the required transition structure, and the remaining geometry optimized. The question then arises as to what the correct geometry of the reacting centres is.

For the simple addition of methyl radical to ethylene, there is general agreement that the reacting centres lie at the vertices of a slightly obtuse triangle on a plane orthogonal to the nodal plane of the $\pi$ system (22). Accurate dimensions are available from ab initio calculations. It is unlikely that precisely the same geometry would apply to the hexenyl transition structures since the arrangement of reactive centres would be affected to an extent by the strain incorporated into the cyclic system. This expectation was confirmed when the MM2 method was applied to model exo and endo transition structures in which C(1), C(5) and C(6) were fixed at positions similar to those found in the ethylene/methyl radical case (viz: C(1)-C(5) = 2.40 Å, C(5)-C(6) = 1.35 Å, C(1)C(5)C(5) = 107° for exo, same dimensions for the endo interacting centres). The geometry of the rest of the molecule was optimized using MM2. The preliminary calculations show that the exo transition structure is lower in energy than the endo, but that the difference has been overestimated by more than 4 kcal mol$^{-1}$ (6.1 kcal mol$^{-1}$ vs the experimental value of 1.72 kcal mol$^{-1}$).

A more realistic estimate of the dimensions of the intimate array of reactive centres was needed. Hexenyl itself is clearly too large to perform reliable ab initio calculations on. We chose, therefore, to determine the exo and endo transition state geometries using a semi-empirical molecular orbital technique.

Until very recently, MNDO (Modified Neglect of Diatomic Overlap) was the latest in a series of semi-empirical molecular orbitals reported by Dewar and co-workers. MNDO is based on the NDDO approximation of the Roothaan-Hall Self Consistent Field-Linear Combination of Atomic Orbital-Molecular Orbital (SCF-LCAO-MO) method, whereas previous methods such as MINDO/3 are based on the INDO approximation also developed by Pople and co-workers.

---

# At this stage only MINDO/3 and STO-3G geometries were available.

## Dewar and co-workers have reported a "third generation" method "Austin Method 1" (AM1) based on the NDDO approximation.
Dewar states that there is "greater theoretical justification for NDDO than for INDO" and that improvements in calculated heats of formation and geometries, especially relating to bond angles, and the more reliable ordering of molecular orbitals are areas in which MNDO is often superior to its predecessor, MINDO/3.

Many systems have been studied using the MNDO method. Generally, a halving in the absolute error of the ground-state heats of formation when compared to MINDO/3 has been observed.

Extension of the MNDO method to an Unrestricted Hartree-Fock (UHF) version suitable for open-shell systems has lead to the successful modelling of the ground states of various radical species.

Modelling transition states, however, is a less certain aspect of the capabilities of the MNDO method. Almost no experimental data exist for the geometries of transition states. Thus, MNDO transition structures can only be compared with those from ab initio methods and only for relatively small systems. Schroeder and Thiel have shown MNDO to be capable of reproducing the qualitative features of potential surfaces with a good degree of correlation with ab initio techniques. Their comparison did not, however, look at radical addition reactions.

In order to ascertain how well MNDO is capable of modelling radical addition transition states, the ethylene/methyl radical system was investigated. It is curious to note that an extensive search of the literature failed to find a study of this system by MNDO.

All MNDO calculations in this work were performed using the standard MNDO-UHF program. All geometries were optimized using the Davidon-Fletcher-Powell algorithm for minima and the gradient-norm minimization technique for transition states. If the gradient-norm procedure failed to converge, transition structures were obtained using the reaction-coordinate method, i.e.: by varying the distance between the radical centre and the terminus of the olefin being attacked to obtain a path of minimum energy with respect to all other internal coordinates. The transition state corresponds to the point of maximum energy along this path.
When the gradient-norm algorithm converged, a force constant analysis\textsuperscript{73b} was performed. The existence of exactly one negative eigenvalue in the molecular force constant matrix was proof of transition state\textsuperscript{81}.

Table 1 compares the MNDO-UHF results for the ethylene/methyl radical transition state (23) with those obtained by other molecular orbital methods.

<table>
<thead>
<tr>
<th>METHOD</th>
<th>r (Å)</th>
<th>θ (°)</th>
<th>R (Å)</th>
<th>ΔE# \textsubscript{calc} (kcal mol\textsuperscript{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>MINDO/3-UHF\textsuperscript{19}</td>
<td>2.36</td>
<td>108.8</td>
<td>1.327</td>
<td>7.9</td>
</tr>
<tr>
<td>MNDO-UHF\textsuperscript{a}</td>
<td>2.22</td>
<td>104.7</td>
<td>1.376</td>
<td>13.7</td>
</tr>
<tr>
<td>STO-3G\textsuperscript{b,71}</td>
<td>2.43</td>
<td>105.3</td>
<td>1.375</td>
<td>5.0</td>
</tr>
<tr>
<td>3-21G\textsuperscript{b,20g,71}</td>
<td>2.27</td>
<td>107.9</td>
<td>1.375</td>
<td>5.4</td>
</tr>
<tr>
<td>4-31G\textsuperscript{22a}</td>
<td>2.23</td>
<td>108.6</td>
<td>1.381</td>
<td>8.7</td>
</tr>
<tr>
<td>6-31G\textsuperscript{*b,71}</td>
<td>2.25</td>
<td>109.1</td>
<td>1.382</td>
<td>9.4</td>
</tr>
</tbody>
</table>

\[ΔE\# \textsubscript{expt} = 7.7 \text{ kcal mol}^{-1}\textsuperscript{c}\]

a. This work.

b. Basis set superposition error\textsuperscript{83} taken into account.

c. See reference 13.

Table 1. Comparison of MNDO with other molecular orbital methods for the ethylene/methyl radical transition state.
Table 2. Comparison of MNDO and MINDO/3 transition structures for the exo and endo cyclization modes of the 5-hexenyl radical.
While the MNDO calculated activation energy of 13.7 kcal mol\(^{-1}\) compares poorly with the experimental value of 7.7 kcal mol\(^{-1}\) for this reaction, the transition state geometry agrees quite well with the highest level of \textit{ab initio} calculation available (6-31G\(^*\)). The internuclear separation \(r\) of 2.22Å compares favourably with the 6-31G\(^*\) value of 2.25Å. The bond length \(R\) is also in good agreement (1.376Å vs 1.382Å). It is clear that MINDO/3 performs considerably more poorly in these areas. Bond angles calculated at all levels agree fairly closely.

These results encouraged the investigation of the 5-hexenyl system by the MNDO method. The MINDO/3 geometries for the \textit{exo} and \textit{endo} transition states as calculated by Bischof\(^4\) were of doubtful value in light of the results obtained for the ethylene/methyl radical system. Unfortunately, the gradient-norm algorithm failed to converge when the \textit{exo} and \textit{endo} transition structures for the cyclization of the 5-hexenyl radical were being determined. Therefore, as previously discussed, the transition structures were determined using the reaction-coordinate approach.

Table 2 compares the MNDO transition structures for the \textit{exo} and \textit{endo} modes of cyclization of the 5-hexenyl radical with those obtained using MINDO/3. Two major improvements over MINDO/3 are apparent. Firstly, MNDO gives a more realistic value for the bond length \(R\) in each case. Secondly, while still overestimating the activation energy for the cyclizations, MNDO, in accordance with experimental observations\(^{28c,56,59b}\), clearly predicts the \textit{exo} mode to be the more favoured for enthalpic reasons, which is an effect that MINDO/3 was insensitive to. Bischof had explained the \textit{exo} predominance on entropic grounds\(^5\).

The MNDO method was also applied to the \textit{exo} and \textit{endo} transition states for the cyclization of 6-heptenyl and 7-octenyl radicals. The dimensions of the intimate array of reactive centres for the two radicals is given in Table 3, along with the 5-hexenyl geometry.

It is interesting to note that there is little variation in the values of \(r\) and \(R\), the interatomic distances, but \(\theta\) appears to be rather sensitive to ring size.

These dimensions were then incorporated into model transition structures and the strain energy of their most stable conformers determined by the MM2 method. Parameters for carbon-centred \(\pi\) radicals were developed by Beckhaus and Ruchart\(^8\) and incorporated into the MM2 Force Field. Figure 1 displays the
structures of lowest strain energy for the exo and endo cyclization modes of 5-hexenyl, 6-heptenyl and 7-octenyl radicals. The recognition of the most stable structures for 5-hexenyl (16,17) and 6-heptenyl exo (26) presented no problems. They resemble the chair form of cyclohexane. The endo structure for 6-heptenyl can assume a number of low energy conformations. MM2 calculations on each of these showed the most stable conformer to be a modified chair structure (27), in contrast to the twist-chair conformation which is the most stable form of cycloheptane64.

![Image of structures](image.png)

**Table 3.** Dimensions\(^a\) of the Intimate Array of Reactive Centres in Cyclic Transition Structures.

<table>
<thead>
<tr>
<th></th>
<th>Exo Structure (24)</th>
<th>Endo Structure (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>r</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>2.20</td>
<td>1.388</td>
</tr>
<tr>
<td>4</td>
<td>2.20</td>
<td>1.392</td>
</tr>
<tr>
<td>5</td>
<td>2.20</td>
<td>1.393</td>
</tr>
</tbody>
</table>

\(^a\) r and R in Å, θ in degrees.

The 7-octenyl structures (28,29) could also adopt a number of conformations. The lowest energy form of the exo structure assumed a cycloheptane-like chair structure (28) while the endo structure (29) appeared different from the standard low-energy forms of cyclooctane64.

In order to obtain results which could realistically be compared with experiment, it was necessary to subtract, from the total strain energy, the strain energy component associated with the movement of the three reacting centres along the reaction coordinate. This is compensated for by favourable electronic interactions which are not included in the MM2 treatment.
Figure 1. Model transition structures for the ring closure of \(\omega\)-alkenyl radicals.
Therefore, subtraction in each case of the strain energy associated with the close approach of the radical centre and the olefinic terminal carbon (C(1)-C(5) in hexenyl exo), and the stretching of the olefinic bond (C(5)-C(6) in hexenyl) from the total MM2 strain energy gave values of $E_s$, the strain energy associated with the transition structure. Subtraction, in each case, of $E_s$(ground), the radical ground-state strain energy, gave values of $\Delta E_s$, the MM2 calculated strain energy component of the activation energy. These are compared in Table 4 for the exo and endo cyclization modes of the 5-hexenyl (1), 6-heptenyl (30) and 7-octenyl (31) radicals.

Inspection of Table 4 clearly reveals that the calculated values for the exo and endo modes of cyclization of the hexenyl radical (1) mirror experimental findings\textsuperscript{28c,56,59b} in accordance with the stereoelectronic hypothesis\textsuperscript{17,52}. The method predicts that the transition state leading to the exo product (16) is more stable than that leading to the endo product (17) by 2.8 kcal mol\textsuperscript{-1}. This difference is slightly larger than that observed experimentally (1.7 kcal mol\textsuperscript{-1}) but this is not unexpected as the method makes no allowance for the more favourable delocalization of spin onto a secondary centre in the endo structure (17).

### Table 4.
Comparison between transition structure strain energies ($\Delta E_s$)\textsuperscript{a} as calculated by MM2 with experimental data\textsuperscript{a} for the cyclization of 5-hexenyl (1), 6-heptenyl (30) and 7-octenyl (31) radicals.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_s$(ground)</th>
<th>$\Delta E_s$(exo)</th>
<th>$\Delta E_s$(endo)</th>
<th>$E_{act}$(exo)</th>
<th>$E_{act}$(endo)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>7.5</td>
<td>10.3</td>
<td>6.8</td>
<td>8.5</td>
<td>28c,56,59b</td>
</tr>
<tr>
<td>30</td>
<td>3.7</td>
<td>9.1</td>
<td>10.8</td>
<td>7.9</td>
<td>8.8</td>
<td>28c,56</td>
</tr>
<tr>
<td>31</td>
<td>4.0</td>
<td>15.0</td>
<td>13.0</td>
<td>b</td>
<td>9.6</td>
<td>56,85c</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Energies in kcal.mol\textsuperscript{-1}.
\textsuperscript{b} Values not available.
\textsuperscript{c} Recent experiments\textsuperscript{85} indicate that the products from this reaction were wrongly identified in earlier work; the values have been transposed accordingly.
The calculations also correctly predict the regiochemistry for the cyclization of the 6-heptenyl radical (30), though over-estimating the activation energy difference between the exo and endo modes. It is significant, however, that the calculations mirror experiment in that the difference in the calculated values of $\Delta E_s$ for the exo and endo modes of cyclization for the heptenyl radical are smaller than those for hexenyl.

The calculated data also indicate that the 7-octenyl radical (31) should cyclize predominantly in the endo mode. This is contrary to earlier experimental findings\textsuperscript{56} and has prompted the re-investigation of this system. Recent experimental data\textsuperscript{85} have indicated that the products from this reaction were wrongly identified and that the reaction does indeed proceed in the endo fashion. This outcome demonstrates the predictive power of the MM2 method.

The calculations allow closer examination of the hypothesis developed by Julia\textsuperscript{51} (see introduction), namely that the 5-hexenyl endo transition structure (17) is destabilized by an unfavourable non-bonded interaction between the pseudo-axial hydrogen at C-2 and the syn hydrogen at C-6.

![Diagram](image)

Inspection of the data available from the MM2 calculations reveals this interaction to be less than 0.1 kcal mol$^{-1}$. This leads to the conclusion that it plays no important role in directing the regiochemistry of this reaction.

In light of recent reports of the cyclization of alkenyl-vinyl\textsuperscript{86}, azetidinonyl\textsuperscript{87} and pyrrolidinonyl\textsuperscript{38b,87} radicals, it was of interest to see whether reliable strain energy values could be obtained for the corresponding transition structures.

The geometry of the intimate array of reactive centres in the transition structures for the exo (32) and endo (33) modes of cyclization of the hexa-1,5-dien-1-yl radical (34) as well as the geometry for the exo (35) and endo (36) modes of
cyclization of the N-(3-butenyl)azetidinonyl (37) and N-(3-butenyl)pyrrolidinonyl (38) radicals were determined by MNDO in the usual way. As was the case with the other cyclizations, convergence of the gradient-norm algorithm could not be achieved. It should be noted that there are two exo modes of cyclization of the heterocyclic radicals (37,38). Only the exo-syn transition structure was determined for 37 and the exo-anti for 38. It is unlikely⁵⁸ that the geometry of the reactive centres would differ significantly for the other exo structure in each case.

![Chemical structures](image)

Table 5. Dimensions$^a$ of the intimate array of reactive centres in cyclic transition structures.

<table>
<thead>
<tr>
<th>Structure</th>
<th>r</th>
<th>R</th>
<th>$\theta$</th>
<th>mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>2.25</td>
<td>1.377</td>
<td>98.3</td>
<td>exo</td>
</tr>
<tr>
<td>33</td>
<td>2.35</td>
<td>1.373</td>
<td>91.8</td>
<td>endo</td>
</tr>
<tr>
<td>35a</td>
<td>2.15</td>
<td>1.395</td>
<td>103.3</td>
<td>exo</td>
</tr>
<tr>
<td>35b</td>
<td>2.15</td>
<td>1.396</td>
<td>110.4</td>
<td>exo</td>
</tr>
<tr>
<td>36a</td>
<td>2.20</td>
<td>1.391</td>
<td>93.3</td>
<td>endo</td>
</tr>
<tr>
<td>36b</td>
<td>2.20</td>
<td>1.390</td>
<td>94.6</td>
<td>endo</td>
</tr>
</tbody>
</table>

$^a$ r and R in Å, $\theta$ in degrees.
Table 5 lists the geometry of the intimate array of reactive centres in the transition structures for the exo and endo modes of cyclization of 34, 37 and 38.

It is interesting to note that the attack distances $r$ in structures 32 and 33 are longer than those for the corresponding 5-hexenyl cases (16, 17). This is due to the greater steric demand required to orientate the radical $\sigma$ orbital as opposed to the $p$ orbital in hexenyl, as well as the more efficient orbital overlap achieved by the $\sigma$ orbital at greater distances due to its directional properties. This is in contrast to the somewhat shorter distances observed in the heterocyclic exo structures (35). The MNDO calculations clearly indicate that in the transition state, the free electron, apart from being delocalized onto the olefinic moiety, is extensively delocalized onto the carbonyl of the heterocyclic ring. Therefore, to obtain efficient orbital overlap at the transition state, the distance $r$ must necessarily be shorter than in the corresponding hexenyl structure. The endo structure, on the other hand, must balance the degree of overlap achieved at the transition state with the strain encountered in achieving the required geometry in that transition structure. It is fortuitous but not surprising that the two effects tend to balance, resulting in a distance $r$ of 2.20Å, the same value as observed in the hexenyl case.

These dimensions were then incorporated into model transition structures and the strain energies of their most stable conformers determined by MM2 in the usual way. Since no parameters for conjugated or $\sigma$ carbon radicals were available, those for an ordinary $sp^2$ centre were employed. The results are summarized in Table 6. The optimized geometries are depicted in Figure 2.

The directionality of the $\sigma$ radical in the exo structure (39) was maintained by ensuring the planarity of atoms 1, 2, 5 and 8. Similar constraints were enforced in the endo structure (40). To ensure the correct geometry in the azetidinonyl transition structures (41, 42, 43), the geometry of the nitrogen atom, which is planar in the starting radical (37) but not in the product, was fixed as suggested by the MNDO calculations. Thus, in structures 41 and 42 the dihedral angle (8, 1, 2, 3) was fixed at 140° while the equivalent angle in structure 43 was held at 160°. No such constraints were needed in the pyrrolidinonyl structures (44, 45, 46) as both starting and product radical nitrogen geometries are planar.
Figure 2. The MM2 optimized transition structures for the various modes of cyclization of the 1,5-hexadien-1-yl (34), N-(3-butenyl)azetidinonyl (37) and N-(3-butenyl)pyrrolidinonyl (38) radicals.
Table 6. Values of $\Delta E_s$ as calculated by MM2 for the exo and endo modes of cyclization of the 1,5-hexadien-1-yl (34), N-(3-butenyl)azetidinonyl (37) and N-(3-butenyl)pyrrolidinonyl (38) radicals.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_s$(ground)</th>
<th>$\Delta E_s$(exo)</th>
<th>$\Delta E_s$(endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>2.0</td>
<td>5.6</td>
<td>7.0</td>
</tr>
<tr>
<td>37</td>
<td>60.3</td>
<td>19.2 (syn)</td>
<td>17.2 (anti)</td>
</tr>
<tr>
<td>38</td>
<td>3.6</td>
<td>8.2 (syn)</td>
<td>8.2 (anti)</td>
</tr>
</tbody>
</table>

a. Strain energies in kcal.mol$^{-1}$.

Unfortunately, no kinetic data are available for the cyclization of 34, 37 and 38. Comparison in a qualitative fashion is however possible.

The 1,5-hexadien-1-yl radical (34) is observed to cyclize fast and exclusively in the exo mode$^{30b}$. This is in agreement with the calculated results.

Analogues of the azetidinonyl radical (37) have been observed by Boate$^{87}$ to cyclize exclusively in the endo mode, again in agreement with the MM2 data. It is unlikely that the value of $\Delta E_s$ of 17.2 kcal mol$^{-1}$ for this reaction accurately reflects the activation energy, but is more likely to indicate deficiencies in the MM2 treatment of 4-membered rings, in particular $\beta$-lactam systems.

Hart and co-workers$^{38b,88}$ have reported that analogues of the pyrrolidinonyl radical (38) cyclize to give both exo and endo cyclized products, also in agreement with the MM2 data.

The transition structures as determined by this method ($16,17,26-29,39-46$) can now be used as parent structures in the investigation of substituent effects in these cyclization reactions. Substitution at positions along the cyclizing chain is unlikely to affect the geometry of the intimate array of reactive centres to a significant extent. This hypothesis is supported by the calculations of Canadell and Igual$^{58}$ who report only minor deviations from the 5-hexenyl transition state geometries for the 2- and 5-methyl substituted cases.
SUMMARY

The discussion in this chapter has focussed on the development of the MM2/MNDO method for the study of free-radical cyclization reactions. It has been shown that incorporation of the MNDO determined geometries of the interacting centres in the transition states for the exo and endo modes of cyclization of a number of parent alkenyl radicals into MM2 model transition structures, has been successful in predicting the outcome of these ring-closures. It has been shown that the method provides excellent agreement with the available experimental data.

It has also been shown that the method provides predictions useful in the identification of the components of the product mixtures observed in these reactions. The example given is that of the 7-octenyl radical (31) which is predicted to cyclize preferentially in the endo mode. Experimental re-investigation of this system has revealed the initial product assignment to have been incorrect, agreeing with the data available from the MM2/MNDO method.

Application of the method to a wide selection of cyclization reactions will be the focus of Chapter 2.
CHAPTER 2

Application of The MM2/MNDO Method.

The previous chapter provided an in-depth discussion of the development of the MM2/MNDO method for the study of radical cyclization reactions. It was seen that the method gives good agreement between theory and experiment for the parent systems discussed.

This chapter aims to provide an idea of the scope of the method. It will be shown that the method can be successfully applied in the study of both regio- and stereo-chemical problems to a large number of systems. Sections of this work have recently been published.89

i. ω-Alkenyl Radicals.

Having concluded that the theoretical method can successfully model the cyclization of the ω-alkenyl radicals (1,30,31), we focussed attention on substituted ω-alkenyl systems. Table 7 compares the rates and regiochemistry of a number of substituted alkenyl radical ring closures as calculated by MM2 with the available experimental data. For each of the radicals (47-58) the intimate arrays of reactive centres for the exo and endo transition structures were held at the dimensions given for the corresponding parent structures as discussed in Chapter 1. The values of $\Delta E_s$ were then obtained in the usual way. For the 5-hexynyl radical (59), the same angles $\theta$ and interatomic distances $r$ as for the hexenyl transition structures (Table 3) were employed, but the C(5)-C(6) distance $R$ was set to 1.215 Å.22a. Theoretical studies suggest that $\theta$ should be larger for additions to acetylenes than for additions to olefins. If this were correct and $\theta$ were increased for the cyclizations of 59, the value of $\Delta E_s$ for the exo mode would be raised slightly, but $\Delta E_s$ for the endo mode would be raised to a much greater extent.

Inspection of Table 7 reveals that while the values of $\Delta E_s$ are generally larger than the corresponding activation energies, there is satisfactory qualitative agreement between theory and experiment. Consequently, the method gives a high degree of correlation between the order of reactivity as predicted by the values of $\Delta E_s$ and the available kinetic data. Thus, the relative order of the rate constants for
Table 7. Comparison between transition structure strain energies, $\Delta E_s^a$, and experimental data$^a$ for the cyclization of various substituted $\omega$-alkenyl and related radicals.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_g$ (ground)</th>
<th>$\Delta E_s$ (exo)</th>
<th>$\Delta E_s$ (endo)</th>
<th>$k_{25}$ (exo)</th>
<th>$k_{25}$ (endo)</th>
<th>$E_{AC}$ (exo)</th>
<th>$E_{AC}$ (endo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>7.4</td>
<td>10.2</td>
<td>$2.3 \times 10^5$</td>
<td>$4.1 \times 10^3$</td>
<td>6.8</td>
<td>8.5</td>
<td>28c,56,59b</td>
</tr>
<tr>
<td>30</td>
<td>3.7</td>
<td>9.1</td>
<td>10.8</td>
<td>$5.4 \times 10^3$</td>
<td>$7.5 \times 10^2$</td>
<td>7.9</td>
<td>8.8</td>
<td>28c,56,59b</td>
</tr>
<tr>
<td>31</td>
<td>4.0</td>
<td>15.0</td>
<td>13.0</td>
<td>$&lt;70$</td>
<td>$1.2 \times 10^2$</td>
<td>a</td>
<td>9.6</td>
<td>56,85</td>
</tr>
<tr>
<td>47</td>
<td>3.4</td>
<td>9.7</td>
<td>9.5</td>
<td>$5.3 \times 10^3$</td>
<td>$9.3 \times 10^3$</td>
<td>8.5</td>
<td>8.0</td>
<td>62,90,91</td>
</tr>
<tr>
<td>48</td>
<td>2.9</td>
<td>7.0</td>
<td>10.2</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>4.8</td>
<td>6.7</td>
<td>13.5</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td>b</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>4.5</td>
<td>7.0</td>
<td>9.2</td>
<td>$3.5 \times 10^5$</td>
<td>$6.0 \times 10^3$</td>
<td>b</td>
<td>b</td>
<td>62,90,91</td>
</tr>
<tr>
<td>51</td>
<td>6.6</td>
<td>6.0</td>
<td>9.7</td>
<td>$3.6 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>5.4</td>
<td>b</td>
<td>59b</td>
</tr>
<tr>
<td>52</td>
<td>6.5</td>
<td>6.1</td>
<td>9.2</td>
<td>$5.1 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>5.1</td>
<td>b</td>
<td>59b</td>
</tr>
<tr>
<td>53</td>
<td>7.0</td>
<td>6.8</td>
<td>8.3</td>
<td>$3.2 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>5.5</td>
<td>b</td>
<td>59b</td>
</tr>
<tr>
<td>54</td>
<td>6.0</td>
<td>6.8</td>
<td>11.1</td>
<td>$8.5 \times 10^6$</td>
<td>$&lt;1 \times 10^5$</td>
<td>4.1</td>
<td>b</td>
<td>92</td>
</tr>
<tr>
<td>55</td>
<td>5.4</td>
<td>7.1</td>
<td>10.6</td>
<td>$2.5 \times 10^4$</td>
<td>$5.1 \times 10^2$</td>
<td>8.4</td>
<td>10.1</td>
<td>93</td>
</tr>
<tr>
<td>56</td>
<td>-0.4</td>
<td>9.8</td>
<td>6.7</td>
<td>$8.7 \times 10^2$</td>
<td>$1.8 \times 10^3$</td>
<td>b</td>
<td>b</td>
<td>94</td>
</tr>
<tr>
<td>57</td>
<td>-1.4</td>
<td>9.4</td>
<td>7.3</td>
<td>c</td>
<td>c</td>
<td>b</td>
<td>b</td>
<td>94</td>
</tr>
<tr>
<td>58</td>
<td>-0.3</td>
<td>7.4</td>
<td>9.7</td>
<td>$7.4 \times 10^4$</td>
<td>$5.0 \times 10^3$</td>
<td>b</td>
<td>b</td>
<td>94</td>
</tr>
<tr>
<td>59</td>
<td>2.3</td>
<td>7.5</td>
<td>14.7</td>
<td>$2.8 \times 10^4$</td>
<td>$&lt;600$</td>
<td>8.3</td>
<td>b</td>
<td>92</td>
</tr>
</tbody>
</table>

a. Energies in kcal.mol$^{-1}$; rate constants at 250$^\circ$ in s$^{-1}$.

b. Experimental data not available.

c. Kinetic data not available. The radical is reported to cyclize almost exclusively in the endo mode$^{34}$. 

Strain arising from $\omega$-alkenyl generally favors the exo structure. This is
the \textit{exo} and \textit{endo} cyclization modes of the hexenyl (1), heptenyl (30) and octenyl (31) radicals is correctly predicted from the values of $\Delta E_s$. The method also correctly predicts the high rate of ring closure of the allyloxyethyl radical (54), and the high degree of regioselectivity observed, as well as the rate enhancing effect of the gem-dimethyl group in the species 51-53. The MM2 data indicate that the increase in the ground-state strain energy, $\Delta E_s$ (ground), associated with the introduction of the gem-dimethyl group outweighs the increase in the strain energy of the corresponding transition state. Consequently, the overall effect is a lowering of $\Delta E_s$ when compared with the unsubstituted system. This effect, as observed in other reactions, has often been referred to as the "Thorpe-Ingold" effect.

Very encouraging is the ability of the method to correctly predict the regiochemistry of those few cases which cyclize preferentially in the \textit{endo} mode. Thus, the 7-octenyl (31), the 5-methylhexenyl (47) and the silicon containing radicals (56, 57) are all correctly predicted to cyclize mainly \textit{endo}. Also pleasing is the prediction that while 47 may cyclize mainly in the \textit{endo} fashion, the oxygen analogue, the 2-methylallyloxyethyl radical (55), is predicted to cyclize mainly \textit{exo}, also in agreement with experimental data.

The high degree of regioselectivity predicted from the values of $\Delta E_s$ for the cyclization of the \textit{cis}-hept-5-enyl radical (49) as opposed to its \textit{trans} isomer (48) reflects the pseudo-axial orientation of the methyl group in the \textit{endo} transition structure of the former, as opposed to the pseudo-equatorial arrangement in the \textit{endo} transition structure of the latter. Unfortunately, no experimental data are available for these cyclizations. However \textit{cis}- and \textit{trans}-5-methylhept-5-enyl radical have been studied\textsuperscript{29b} and, as expected on the basis of the calculations, the \textit{cis} isomer cyclizes exclusively in the \textit{exo} mode, whereas the \textit{trans} isomer reacts to give both \textit{exo} and \textit{endo} cyclized products.

Table 8 compares the components of the total transition state strain energy, $\Delta E_s$, for the \textit{exo} and \textit{endo} modes of cyclization of the systems of particular interest. Generally, the compression strain term is not a significant contributor to the overall strain energy, reflecting fairly ordinary values for the bond lengths in both \textit{exo} and \textit{endo} transition structures. The Van der Waals (VDW) strain terms are significant. Strain arising from 1,4 interactions generally disfavour the \textit{exo} structure. This is not
Table 8. Selected components of the transition state strain energies for the cyclization of some ω-alkenyl and related radicals.

<table>
<thead>
<tr>
<th>Compression</th>
<th>Bending</th>
<th>VDW(^a) 1,4</th>
<th>VDW(^a) other</th>
<th>Torsion</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-exo</td>
<td>0.22</td>
<td>1.36</td>
<td>4.21</td>
<td>2.60</td>
<td>2.00</td>
<td>0.05</td>
</tr>
<tr>
<td>1-endo</td>
<td>0.42</td>
<td>2.00</td>
<td>2.98</td>
<td>4.77</td>
<td>2.99</td>
<td>0.06</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.20</td>
<td>+0.74</td>
<td>-1.23</td>
<td>+2.17</td>
<td>+0.99</td>
<td>+0.03</td>
</tr>
<tr>
<td>30-exo</td>
<td>0.31</td>
<td>2.52</td>
<td>3.58</td>
<td>3.57</td>
<td>2.71</td>
<td>0.15</td>
</tr>
<tr>
<td>30-endo</td>
<td>0.37</td>
<td>3.43</td>
<td>3.74</td>
<td>4.10</td>
<td>2.63</td>
<td>0.20</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.06</td>
<td>+0.91</td>
<td>+0.16</td>
<td>+0.53</td>
<td>-0.35</td>
<td>+0.05</td>
</tr>
<tr>
<td>31-exo</td>
<td>0.41</td>
<td>4.66</td>
<td>5.10</td>
<td>3.62</td>
<td>5.30</td>
<td>0.25</td>
</tr>
<tr>
<td>31-endo</td>
<td>0.47</td>
<td>3.18</td>
<td>5.12</td>
<td>3.95</td>
<td>4.33</td>
<td>0.21</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.06</td>
<td>-1.48</td>
<td>+0.02</td>
<td>+0.33</td>
<td>-0.97</td>
<td>-0.04</td>
</tr>
<tr>
<td>47-exo</td>
<td>0.40</td>
<td>2.12</td>
<td>4.82</td>
<td>1.92</td>
<td>3.77</td>
<td>0.03</td>
</tr>
<tr>
<td>47-endo</td>
<td>0.44</td>
<td>2.12</td>
<td>3.33</td>
<td>4.15</td>
<td>2.76</td>
<td>0.10</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.04</td>
<td>0.00</td>
<td>-1.49</td>
<td>+2.23</td>
<td>-1.01</td>
<td>+0.07</td>
</tr>
<tr>
<td>54-exo</td>
<td>0.26</td>
<td>1.36</td>
<td>5.46</td>
<td>2.55</td>
<td>0.77</td>
<td>0.79</td>
</tr>
<tr>
<td>54-endo</td>
<td>0.62</td>
<td>3.17</td>
<td>3.91</td>
<td>5.49</td>
<td>3.06</td>
<td>0.87</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.36</td>
<td>+1.81</td>
<td>-1.55</td>
<td>+2.94</td>
<td>+2.29</td>
<td>+0.08</td>
</tr>
<tr>
<td>56-exo</td>
<td>0.26</td>
<td>1.49</td>
<td>1.01</td>
<td>2.35</td>
<td>1.24</td>
<td>-0.12</td>
</tr>
<tr>
<td>56-endo</td>
<td>0.26</td>
<td>1.49</td>
<td>0.21</td>
<td>1.77</td>
<td>1.77</td>
<td>0.48</td>
</tr>
<tr>
<td>endo-exo</td>
<td>-0.07</td>
<td>-2.11</td>
<td>-1.08</td>
<td>+1.31</td>
<td>-1.28</td>
<td>+0.10</td>
</tr>
<tr>
<td>57-exo</td>
<td>0.24</td>
<td>3.04</td>
<td>0.99</td>
<td>1.05</td>
<td>2.23</td>
<td>0.47</td>
</tr>
<tr>
<td>57-endo</td>
<td>0.18</td>
<td>1.49</td>
<td>0.21</td>
<td>1.77</td>
<td>1.77</td>
<td>0.48</td>
</tr>
<tr>
<td>endo-exo</td>
<td>-0.06</td>
<td>-1.55</td>
<td>-0.78</td>
<td>+0.72</td>
<td>-0.46</td>
<td>+0.01</td>
</tr>
<tr>
<td>58-exo</td>
<td>0.28</td>
<td>1.73</td>
<td>3.07</td>
<td>0.64</td>
<td>1.51</td>
<td>-0.12</td>
</tr>
<tr>
<td>58-endo</td>
<td>0.36</td>
<td>2.33</td>
<td>1.05</td>
<td>2.44</td>
<td>3.33</td>
<td>-0.12</td>
</tr>
<tr>
<td>endo-exo</td>
<td>+0.08</td>
<td>+0.60</td>
<td>-2.02</td>
<td>+1.80</td>
<td>+1.82</td>
<td>0.00</td>
</tr>
</tbody>
</table>

a. Van der Waals energies.
surprising as the endo structure is generally larger than the exo; accordingly, 1,4 terms are likely to be less important. The other VDW interactions generally disfavour the endo mode of cyclization with the net VDW effect often being small.

The major controlling factors appear to be bending and torsion which, almost without exception, favour the transition structure of lowest overall strain energy, $\Delta E$.

Further examination of the bending and torsion terms reveal that the bending energy is largely associated with ring strain and the torsion energy, with deformation about the $\pi$ bond. Thus, the high rate of cyclization and the high degree of regioselectivity observed for the allyloxyethyl radical (54) reflects the favourable effect of the relatively short C-O bond length (1.41Å) and small C-O-C angle (106.8°) on the bending and torsion strain in the exo structure (cf. C-C-C bonds: 1.52Å; angle: 109.5°). This favourable C-O length and C-O-C angle is also responsible for the exo preference in the cyclization of the 2-methylallyloxyethyl radical (55), as opposed to the endo preference observed for the carbon analogue (47).

The effect of the relatively long C-Si bond length (1.87Å) is dependent upon the position of the silicon atom in the molecule. Accordingly, in structures 56 and 57 the effect is to raise the energy of the exo structure, while in 58 the energy of the endo structure is raised. Inspections of models clearly reveal that in structures 56 and 57, the longer C-Si bond lengths favour alignment of the radical centre for approach at the unsubstituted end of the olefin (ie. endo cyclization) while the reverse is true in structure 58, the exo approach is favoured. Thus, the MM2 calculated results agree with the available experimental data, in agreement with the stereo-electronic hypothesis\(^\text{17}\).

ii. Alkenylaryl and Related Radicals.

Recent experimental data on the cyclization of alkenylaryl\(^{95,96}\) and alkenylvinyl\(^{86}\) radicals prompted the investigation of these systems by the MM2/MNDO method. In each transition structure for each radical (60-63,65-66) the geometry of the intimate array of reactive centres was fixed as for the exo and endo transition structures of the parent radical, 1,5-hexadien-1-yl (34) (see Table 5).
The choice of $34$ as the parent seemed reasonable as in each case ($60$-$66$) the unpaired electron is localized in a $\sigma$ orbital. In the $o$-(3-butenyloxy)phenyl case ($64$), the transition structures are heptenyl like. Accordingly the dimensions of the intimate array of reactive centres for the exo and endo transition structures of the 6-heptenyl radical (30) (see Table 3) were employed, as no other dimensions were available. Typical transition structures are shown in Figure 3.

Table 9 compares the calculated values of $\Delta E_s$ for the exo and endo modes of cyclization of the radicals ($60$-$66$) with the available experimental data. The comparison reveals excellent agreement between theory and experiment in that the

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_s$(ground)</th>
<th>$\Delta E_s$(exo)</th>
<th>$\Delta E_s$(endo)</th>
<th>$k_{25}$(exo)</th>
<th>$k_{25}$(endo)</th>
<th>$E_{ac}$(exo)</th>
<th>$E_{ac}$(endo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$60$</td>
<td>0.8</td>
<td>4.5</td>
<td>6.3</td>
<td>$3.1 \times 10^8$</td>
<td>$&lt;6 \times 10^6$</td>
<td>3.7</td>
<td>$b$</td>
<td>95</td>
</tr>
<tr>
<td>$61$</td>
<td>4.3</td>
<td>1.8</td>
<td>6.1</td>
<td>$5.3 \times 10^9$</td>
<td>$&lt;5 \times 10^7$</td>
<td>3.1</td>
<td>$b$</td>
<td>95</td>
</tr>
<tr>
<td>$62$</td>
<td>1.1</td>
<td>5.1</td>
<td>5.7</td>
<td>$b$</td>
<td>$b$</td>
<td>e</td>
<td>e</td>
<td>96</td>
</tr>
<tr>
<td>$63$</td>
<td>3.7</td>
<td>2.3</td>
<td>5.6</td>
<td>$1.7 \times 10^9$</td>
<td>$3.6 \times 10^7$</td>
<td>3.1</td>
<td>5.9</td>
<td>95</td>
</tr>
<tr>
<td>$64$</td>
<td>4.7</td>
<td>5.6$^c$</td>
<td>7.6$^c$</td>
<td>$3.1 \times 10^8$</td>
<td>$d$</td>
<td>3.6</td>
<td>$d$</td>
<td>95</td>
</tr>
<tr>
<td>$34$</td>
<td>2.0</td>
<td>5.6</td>
<td>7.0</td>
<td>$b$</td>
<td>$b$</td>
<td>$b$</td>
<td>$b$</td>
<td>30b</td>
</tr>
<tr>
<td>$65$</td>
<td>2.4</td>
<td>4.2</td>
<td>4.8</td>
<td>$5.6 \times 10^7$</td>
<td>$d$</td>
<td>4.0</td>
<td>$d$</td>
<td>86</td>
</tr>
<tr>
<td>$66$</td>
<td>5.6</td>
<td>2.4</td>
<td>5.1</td>
<td>$2.5 \times 10^8$</td>
<td>$d$</td>
<td>3.0</td>
<td>$d$</td>
<td>86</td>
</tr>
</tbody>
</table>

a. Energies in kcal.mol$^{-1}$; rate constants at 25$^\circ$ in s$^{-1}$.
b. Experimental data not available.
c. Determined for transition structures with dimensions of the intimate array identical with those for the cyclization of 6-heptenyl radical (see chapter 1).
d. Not observed.
e. Preliminary experiments reveal the exo/endo ratio to be about unity.$^{96}$

The choice of $34$ as the parent seemed reasonable as in each case ($60$-$66$) the unpaired electron is localized in a $\sigma$ orbital. In the $o$-(3-butenyloxy)phenyl case ($64$), the transition structures are heptenyl like. Accordingly the dimensions of the intimate array of reactive centres for the exo and endo transition structures of the 6-heptenyl radical (30) (see Table 3) were employed, as no other dimensions were available. Typical transition structures are shown in Figure 3.

Table 9 compares the calculated values of $\Delta E_s$ for the exo and endo modes of cyclization of the radicals ($60$-$66$) with the available experimental data. The comparison reveals excellent agreement between theory and experiment in that the
calculations correctly predict the preferred exo mode of cyclization in almost all cases\textsuperscript{86,95} and the roughly equal amounts of exo and endo for the radical 62\textsuperscript{96}. The calculations also correctly predict that these reactions occur at a greater rate than those in the corresponding alkenyl series.

**Figure 3.** Model transition structures for exo and endo cyclization of \(\alpha\)-(3-butenyl)phenyl radical (60).

Examination of the components of the alkenylaryl transition state strain energies reveal that exo cyclization is favoured over endo mainly because of more favourable bending and torsion energies, again indicating that these strain energy components are the major controlling factors.

**Table 10.** Transition structure strain energy components\textsuperscript{a} for the exo cyclization mode of the 5-hexenyl (1) and \(\alpha\)-butenylphenyl (60) radicals.

<table>
<thead>
<tr>
<th></th>
<th>5-Hexenyl (1)</th>
<th>(\alpha)-Butenylphenyl (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(E_s) (ground)</td>
<td>(E_s) (exo)</td>
</tr>
<tr>
<td>Compression</td>
<td>0.17</td>
<td>0.22</td>
</tr>
<tr>
<td>Bending</td>
<td>0.40</td>
<td>1.36</td>
</tr>
<tr>
<td>VDW (1,4)</td>
<td>2.52</td>
<td>4.21</td>
</tr>
<tr>
<td>VDW (other)</td>
<td>-0.65</td>
<td>2.60</td>
</tr>
<tr>
<td>Torsion</td>
<td>0.43</td>
<td>2.00</td>
</tr>
<tr>
<td>Other</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>2.94</strong></td>
<td><strong>10.44</strong></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Energies in kcal.mol\textsuperscript{-1}.
Comparison between the strain energy components for the **exo** cyclization of the hexenyl (1) and o-butenylphenyl (60) radicals should indicate why the alkenylaryl series react so much faster than the corresponding alkyl series. This has been done. Table 10 compares the strain energy components for the exo transition structures in the cyclization of 1 and 60. The comparison reveals that the high rates of cyclization are not just a reflection of the high intrinsic reactivity of σ-radicals as compared with π-radicals, although this is probably quite significant. The major factor is undoubtedly the low values of $\Delta E_s^{(exo)}$ in the alkenylaryl cases as compared with the corresponding alkenyl cases. Table 10 demonstrates that $\Delta E_s^{(exo)}$ for o-butenylphenyl (60) is lower than $\Delta E_s^{(exo)}$ for 5-hexenyl (1) mainly because of favourable bending and VDW terms. Closer inspection of the MM2 data shows that the presence of hydrogens on C(1) and C(2) in the alkenyl systems give rise to unfavourable interactions which do not occur in the alkenylaryl cases.

iii. Stereochemistry.

Factors affecting the stereochemical outcome of the cyclization of substituted ω-alkenyl radicals are more subtle than those affecting the regiochemistry. Beckwith and co-workers have argued that 3-substituted hexenyl radicals cyclize preferentially to give the cis disubstituted product, while the 2- and 4-substituted radicals give mainly the trans product. This explanation rests on the hypothesis that the exo hexenyl transition structure resembles the chair form of cyclohexane. Thus, on stereo-electronic grounds, the exo structures bearing pseudo-equatorial substituents are the more stable. Therefore, substitution at position 3 yields mainly the cis product, while substitution at positions 2 and 4 affords mainly trans.

Our calculations strongly support this view. The model transition structure for the exo cyclization of the 5-hexenyl radical does indeed resemble the chair form of cyclohexane (see Figure 1) and bears clearly distinguishable pseudo-axial and pseudo-equatorial hydrogens at positions 2, 3 and 4. Figure 4 clearly displays the pseudo-axial and equatorial positioning of the methyl group in the two conformationally distinct exo transition structures for the cyclization of 3-methylhex-5-en-yl radical (68).
The data in Table 11 indicate that for the radicals 67-69, the conformer of the transition structure containing the methyl group in the pseudo-equatorial position is of lower energy than that containing the methyl group in the pseudo-axial position, in excellent agreement with the available experimental data\textsuperscript{59b}. Closer inspection of the MM2 results also indicate that the conformers of the transition structure containing the pseudo-axial methyl groups are not only disfavoured by VDW interactions, but also by bending and torsion strain energy terms.

**Table 11.** Comparison between transition structure strain energies, $\Delta E_\text{s}$\textsuperscript{a}, and experimental data\textsuperscript{a} for the cyclization of various substituted $\omega$-alkenyl radicals.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_\text{a}(\text{ground})$</th>
<th>$\Delta E_\text{s}$(cis)</th>
<th>$\Delta E_\text{s}$(trans)</th>
<th>$k_25$(cis)</th>
<th>$k_25$(trans)</th>
<th>$E_\text{act}$(cis)</th>
<th>$E_\text{act}$(trans)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\cdot\cdot\cdot$ 18</td>
<td>3.4</td>
<td>7.3</td>
<td>7.5</td>
<td>$1.1 \times 10^5$</td>
<td>$4.2 \times 10^4$</td>
<td>6.9</td>
<td>7.6</td>
<td>62,90</td>
</tr>
<tr>
<td>$\cdot\cdot\cdot$ 67</td>
<td>4.7</td>
<td>7.3</td>
<td>6.3</td>
<td>$2.4 \times 10^5$</td>
<td>$4.5 \times 10^5$</td>
<td>6.5</td>
<td>6.1</td>
<td>59b</td>
</tr>
<tr>
<td>$\cdot\cdot\cdot$ 68</td>
<td>4.5</td>
<td>6.1</td>
<td>7.7</td>
<td>$7.0 \times 10^5$</td>
<td>$2.4 \times 10^5$</td>
<td>6.0</td>
<td>6.4</td>
<td>59b</td>
</tr>
<tr>
<td>$\cdot\cdot\cdot$ 69</td>
<td>5.0</td>
<td>7.9</td>
<td>6.2</td>
<td>$7.5 \times 10^4$</td>
<td>$3.6 \times 10^5$</td>
<td>7.7</td>
<td>6.6</td>
<td>59b</td>
</tr>
<tr>
<td>$\cdot\cdot\cdot$ 70</td>
<td>4.0</td>
<td>9.0</td>
<td>9.7</td>
<td>$5.7 \times 10^3$</td>
<td>$2.1 \times 10^3$</td>
<td>8.4</td>
<td>9.0</td>
<td>30b</td>
</tr>
<tr>
<td>$\cdot\cdot\cdot$ 71</td>
<td>6.4</td>
<td>8.5</td>
<td>8.0</td>
<td>$2.8 \times 10^4$</td>
<td>$8.7 \times 10^4$</td>
<td>8.7</td>
<td>5.5</td>
<td>b</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Energies in kcal.mol$^{-1}$; rate constants at 25$^\circ$ in s$^{-1}$.

The effects controlling the stereochemistry of the 1-substituted hexenyl radicals are less clear. The calculations correctly predict that the hept-6-en-2-yl radical (18) cyclizes preferentially cis and that the 2,2-dimethylct-7-en-3-yl radical (71) cyclizes mainly trans. These preferences cannot be attributed to pseudo-axial and equatorial orientation of substituents as the positioning at C(1) is not clearly defined. Closer inspection of the MM2 data reveals a delicate balance between unfavourable torsion terms in the trans transition structures and unfavourable VDW terms in the cis structures. Thus, the data for the cyclization of 71 reveal two low
Figure 4. Showing the pseudo-axial and equatorial arrangements of the methyl group in the cis and trans exo transition structures for the cyclization of 3-methylhex-5-enyl radical.
energy conformations of the trans transition structure (72, 73) and one low energy conformation of the cis structure (74). In the trans structure 72, there is clear eclipsing between atoms marked a, b, c and d while in 73 eclipsing occurs between e, f, g and h resulting in unfavourable torsion energies. The cis structure (74) suffers from no such eclipsing. However, unfavourable steric interaction between the t-butyl group and the methylene moiety (c-h in 74) results in unfavourable VDW energies. For the cyclization of 71, the forces are balanced such that VDW terms dominate, resulting in mainly trans cyclization. This is not unexpected due to the steric demand imposed by the t-butyl group. When the substituent at position 1 is less sterically demanding (ie: radicals 18, 70), the torsion terms become the major controlling factor and cyclization proceeds mainly in the cis fashion.

Thus, it appears that the stereochemistry of the cyclization of 1-substituted hexenyl radicals is also controlled by steric factors, as opposed to previous suggestions of orbital or polar control (see Introduction).

This hypothesis will be further discussed in Chapter 4 of this work.


a. Substituted Butenylperoxy Radicals.
The success of the MM2/MNDO method in predicting the regio- and stereo-chemistry of a variety of systems encouraged the investigation of more complex systems.

Beckwith and Wagner\(^{46d}\) have reported that the thiol/oxygen co-oxidation of the triene (75) gives only one (76) of four possible products.

This has been explained in terms of rapid equilibrium between the two diastereomeric intermediate peroxy radicals (77, 78) via the addition/elimination of molecular oxygen.

The peroxy radicals (77, 78) can cyclize in the exo fashion to give four possible products. The ultimate observed product is determined by the relative heights of the activation energy barriers. This hypothesis can be tested using the MM2/MNDO method.

The strain energies, $E_s$ and $\Delta E_s$ for the peroxy radicals (77, 78) and the geometries of the various transition structures were calculated on the assumption that the intimate array of reactive centres would be similar to those of the hexenyl exo transition structure (see Table 3). Although experimental work was conducted with arenethiols\(^{46d}\), calculations were performed on the methyl analogues, for simplicity. The results are summarized in Figure 5.

Interestingly, the peroxy radical leading to the ultimate product is the one of lower energy, but this is of no consequence, as the rapid equilibrium funnels the reaction through 78 to give eventually the same product as that (76) observed
experimentally. Closer inspection of the transition structure leading to 76, (79), reveals it to be the only one having all substituents in pseudo-equatorial positions. It is not surprising, therefore, that this route should lead to the eventual product.

![Transition structure](image)

b. Formation of Tetrahydroindanes.

Table 12. Transition state strain energies $\Delta E_s$ for the **exo** cyclizations of the cyclohexadienylalkyl radicals 80 and 81.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_s$(ground)</th>
<th>$\Delta E_s$(cis)</th>
<th>$\Delta E_s$(trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>15.7</td>
<td>5.1</td>
<td>30.6</td>
</tr>
<tr>
<td>81</td>
<td>16.2</td>
<td>9.5</td>
<td>21.6</td>
</tr>
</tbody>
</table>

a. Energies in kcal.mol$^{-1}$.

The cyclization of radicals 80–82 generated from precursors available from Birch reductive alkylations of aromatic esters provides a convenient route into tetrahydroindane and related systems$^97$. The stereochemistry of the newly formed ring junction has been observed to be strictly cis$^97$. The data in Table 12 clearly show why this is the case.

For the **exo** cyclization of 80 or 81, only the value of $\Delta E_s$ for the cis mode is low enough to allow the reaction to occur. In the trans case, the transition structure is clearly too highly strained to make this cyclization route feasible.
c. Formations of Triquinnanes by Consecutive Radical Cyclization.

Linearly fused triquinane natural products have attracted considerable attention in recent years both from a synthetic and biological point of view. The architecturally unique assembly of five-membered rings has, in some instances, exhibited biological activity. Reports concerning the syntheses of these systems have recently appeared in the literature, using both conventional chemical approaches and free-radical methodology (see Introduction). Much current interest in radical chemistry is focussed on the construction of polycyclic systems. Hence, it would be of considerable utility to be able to predict the regio- and stereo-chemical outcome of these reactions before embarking upon an elaborate synthesis. Thus, we have completed a theoretical study of the consecutive cyclization of the dodeca-1,8,11-trien-4-yl radical (83). The aim was to predict the possible products in the reaction scheme. It should be noted that the ultimate product (eg. 93) is capable of existing in 16 different diastereomeric forms.

As expected, the results depicted in Figure 6 predict that 83 should cyclize, in the first instance, exclusively in the exo mode; $\Delta E_s^{(\text{exo})}$ is much lower than $\Delta E_s^{(\text{endo})}$. Also predicted is that 84(cis) should be formed in preference to 84(trans). Further calculations on the cyclization of 84(trans) reveal no low energy pathways for further cyclization. Thus, 84(trans) is not a suitable precursor for triquinnane formation. The small amount of 84(trans) predicted to form should eventually end up, after hydrogen atom transfer, as the diene (96).

Further cyclization of 84(cis) can result in four possible product radicals (85-88) resulting from exo cyclization, all having similar values of $\Delta E_s$. The endo mode has a considerably higher value of $\Delta E_s$ and is unlikely to yield significant quantities of products.
Figure 6. Possible products and values of $\Delta E_s$ (kcal.mol$^{-1}$) (in parentheses) for the various reaction paths of the cyclization of the trienyl radical 83.
Further cyclization of 85 can result in two possible \textit{exo} products (89), the \textit{endo} process being sterically considerably less feasible ($\Delta E_\text{s} = 9.5$ kcal mol$^{-1}$). Radical 86 has realistically only one route open to it, the formation of 90(\(\alpha\)-Me). Formation of both 90(\(\beta\)-Me) and the \textit{endo} product are energetically more costly ($\Delta E_\text{s} = 9.0$ and 8.2 kcal mol$^{-1}$ respectively). In comparison, the \textit{endo} cyclization of 87 to give 92 is as feasible as the \textit{exo} process leading to 91(\(\beta\)-Me). Finally, the radical 88 has only high energy cyclization processes open to it and is therefore predicted to react by intermolecular hydrogen atom transfer, to give the alkene (95).

In summary, the method predicts that the trienyl radical (83) should not react cleanly to give one product, but should afford seven major and possibly one minor product and perhaps some of the diene (96). The expected major products are four triquinnanes (ie. the two isomers of 89, 90(\(\alpha\)-Me) and 91(\(\beta\)-Me), and two \textit{endo} cyclized tricyclic products (92 and 94). The possible minor product is expected to be 91(\(\alpha\)-Me).

Beckwith and co-workers have recently reported the results of the cyclization of 83\textsuperscript{89c}. Their preliminary experiments have shown that the reaction of tri-n-butylgermanium hydride with the trienyl bromide (97) affords four triquinnanes (yields: 18\%, 9\%, 12\%, 6\%) of which the first two have been identified as the isomers of 89 and the third is tentatively assigned the structure 90(\(\alpha\)-Me).

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {Br};
  \draw [thick] (0,0) -- (1,0) -- (2,0) -- (3,0) -- (4,0) -- (5,0);
  \node at (2,0) {97};
\end{tikzpicture}
\end{center}

Two \textit{endo} cyclized tricyclic products have also been observed (10\%, 24\%), tentatively assigned to be 92 and 94, and one bicyclic product (14\%) tentatively identified as 95.

The ability of the method to correctly predict the structure of two products and the type and number of four others provides powerful evidence of the utility of the method.
Conclusion

In this chapter, the scope and power of the MM2/MNDO method, the development of which was discussed in Chapter 1, have clearly been demonstrated. Excellent agreement between theoretical and experimental data has been observed for a large number of systems. The ability of the method to solve stereochemical problems and to predict correctly the course of a complex cyclization process provides powerful evidence of the utility of the method as a tool for the study of radical cyclization reactions, both from a physical and from a synthetic approach.
CHAPTER 3

The Effect of Radical Geometry on the Rate and Stereochemistry of Ring Closure.

i. Conformational Acceleration - The Methylene-cyclo-decyl Radical.

In their studies of the β-fission of 9-decalinoxy radicals, Beckwith and co-workers report that the cyclization of the 6-oxo-cyclo-decyl radical (98a) in the presence of tri-n-butyltin hydride gives cis- and trans- 9-decalinol (99a, 100a) (Scheme 11).

The cyclization reaction competes very effectively with hydrogen atom transfer from the tin hydride to give good yields of the cyclized material and only 4% of the uncyclized material, cyclo-decanone (101a) at 60° using 1.3M tin hydride. From these results, the rate constants for the cis and trans modes of cyclization were determined to be $6 \times 10^7$ s$^{-1}$ and $2 \times 10^7$ s$^{-1}$ at 60° respectively. This is therefore a fast radical cyclization process, by comparison with the hexenyl radical (1) itself, which has a rate constant of only $-4 \times 10^5$ s$^{-1}$ at 60°. Also curious is the predominance of the cis product (99a). Presumably these results reflect favourable energy and entropy factors associated with trans-annular bond formation. However, the observation that the cis product is formed at a faster rate than the trans product is not in accord with intuition as the trans product (100a) is more...
thermodynamically stable. Also, comparison, in each case, of models of the expected transition structure and the corresponding decalin product reveals a remarkable similarity between the two. On the basis of this similarity, the relative energies of the transition structures are expected to reflect the relative energies of the products, suggesting that the trans product (100a) is also favoured kinetically.

It was of interest to investigate whether the conformational effects noticed for 98a are more generally observable. Accordingly, a study of the cyclization of the 6-methylenecyclodecyl radical (98b) was initiated.

As radicals are readily generated from the corresponding halide and since the halides are readily prepared from the corresponding alcohol, 6-methylenecyclodecanol (102b) was seen as the initial synthetic target.

Numerous reports have appeared in the literature\textsuperscript{101} detailing the preparation of 6-hydroxycyclodecanone (103) which has successfully been converted into 102b by Wittig methodology\textsuperscript{102}. The synthetic strategy chosen for the preparation of 102b is shown in Scheme 12.

Treatment of decalyl-9-hydroperoxide (104) with benzoyl chloride in pyridine afforded the perbenzoate ester which was readily rearranged in methanol under reflux to give 11-oxabicyclo[4.4.1]undec-1-yl benzoate (105) in good yield. Further treatment with potassium hydroxide in methanol at reflux yielded 6-hydroxycyclodecanone (103) which was methylenated using methylene triphenylphosphorane in dimethylsulfoxide (DMSO) to give the desired 6-methylenecyclodecanol (102b).
The next step involved conversion of the alcohol (102b) into a suitable halide. However, $^1$H NMR spectroscopy indicated that treatment of the alcohol with N-bromosuccinimide/ triphenylphosphine (NBS/Ph$_3$P) in acetonitrile gave only saturated material. Similar results were observed with sodium iodide /chlorotrimethylsilane in acetonitrile.

Becker and Chappius$^{102}$ have shown that thermolysis of 102b results in rearrangement to give the bicyclo[4.4.1]undecyl alcohol (106a). Other work$^{103}$ has shown that solvolysis of the cyclodecyl tosylate (102c) results in similar rearrangement to afford 106b. This presumably suggests that the intermediate phosphonium salt or silyl ether in the halogenation of 102b can rearrange in similar fashion to give the saturated halide 106c (Scheme 13).
The relative ease of occurrence of this unwanted reaction suggests that attempted preparation of the halide (102a) by other means would also encounter difficulties.

As an alternative to halides, dithiocarbonates\textsuperscript{104} (107a,b) and thionocarbonates (107c) are readily prepared, efficient precursors of free-radicals. The methyldithiocarbonate (107a) was prepared by treatment of the alcohol (102b) with sodium hydride in ether followed by quenching of the alkoxide formed with carbon disulfide and methyl iodide. The phenyldithiocarbonate (107b) and phenylthionocarbonate (107c) were prepared by the treatment of 102b with (phenylthio)thiocarbonyl chloride or phenylchlorothionocarbonate respectively in pyridine/ dichloromethane as depicted in Scheme 14.

The dithio- and thionocarbonates react with tri-n-butyltin hydride to give an intermediate carbon-centred radical which decomposes to give the desired alkyl radical\textsuperscript{104} (Scheme 15).
Barker and Beckwith\textsuperscript{105} have proposed an alternative low-temperature mechanism for the decomposition of dithiocarbonates based on ESR evidence (Scheme 16).

\begin{equation*}
\begin{array}{c}
\text{S} = \text{C}^\text{OR} \\
\text{SnBu}_3 \\
\text{Bu}_3\text{SnSR'} + R - \text{O} - \text{C}^\text{S} \\
\rightarrow R^* + \text{COS}
\end{array}
\end{equation*}

\textbf{Scheme 16}

Treatment of 107 with ten equivalents of tri-n-butyltin hydride in benzene (pseudo first-order conditions, see Appendix A) and analysis of the subsequent reaction mixture by gas-chromatography (GC) revealed the presence of two major products identified as cis- and trans- 9-methyldecalin (99b, 100b) by comparison with authentic samples. The reaction yields were in excess of 90\% as compared with an internal standard (1,2,4,5-tetramethylbenzene). A sample of 99b was prepared by the reduction of cis-9-(2-bromomethyl)decalin (99c) with lithium aluminium hydride, while a sample of 100b was prepared by the action of tetramethylsilane/ aluminium chloride on decalin, as described by Kursanov et al.\textsuperscript{106}.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{CH}_2\text{Br}}; \node (b) at (1,0) {\text{LiAlH}_4}; \node (c) at (2,0) {\text{H}};
  \draw[->] (a) -- (b); \draw[->] (b) -- (c);
  \node (d) at (3,0) {\text{CH}_3}; \node (e) at (2,0) {\text{99c}};
  \draw[->] (e) -- (d);
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{CH}_3}; \node (b) at (1,0) {\text{LiAlH}_4}; \node (c) at (2,0) {\text{H}};
  \draw[->] (a) -- (b); \draw[->] (b) -- (c);
  \node (d) at (3,0) {\text{H}};
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {\text{CH}_3}; \node (b) at (1,0) {\text{TMS/ AlCl}_3}; \node (c) at (2,0) {\text{H}};
  \draw[->] (a) -- (b); \draw[->] (b) -- (c);
  \node (d) at (3,0) {\text{100b}};
\end{tikzpicture}
\end{center}

The reduction of the carbonates (107a,c) also produced small amounts of material initially assumed to be 6-methyleneoctadec-1-ene (108) arising via an elimination process. In confirmation of this hypothesis, distillation of the
methyldithiocarbonate (107a) gave 108 as the only isolable material. The phenyldithiocarbonate (107b) underwent no such elimination under the reaction conditions and was therefore used in subsequent kinetic experiments.

![Diagram](image)

Although the uncyclized (directly reduced) methylenecyclodecane (101b) was not detected at the concentrations of the tin hydride used (0.1M) there was a possibility that it might be observed at higher concentrations. However, even in neat tin hydride (~3.4M) no amount of 101b could be detected, indicating that the ring closure of 98b is considerably faster than that for the corresponding ketone radical (98a).

As was observed for the ketone radical (98a), the cis isomer was the major product in the cyclization of the methylenecyclodecyl radical (98b), dominating by a factor of 3.0 at 80°. As expected, the cis/trans ratio was temperature dependent, ranging from 3.5 at 60° to 2.3 at 122°. Experimental data are tabulated in Appendix A.

Assuming that gas chromatography (GC) is capable of detecting 1% of 101b if it were present, we can reliably take this value as an upper limit to the amount of uncyclized material present. The appropriate integrated rate equation (see Appendix A), namely:

\[
\frac{[C]}{[U]} = \frac{k_c}{k_H [Bu_3SnH]} \quad \ldots A3
\]

where [C] and [U] denote cyclized and uncyclized material concentrations respectively, \( k_c \) is the rate constant for ring closure, \( k_H \) is the rate constant for hydrogen abstraction from the tin hydride, standard values of which were obtained from the work of Ingold and co-workers\(^{28c}\), was applied to the data. Lower limits for the cyclization rate constants were determined to be:
Bowry\textsuperscript{107}, using a radical trapping technique\textsuperscript{109}, has recently determined the total cyclization rate constant for these reactions to be $5 \times 10^{10}$ s$^{-1}$, the fastest cyclization rate constant yet observed for an alkenyl radical and clearly too rapid to allow the formation of uncyclized material (101b) under the conditions used. Application of the Arrhenius equation (A10, see Appendix A) to the experimental data suggested that while the cis isomer is energetically favoured over the trans by 1.8 kcal mol$^{-1}$, the trans isomer is entropically favoured (logA difference: 0.63), the balance of factors favouring the cis isomer over the temperatures used in the kinetic study.

With the successes of the MM2/MNDO transition structure modelling method, as described in Chapters 1 and 2, in mind, strain energy calculations were performed on a number of low energy conformations of possible transition structures leading to the cis and trans products (99,100) in the hope that theory would provide a satisfactory explanation for the observed preference for the cis stereochemistry. The conformers of lowest energy, viz (109,110), were remarkably similar to models of the observed products. As expected, on the basis of the thermodynamic stabilities of the products, the transition structure for the trans cyclization mode was calculated to be 1.4 kcal mol$^{-1}$ more favourable than the cis structure (110) of lowest energy. Clearly, if the products arise from the same ground-state distribution of conformers, the calculations predict the trans isomer (100) to predominate, contrary to the available experimental data.
NMR\textsuperscript{109}, crystal structure\textsuperscript{110} and strain energy\textsuperscript{64,111} evidence point to the "diamond lattice" boat-chair-boat (BCB) conformation of cyclodecane, having the fewest number of trans-annular interactions, as being of lowest energy.

Figure 7 clearly reveals that the BCB form of cyclodecane has three different kinds of carbon atom present. Out of these, C(3) (and C(4,8,9) by symmetry) is involved in the majority of unfavourable trans-annular interactions. Thus, by analogy with cyclodecanone\textsuperscript{109}, the methylenecyclodecyl radical (98b) would be expected to exist in the BCB-3 form, eliminating two sets of unfavourable trans-annular H-H interactions at positions 3 and 8, as depicted in Figure 7. The BCB-1 and BCB-2 forms, having the methylene functionality at C(1) and C(2) respectively, do not benefit by the reduction in trans-annular interactions as observed for the BCB-3 form.

![Cyclodecane BCB and 6-methylenecyclodecyl radical BCB-3](image)

**Figure 7.** Depicting the most stable conformers of cyclodecane and the 6-methylenecyclodecyl radical.

Anet and co-workers\textsuperscript{109} have determined the rate constant for pseudorotation between low energy conformations of cyclodecanone to be in the region of $2 \times 10^5$ s\textsuperscript{-1} at 80°. It is unlikely that conformers of the methylenecyclodecyl radical would interconvert at significantly different rates from those observed for cyclodecanone. Thus, it would appear, since the cyclization rate constant ($5 \times 10^{10}$ s\textsuperscript{-1}) is about five orders of magnitude faster than pseudorotation, that conformational interconversion of the methylenecyclodecyl radical would be too slow to compete with cyclization. Consequently, the product distribution is expected to
reflect the conformational distribution of the radical ground-state, which in turn reflects the conformational distribution of the radical precursor, provided that the initiation process does not differ significantly between conformers, as the radical cannot pseudorotate before cyclization occurs.

**Figure 8.** Low energy conformations of 6-iodomethylenecyclodecane and associated strain energies (kcal mol$^{-1}$) as calculated by MM2.

As the precursor of the ketone radical (98a) in the study of Beckwith et al.\textsuperscript{100} was the corresponding bromide and since both 98a and 98b show similar stereochemical preferences, strain energy calculations were performed on low energy conformations of 6-iodomethylenecyclodecane, a convenient heavy-atom precursor.
Figure 8 depicts the two lowest energy conformations capable of cyclizing in trans fashion, the BCB-3 and crown (TCCC)\textsuperscript{109} forms and the lowest energy conformation leading to the cis product, the CBC-3 form. As is observed for cyclodecanone\textsuperscript{109}, the calculations reveal the BCB-3 form to be the most stable, with the CBC-3 form being 3.76 kcal mol\textsuperscript{-1} less favourable.

The calculations give no satisfactory explanation for the observed stereochemical preferences in the cyclizations of 98a,b predicting, in both transition state and ground-state studies, the incorrect stereo-preferences. Perhaps this is an example of a cyclization reaction in which factors other than steric dominate. Allinger\textsuperscript{64} suggests that there are too many conformations available in these systems to ever hope to effect a systematic study of them all. It is possible that the true ground- and transition state conformational preferences reflect none of those considered. With so many conformations available it becomes clear that any force-field analysis must, out of necessity, be incomplete. Whatever the case may be, no satisfactory explanation has been arrived at to account for the observed stereochemical preferences.


As was shown in Chapter 2, MM2/MNDO calculations predict the Z-hept-5-enyl radical (49) to cyclize slightly faster than the corresponding E- isomer (48) and with greater regiospecificity.

We decided, therefore, to investigate whether geometrical isomerism of the olefin has any effect on the overall stereo-selectivities and rates of these cyclization reactions. Prior to commencing an experimental programme, strain-energy calculations, as described in Chapters 1 and 2, were performed on the cis- and trans-modes of cyclization of the E- and Z- oct-6-en-2-yl radicals (111, 112). These calculations, the results of which are displayed in Table 13, suggest that both isomers are expected to cyclize preferentially in the cis mode, however, the calculated data do not predict a high degree of preference. The data also suggest that the Z- isomer should cyclize slightly faster than the E- isomer, although the difference in rates is not expected to be great.
Table 13. MM2 calculated strain energies, $\Delta E_s$ a for the cis and trans modes of cyclization of the oct-6-en-2-y1 radicals 111 and 112.

<table>
<thead>
<tr>
<th>Radical</th>
<th>$E_s$(ground)</th>
<th>$\Delta E_s$(cis)</th>
<th>$\Delta E_s$(trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>111</td>
<td>3.21</td>
<td>6.88</td>
<td>6.98</td>
</tr>
<tr>
<td>112</td>
<td>5.02</td>
<td>6.62</td>
<td>6.82</td>
</tr>
</tbody>
</table>

a. Strain energies in kcal.mol$^{-1}$.

In order to test the theoretical predictions a, an investigation into the cyclization of the E- and Z- 2-(hex-2-en-1-oxy)- ethyl radicals (113, 114) was initiated.

Scheme 17
These radicals were chosen because they are easy to generate and are of the correct structures for the investigation of the desired effect. Scheme 17 depicts the route chosen for the preparation of the bromides (115)- suitable precursors of 113 and 114. Treatment of ethylene glycol with sodium hydride followed by E- or Z-1-bromohex-2-ene afforded the β-hydroxyether (116) which was converted to the desired bromide by the action of phosphorous tribromide in ether.

![Scheme 17](image)

The alcohol (116) was isolated from a binary mixture by medium pressure liquid chromatography (MPLC). The NMR data for the other product is consistent with the conjugate substitution product (117).

Prepared by this method, the Z- alcohol (116b) was contaminated with 20\% of the E- isomer (116a) as determined by \(^{13}\)C NMR spectroscopy. This contamination was carried through to the bromide (115b). Isomerism probably occurs via the alcohol (117) followed by re-substitution to give the thermodynamically more stable olefin (Scheme 18).

![Scheme 18](image)
Treatment of the bromides (115) with ten equivalents of tri-n-butyltin hydride in hexane at various temperatures followed by GC analysis of the reaction mixtures revealed two major products in each case. These were identified, by comparison with authentic samples, as 3-n-butyltetrahydrofuran (118) and the olefin (119) derived from the direct hydrogen atom transfer from the tin hydride to the radical in each case (Scheme 19). The tetrahydrofuran (118) was isolated from the reaction mixture by preparative gas chromatography and fully characterized, while 119 was prepared by treatment of the appropriate hex-2-en-1-ol with sodium hydride and ethyl iodide.

The bromo precursors (115) needed to be introduced into the tin hydride solution at the desired temperature of reaction (see Method B, experimental section). This was mainly to overcome the erratic results observed under the normal conditions used (see Method A, experimental section) as the radical reaction appeared to initiate at a rate such that complete cyclization would have occurred before the solution had reached the desired temperature. Normally the initiation step
is sufficiently slow to allow the pre-prepared solution to warm to the desired temperature.

Table 14 lists the results of the kinetic experiments involving 113 and 114. The rate constants, $k_c$, have been derived from equation A3 (see Appendix A) using standard values of the hydrogen abstraction rate constant from tin hydride, $k_H$ for alkyl radicals as determined by Ingold and co-workers\textsuperscript{28c}.

![Chemical structures of 115a and 115b]

Table 14. Kinetic data for the cyclization of the E- and Z- 2-(Hex-2-en-1-oxy)ethyl radical.

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Temp (°C)</th>
<th>[118]/[119]</th>
<th>$k_c$</th>
<th>$k_c(s^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$k_c/k_H$</td>
<td></td>
</tr>
<tr>
<td>115a</td>
<td>51</td>
<td>0.89</td>
<td>2.55 (± 6%)</td>
<td>9.9 x 10^6</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1.01</td>
<td>2.90</td>
<td>1.3 x 10^7</td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>1.10</td>
<td>3.16</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>1.21</td>
<td>3.47</td>
<td>2.2</td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>1.36</td>
<td>3.90</td>
<td>2.8</td>
</tr>
<tr>
<td>115b</td>
<td>50</td>
<td>0.79</td>
<td>2.27 (± 1%)</td>
<td>8.8 x 10^6</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>0.85</td>
<td>2.44</td>
<td>1.1 x 10^7</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>0.96</td>
<td>2.76</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>91</td>
<td>1.02</td>
<td>2.93</td>
<td>2.1</td>
</tr>
</tbody>
</table>

$[\text{Bu}_3\text{SnH}] = 2.87\text{M}$

Application of the Arrhenius equation (A10, see Appendix A) to the data in Table 14 reveals that the E- isomer (113) cyclizes with an energy of activation of 6.2 ± 0.5 kcal mol\textsuperscript{-1} and logA of 11.2 ± 0.5 while the Z isomer (114) cyclizes with 5.2 ± 0.5 kcal mol\textsuperscript{-1} and 10.4 ± 0.4 as the energy of activation and logA terms respectively.

Although the data in Table 14 also indicate that 113 cyclizes at a faster rate than 114 over the temperature range of the study, this is not clear from the activation parameters. The parameters indicate that the E- isomer (113) cyclizes...
faster than the Z- isomer (114) mainly because of entropic factors, although, when the error bars are included, the data appear to be essentially the same in each case. It is clear that no profound rate difference is observed for the geometrically isomeric radicals (113,114).

In order to determine what role geometrical isomerism plays in directing the stereochemistry of these radical cyclization reactions, the reactions of the E- and Z- isomers of the 1-(hex-2-en-1-oxy)hex-2-yl radical (120,121) were investigated.

These radicals were envisaged as arising from the thionocarbonate precursors (122) prepared as outlined in Scheme 20 for the E- isomer.

Reaction of E-hex-2-en-1-ol with sodium hydride followed by n-butyloxirane yielded the β-hydroxyether (123a) which was converted into the desired thionocarbonate using phenylchlorothionocarbonate in the usual way. While the preparation of the E- thionocarbonate (122a) proceeded smoothly, its reaction with excess tri-n-butyltin hydride in hexane in the usual way, as monitored by GC, proceeded poorly, requiring many additions of the radical initiator, azo-bis-isobutyronitrile (AIBN), to maintain the decomposition. It is unclear what exactly is inhibiting the radical chain process, as this effect has not been previously reported for thionocarbonates.

\[
\begin{align*}
\text{Scheme 20}
\end{align*}
\]
Attempted preparation of the corresponding halide using phosphorous tribromide or NBS/ carbon tetrachloride resulted in an unidentifiable mixture of compounds.

Phenylselenides have also been reported\textsuperscript{113} as efficient radical precursors. As the conversion of the alcohol (123a) to the phenylselenide (124a) proceeded smoothly (Scheme 21) and as subsequent decomposition proceeded to completion, it was chosen as the radical precursor for kinetic studies.

\[
\begin{align*}
\text{O} & \quad \text{OH} & \quad \text{SePh} \\
123a & \quad 124a
\end{align*}
\]

\[
\begin{align*}
\text{MeSO}_2\text{Cl} & \quad \text{Et}_3\text{N} \\
\text{OSO}_2\text{Me} & \quad \text{NaBH}_4 \\
(\text{PhSe})_2 & \quad \text{EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{SePh} \\
123a & \quad 124a
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{SePh} \\
123a & \quad 124a
\end{align*}
\]

\[
\begin{align*}
\text{MeSO}_2\text{Cl} & \quad \text{Et}_3\text{N} \\
\text{OSO}_2\text{Me} & \quad \text{NaBH}_4 \\
(\text{PhSe})_2 & \quad \text{EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{SePh} \\
123a & \quad 124a
\end{align*}
\]

\[
\begin{align*}
\text{MeSO}_2\text{Cl} & \quad \text{Et}_3\text{N} \\
\text{OSO}_2\text{Me} & \quad \text{NaBH}_4 \\
(\text{PhSe})_2 & \quad \text{EtOH}
\end{align*}
\]

Reaction of the alcohol (123a) with methanesulfonyl chloride/ triethylamine gave the corresponding mesylate which was converted to the desired phenylselenide (124a) by the action of diphenyldiselenide/ sodium borohydride in ethanol.

Attempted preparation of the Z- alcohol (123b) in a similar manner to that outlined in Scheme 20 resulted in an inseparable mixture of compounds. Thus, an alternative synthetic route was established (Scheme 22).

Treatment of Z-hex-2-en-1-ol with two equivalents of sodium hydride followed with bromoacetic acid yielded the acid (125) in good yield and in an isomerically pure state as determined by $^{13}$C nmr spectroscopy. Reduction of 124 to the corresponding alcohol followed by Swern oxidation\textsuperscript{114} with oxalyl chloride/ dimethyl sulfoxide (DMSO) to the corresponding aldehyde, which was not isolated but treated directly with $\text{n}$-butylmagnesium bromide to give the alcohol (123b) in
16% overall yield from the acid (125). The alcohol (123b) was readily converted to the phenylselenide (124b) in similar fashion to the preparation of 124a.

Scheme 22

The phenylselenides (124), like the β-bromoethers (115), initiated extremely rapidly in their reaction with tin hydride in hexane to give the desired radicals (120,121) which reacted to give cis and trans-3,4-di-n-butyltetrahydrofuran (126a,b) and the directly reduced product (126c,d) as determined by GC comparison with authentic samples (Scheme 23). Therefore Method B (see experimental section) as previously discussed for 115 was employed in the kinetic studies. Even so, the experimental data for the Z- isomer (121) was so scattered that only rough estimates of the reaction rates and the product ratios could be determined.

Results for the E- isomer (120) were also unreliable, allowing only rough rate constants, k,c, to be determined and were too scattered for reliable application of
the Arrhenius equation (A10, see Appendix A) for the determination of activation parameters.

![Scheme 23](image)

Authentic samples of $^{126}$a and $^{126}$b were separated from the reaction mixture by preparative gas chromatography and fully characterized. $^{126}$c and $^{126}$d were prepared by treating the appropriate hex-2-en-1-ol with sodium hydride followed by n-hexylmethanesulfonate.

![Reaction Scheme](image)

Barton and co-workers$^{115}$ have recently reported the rate enhancing effect of $\beta$ carbon-oxygen bonds in the initiation of radical reactions from dithiocarbonates in the presence of tri-n-butyltin hydride. They have observed that primary dithiocarbonates react at $110^\circ$, provided that a $\beta$-ether linkage is present and go on to suggest extra radical stability due to some effect of the $\beta$-oxygen. Primary dithiocarbonates are usually inert under these conditions$^{104}$.

Both $^{115}$ and $^{124}$ have $\beta$-ether linkages, thus, the rate enhancement of initiation observed is not unexpected. As $^{124}$ leads to a secondary radical and $^{115}$ to a primary, it is also not surprising to find that $^{124}$ is observed to initiate at, what appears to be, a faster rate than $^{115}$. The scatter in the data for $^{124}$ probably reflects reaction occurring during the mixing process involved in dissolving the precursor in the tin hydride solution.

Table 15 lists the available kinetic data for the reaction of
1-\((\text{E}-\text{hex-2-en-1-oxy})\)-2-(phenylseleno)hexane \((124a)\) with tri-n-butyltin hydride in hexane at various temperatures.

**Table 15.** Kinetic data for the reaction of 1-\((\text{E}-\text{hex-2-en-1-oxy})\)-2-(phenylseleno)hexane \((124a)\) in hexane.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu3SnH] ([\text{M}])</th>
<th>([\text{cis}]/[\text{trans}])</th>
<th>([126]/[127])</th>
<th>(k_c/k_H)</th>
<th>(k_c (s^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>-33</td>
<td>0.98</td>
<td>1.2</td>
<td>2.23</td>
<td>2.27 ((\pm 73%))</td>
<td>7.9 x10^5</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
<td>1.2</td>
<td>2.16</td>
<td>2.12</td>
<td>2.0 x10^6</td>
</tr>
<tr>
<td>26</td>
<td>0.98</td>
<td>1.2</td>
<td>2.62</td>
<td>2.56</td>
<td>3.7</td>
</tr>
<tr>
<td>60</td>
<td>1.81</td>
<td>1.2</td>
<td>2.32</td>
<td>4.20</td>
<td>1.1 x10^7</td>
</tr>
<tr>
<td>90</td>
<td>1.81</td>
<td>1.2</td>
<td>2.59</td>
<td>4.69</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The data for \(k_c\), the total cyclization rate constant, indicate that \(124a\) cyclizes faster than the corresponding alkenyl radicals (e.g., hexenyl), but this is not unexpected as the ether linkage reduces the exo transition structure strain energy due to the more favourable C-O-C bond angle (see Chapter 2 for a detailed discussion). The data also show that the cyclization proceeds to afford mainly the cis-disubstituted product, however, the cis/trans ratio of 1.2 suggests that the activation parameters of the two cyclization routes are fairly comparable. It is curious to note the invariance of the cis/trans ratio with temperature; however, it is not certain whether or not this observation is a manifestation of the averaging of the scattering in the raw data.

The crude data available for the \(Z\)-isomeric radical \((121)\) indicate that cyclization occurs with a rate constant of about \(4 \times 10^6 \text{ s}^{-1}\) at 25° with a cis/trans ratio of 1.3. Also suggested is a ratio of 1.5 at 80°. These results compare favourably with those obtained for the E-isomer \((120)\) indicating that there is no profound rate difference between the two geometric isomeric radicals and that the stereochemical control in these reactions appears to be essentially independent of the double bond geometry.

**Summary**

This chapter has investigated the effect of radical geometry on the rates and stereochemistry of cyclization. It has been shown that the 6-methylene-cyclodecyl radical \((98b)\) cyclizes with rate constants considerably larger than those of
other alkenyl radicals suggesting rate enhancement due to favourable entropic and enthalpic factors associated with trans-annular ring closure. It is not clear why the cyclization affords mainly the cis stereochemistry of products.

It has also been observed that E- and Z- isomeric alkenyloxy-alkyl radicals (113, 114, 120, 121) show essentially no difference in their cyclization rates and appear to cyclize in essentially identical modes to afford mainly cis-disubstituted tetrahydrofurans. These results agree favourable with the strain energy calculations performed on the parent system, the E- and Z- oct-6-en-2-yl radicals.
CHAPTER 4

The Effect of Substitution at Position 1 in the Cyclization of Alkenyl Radicals.

As was discussed in earlier chapters, the factors controlling the stereoselectivity of 1-substituted hexenyl-type radicals are still not clear. Few hypotheses have been suggested. Among these we find explanations incorporating the importance of secondary orbital effects and polarity in the various transition states (see Introduction). An alternative explanation, based on strain-energy calculations performed on appropriately substituted hexenyl radicals, has been suggested in Chapter 2. This hypothesis rests on the premise that the stereoselectivity is the result of a delicate balance between opposing unfavourable steric interactions in the respective cis- and trans- transition structures.

This chapter discusses the experimental evidence for and against the various suggested hypotheses. It will be seen that the nature of the substituent can have a major effect on both the rate of cyclization and stereochemical outcome of these reactions.

The chapter is divided into three sections. The first of these details the reactions performed in non-polar solvents such as hexane and benzene, and discusses the evidence supporting the stereo-electronic hypothesis concerning the stereochemistry of these cyclizations. The next section covers the effect of solvent on the observed stereochemistries, where it will be seen that polar solvents tend to increase the stereoselectivity in some systems. The third and last section discusses the experimental problems encountered in the project, including the syntheses of the various radical precursors and product standards.

i. The Effect of Substituent in Non-Polar Solvent.

A variety of free-radical precursors were prepared for this study. These include halides, thionocarbonates and thiohydroxamic esters which were prepared as described in part iii. of this chapter. Figure 7 depicts the radicals and corresponding precursors studied in this work. The radical (121), generated from the phenylselenide (124b), as discussed in Chapter 3, has been included for
<table>
<thead>
<tr>
<th>Radical</th>
<th>Precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Radical 18" /></td>
<td><img src="image2" alt="Precursor 127" /></td>
</tr>
<tr>
<td><img src="image3" alt="Radical 71" /></td>
<td><img src="image4" alt="Precursor 128" /></td>
</tr>
<tr>
<td><img src="image5" alt="Radical 129" /></td>
<td><img src="image6" alt="Precursor 129" /></td>
</tr>
<tr>
<td><img src="image7" alt="Radical 131" /></td>
<td><img src="image8" alt="Precursor 132" /></td>
</tr>
<tr>
<td><img src="image9" alt="Radical 133" /></td>
<td><img src="image10" alt="Precursor 134" /></td>
</tr>
<tr>
<td><img src="image11" alt="Radical 135" /></td>
<td><img src="image12" alt="Precursor 136" /></td>
</tr>
<tr>
<td><img src="image13" alt="Radical 137" /></td>
<td><img src="image14" alt="Precursor 138" /></td>
</tr>
<tr>
<td><img src="image15" alt="Radical 139" /></td>
<td><img src="image16" alt="Precursor 140" /></td>
</tr>
<tr>
<td><img src="image17" alt="Radical 121" /></td>
<td><img src="image18" alt="Precursor 124b" /></td>
</tr>
</tbody>
</table>

**Figure 7.** Depicting the radicals and their corresponding precursors in this study.
completeness. The systems studied represent a variety of sterically demanding and electronically interacting 1-substituted hexenyl radicals.

Free-radical reactions were generally performed under pseudo first-order conditions using a ten-fold excess of tri-n-butyltin hydride in either hexane or benzene as detailed in Appendix A. Reaction yields were in excess of 90% as determined by GC analysis of the product mixtures and comparison with incorporated octane, decane, dodecane or pentadecane internal standards as appropriate. Products were identified by GC comparison with authentic samples as discussed in part iii. of this chapter. Rate constants and activation parameters were determined by the application of the appropriate integrated rate equation for irreversible cyclization under pseudo first-order conditions (A3) and the Arrhenius equation (A10) respectively as discussed in Appendix A.

\[
\frac{[C]}{[U]} = \frac{k_c}{k_H} \frac{1}{[Bu_3SnH]} \quad \text{...A3}
\]

\[
k = Ae^{-(E_a/RT)} \quad \text{...A10}
\]

Standard values of \(k_H\), as determined by Ingold and co-workers\(^{28c}\) for alkyl radical hydrogen abstraction from tin hydride, were employed in the determination of the cyclization rate constant, \(k_c\) (see Appendix A). Detailed kinetic data for the reactions studied in this work appear in Appendix A.

Scheme 24
As expected on the basis of the work of Julia and co-workers\textsuperscript{117}, the delocalized radicals (129, 133) proved to cyclize reversibly. This was inferred from the experimental data which did not appear to fit equation A3 and from dilution experiments in which it was observed that when the concentration of tin hydride was small (−0.01 M), the thermodynamically more stable endo cyclized product (141) appeared in the reaction mixture of the cyclization of 129. Clearly both pathways to give exo and endo products (Scheme 24) are unimolecular. As we were observing a concentration dependence favouring the thermodynamically more stable product at lower tin hydride concentrations, reversibility of the cyclization step is occurring and cannot be neglected.

Similar results were observed with 133 which cyclized exclusively in the exo mode and showed preferential formation of the trans cyclized product (142), the thermodynamically more stable of the possible exo products, at lower tin hydride concentration.

Thus, for 129 and 133 reactions were performed under pseudo first-order and second-order (1.0 equivalent of tin hydride) conditions as discussed in Appendix A. Application of the appropriate (reversible) integrated rate equations A7 and A9\textsuperscript{9}, for pseudo first-order and second-order conditions respectively, to the results obtained for 129, as tabulated in Appendix A, yielded values of the cyclization rate constant, \( k_c \) and hydrogen abstraction rate constant, \( k_H \) which, when applied with the Arrhenius equation (A10) yielded the desired activation parameters.

\[
\frac{[C]}{[U]} = \frac{k_H}{k_H} \left( \frac{1}{K_E} \right) + \frac{k_H}{k_c} [\text{Bu}_3\text{SnH}] \quad \ldots \text{A7}
\]

\[
\frac{1}{[C]_f} = \frac{1 + \theta}{[\text{Bu}_3\text{SnH}]} + \frac{1}{2r} \quad \ldots \text{A9}
\]

# For explanations of the symbols used, consult Appendix A.
For radical (133) the data obtained were too scattered to allow the derivation of reliable values of the hydrogen abstraction rate constant, $k_H$. This, we believe, is mainly due to the lesser extent of reversibility exhibited by 133 as opposed to 129. As the determination of $k_H$ requires the determination of the equilibrium constant $K_E$, which in turn is related to the intercept in equation A7, scatter in this intercept would eventually be reflected as scatter in the values of $k_H$. As the lesser degree of reversibility (ie. larger $K_E$) results in a smaller value of the intercept of equation A7, any scatter in that intercept for 133 would show a larger percentage error in $k_H$ than that for 129. Accordingly, only relative activation parameters were obtained for 133.

Recently, Bowry$^{107}$, using a radical trapping technique$^{108}$ has studied the cyclization of 133 and has determined the total (cis + trans) cyclization rate constant to be $1.4 \times 10^5 \text{ s}^{-1}$ at 80°, leading to a value of the hydrogen abstraction rate constant, $k_H$ of $1.0 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 80°. This is somewhat slower than that observed by Ingold et al.$^{28c}$ for ordinary secondary alkyl radicals ($3.6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 80°) possibly because 133 is a delocalized radical, necessitating a later transition structure for hydrogen atom transfer from tri-n-butyltin hydride.

Surprisingly, the cyclization of the methoxy substituted radical (135) exhibited no reversibility, as it too is expected to be delocalized. The cis/trans ratio proved to be concentration (of tin hydride) independent at a given temperature and the kinetic data fitted equation A3. Supporting this observation, Glover and Pigou$^{118}$ failed to observe reversibility in the cyclization of the 3-butenyloxymethyl radical (143) using both conventional and ESR techniques.
As no values of $k_H$ were available for secondary $\alpha$-oxygen substituted radicals (i.e. 135) the value determined by Glover and Pigou\textsuperscript{118} for radical 143 ($3.5 \times 10^5$ M$^{-1}$ s$^{-1}$ at 25°) was used in this work.

Table 16 lists the calculated cis and trans rate constants at 25° for the cyclization of the radicals depicted in Figure 7 as determined from the data contained in Appendix A.

A number of interesting trends become apparent. Firstly, as previously discussed, radicals 129, 133 and 135 are expected to be conjugated. Accordingly, the transition states in each case must occur later along the reaction path, in order to maintain efficient orbital overlap between the radical $p$ orbital and the olefinic $\pi$ system. This effect would tend to increase the transition state strain energy as compared to the ground-state energy mainly because of the steric demand imposed by the shorter distance between C(1) and C(5) in the transition structure. This distance is dependent upon the extent of delocalization in the radical. Thus, the doubly delocalized radical (129) is observed to cyclize more slowly than the mono-delocalized system (133). The observation that the ester radical (133) cyclizes more slowly than the methoxy substituted radical (135), in both the cis and trans modes, probably reflects the relative stabilities of the radicals in each case. Thus, it is reasonable to conclude that the methoxy group is less stabilizing to the unpaired electron than is the ester functionality. This is in agreement with the observation that 133 cyclizes reversibly whereas 135 does not under the reaction conditions employed.

Secondly, inspection of Table 16 reveals that both modes of cyclization generally exhibit the trends expected on the basis of steric interference. The strain-energy analysis presented in Chapter 2 suggests that a delicate balance between opposing steric forces exist in the cyclization of 1-substituted hexenyl radicals. Thus, as expected, the cis transition structures are disfavoured by Van der Waals (VDW) interactions between the substituent at position 1 and C(6), while the trans transition structures are disfavoured by the unfavourable eclipsing of neighbouring groups (see discussion on pages 37-39). The net result is preferential formation of the trans product when the substituent at position 1 is sterically demanding, and formation of the cis product when the substituent is small.
Table 16. The rates of cyclization of various substituted \( \omega \)-alkenyl radicals in non-polar solvent.

<table>
<thead>
<tr>
<th>Radical</th>
<th>( k_{cis} )</th>
<th>( k_{trans} ) (s(^{-1})) at 25°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CO}_2\text{Et} )</td>
<td>( \sim 4 \times 10^4 )</td>
<td>-</td>
</tr>
<tr>
<td>( \text{CO}_2\text{Et} )</td>
<td>2.6 ( \times 10^4 )</td>
<td>4.9 ( \times 10^4 )</td>
</tr>
<tr>
<td>( \text{CO}_2\text{Et} )</td>
<td>( \sim 3 \times 10^4 )</td>
<td>( \sim 4 \times 10^4 )(^a)</td>
</tr>
<tr>
<td>( \text{OMe} )</td>
<td>2.8 ( \times 10^4 )</td>
<td>8.7 ( \times 10^4 )</td>
</tr>
<tr>
<td>( \text{OMe} )</td>
<td>6.7 ( \times 10^4 )</td>
<td>7.1 ( \times 10^4 )(^b)</td>
</tr>
<tr>
<td>( \text{CF}_3 )</td>
<td>7.1 ( \times 10^4 )</td>
<td>1.3 ( \times 10^5 )</td>
</tr>
<tr>
<td>( \text{CH}_3 )</td>
<td>1.3 ( \times 10^5 )</td>
<td>1.1 ( \times 10^5 )</td>
</tr>
<tr>
<td>( \text{O} )</td>
<td>1.9 ( \times 10^5 )</td>
<td>5.8 ( \times 10^4 )</td>
</tr>
<tr>
<td>( \text{O} )</td>
<td>4 ( \times 10^6 )</td>
<td>3 ( \times 10^6 )</td>
</tr>
</tbody>
</table>

\(^a\) From the work of Bowry\(^{107}\) as discussed in the text.
\(^b\) Assuming a value of \( k_H = 3.5 \times 10^5 \) l mol\(^{-1}\) s\(^{-1}\) at 25°C as determined by Glover and Pigou\(^{118}\) for the reaction of 3-butenyloxymethyl radical with tri-n-butyltin hydride as discussed in the text.
While the data displayed in Table 16 generally support this view, it becomes clear that this explanation is not solely responsible for the observed trends. Closer inspection of the data indicate that for the non-conjugated radicals studied (18, 71, 131, 137, 139), the rate constant for cis cyclization ($k_{cis}$) increases as the steric bulk of the substituents is decreased. Thus, the dicyclohexyl substituted system (131), being most sterically demanding, has a smaller value of $k_{cis}$ than the $t$-butyl substituted case (71). This trend is continued until the least demanding system (18) is reached, which cyclizes fastest, in the cis mode, of the radicals in question. These observations are as expected on the basis of the previously discussed stereo-electronic hypothesis. As the steric bulk decreases, so do the VDW interactions, resulting in faster cyclization.

Inspection of the data for the trans mode of cyclization reveals an unexpected trend. The bulkier systems (71, 131) have lower values for the trans cyclization rate constant ($k_{trans}$) than do the intermediate cases (137, 139). This is as expected on the basis of the hypothesis, bulkier substituents lead to increased torsion strain due to unfavourable neighbouring group eclipsing.

Unexpected, though, is the decrease in $k_{trans}$ observed as the substituent bulk is reduced even further. Thus, the least demanding case (18) is observed to cyclize, in the trans mode, even more slowly than the $t$-butyl substituted system (71). It is clear that the stereo-electronic hypothesis, developed in Chapter 2, cannot account for this observation. Some effect, disfavouring the trans mode of cyclization, beyond the steric factors already discussed, is operating, and increasingly so, as the steric bulk of the substituents is reduced.

It is not clear as to what other factors disfavouring the trans mode of cyclization are operating. Perhaps the effect is polar in nature. In any case, further work on suitably substituted systems is necessary, in order to fully understand the
effects in operation. Systems such as 144 and 145 have the potential of being able
to provide information on the importance of polar effects on the stereochemistry of
these reactions.

What is clear at this point is that the cis products, in the cyclization of
systems such as 18 and 139, are seen to predominate, not because the cis mode of
cyclization is favoured over the trans\textsuperscript{17,53} (as discussed in the Introduction), but
because the trans mode of cyclization is disfavoured over the cis. While steric factors
are important contributors to this observation, they can only partly account for the
experimental data.

The third effect is a result of the overall architecture of the transition
structures involved in the cyclization reactions. Thus, the oxygen containing system
(121), in which strain in the transition structure is relaxed by the favourable oxygen
atom geometry (see discussion in Chapter 2), is observed to cyclize fastest of all.
The effect is dramatic, 121 cyclizes almost 40 times faster than the carbon analogue
(137) at 25°.

Having investigated the factors affecting the observed rate constants, the
stereochemical preferences of the various systems were examined.

Table 17 lists the observed ratios of the cis and trans cyclization rate
constants (k\textsubscript{cis}/k\textsubscript{trans}) for the systems of interest at various temperatures. Further
details can be found in Appendix A.

Inspection of Table 17 reveals a number of trends. Firstly, as expected, in
all cases stereoselectivity increases with decreasing temperature. This is
exceptionally noticeable for the t-butyl-substituted system (71) which shows a
cis/trans ratio of 0.80 at 80°, 0.31 at 25° and 0.064 at -33°, a variation of a factor
of almost 13 over the temperature range in question.

Secondly, the delocalized radicals (133, 135) show little stereoselectivity
over the temperature range of the study. This suggests that both the cis and trans
modes of cyclization are essentially energetically identical.

Finally the oxygen containing system (121) is observed to cyclize
preferentially in the cis mode, as opposed to the carbon analogue (137). This
observation cannot readily be explained as the overall effect of transition structure
architecture, a result of the oxygen atom geometry, is not fully understood.
Presumably, as the factors affecting the stereochemical outcome of these reactions are subtle, slight increases in the degree of unfavourable eclipsing observed in the trans transition structure, could reverse the preferential trans stereochemistry observed for 137 to the cis stereochemistry observed for 121.

$$\begin{array}{c|c|c|c|c}
\text{Temperature} & -33^\circ & 0^\circ & 25^\circ & 80^\circ \\
\hline
131 & - & - & 0.48 & 0.60 \\
133 \text{ CO}_2\text{Et} & - & 0.88 & 0.87 & 0.90 \\
71 \text{ OMe} & 0.064 & 0.22 & 0.31 & 0.80 \\
135 \text{ CF}_3 & - & 0.96 & 0.96 & 0.96 \\
137 & - & 0.53 & 0.58 & 0.71 \\
139 \text{ CH}_3 & - & 1.33 & 1.20 & 1.07 \\
18 & - & - & 3.30 & 2.71 \\
121 & - & - & 1.5 & 1.3 \\
\end{array}$$

Table 17. Showing the values of $k_{\text{cis}}/k_{\text{trans}}$ for the cyclization of various substituted $\omega$-alkenyl radicals in non-polar solvent.

The data also allow closer examination of the hypothesis involving favourable secondary orbital interactions (see introduction). As discussed, Beckwith and co-workers$^{17,53}$ have suggested that the preferential cis mode of cyclization observed for 18 is a result of a favourable secondary orbital effect in the cis transition structure (19a) which does not occur in the trans.
This effect would be expected to operate in any system in which hydrogen atoms on the substituent at position 1 are \( \alpha \) to the radical centre. Thus, 137, on the basis of this model, would be expected to cyclize preferentially in the \textit{cis} mode. This is not observed, suggesting that the secondary orbital effect plays no important role in these reactions.

As the stereo-electronic model offers only partial explanation for the observed modes of cyclization for the hydrocarbon radicals studied, it would seem appropriate to conclude that further work in this area, concerning the nature of the factors disfavouring the \textit{trans} mode of cyclization, is necessary.

ii. The Effect of Solvent on the Cyclization of Substituted Hexenyl Radicals.

We were surprised to find that some of the systems studied exhibited varying stereoselectivities in solvents of varying polarity. Solvent effects have rarely been considered in radical reactions, which have generally been thought of as being non-polar and therefore mostly unaffected by the nature of the solvent.

Table 18 lists the observed \textit{cis}/\textit{trans} cyclized product ratios for the systems of interest. The data displayed represent a study at a variety of temperatures, of which samples at 25° and 80° in a variety of solvents of increasing polarity, ranging from hexane to \( n \)-propanol are given. Solvent polarity was gauged on the basis of
The solvents displayed are in increasing order of polarity. It should be noted that for solubility reasons, as discussed in part iii. of this chapter, 135 was studied in benzene as the non-polar solvent. Further details are found in Appendix A.

<table>
<thead>
<tr>
<th></th>
<th>hexane 25°</th>
<th>ether 25°</th>
<th>DME 25°</th>
<th>ethanol 25°</th>
<th>n-propanol 25°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80°</td>
<td>80°</td>
<td>80°</td>
<td>80°</td>
<td>80°</td>
</tr>
<tr>
<td>131</td>
<td>0.48</td>
<td>0.60</td>
<td>0.55</td>
<td>0.55</td>
<td>0.60</td>
</tr>
<tr>
<td>132</td>
<td>0.31</td>
<td>0.80</td>
<td>0.37</td>
<td>0.58</td>
<td>0.29</td>
</tr>
<tr>
<td>135</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
</tr>
<tr>
<td>137</td>
<td>0.58</td>
<td>0.71</td>
<td>0.57</td>
<td>0.73</td>
<td>0.57</td>
</tr>
<tr>
<td>139</td>
<td>1.20</td>
<td>1.07</td>
<td>1.86</td>
<td>1.51</td>
<td>1.70</td>
</tr>
<tr>
<td>18</td>
<td>3.30</td>
<td>2.71</td>
<td>3.51</td>
<td>2.75</td>
<td>3.56</td>
</tr>
<tr>
<td>121</td>
<td>1.5</td>
<td>1.3</td>
<td>1.5</td>
<td>1.3</td>
<td>1.5</td>
</tr>
</tbody>
</table>

a. Reaction performed in benzene as the non-polar solvent.

Table 18. The solvent and temperature dependence of the cis/trans ratio for the cyclization of various substituted o-alkenyl radicals.

Inspection of Table 18 reveals that most of the systems studied exhibit no solvent effect. The stereoselectivity is independent of the solvent used. There are however, three notable exceptions. Radicals (18, 71, 139) clearly display a solvent dependent stereoselectivity with greater selectivity correlating with increasing solvent polarity. Accordingly, the t-butyl-substituted case (71) shows a cis/trans ratio of 0.31 in hexane, 0.29 in DME, 0.23 in ethanol and 0.17 in n-propanol at 25°. Thus, 71 displays an almost two-fold increase in the stereoselectivity of cyclization in...
progressing from the non-polar solvent, hexane to the relatively polar case, propanol. Presumably, this stereoselectivity would show an even further increase in even more polar solvents, however, experiments designed to test this hypothesis were unsuccessful due to the limited solubility shown by tri-n-butyltin hydride in these polar solvents. Similar, but less dramatic, solvent dependences are exhibited by 18 and 139.

![Figure 8. Relative Arrhenius plots for comparison of the cis and trans modes of cyclization of the 2,2-dimethyloct-7-en-3-yl radical (71) in various solvents.](image)

In order to gain an understanding of the factors responsible for this effect, we focused our attention on radical (71), exhibiting the most pronounced effect.

We chose to examine the trends observed in the activation parameters as the solvent polarity was altered. The results are shown in Figure 8 in which plots of the logarithm of the trans/cis ratio as a function of reciprocal temperature for the various solvents studied are displayed. Inspection of Figure 8 reveals that the nature of the solvent has little effect on the activation energy associated with each mode of cyclization, the observed slopes of the plots are generally similar. It is of interest to note, however, that the ethereal solvents (ether, DME) appear to form a set of different slope to the others. This suggests, as the slope of the plots decrease...
slightly in going from the "ordinary" to the ethereal solvents, that the cis and trans modes of cyclization are energetically more equivalent in the ethers.

The most important effect suggested by Figure 8 concern the intercepts of the plots, which vary significantly in moving from non-polar to more polar solvent. This, in turn, suggests that the major factor responsible for the observed increase in stereoselectivity is entropic in nature. Similar conclusions are reached by examination of the data for 18 and 139. The data clearly indicate that the entropies of activation of the two modes of cyclization become less equivalent as the solvent polarity increases.

It is difficult to reach a satisfactory explanation for this effect, especially when considering the observation that the effect seems to increase the observed stereoselectivity in each case and that only non-conjugated systems lacking a substituent at position 6 appear to show this effect at all.

To the synthetic chemist wishing to design stereoselective syntheses based on radical cyclization methodology, this work suggests the following:

i. If a solvent effect is to be observed, then stereo-selectivity would be expected to be enhanced in polar solvents such as propanol rather than hexane or benzene.

ii. Stereoselectivity is also improved at lower temperatures. The advice, therefore, is to perform the cyclization reaction in a polar solvent, such as propanol, at low temperatures, such as 0° or lower.

It was also of interest to compare the relative cyclization rate constants for the various radicals in various solvents. As no values of $k_H$ are available for alkyl radicals abstracting hydrogen from tin hydride in solvents other than non-polar, only values of the cyclization rate constant relative to $k_H$ could be determined. These values are displayed in Table 19 in which the ratios of the cis and trans cyclization rate constant ($k_{cis}$, $k_{trans}$) to the hydrogen abstraction rate constant ($k_H$) are tabulated at 80° for the various systems of interest in solvents of varying polarity.

Inspection of Table 19 reveals that in all cases, except 139, the ratio of the cyclization rate constant ($k_c$) to $k_H$ (ie: $k_c/k_H$) decreases, for both modes of cyclization, as solvent polarity increases. This observation can be explained as a result of an increase in $k_H$ in the more polar solvents.
Table 19. Showing the solvent dependence of $k_{cis}/k_H$ and $k_{trans}/k_H$ for various $\omega$-alkenyl radicals in various solvents at 80°.

If we consider the radical addition process for ordinary hydrocarbon radicals as being the result of the p (SOMO) radical orbital interacting with the LUMO orbital of the $\pi$ system, the addition is nucleophilic in nature and the transition structure, if it were to be polarized, would be so as depicted in 146a. It is unlikely, however, that the magnitude of the polarization would be great, as no charge stabilizing substituents are present in the structure. Similarly, due to hyperconjugation by the groups R and R' and the favourable formation of a partial positive charge on the tin atom, the hydrogen atom transfer transition structure is likely to be as depicted in 147a. Accordingly, as solvent polarity increases, 147a is likely to be more effectively stabilized than the cyclization transition state (146a).

Thus, the hydrogen atom transfer process is likely to become faster relative to the cyclization process, resulting in a lowering of the value of $k_{cis}/k_H$, for both modes of
cyclization, in polar solvents, as is observed. The high values of $k_c/k_H$ observed for the methoxy-substituted system (135) reflects the lower values of $k_H$ associated with the conjugated radical, as previously discussed.

Inspection of Table 19 also reveals that the trifluoromethyl substituted system (139) exhibits a reverse solvent dependence. The values of $k_c/k_H$ increase with increasing solvent polarity for both modes of cyclization. This effect can be rationalized in terms of the electron-withdrawing ability of the CF$_3$ group which would result in a reversal of polarity in the cyclization transition structure (146b). The hydrogen atom transfer transition structure (147a) is likely to be destabilized when $R = CF_3$ and therefore reduced in polarity, or even polarity reversed, as shown in 147b. The tin atom in 147b would be less likely to accommodate a partial negative than a partial positive charge. Therefore, 147b, like 147a($R = CF_3$), is expected to be less polarized than 147a. Consequently, the hydrogen atom transfer rate constant, $k_H$, is expected to show a reduced solvent dependence when $R = CF_3$.

Likewise, due to the presence of the CF$_3$ group in 146b, it is likely to be more polarized and in the reverse sense to 146a. Thus, the rate of cyclization would be expected to increase in more polar solvents, resulting in the values of $k_c/k_H$ increasing as the solvent polarity in increased, as is observed for 139, for both modes of cyclization.

Previously discussed has been the idea that the observed preferential cis mode of cyclization for the methyl-substituted case (18) is the result of favourable
electrostatic interactions in a polar transition state^{17} (see Introduction). The data displayed in Table 19 show too little variation in the values of $k_c/k_H$ for the cyclization of 18 in solvents of increasing polarity, to support this view. Also, in light of the discussion in part i. of this chapter, the observed stereopreferences have been explained in terms of a disfavoured trans mode of cyclization, rather than a favoured cis mode of cyclization.

In summary, the data presented in part ii. of this chapter suggest that in certain instances, the stereoselectivity of the cyclization of 1-substituted alkenyl radicals increases in more polar solvents. This effect appears to be the result of favourable entropic factors operating in the more polar solvents. We have been unable to offer an explanation for these observations.

The data also suggest that polar solvents have an effect on the hydrogen atom transfer rate constant, $k_H$, for ordinary alkenyl radicals. Accordingly, $k_H$ appears to increase relative to $k_c$ in the more polar solvents. The reverse is true for the trifluoromethyl-substituted case (139) in which significant polar effects are expected to operate. These observations have been explained in terms of differing degrees of polarity in the various cyclization and hydrogen atom transfer transition states.

iii. The Preparation of Radical Precursors and Product Standards.

Of the radicals and corresponding precursors depicted in Figure 7, only the hept-6-en-2-yl (18), 1,1-diethoxy carbonyl hex-5-en-1-yl (129) and 1-ethoxy- carbonyl hex-5-en-1-yl (133) radicals have been studied previously. The radical (18) was re-investigated in this work as the initial work of Beckwith et al.^{53} did not include a solvent effect study, while the original work of Julia and Maumy^{117} into 129 and 133 did not involve the determination of any activation parameters.

The following sections describe the syntheses of the various free-radical precursors employed in this study and their subsequent reactions with tri-n-butyltin hydride. Full details of product ratios and activation parameters are found in Appendix A.
a. The Hept-6-en-2-yl Radical (18).

As this system had been studied previously\textsuperscript{53}, the bromo-precursor (127) was readily available.

Treatment of 127 with ten equivalents of tri-n-butyltin hydride (azo-bis-isobutyronitrile, AIBN, as initiator) in hexane (0.1M) afforded a mixture of products identified as cis- and trans- 1,2-dimethylcyclopentane (148, 149) (57%, 21% respectively) and 1-heptene (150, 22%) (Scheme 25). The products were identified by gas chromatographic comparison with authentic, commercially available\textsuperscript{119} product standards.

\[
\begin{align*}
\text{Br} & \quad \text{Bu}_3\text{SnH (0.1M)} \\
\text{hexane, 80°} & \quad \text{127} \\
& \quad \text{148} \quad 57\% \\
& \quad + \\
& \quad \text{149} \quad 21\% \\
& \quad + \\
& \quad \text{150} \quad 22\%
\end{align*}
\]

**Scheme 25**

These results lead, by the application of the appropriate integrated rate equation (see Appendix A), to a total (cis + trans) cyclization rate constant of 1.2 x 10^6 s\textsuperscript{-1} at 80°, in good agreement with the previously determined\textsuperscript{53} value of 1 x 10^6 s\textsuperscript{-1} at 80°. The cis/trans ratio of 2.7 at 80° also compares favourably with the already determined\textsuperscript{90} value of 2.0 at 80°. The latter value may reflect previous difficulties in resolving 149 and 150 during gas chromatography.

\[
\begin{align*}
\text{OH} & \quad \text{152} \\
\text{PhOC(S)Cl / py} & \quad \text{151}
\end{align*}
\]

**Scheme 26**

As in certain cases, thionocarbonates were used as the radical precursors, it was of interest to compare their decomposition with the decomposition of the more
conventional halides. Therefore, \( \text{O-(hept-6-en-2-yl)-O-phenylthionocarbonate (151)} \) was prepared from the corresponding alcohol (152) and phenylchlorothionocarbonate in the usual way, as depicted in Scheme 26.

Reaction of the thionocarbonate (151) with tin hydride, under identical conditions to those depicted in Scheme 25 for 127, gave identical results to those obtained for the halide (127). These results were encouraging and indicated that thionocarbonates do indeed decompose to give the desired radicals which react further to give products which are independent of the nature of the precursor.

b. The 1,1-Diethoxycarbonylhex-5-en-1-yl (129) and 1-Ethoxycarbonylhex-5-en-1-yl (133) Radicals.

The desired halide precursors to the radicals (129, 133) were prepared as outlined in Scheme 27.

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
& \quad \text{i. NaH} \\
& \quad \text{ii. Br} \\
\rightarrow & \quad 153 \quad 75\% \\
\end{align*}
\]

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
& \quad \text{i. NaH} \\
& \quad \text{ii. NXS} \\
\rightarrow & \quad 130 \quad X = \text{Cl} \quad 81\% \\
& \quad 154 \quad X = \text{Br} \quad 78\% \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \text{CO}_2\text{Et} \\
& \quad \text{i. NaOH} \\
& \quad \text{ii. } \Delta \\
\rightarrow & \quad 134 \quad X = \text{Cl} \quad 69\% \\
& \quad 156 \quad X = \text{Br} \quad 16\% \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \text{CO}_2\text{H} \\
& \quad \text{i. SOCl}_2 \\
& \quad \text{ii. EtOH} \\
\rightarrow & \quad 155 \\
\end{align*}
\]

**Scheme 27**

Diethyl malonate was alkylated using 5-bromopentene to give diethyl hex-5-en-1,1-dicarboxylate (153) in good yield. Treatment of 153 with sodium hydride in dimethylformamide (DMF) followed by N-chloro- or N-bromo- succinimide gave the halide precursors (130, 154) to the radical 129. Hydrolysis of the ester groups in each case followed by thermal decarboxylation yielded the \( \alpha \)-halo acid (155) which was converted to the required ethyl ester (134, 156) by the action of thionyl chloride followed by ethanol.
As it turns out, either the chlorides (130, 134) or the bromides (154, 156) are suitable precursors for generating the desired radical, which then reacts to give both cyclized and uncyclized products. However, the bromides (154, 156) initiate far too readily for use in kinetic studies. The high reactivity of the bromides in these cases probably reflects the stability of the radicals being generated. Consequently, the less reactive chlorides\textsuperscript{113} (130, 134) were used as the precursors in this study.

Treatment of 130 with one equivalent of tri-n-butyltin hydride (AIBN initiator) in benzene at an initial concentration of 0.13M at 80° yielded two products which were identified as diethyl 2-methylcyclopentane-1,1-dicarboxylate (157, 41%) and the directly reduced diester (153, 59%) depicted in Scheme 28.

![Scheme 28](image)

All products were identified by gas chromatographic comparison with authentic samples. When the tin hydride concentration was reduced to 0.01M, a third product appeared in the reaction mixture (≈5%) identified as diethyl cyclohexane-1,1-dicarboxylate (141). The presence of 141 in the reaction mixture at low tin hydride concentrations is proof of reaction reversibility, as previously discussed. An authentic sample of 157 was isolated from the above reaction mixture (Scheme 28) by preparative gas chromatography, using the bromide (154) as the radical precursor and a tin hydride concentration of 0.06M in benzene. Isolated in this manner, 157 proved to be identical to that previously reported\textsuperscript{117}.

An authentic sample of 141 was prepared by the method of Bergson and Biezaïs\textsuperscript{120} as shown in Scheme 29.

![Scheme 29](image)
Treatment of diethyl malonate with two equivalents of sodium ethoxide in ethanol followed by 1,5-dibromopentane afforded the desired diester (141) in 21% yield.

The chloro-ester (134) also reacted smoothly with tri-\textit{n}-butylin hydride (10 equiv., 0.18M) in benzene at 70° to give three products identified in the usual way as ethyl \textit{cis}-2-methylcyclopentane-carboxylate (158, 18%), its \textit{trans} isomer (142, 21%) and the directly reduced product, ethyl hept-6-enoate (159, 61%) (Scheme 30).

![Scheme 30](image)

An authentic sample of 159 was prepared by the sodium chloride/ DMSO/ water decarboxylation\textsuperscript{11d} of the diester (153) (Scheme 31) while an authentic sample of 142 was prepared by the method of Nenitzescu and Ionescu\textsuperscript{121} as depicted in Scheme 32.

![Scheme 31](image)

Reaction of cyclohexane with aluminium chloride and acetyl chloride yielded the ketone (160) which was degraded with sodium hypobromite to the \textit{trans} carboxylic acid (161). \textsuperscript{1}H nmr spectroscopy indicated that the acid (161) was contaminated with ~ 5% of the \textit{cis} isomer. Conversion of 161 into the desired ester (142) using thionyl chloride followed by ethanol proceeded smoothly. \textsuperscript{1}H nmr
spectroscopy revealed that the cis contamination observed for the acid (161) was carried through into the ester (142).

Scheme 32

In order to prove the assignment of the cis structure (158), it was isolated from the reaction mixture by preparative gas chromatography, after treating ethyl 2-(4-methyl-phenylthio)hept-6-enoate (162) with tin hydride (Scheme 33). Substantial quantities of 162 were originally prepared, by the alkylation of ethyl 2-(4-methylphenylthio)acetate (163) with 5-bromopentene, in the hope that it would be a suitable precursor to the radical (133). While 133 was generated from 162, the
radical chain process proved too inefficient for kinetic studies, requiring repeated additions of the radical initiator (AIBN) to effect complete reaction. Phenylthiolates are well known to be inefficient radical precursors\(^{113}\).

c. The 2,2-Dimethyloct-7-en-3-yl Radical (71).

It was our initial intention to generate the title radical (71) from 3-bromo-2,2-dimethyloct-7-ene (164). However, 164 could not be prepared from the readily available 2,2-dimethyloct-7-en-3-ol (165). Even when the method of Bunnett and co-workers\(^{122}\), using tetrabutylammonium bromide in acetone, a method successful at converting primary neo-pentyl mesylates and tosylates into their corresponding bromides, was employed, no bromide (164) was isolated (Scheme 34).

The alcohol (165) was prepared by the addition of 4-pentenylmagnesium bromide to trimethylacetaldehyde. As an alternative to the bromide (164), 165 was converted into the thionocarbonate (128) as depicted in Scheme 35.

Treatment of the thionocarbonate (128) with ten equivalents of tri-n-butyltin hydride (0.09M) in hexane at 60° yielded three products identified as cis-1-1-butyl-2-methylcyclopentane (166, 22%), its trans isomer (167, 35%) and the directly reduced 7,7-dimethyloct-1-ene (168, 43%) as illustrated in Scheme 36.
Scheme 36

When the reaction was repeated using 3.0M tin hydride, only a single product was detected. This product was isolated by preparative gas chromatography and fully characterized. Nmr spectral analysis showed this product to be the olefin (168).

Identification of the cis and trans cyclic products (166, 167) proved to be more difficult. They were eventually isolated by preparative gas chromatography after 128 was reduced with 0.06M tri-n-butyltin hydride in hexane. Unfortunately, it was not possible to assign the stereochemistries to 166 and to 167 on the nmr evidence alone. The major isomer, of higher gas chromatographic retention time, contained a doublet (δ 0.85, J=7.1Hz) corresponding to the methyl group and a singlet (δ 0.93) corresponding to the t-butyl group in the 1H nmr spectrum. The minor isomer revealed a doublet (δ 0.97, J=6.8Hz) and a singlet (δ 0.84) for the equivalent groups in its structure. Also 13C nmr spectroscopy on the two isomers proved to be of limited use. The major product showed signals at δ 54.7, 35.5, 34.8, 29.3, 23.0 and 16.8 ppm, while the minor isomer had signals at δ 57.6, 36.3, 34.4, 29.4, 27.9, 25.6 and 23.8 ppm in its 13C nmr spectrum. Unlike cyclohexane derivatives, where shielding effects are readily recognizable due to the clearly defined axial and equatorial positioning of groups, cyclopentane derivatives do not allow clear spectral interpretation as the 5-membered ring is much flatter than the 6-membered system. Accordingly, pseudo-axial and pseudo-equatorial positions are much more equivalent in the cyclopentane series. Thus, proof of structure was obtained by an alternative approach, depicted in Scheme 37.
Cyclopentanone was converted into its trimethylsilyl ether derivative (169) with chlorotrimethylsilane and triethylamine in DMF\textsuperscript{124}. Reaction of 169 with 1-butyl chloride and titanium tetrachloride as described by Reetz and co-workers\textsuperscript{125} afforded 2-1-butylcyclopentanone (170) in moderate yield. Methylenation of the ketone (170) using freshly prepared zinc/titanium tetrachloride/dibromomethane reagent, as described by Lombardo\textsuperscript{126}, resulted in the smooth conversion of 170 into the corresponding olefin (171). Hydrogenation of 171 using hydrogen and 10% palladium on carbon gave two compounds as evident by gas chromatography. Nmr spectral analysis of the reaction mixture revealed that the major isomer (95%) corresponded to the minor cyclic isomer in Scheme 36.

On the basis of the hydrogenation reaction, the minor isomer in Scheme 36 is assigned to be cis-1-1-butyl-2-methylcyclopentane (166) with the major cyclic isomer, corresponding to the minor (5%) product in Scheme 37, assigned to be trans-1-1-butyl-2-methylcyclopentane (167).

d. The Z-Tridec-9-en-5-yl Radical (137).

The title radical was generated from the corresponding thionocarbonate (138), prepared as outlined in Scheme 38.

Reaction of 2-hydroxytetrahydropyran with n-butylidenetriphenylphosphorane in DMSO gave Z-non-5-en-1-ol (172) in 47% yield. $^{13}$C nmr
spectroscopy indicated that 172 was contaminated with ~8% of the isomeric E-olefin. This observation is consistent with the work of Ohloff et al. who report a similar isomeric contamination in this Wittig reaction127.

Pyridinium dichromate oxidation of the alcohol (172) to the corresponding aldehyde followed by Grignard reaction with n-butylmagnesium bromide, afforded Z-tridec-9-en-5-ol (173) in 40% overall yield. The alcohol (173) was converted to the thionocarbonate (138) in the usual way.

Scheme 38

The thionocarbonate (138) was contaminated with ~8% of the E- isomer. The purity of 138 was considered sufficient for our purposes, as the relative errors resulting from the E-isomer contamination are likely to be smaller than the relative errors in the activation parameters arising from the experimental conditions, and errors in the reported values of the hydrogen transfer (from tin hydride) activation parameters28c.

Scheme 39
Treatment of the thionocarbonate (138) with ten equivalents of tri-n-butyltin hydride (0.2M) in hexane (AIBN initiator) at 80° yielded three products. These were identified, by gas chromatography in the usual way, as cis-1,2-di-n-butylcyclopentane (174, 27%), its trans isomer (175, 37%) and the directly reduced product, Z-tridec-4-ene (176, 36%) (Scheme 39).

The olefin (176) was identified by comparison with an authentic sample, prepared by the action of n-butylidenetriphenylphosphorane on n-nonanal in DMSO as depicted in Scheme 40.

The isomeric cyclic products (174, 175) were identified by the hydrogenation of appropriate alkenes as shown in Schemes 41 and 42.

Conversion of cyclopentanone into its morpholine enamine derivative (177) by the method of Stork and co-workers128, followed by reaction with 1-bromobut-2-
ene and then hydrogenation using hydrogen with 10% palladium on carbon in pentane, afforded 2-n-butylcyclopentanone (178) in moderate yield. Treatment of the ketone (178) with n-butylmagnesium bromide in ether gave the diastereomeric pair of alcohols (179) in 35% yield, which were then dehydrated to give primarily 1,2-di-n-butylcyclopent-1-ene (180, 80%) as well as other olefinic isomers, in near quantitative yield.

The olefin (180) could not be reduced with hydrogen and palladium on carbon in pentane, an observation attributed to the tetra-substituted double bond. When the hydrogenation was performed in acetic acid over a period of 48 hours, 180 was converted to the isomeric mixture of cyclic hydrocarbons (174, 175). 13C nmr spectral analysis of the mixture revealed two distinct sets of signals. The major set (δ 46.1, 35.5, 32.5, 30.9, 24.0, 14.3) was tentatively assigned to the cis isomer (174) while the minor set (δ 42.6, 35.5, 32.3, 30.2, 29.0, 14.1) was assigned to the trans isomer (175). Conclusive assignments could not be made as the hydrogenation conditions used (H2/Pd-C/AcOH) facilitate double bond migration during the reaction129 and it is unclear what effect this would have on the stereochemistry of hydrogenation.

Therefore, an alternative olefin (181) was prepared as outlined in Scheme 42.

Treatment of 2-n-butylcyclopentanone (178) with n-butylidenediarylphosphorane in DMSO gave an isomeric mixture of 1-n-butyl-2-n-butylidenecyclopentanes (181) in 29% yield. Hydrogenation of these olefins (181) under non-bond migratory conditions (H2/Pd-C/pentane) yielded the two expected cyclic hydrocarbons (174, 175) with the major product constituting 91% of the mixture and assigned to be the cis isomer (174). The experiment outlined in Scheme 42 confirms the assignments made on the basis of the previous hydrogenation reaction, depicted in Scheme 41.

Scheme 42
The mixture of cis and trans cycloalkanes (174, 175) obtained from the hydrogenation of the olefinic precursors (180, 181) was compared by gas chromatography with the mixture derived from the reaction of the thionocarbonate (138) with tin hydride (Scheme 39). This comparison confirmed that the major cyclic hydrocarbon product in the radical reaction mixture is indeed trans-1,2-di-n-butylcyclopentane (175), with the minor cyclic product being the cis isomer (174).

e. The 1-Methoxyhex-5-en-1-yl Radical (135).

The title radical was initially envisaged as being generated from the chloride precursor (182). However, attempted preparation of 182 from the aldehyde (183) and hydrogen chloride in methanol, as described by Klages and Muehlbauer did not achieve the required conversion. \(^{1}\)H nmr analysis of the product mixture indicated an absence of unsaturated material. The spectrum is consistent with rearrangement to give the cyclohexane derivative (184), probably through the hemi-acetal intermediate (185) via the mechanism depicted in Scheme 43.

As the halide precursor could not be synthesized, and as the thionocarbonate could also not be prepared due to the sensitivity of the necessary hemi-acetal precursor (185), the thiohydroxamic ester (136) was prepared as outlined in Scheme 44.
Treatment of the bromoester (156) with excess sodium methoxide in methanol gave 2-methoxyhept-6-enoic acid (186). Presumably hydrolysis of the ester functionality occurs by trans-esterification followed by nucleophilic attack of methoxide, as depicted in Scheme 45. The acid (186), upon treatment with thionyl chloride followed by 1-hydroxy-5-methyl-(1H)-thiazolin-2-thione and dimethylaminopyridine (DMAP) in ether afforded the required thiohydroxamic ester (136).

Thiohydroxamic esters are efficient radical precursors, as reported by Barton and co-workers. They decompose and react with tin hydride, producing radicals in the manner shown in Scheme 46.
When the thiohydroxamic ester (136) was treated with tri-n-butyltin hydride (0.18M) in benzene (AIBN initiator) at 45°, three products were detected by gas chromatography in the usual way. These were identified as being cis-1-methoxy-2-methylcyclopentane (187, 37%), its trans isomer (188, 39%) and the directly reduced 1-methoxyhex-5-ene (189, 24%), as illustrated in Scheme 47. It should be noted that 136 is not soluble in hexane.

![Scheme 47](image)

An authentic sample of 189 was prepared by treating hex-5-en-1-ol with sodium hydride in dimethoxyethane (DME) followed by the addition of iodomethane (Scheme 48).

![Scheme 48](image)

The isomeric ethers (187, 188) were identified by gas chromatographic comparison with an authentic sample of a known mixture of ethers (187, 188) as shown in Scheme 49.

Reduction of 2-methylcyclopentanone with lithium aluminium hydride in ether at 0° is well known\(^{132}\) to afford an 80:20 mixture of trans- and cis-2-methylcyclopentanols (190) respectively. This expectation was confirmed when \(^1H\) and \(^13C\) nmr analyses agreed with those reported\(^{132}\). Treatment of this mixture of alcohols (190) with sodium hydride followed by iodomethane yielded a mixture of
the required ethers (187, 188). $^{13}$C nmr spectroscopy confirmed that the original isomer ratio had been retained. Thus, comparison by gas chromatography of this known mixture with that from the tin hydride reduction (Scheme 47) revealed that the major product in each case was indeed the trans ether (188).

$$\text{Scheme 49}$$

i. $\text{NaH}$

ii. $\text{MeI}$

$190a$: cis 20%

$187$: cis 20%

$188$: trans 80%

$\text{f. The 1,1,1-Trifluorohept-6-en-2-yl Radical (139).}$

The title radical was generated from its thionocarbonate precursor (140), prepared as outlined in Scheme 50.

$$\text{Scheme 50}$$

Reaction of ethyl trifluoroacetate with two equivalents of 4-pentenylmagnesium bromide in ether gave the secondary alcohol (191) in 56% yield which was then converted, in the usual way, into the corresponding thionocarbonate (140).

The Grignard reaction, depicted in Scheme 50, requires two equivalents of the Grignard reagent. The first equivalent adds to the ester, while the second equivalent presumably reduces the ketone thus formed to the required alcohol (Scheme 51). This process is well documented for $\alpha$-tri-fluoromethyl ketones.$^{133}$
Treatment of the thionocarbonate (140) with ten equivalents of tri-n-butyltin hydride (0.2M) in hexane at 80° in the usual way afforded three products as evident by gas chromatography. Two of these products were identified as cis-1-methyl-2-trifluoromethylcyclopentane (192, 32%) and the trans isomer (193, 29%) by comparison with authentic samples. The third product (39%) was assigned to be the directly reduced product, 1,1,1-trifluorohept-6-ene (194). Only this third product was removed from the reaction mixture upon treatment with excess bromine. It is highly likely, therefore, that this third compound is the olefin (194) (Scheme 52).

\[ \text{OC(S)OPh} \]  
\[ \text{CF}_3 \]

\[ \text{140} \]  
\[ \text{hexane, 80°} \]  
\[ \text{0.2M Bu}_3\text{SnH} \]

\[ \text{CF}_3 \]

\[ \text{192} \]  
\[ 32\% \]

\[ \text{193} \]  
\[ 29\% \]

\[ \text{194} \]  
\[ 39\% \]

\[ \text{+} \]  
\[ \text{cis} \]

\[ \text{trans} \]

Scheme 52

Identification of the two cyclopentane derivatives (192, 193) was achieved as illustrated in Scheme 53.

\[ \text{CO}_2\text{H} \]  

\[ \text{161} \]  
\[ 5\% \text{ cis} \]
\[ 95\% \text{ trans} \]

\[ \text{SF}_4 \]  
\[ \text{120°} \]

\[ \text{192} \]  
\[ 5\% \text{ cis} \]
\[ 193 \]  
\[ 95\% \text{ trans} \]

Scheme 53

Reaction of the trans acid (161), containing 5% of the cis isomer, with sulfur tetrafluoride at 120° for 10 hours yielded trans-1-methyl-2-trifluoromethylcyclopentane (193) containing 5% of the cis isomer (192). This isomer distribution was confirmed by $^{13}$C nmr spectroscopy.

Comparison of this mixture with that obtained by the tin hydride reduction of the thionocarbonate (140) (Scheme 52) revealed that the dominant product in the tin hydride reduction was indeed the cis isomer (192).
g. The 1-Cyclohexyl-5-cyclohexylidenepent-1-yl Radical (131).

The thionocarbonate (132) was prepared as the precursor of the title radical (Scheme 54).

```
\begin{center}
\begin{tikzpicture}
  \node[anchor=east] at (0,0) {\text{Wittig reaction of cyclohexanone with (4-carboxybutyl)triphenylphosphonium bromide and sodium hydride followed by reduction of the product acid with lithium aluminium hydride, afforded 5-cyclohexylidenepentan-1-ol (195) in 31\% yield. This alcohol (195) was oxidized to the corresponding aldehyde, using pyridinium dichromate, and then reacted with cyclohexylmagnesium bromide to give 1-cyclohexyl-5-cyclohexylidenepentan-1-ol (196). The alcohol (196) was converted into the corresponding thionocarbonate (132) by the action of phenylchlorothionocarbonate and pyridine in dichloromethane.}}

Wittig = \text{Ph}_3\text{P} \equiv \text{CO}_2^-

\begin{align*}
\text{Wittig reaction of cyclohexanone with (4-carboxybutyl)triphenylphosphonium bromide and sodium hydride followed by reduction of the product acid with lithium aluminium hydride, afforded 5-cyclohexylidenepentan-1-ol (195) in 31\% yield. This alcohol (195) was oxidized to the corresponding aldehyde, using pyridinium dichromate, and then reacted with cyclohexylmagnesium bromide to give 1-cyclohexyl-5-cyclohexylidenepentan-1-ol (196). The alcohol (196) was converted into the corresponding thionocarbonate (132) by the action of phenylchlorothionocarbonate and pyridine in dichloromethane.}
\end{align*}
\end{center}
```
The olefin (197) was readily identified. It was prepared by the reduction of the methanesulfonate (200) (Scheme 56).

Identification of the cyclized products (198, 199) proved very difficult. As no straight-forward synthesis of either 198 or 199 could be envisaged, preparative gas chromatography of the radical cyclization reaction mixture was attempted.

The cyclization reaction (Scheme 55) was repeated on a larger scale using one equivalent of 0.03M tin hydride. Under these reaction conditions, only very small amounts of the olefin (197) were detected. Preparative gas chromatography
proved unable to separate the cyclic isomers (198, 199), which were collected as a binary mixture (2:1). 200 MHz $^1$H nmr spectroscopy proved unable to resolve any signals of interest. $^{13}$C nmr spectroscopy showed two distinct sets of lines. The major set showed absorbtion signals at $\delta$ 47.5, 42.0, 33.0, 29.1, 28.9, 27.2, 27.0, 26.9 and 26.8 ppm, while the minor isomer absorbed at $\delta$ 48.2, 37.8, 33.6, 31.1, 28.3, 28.1, 26.1, 25.7 and 23.8 ppm. Due to symmetry and the near planarity of the cyclopentane ring, as previously discussed, it was not possible to unambiguously assign structures to the two isomers (198, 199) on the basis of the nmr data.

However, considering the steric bulk of the substituents on radical 131 and bearing in mind the stereochemical discussions presented in Chapter 2 and part i. of this chapter, it is unlikely that 131 would prefer to cyclize in the cis mode. Consequently, the major product in the cyclization of 131 has been assigned the trans structure (199) while the minor product has been assigned the cis structure (198).

![131](image)

When kinetic experiments involving 131 were performed, the derived kinetic data were too scattered to allow reliable determination of activation parameters. This, we believe, is a reflection of the poor gas chromatographic separation achieved for the three observed products. Consequently, gas chromatographic peak integration contained non-negligible errors. Appendix A lists the data as obtained for 131.

**Summary**

This section of this chapter has served to highlight the syntheses of the various radical precursors and product standards employed in this work. The methods used and problems encountered in preparing the precursors, generating the radicals and identifying the products have also been discussed.
EXPERIMENTAL SECTION

General

a. Melting points were determined on a Kofler Hot Stage microscope apparatus. Melting and boiling points are uncorrected.

b. Elemental analyses were performed by the A.N.U. Analytical Service.

c. Infra-red spectra were recorded on a Beckman IR-10 Infra-Red Spectrophotometer. Significant absorptions (cm⁻¹) are reported.

d. Electron Impact (EI) Mass Spectra were measured on a VG Micromass 7070-F Mass Spectrometer operating at 70 eV. The molecular ion (M⁺) and selected fragment ions are reported as their mass/charge ratios (m/z) followed by their relative intensities as compared with the base (100%) fragment. All mass spectra are EI unless otherwise indicated.

Chemical Ionization (CI) Mass Spectra were measured on the above instrument employing ammonia as the reagent gas.

High Resolution Mass Spectra were determined on an AEI MS 902 High Resolution Mass Spectrometer.

e. Proton (¹H) nmr spectra were measured on either:

1) A JEOL PNM FX-200 spectrometer operating at 200 MHz.
2) A JEOL MH-100 spectrometer operating at 100 MHz.
3) A JEOL JNM-PMX60 spectrometer operating at 60 MHz.

Spectra were recorded in deuterochloroform (CDCl₃, 99.5% deuterium incorporation), unless otherwise stated, and reported as: spectrometer (60, 100, 200) followed by the proton signal chemical shift (δ) in parts per million (ppm) downfield from an internal tetramethylsilane (TMS) standard. Assignments, intensities (number of protons) and coupling constants (J Hz), where appropriate, follow the reported chemical shifts in parentheses. Abbreviations used include:

s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

f. Carbon-13 (¹³C) nmr spectra were recorded on the JEOL PNM FX-200 spectrometer operating at 50.1 MHz in deuterochloroform as described above. Chemical shifts (δ) are reported in parts per million (ppm) downfield from an internal TMS standard. Assignments and coupling constants (where appropriate) follow in parentheses.

g. Preparative Thin Layer Chromatographies (TLC) were performed with pre-coated glass plates (30x20 cm) of Merck Kieselgel 60 F₂₅₄ (0.2 cm thickness).
General

a. Melting points were determined on a Reichert Hot-Stage microscope apparatus. Melting and boiling points are uncorrected.

b. Elemental analyses were performed by the A.N.U. Analytical Service.

c. Infra-red spectra were measured on a Perkin-Elmer 683 Infra-Red Spectrophotometer. Significant absorbtions (cm$^{-1}$) are reported.

d. Electron Impact (EI) Mass Spectra were measured on a VG Micromass 7070 F Mass Spectrometer operating at 70 eV. The molecular ion (M$^+$) and selected fragment ions are reported as their mass/charge ratios (m/e) followed by their relative intensities as compared with the base (100%) fragment. All mass spectra are EI unless otherwise indicated.

Chemical Ionization (CI) Mass Spectra were measured on the above instrument employing ammonia as the reagent gas.

High Resolution Mass Spectra were determined on an AEI MS 902 High Resolution Mass Spectrometer.

e. Proton (1H) nmr spectra were measured on either:
   i) A JEOL PNM FX-200 spectrometer operating at 200 MHz.
   ii) A JEOL MH-100 spectrometer operating at 100 MHz.
   iii) A JEOL JNM-PMX60 spectrometer operating at 60 MHz.

Spectra were recorded in deuterochloroform (CDCl$_3$, 99.8% deuterium incorporation), unless otherwise stated, and reported as: spectrometer (60, 100, 200) followed by the proton signal chemical shift (δ) in parts per million (ppm) downfield from an internal tetramethylsilane (TMS) standard. Assignments, intensities (number of protons) and coupling constants (J (Hz), where appropriate) follow the reported chemical shifts in parentheses. Abbreviations used include: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

f. Carbon-13 (13C) nmr spectra were recorded on the JEOL PNM FX-200 spectrometer operating at 50.1 MHz in deuterochloroform as described above. Chemical shifts (δ) are reported in parts per million (ppm) downfield from an internal TMS standard. Assignments and coupling constants (where appropriate) follow in parentheses.

g. Preparative Thin Layer Chromatographies (TLC) were performed with pre-coated glass plates (20x20 cm) of Merck Kieselgel 60 F$_{254}$ (0.2 cm thickness).
h. Medium Pressure Liquid Chromatography (MPLC) was performed using a Merck LiChroprep Si 60 (40-63 µm) column. Compounds were detected using a Waters R-403 differential refractometer.

i. Gas Chromatographies were performed with capillary columns purchased from Scientific Glass Equipment, Melbourne, Australia or with ordinary packed columns as described. All columns were used in a Varian 6000 or Varian 3400 gas chromatograph equipped with Hewlett-Packard 3390A integrator.
Compound Index

<table>
<thead>
<tr>
<th>Compound</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- Bromo-2-(E-hex-2-en-1-oxy)ethane (115a)</td>
<td>18.</td>
</tr>
<tr>
<td>1- Bromo-2-(Z-hex-2-en-1-oxy)ethane (115b)</td>
<td>23.</td>
</tr>
<tr>
<td>E-1- Bromohex-2-ene</td>
<td>16.</td>
</tr>
<tr>
<td>Z-1- Bromohex-2-ene</td>
<td>21.</td>
</tr>
<tr>
<td>2-(But-2-en-1-yl)cyclopentanone</td>
<td>66.</td>
</tr>
<tr>
<td>3-(1-n-Butyl)-2,3,4,5-tetrahydrofuran (118)</td>
<td>20.</td>
</tr>
<tr>
<td>E- &amp; Z-1-n-Butyl-2-butylidenecyclopentane (181)</td>
<td>71.</td>
</tr>
<tr>
<td>Cis-1-t-Butyl-2-methylcyclopentane (166)</td>
<td>54, 59.</td>
</tr>
<tr>
<td>Trans-1-t-Butyl-2-methylcyclopentane (167)</td>
<td>54, 59.</td>
</tr>
<tr>
<td>2-t-Butylcyclopentanone (170)</td>
<td>56.</td>
</tr>
<tr>
<td>2-n-Butylcyclopentanone (178)</td>
<td>67.</td>
</tr>
<tr>
<td>2-n-Butyloxirane</td>
<td>25.</td>
</tr>
<tr>
<td>n-Butyltriphenylphosphonium iodide</td>
<td>60.</td>
</tr>
<tr>
<td>(4- Carboxybutyl)triphenylphosphonium bromide</td>
<td>83.</td>
</tr>
<tr>
<td>1-Cyclohexyl-5-cyclohexyldienepent-1-yl methanesulfonate (200)</td>
<td>87.</td>
</tr>
<tr>
<td>O-[1-Cyclohexyl-5-cyclohexyldienepent-1-yl]-O-phenylthionocarbonate</td>
<td>86.</td>
</tr>
<tr>
<td>1-Cyclohexyl-5-cyclohexyldienepentan-1-ol (196)</td>
<td>85.</td>
</tr>
<tr>
<td>1-Cyclohexyl-5-cyclohexyldienepentane (197)</td>
<td>87.</td>
</tr>
<tr>
<td>5-Cyclohexyldienepentanol (195)</td>
<td>84.</td>
</tr>
<tr>
<td>4-(Cyclopenten-1-yl)morpholine (177) Decahydonaphthalene-9-yl perbenzoate</td>
<td>2.</td>
</tr>
<tr>
<td>Cis-3,4-Di-n-butyl-2,3,4,5-tetrahydrofuran (126a)</td>
<td>28.</td>
</tr>
<tr>
<td>Trans-3,4-Di-n-butyl-2,3,4,5-tetrahydrofuran (126b)</td>
<td>28.</td>
</tr>
<tr>
<td>Cis-1,2-Di-n-butylcyclopentane (174)</td>
<td>70, 72.</td>
</tr>
<tr>
<td>Trans-1,2-Di-n-butylcyclopentane (175)</td>
<td>70, 72.</td>
</tr>
<tr>
<td>1,2-Di-n-butylcyclopentanol (179)</td>
<td>68.</td>
</tr>
<tr>
<td>1,2-Di-n-butylcyclopentene (180)</td>
<td>69.</td>
</tr>
<tr>
<td>Cis-1,2-Dicyclohexylcyclopentane (198)</td>
<td>88.</td>
</tr>
<tr>
<td>Trans-1,2-Dicyclohexylcyclopentane (199)</td>
<td>88.</td>
</tr>
<tr>
<td>Diethyl 1-bromohex-5-en-1,1-dicarboxylate (154)</td>
<td>38.</td>
</tr>
<tr>
<td>Diethyl 2-methylcyclopentan-1,1-dicarboxylate (157)</td>
<td>41.</td>
</tr>
<tr>
<td>Diethyl cyclohexane-1,1-dicarboxylate (141)</td>
<td>40.</td>
</tr>
<tr>
<td>Diethyl hex-5-en-1,1-dicarboxylate (153)</td>
<td>37.</td>
</tr>
<tr>
<td>Diethyl-1-chlorohex-5-en-1,1-dicarboxylate (130)</td>
<td>39.</td>
</tr>
<tr>
<td>7,7-Dimethyloct-1-ene (168)</td>
<td>53.</td>
</tr>
<tr>
<td>2,2-Dimethyloct-7-en-3-ol (165)</td>
<td>50.</td>
</tr>
<tr>
<td>O-(2,2-Dimethyloct-7-en-3-yl)-O-phenylthionocarbonate (128)</td>
<td>52.</td>
</tr>
<tr>
<td>1-Ethoxy-E-hex-2-ene (119a)</td>
<td>19.</td>
</tr>
<tr>
<td>1-Ethoxy-Z-hex-2-ene (119b)</td>
<td>24.</td>
</tr>
</tbody>
</table>
Ethyl (4-methylphenylthio)acetate (163)
Ethyl 2-(4-methylphenylthio)hept-6-enolate (162)
Ethyl 2-bromohept-6-enolate (156)
Ethyl 2-chlorohept-6-enolate (134)
Trans-Ethyl 2-methylcyclopentan-1-carboxylate (142)
Cis-Ethyl 2-methylcyclopentan-1-carboxylate (158)
Ethyl hept-6-enolate (159)
O-(Hex-6-en-2-yl)-O-phenylthionocarbonate (151)
Hex-1-oxy-E-hex-2-ene (126c)
Hex-1-oxy-Z-hex-2-ene (126d)
1-(E)-Hex-2-en-1-oxy)-2-(phenylseleno)hexane (124a)
2-(E)-Hex-2-en-1-oxy)ethanol (116a)
2-(Z)-Hex-2-en-1-oxy)ethanol (116b)
O-[1-(E)-Hex-2-en-1-oxy)hex-2-yl]-O-phenylthionocarbonate (122a)
1-(E)-Hex-2-en-1-oxy)hexan-2-ol (123a)
1-(Z)-Hex-2-en-1-oxy)hexan-2-ol (123b)
1-(Z)-Hex-2-en-1-oxy-2-(phenylseleno)hexane (124b)
Z-Hex-2-en-1-oxyacetic acid (125)
5-Hexenal (183)
n-Hexyl methanesulfonate
9-Hydroperoxydecahydronaphthalene (104)
6-Hydroxycyclodecanone (103)
Cis-I-Methoxy-2-methylcyclopentane (187)
Trans-I-Methoxy-2-methylcyclopentane (188)
2-Methoxyhept-6-enoic acid (186)
1-(2-Methoxyhept-6-enoyl)-5-methyl-(1H)-thiazolin-2-thione (136)
1-Methoxyhex-5-ene (189)
Trans-I-Methyl-2-trifluoromethylcyclopentane (193)
Trans-2-Methylcyclopentanecarboxylic acid (161)
2-Methylcyclopentanol (190)
Trans-9-Methyldecahydronaphthalene (100b)
Cis-9-Methyldecahydronaphthalene (99b)
1-Methylene-2-t-butylcyclopentane (171)
6-Methyleneacyclocdec-1-ene (108)
Methyleneacyclocdecane
6-Methyleneacyclocdecanol (102b)
O-(6-Methyleneacyclodecyl)-O-phenylthionocarbonate (107c)
O-(6-Methyleneacyclocdecyl)-S-methylidithiocarbonate (107a)
O-(6-Methyleneacyclocdecyl)-S-phenylidithiocarbonate (107b)
Z-Non-5-en-1-ol (172)
Compound Index...

<table>
<thead>
<tr>
<th>Compound</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>11- Oxabicyclo[4.4.1]undec-1-yl benzoate (105)</td>
<td>3</td>
</tr>
<tr>
<td>O- Phenyl-O-(1,1,1-trifluorooct-6-en-2-yl)thionocarbonate (140)</td>
<td>81</td>
</tr>
<tr>
<td>O- Phenyl-O-(Z-tridec-9-en-5-yl)thionocarbonate (138)</td>
<td>63</td>
</tr>
<tr>
<td>(Phenylthio)thiocarbonyl chloride</td>
<td>8</td>
</tr>
<tr>
<td>Z- Tridec-4-ene (176)</td>
<td>64</td>
</tr>
<tr>
<td>Z- Tridec-9-en-5-ol (173)</td>
<td>62</td>
</tr>
<tr>
<td>1,1,1-Trifluorohept-6-en-2-ol (191)</td>
<td>80</td>
</tr>
<tr>
<td>1-(Trimethylsilyloxy)cyclopentene (169)</td>
<td>55</td>
</tr>
</tbody>
</table>

Section 3.81.63.64.62.80.55.
Synthesis of Radical Precursors and Product Standards.

1. 9-Hydroperoxydecahydronaphthalene (104).

Benzoylperoxide (2.0g) was added to decahydronaphthalene (750 ml) with stirring at 100°. Oxygen was introduced at a moderate rate and stirring continued for 18h. The mixture was cooled, washed with 10% sodium hydroxide (3x), ethane-1,2-diol (3x), 10% sulfuric acid, water and dried (MgSO₄). The product was isolated by silica column chromatography (500g, 100-200 mesh). The decahydronaphthalene was removed by applying a pressure of 20kPa to the column followed by elution with hexane. Further elution with dichloromethane yielded, after evaporation and recrystallization from hexane, the title compound (13.2g, ca 2%), mp = 91-93° (lit¹⁰¹a: mp = 95-96°).

¹H nmr(60,CCl₄): δ 6.88 (1H, s, OOH); 0.63-2.30 (17H, m, RH).

2. Decahydronaphthalen-9-yl perbenzoate.

To a solution of 9-hydroperoxydecahydronaphthalene (104) (10.0g, 59 mmol) in pyridine (25 ml) was added benzoyl chloride (9.1g, 65 mmol) dropwise over a 5 min period with stirring at ice-bath temperatures. The mixture was stirred at room temperature for a further 60 min after which it was poured into 15% sulfuric acid (200 ml) and extracted with ether (2x). The combined organic phases were washed with saturated sodium bicarbonate, dried (MgSO₄) and the solvent removed to give the title perbenzoate (16.0g, 99%).

¹H nmr(60,CCl₄): δ 7.20-8.25 (5H, m, ArH); 0.83-2.23 (17H, m, RH).

3. 11-Oxabicyclo[4.4.1]undec-1-yl benzoate (105).

Decahydronaphthalen-9-yl perbenzoate, prepared in part 2, (16.0g, 58.4 mmol) was heated under reflux in methanol (80 ml) for 2h. Concentration of the solution at reduced pressure resulted in crystallization. After storing at 0° overnight, the crystals were collected and identified as the title benzoate (9.6g, 60%), mp = 93-96° (lit¹⁰¹a: mp = 95.5-97°).

¹H nmr(60,CCl₄): δ 7.83-8.10 (2H, m, ArH-2); 7.17-7.48 (3H, m, ArH-3,4); 3.30-3.77 (1H, m, H-6); 2.60-3.10 (2H, m, H-2); 1.05-2.17 (14H, m, RH).
13C nmr: δ 165.0 (C=O); 132.7 (C-4'); 131.4 (C-1'); 129.6 (2x C-2'); 128.2 (2x C-3'); 108.3 (C-1); 75.0, (C-6); 39.4 (2x C-2); 33.1 (2x C-5); 29.3 (2x C-3); 28.0 (2x C-4).

4. 6-Hydroxycyclodecanone (103)

11-Oxabicyclo[4.4.1]undec-1-yl benzoate (105) (1.44g, 3.6 mmol) was heated under reflux in methanol (40 ml) and water (1 ml) containing 1.4% potassium hydroxide for 15 h. The mixture was cooled and neutralized with 10% sulfuric acid and concentrated at reduced pressure. Dichloromethane (20 ml) and 10% sodium hydroxide (20 ml) were added to the residue and shaken well. The two phases were separated and the aqueous phase extracted with dichloromethane (2x). The combined organic phases were dried (MgSO₄) and the solvent removed to give the title ketone as a white crystalline solid. (860 mg, 96%), mp = 66-68° (lit 101a: mp = 69-70°).

v max: 1685, 3380, 3420 cm⁻¹.

1H nmr (60, CDCl₃): δ 3.90 (1H, m, H-6); 3.01 (1H, s (broad), OH); 1.20-2.66 (16H, m, RH).

5. 6-Methylenecyclodecanol (102b).

Sodium hydride (240 mg, 10.0 mmol) was stirred in dry dimethylsulfoxide (DMSO) (10 ml) at 70° until the evolution of hydrogen had ceased (45 min). Methyltriphenylphosphonium iodide (4.0g, 11.0 mmol) in dry DMSO (15 ml) was added to the mixture and stirring continued for 10 min. 6-Hydroxycyclodecanone (103) (860 mg, 5.1 mmol) in dry DMSO (15 ml) was added and the mixture stirred at 70° for 2h. The reaction mixture was cooled, poured into water (50 ml) and extracted with pentane (5x). The combined extracts were washed with saturated sodium chloride, dried (MgSO₄) and the solvent removed to give a yellow oil identified as mainly title alcohol by 1H nmr spectroscopy. The product was isolated by flash chromatography (dichloromethane) to give the title alcohol as a white crystalline solid (740 mg, 87%), mp = 40-41° (lit 102: mp = 41-42°).

v max: 1640, 3350 (broad) cm⁻¹.

1H nmr(60): δ 4.83 (2H, s, C=CH₂); 3.87 (1H, m, H-1); 1.22-2.33 (18H, m, RH).
13C nmr: δ 148.5 (C-6); 110.9 (C=C\text{CH2}); 70.4 (C-1); 34.1 (C-2); 33.8 (C-5); 24.6 (C-3); 21.9 (C-4).

6. Reaction of 6-methylenecyclodecanol with N-bromosuccinimide and triphenylphosphine

N-Bromosuccinimide (76 mg, 427 µmol) was added to a stirred suspension of triphenylphosphine (126 mg, 481 µmol) in a solution of 6-methylenecyclodecanol (102b) (50 mg, 298 µmol) in acetonitrile (0.5 ml) for 3 h. The crude reaction mixture was separated by preparative TLC (hexane) to give an unidentified colourless oil (15 mg) having only saturated proton resonances by 1H nmr spectroscopy.

7. Reaction of 6-methylenecyclodecanol with sodium iodide and chlorotrimethylsilane

6-Methylenecyclodecanol (102b) (50 mg, 298 µmol) and sodium iodide (45 mg, 300 µmol) were dissolved in acetonitrile (0.3 ml). The system was flushed with nitrogen and chlorotrimethylsilane (33 mg, 304 µmol) slowly added. The mixture was stirred for 45 min and taken up into ether (10 ml), washed with water, saturated sodium chloride, dried (MgSO₄) and the solvent removed to yield a yellow oil which showed only aliphatic protons by 1H nmr spectroscopy.

8. (Phenylthio)thiocarbonyl chloride

The title compound was prepared from thiophenol (8.8g, 80.0 mmol), 4N sodium hydroxide (20 ml) and thiophosgene (9.1g, 79.1 mmol) by the method of Hayashi et al. to give (phenylthio)thiocarbonyl chloride (4.6g, 31%), bp = 100-102°/2.5mm. (lit: bp = 95-96°/2mm.)

νₘₐₓ: 1110, 1440, 1475, 1575 cm⁻¹.

1H nmr(60): δ 7.44 (s, ArH).

MS: m/e = 188/190 (85%, M⁺); 153 (100%); 109 (33%).

6-Methylenecyclodecanol (102b) (200 mg, 1.19 mmol) was dissolved in dry tetrahydrofuran (6.0 ml) and the system flushed with nitrogen. Dry sodium hydride (50 mg, 2.08 mmol) and imidazole (ca 2 mg) were added and the mixture heated to reflux under nitrogen for 3.5 h. Carbon disulfide (0.4 ml, 6.6 mmol) was added with further heating at reflux for 30 min. Methyl iodide (0.4 ml, 6.5 mmol) was added and reflux heating continued for 30 min. The mixture was cooled, quenched with water (10 ml) and extracted with dichloromethane (2x). The combined organic phases were washed with saturated sodium bicarbonate, dilute hydrochloric acid and saturated sodium chloride, dried (MgSO₄) and the solvent removed to yield a yellow oil which was purified by preparative TLC (dichloromethane) and left standing for 2 months, to give the title dithiocarbonate (165 mg, 54%).

\[ \nu_{\text{max}}: \ 1640 \text{ cm}^{-1}. \]

\(^1\text{H nmr (60)}: \delta 5.93 (1H, m, H-1); 4.87 (2H, s, C=CH₂); 2.48 (3H, s, SCH₃); 1.22-2.43 (16H, m, RH). \]

\(^1^3\text{C nmr:} \delta 215.5 (C=S); 148.2 (C-6); 111.0 (C=CH₂); 83.9 (C-1); 33.9 (C-2); 30.0 (C-5,3); 22.0 (C-4); 18.7 (SCH₃).

MS(CI): \(m/e = 259 \text{ (0.2\%, [M+H]⁺) \}; 151 \text{ (77\%) \}; 95 \text{ (100\%)}. \)

\((C_{13}H_{22}OS_2 \text{ requires: [M+H]⁺} = 259.1190. \text{ Found: [M+H]⁺} = 259.1189 \)


Pyridine (350 mg, 4.4 mmol) was added to a solution of 6-methylenecyclodecanol (102b) (200 mg, 1.19 mmol) in dry dichloromethane (7.0 ml). The system was flushed with nitrogen, (phenylthio)thiocarbonyl chloride (245 mg, 1.30 mmol) added and the mixture heated at reflux for 48h. The reaction mixture was cooled, washed with 10% sulfuric acid, sat. sodium bicarbonate and sat. sodium chloride, dried (MgSO₄) and the solvent removed to give a yellow oil which was quickly filtered through a short silica column (10% dichloromethane/hexane). The filtrate was concentrated at reduced pressure and the products separated by preparative TLC (10% dichloromethane/hexane). The second lowest band proved, on elution, to contain the title dithiocarbonate which was isolated as a yellow oil and crystallized on standing (125mg, 33%), \( \text{mp} = 41-42.5^\circ. \)
112.

$\nu_{\text{max}}$: 1250, 1440, 1470, 1635 cm$^{-1}$.

$^1$H nmr(60): $\delta$ 7.36 (5H, s, ArH); 5.81 (1H, m, H-1); 4.79 (2H, s, C=$\text{CH}_2$); 1.20-2.31 (16H, m, RH).


Pyridine (350 mg, 4.4 mmol) was added to a solution of 6-methylenecyclodecanol (102b) (200 mg, 1.19 mmol) in dry dichloromethane (7.0 ml). The system was flushed with nitrogen, phenylchlorothionocarbonate (225 mg, 1.30 mmol) added and the reaction mixture stirred under nitrogen at room temperature for 1h. The mixture was partitioned between ethyl acetate and water and the organic phase washed with cold 10% hydrochloric acid (3x), sat. sodium bicarbonate (3x), sat. sodium chloride and dried ($\text{Na}_2\text{SO}_4$). Removal of the solvent yielded a green oil identified as the crude product by $^1$H nmr spectroscopy. The product was purified by preparative TLC (10% dichloromethane/hexane) to give the title thionocarbonate as a pale oil (215 mg, 62%).

$^1$H nmr(60): $\delta$ 7.01-7.54 (5H, m, ArH); 5.63 (1H, m, H-1); 4.88 (2H, s, C=$\text{CH}_2$); 1.23-2.23 (16H, m, RH).

MS: 202 (7%, $\text{C}_{12}\text{H}_{10}\text{O}$); 151 (19%, $\text{C}_{11}\text{H}_{19}$); 95 (100%).

No molecular ion could be detected in the mass spectrum using chemical ionization techniques.

($\text{C}_{18}\text{H}_{24}\text{O}_{2}\text{S}$ requires: [M-$\text{PhCO}_2\text{S}$]$^+$ = 151.1487. Found: [M-$\text{PhCO}_2\text{S}$]$^+$ = 151.1482.)


Cis-9-(2-Bromomethyl)decahydronaphthalene (99c) (1.08 g, 4.7 mmol) was added to a quartz round-bottom flask fitted with stirrer and reflux condenser. The system was flushed with nitrogen, a solution of 1.0M lithium aluminium hydride (12.0 ml, 12.0 mmol) in THF was introduced and stirring commenced. Di-tert-butylperoxide (5.0 ml) was added and the mixture irradiated with a 250W mercury lamp at a distance of 300 mm for 2h. The reaction mixture was examined by GC to
reveal the absence of starting material. The reaction mixture was cautiously quenched with water, extracted with pentane (5x), dried (Na$_2$SO$_4$) and the solvent removed to yield a pale oil (760mg) identified as crude title compound.

A sample of the crude product (260mg) was separated by preparative TLC (30/40° light petroleum). The highest band gave, on elution, the title compound (140 mg, 57%).

$\nu_{\text{max}}$: 1450, 1465, 2930, 2960 cm$^{-1}$.

$^1$H nmr(60): $\delta$ 0.8-2.0 (17H, s, RH); 0.94 (3H, s, CH$_3$).

$^{13}$C nmr: $\delta$ 41.3 (C-10); 34.0 (C-8); 32.8 (C-9); 29.7 (C-1); 28.1 (C-4:CH$_3$); 27.7 (C-5:6); 26.8 (C-3); 22.3 (C-2,7).

The spectral data are consistent with literature sources$^{136,137}$.

13. Trans-9-Methyldecahydronaphthalene (100b).

Aluminium chloride (3.0g, 22 mmol) was added to a solution of tetrahydronaphthalene (1.0g, 7.3 mmol) in dichloromethane (20 ml), tetramethylsilane (10 ml) added and the mixture heated for 6h under reflux. Further tetramethylsilane (10 ml) was added, and the mixture left at room temperature for 15h after which 47% cis and trans products were observed by GC (2% OV17 on Chromosorb Q (60-80 mesh)). The mixture was cautiously poured into water (20 ml), extracted with dichloromethane (2x), dried (MgSO$_4$) and the solvent removed to give a yellow oil which was purified by preparative GC (2% OV17-Chromosorb Q (60-80 mesh)) to give the title compound as indicated by $^{13}$C nmr spectroscopy.

$^1$H nmr(60): $\delta$ 0.8-2.0 (17H, m, RH); 0.82 (3H, s, CH$_3$).

$^{13}$C nmr: $\delta$ 45.8 (C-10); 42.1 (C-1); 33.9 (C-9); 29.1 (C-4); 27.2 (C-3); 22.0 (C-2); 15.7 (CH$_3$).

The spectra are consistent with literature sources$^{135}$.


Sodium hydride (180 mg, 7.5 mmol) was added to dry DMSO (5 ml) and the system flushed with nitrogen. The mixture was stirred at 70° until the evolution of hydrogen had ceased (ca. 45 min). Methyl triphenyl phosphonium iodide (2.0g, 4.95 mmol) in dry DMSO (15 ml) was added and the mixture stirred at 70° for 15
min. Cyclodecanone (400 mg, 2.6 mmol) in dry DMSO (5 ml) was added and the mixture stirred for a further 2h. The orange solution was cooled, poured into water (50 ml) and acidified with 15% sulfuric acid. The mixture was extracted with pentane (5x), the combined organic phases washed with water (2x), dried (Na₂SO₄) and the solvent removed to yield a pale oil identified as the title compound.

ν<sub>max</sub>: 885, 1640, 2960, 3070 cm<sup>-1</sup>.

<sup>1</sup>H nmr(60): δ 5.85 (2H, s, C=CH<sub>2</sub>); 2.20 (4H, m, H-2,10); 1.30-1.80 (14H, m, RH).

<sup>13</sup>C nmr: δ 149.12 (C-1); 111.07 (C=CH<sub>2</sub>); 34.68 (C-2,10); 25.05 24.49, 24.41 (C-3,4,5,6,7,8,9).

The spectra are consistent with literature sources<sup>138</sup>.

15. 6-Methylenecyclodec-1-ene (108)

Attempted distillation of crude O-(6-methylenecyclodecyl)-S-methyldithiocarbonate (107a) (1.65g) gave a mixture of dimethyltrithiocarbonate and the title olefin which was isolated by flash chromatography (hexane) and redistilled by bulb-bulb distillation (Kuegelrohr) (100°/25mm) to give a colourless oil. (300mg, 34%).

ν<sub>max</sub>: 1635, 2960, 3320 cm<sup>-1</sup>.

<sup>1</sup>H nmr(60): δ 5.39 (2H, m, H-1,2); 4.81 (2H, s, C=CH<sub>2</sub>); 1.05-2.28 (14H, m, RH).

(C₁₁H₁₈ requires: C, 87.93; H, 12.07%. Found C, 87.71; H, 12.25%).


The title compound was prepared by the method of Ijima et. al.<sup>139</sup> as follows:

Phosphorous tribromide (3.52g, 13 mmol) was added to a solution of E-hex-2-en-1-ol (3.0g, 33 mmol) in ether (100 ml) and the mixture stirred in an ice-bath for 1h. The mixture was concentrated to 10 ml, pyridine (100 µl) added and stirring continued for 2h. The mixture was poured into 10% hydrochloric acid (50 ml), extracted with ether (3x), the combined ethereal extracts washed with sat. sodium bicarbonate, sat. sodium chloride and dried (MgSO₄). Removal of the
solvent yielded a yellow oil identified as the title bromide and of sufficient purity not to require further purification (3.7g, 76%).

\[ \nu_{\text{max}}: 962, 1202, 1435, 1463, 1660 \text{ cm}^{-1}. \]

\( ^1 \text{H nmr}(100): \delta 5.64-5.80 (2\text{H, m, H-2,3}); 3.89-3.96 (2\text{H, m, 2xH-1}); 1.91-2.16 (2\text{H, m, 2xH-4}); 1.32-1.63 (2\text{H, m, 2xH-5}); 0.81-0.98 (3\text{H, m, 3xH-6}). \)

17. 2-(E-Hex-2-en-1-oxy)ethanol (116a).

Dry ethane-1,2-diol (16 ml) was added to sodium hydride (465 mg, 19.0 mmol) with vigorous stirring. When the evolution of hydrogen had ceased, E-1-bromohex-2-ene (3.0g, 18.0 mmol) was added, the mixture stirred at 100° overnight and then cooled. The ethane-1,2-diol was removed by filtration through a short silica column eluted with ethyl acetate. Removal of the solvent afforded a brown oil which was separated by MPLC (50% ethyl acetate/dichloromethane). The third major fraction proved to contain, after removal of the solvent and distillation, the title alcohol as a colourless oil (2.0g, 75%), bp ~ 130°/40mm (Kuegelrohr).

\[ \nu_{\text{max}}: 1360, 1455, 1670, 3420(\text{broad}) \text{ cm}^{-1}. \]

\( ^1 \text{H nmr}(200): \delta 5.48-5.78 (2\text{H, m, H-2',3'}); 3.97 (2\text{H, d, J=5.9Hz, 2xH-1'}); 3.69-3.74 (2\text{H, m, 2xH-1}); 3.49-3.54 (2\text{H, m, 2xH-2}); 3.21 (1\text{H, s(broad), OH}); 1.97-2.08 (2\text{H, m, 2xH-4'}); 1.32-1.46 (2\text{H, m, 2xH-5'}); 0.90 (3\text{H, t, J=7.3Hz, 3xH-6'}). \)

\( ^{13} \text{C nmr: } \delta 134.9, 126.2 (\text{C-2',3'}); 71.9, 71.2, 61.6 (\text{C-1,2,1'}); 34.4 (\text{C-4'}); 22.3 (\text{C-5'}); 13.7 (\text{C-6'}). \)

\( (\text{C}_8\text{H}_{16}\text{O}_2 \text{ requires: C, 66.63; H, 11.18%. Found: C, 66.49; H, 10.97%}). \)


Phosphorous tribromide (220 mg, 820 \( \mu \text{mol} \)) was added to a solution of 2-(E-hex-2-en-1-oxy)ethanol (116a) (300 mg, 2.08 mmol) in ether (10 ml). Pyridine (160 \( \mu \text{l} \)) was added and the mixture stirred at room temperature overnight. The mixture was poured into 10% hydrochloric acid (20 ml), extracted with pentane (2x), the combined extracts washed with sat. sodium bicarbonate, sat. sodium chloride, dried (MgSO\(_4\)) and the solvent removed. The brown residue was separated by flash chromatography (40% pentane/dichloromethane) to give the title bromide as a colourless oil (65 mg, 15%).
\[ \nu_{\text{max}}: 1275, 1630, 1460, 1660 \text{ cm}^{-1}. \]

\[ ^1H \text{ nmr}(200): \delta 5.49-5.72 (2H, m, H-2',3'); 3.79-4.01 (2H, m, 2xH-1'); 3.70-3.76 (2H, m, 2xH-1); 3.43-3.49 (2H, m, 2xH-2); 1.97-2.10 (2H, m, 2xH-4'); 1.34-1.49 (2H, m, 2xH-5'); 0.91 (3H, t, J=7.3Hz, 3xH-6'). \]

\[ ^{13}C \text{ nmr: } s 135.3, 125.9 (C-2',3'); 71.9 (C-1'); 69.6 (C-2); 34.3 (C-1); 30.4 (C-4'); 22.2 (C-5'); 13.7 (C-6'). \]

\[ \text{MS: } m/e = 206/208 (2\%, M^+); 163/165 (63\%); 107/109 (100\%). \]

(C\(_8\)H\(_{15}\)Br\(^7\)O requires: M\(^+\) = 206.0306. Found M\(^+\) = 206.0299).


E-Hex-2-en-1-ol (1.0g, 10.0 mmol) was added to a suspension of sodium hydride (240 mg, 10.0 mmol) in iodoethane (10 ml) and the mixture sonicated until the evolution of hydrogen had ceased. The mixture was heated for 4.5h under reflux conditions, filtered, the filtrate collected and the solvent removed to give a pale oil which was separated by flash chromatography (dichloromethane) and distilled by bulb-bulb distillation to afford the title ether as a colourless oil (300 mg, 23%), bp ~ 140°/100mm (Kuegelrohr).

\[ \nu_{\text{max}}: 1350, 1372, 1455, 1670 \text{ cm}^{-1}. \]

\[ ^1H \text{ nmr}(200): \delta 5.51-5.69 (2H, m, H-2,3); 3.89-3.92 (2H, m, 2xH-1); 3.47 (2H, q, J=7.1Hz, OCH\(_2\)CH\(_3\)); 1.95-2.10 (2H, m, 2xH-4); 1.35-1.46 (2H, m, 2xH-5); 1.21 (3H, t, J=7.1Hz, OCH\(_2\)CH\(_3\)); 0.90 (3H, t, J=7.3Hz, 3xH-6). \]

\[ ^{13}C \text{ nmr: } s 134.3, 126.7 (C-2,3); 71.5 (C-1); 65.4 (OCH\(_2\)CH\(_3\)); 34.5 (C-4); 22.3 (C-5); 15.2 (OCH\(_2\)CH\(_3\)); 13.7 (C-6). \]

(C\(_8\)H\(_{16}\)O requires: C, 77.94; H, 12.58%. Found: C, 77.81; H, 12.34%).

20. 3-(1-n-Butyl)-2,3,4,5-tetrahydrofuran (118).

1-Bromo-2-(E-hex-2-en-1-oxy)ethane (115a) (60 mg, 290 \(\mu\)mol) was dissolved in hexane (1.0 ml), tri-n-butyltin hydride (88 mg, 300 \(\mu\)mol) and a few crystals of AIBN added, the mixture sealed in a glass tube and heated at 80° overnight. The mixture was cooled, separated by preparative GC (20% SE-30 on chromosorb W), the major product collected and identified as the title compound (22 mg, 59%).

\[ \nu_{\text{max}}: 1380, 1455, 1465 \text{ cm}^{-1}. \]
117.

$^1$H nmr(200): δ 3.68-3.94 (4H, m, 2xH-2,5); 3.28-3.35 (1H, m, H-3); 1.95-2.28 (2H, m, 2xH-4); 0.90-1.35 (9H, m, n-CH$_2$CH$_2$CH$_2$CH$_3$).

$^{13}$C nmr: δ 73.5, 67.9 (C-2,5); 39.4, 33.0 (C-3,4); 32.5, 30.8, 22.8, 14.0 (n-CH$_2$CH$_2$CH$_2$CH$_3$).

MS: m/e = 127 (5%, [M-H]$^+$); 81 (53%); 56 (100%).

(C$_8$H$_{16}$O requires: C, 74.94%; H, 12.58%; [M-H]$^+$ = 127.1123. Found: C, 75.05%; H, 12.08%; [M-H]$^+$ = 127.1122.)


The title compound was prepared by the method of Ijima et. al.$^{139}$ in identical manner to that of E-1-bromohex-2-ene, as described in part 16, using phosphorous tribromide (2.35g, 9.0 mmol), Z-hex-2-en-1-ol (2.0 g, 20.0 mmol) and ether (60 ml). The title bromide was obtained in sufficient purity not to require further purification (2.3 g, 71%).

$\nu_{\max}$: 1205, 1380, 1455, 1465, 1645 cm$^{-1}$.

$^1$H nmr(200): δ 5.53-5.81 (2H, m, H-2,3); 3.99 (2H, d, J=7.8Hz, 2xH-1); 2.06-2.18 (2H, m, 2xH-4); 1.34-1.53 (2H, m, 2xH-5); 0.93 (3H, t, J=7.3Hz, 3xH-6).

22. 2-(Z-Hex-2-en-1-oxy)ethanol (116b).

The title compound was prepared in identical manner to that of 2-(E-hex-2-en-1-oxy)ethanol (116a) as described in part 17. using ethane-1,2-diol (15 ml), sodium hydride (310 mg, 12.9 mmol) and Z-1-bromohex-2-ene (2.0 g, 12.3 mmol). The title alcohol was isolated as a colourless oil (2.0g, 75%), bp ~ 130°/40mm (Kugelrohr) which proved to contain 20% E- isomer by $^{13}$C nmr spectroscopy.

$\nu_{\max}$: 1460, 1660, 3420(broad) cm$^{-1}$.

$^1$H nmr(200): δ 5.45-5.80 (2H, m, H-2',3'); 4.05-4.10 (1.6H, m, 2xH-1': Z- isomer); 3.95-4.00 (0.4H, m, 2xH-1': E- isomer); 3.65-3.80 (2H, m, 2xH-1'); 3.45-3.60 (2H, m, 2xH-2'); 3.05 (1H, s(broad), OH); 1.95-2.10 (2H, m, 2xH-4'); 1.30-1.50 (2H, m, 2xH-5'); 0.90 (3H, t, J=7.3Hz, 3xH-6').

$^{13}$C nmr: δ 133.7, 126.0 (C-2',3': Z- isomer); 134.9, 126.2 (C-2',3': E- isomer); 71.4, 66.7, 61.6 (C-1,2,1': Z- isomer); 71.9, 71.2, 61.6 (C-1,2,1': E-
isomer); 29.6 (C-4': Z- isomer); 34.4 (C-4': E- isomer); 22.6 (C-5': Z- isomer);
22.3 (C-5': E- isomer); 13.7 (C-6').


The title compound was prepared in identical manner to 1-bromo-2-(E-hex-2-en-1-oxy)ethane (115a) with the exception that 2-(Z-hex-2-en-1-oxy)ethanol (116a) was used. The title ether was isolated as a colourless oil (64 mg, 15%) and shown to contain 20% E- isomer by $^{13}$C nmr spectroscopy.

$^{1}$H nmr(200): δ 5.49-5.71 (2H, m, H-2',3': Z- isomer); 3.97 (0.4H, d, J=5.9Hz, 2xH-1': E- isomer); 3.68-3.77 (2H, m, 2xH-1'); 3.44-3.49 (2H, m, 2xH-2'); 1.95-2.13 (2H, m, 2xH-4'); 1.32-1.50 (2H, m, 2xH-5'); 0.91 (3H, t, J=7.1Hz, 3XH-6').

$^{13}$C nmr: δ 134.1, 125.6 (C-2',3': Z- isomer); 135.3, 125.9 (C-2',3': E- isomer); 69.8, 66.6 (C-2,1': Z- isomer); 71.9, 69.6 (C-2,1': E- isomer); 30.4 (C-4'); 29.6 (C-1: Z- isomer); 34.3 (C-1: E- isomer); 22.6 (C-5': Z- isomer); 22.2 (C-5': E- isomer); 13.7 (C-6').

(C$_8$H$_{15}$BrO requires: M$^+$ = 206.0306. Found: M$^+$ = 206.0295.)


The title compound was prepared in identical manner to 1-ethoxy-E-hex-2-ene (119a), as described in part 19, with the exception that Z-hex-2-en-1-ol was used instead of the E-alcohol.

$^{1}$H nmr(200): δ 5.50-5.60 (2H, m, H-2,3); 4.01-4.04 (2H, m, 2xH-1); 3.48 (2H, q, J=7.1Hz, OCH$_2$CH$_3$); 1.99-2.16 (2H, m, 2xH-4); 1.31-1.51 (2H, m, 2xH-5); 1.21 (3H, t, J=7.1Hz, OCH$_2$CH$_3$); 0.91 (3H, t, J=7.3Hz 3xH-6).

$^{13}$C nmr: δ 133.1, 126.5 (C-2,3); 66.2, 65.5 (C-1, OCH$_2$CH$_3$); 29.6 (C-4); 22.7 (C-5); 15.3, 13.7 (C-6, OCH$_2$CH$_3$).

(C$_8$H$_{16}$O requires: C, 74.94; H, 12.58%. Found: C, 75.30; H, 12.30%).

25. 2-n-Butyloxirane.

3-Chloroperbenzoic acid (21.3g of 80%, 100 mmol) was added portionwise to a solution of 1-hexene (7.5g, 90 mmol) in dichloromethane (30 ml) and the
mixture stirred overnight. The addition was highly exothermic. The mixture was washed with 4N sodium hydroxide, sat. sodium chloride, dried (MgSO₄) and fractionally distilled. The second fraction proved to be the title compound which was collected as a colourless oil (5.8g, 65%), bp = 118-119° (lit.: 140: 117-119°).

\(^1\)H nmr(60): \(\delta\) 2.3-3.0 (3H, m, H-1; 2xH-2); 0.87-1.77 (9H, m, n-CH₂CH₂CH₂CH₃).


E-Hex-2-en-1-ol (2.0g, 20.0 mmol) was added dropwise with stirring to a suspension of sodium hydride (520 mg, 22.0 mmol) in dry dimethoxyethane (DME) (15 ml) and stirring continued until the evolution of hydrogen had ceased. The system was flushed with nitrogen, 2-n-butyloxirane, as prepared in part 25, (2.0g, 20.0 mmol) added and the mixture heated under nitrogen at reflux for 48h, then cooled. The mixture was poured into 10% hydrochloric acid (200 ml), extracted with pentane (3x), the combined extracts washed with sat. sodium bicarbonate, sat. sodium chloride, dried (MgSO₄) and the solvent removed. The residue was separated by MPLC (30% ethyl acetate/dichloromethane). The second major fraction proved to contain the title alcohol which was isolated as a pale oil after the removal of the solvent (1.60g, 40%). A sample was distilled by bulb-bulb distillation to give the title alcohol as a colourless oil in an analytically pure state, bp ~ 100°/0.1mm (Kuegelrohr).

\(v_{max}\): 1455, 1465, 1670, 3440(broad) cm\(^{-1}\).

\(^1\)H nmr(200): \(\delta\) 5.45-5.68 (2H, m, H-2',3'); 3.94-3.98 (2H, m, 2xH-1'); 3.65-3.73 (1H, m, H-2); 3.40-3.47 (1H, m, H-1a); 3.20-3.29 (1H, m, H-1b); 2.73 (1H, m, OH); 1.96-2.09 (2H, m, 2xH-4'); 1.25-1.54 (8H, m, 2xH-3,4,5,5'); 0.87-0.94 (6H, m, 3xH-6,6').

\(^13\)C nmr: \(\delta\) 134.8, 126.9 (C-2',3'); 77.4, 72.0, 70.3 (C-1,2,1'); 34.4, 33.0 (C-3,4'); 27.8 (C-4); 22.8, 22.2 (C-5,5'); 14.0, 13.7 (C-6,6').

MS: m/e = 200 (1%, M\(^+\)); 99 (52%); 83 (66%); 69 (100%).

(C\(_{12}\)H\(_{24}\)O\(_2\) requires: C, 71.95; H, 12.08%. Found: C, 71.94; H, 11.99%.)

Phenylchlorothionocarbonate (260 mg, 1.50 mmol) was added to a stirred solution of 1-(E-hex-2-en-1-oxo)hexan-2-ol (123a) (272 mg, 1.36 mmol) and pyridine (400 mg) in dichloromethane (10 ml) and the mixture stirred under nitrogen for 1h. The mixture was poured into water (30 ml), extracted with ethyl acetate (2x), the combined organic phases washed with 10% hydrochloric acid (3x), sat. sodium bicarbonate (3x), sat. sodium chloride, dried (Na$_2$SO$_4$) and the solvent removed. The residue was separated by flash chromatography (40% dichloromethane/pentane) to give the title thionocarbonate as a pale oil (320 mg, 70%).

$\nu_{max}$: 1490, 1595, 1670 cm$^{-1}$.

$^1$H nmr(200): $\delta$ 7.08-7.43 (5H, m, Ar-H); 5.46-5.67 (3H, m, H-1,2',3'); 3.96-3.98 (2H, m, 2xH-1'); 3.64 (2H, d, J=4.9Hz, 2xH-1); 1.96-2.11 (2H, m, 2xH-4'); 1.70-1.85 (2H, m, 2xH-3); 1.28-1.50 (6H, m, 2xH-4,5,5'); 0.82-0.96 (6H, m, 2xH-6,6').

$^{13}$C nmr: $\delta$ 194.8 (C=O); 153.4 (Ar-C-1); 134.8-126.1 (C-2',3'); 129.6, 126.4, 121.9 (Ar-C); 83.9, 72.0, 69.7 (C-1,2,1'); 34.3, 30.2, 27.2, 22.6, 22.2 (C-3,4,5,4',5'); 13.9, 13.7 (C-6,6').

MS(CI): m/e = 337 (3%, [M+H]$^+$); 237 (100%); 183 (34%).

(C$_{19}$H$_{28}$O$_3$S requires: [M+H]$^+$ = 337.1837. Found: [M+H]$^+$ = 337.1838).

28. Cis- and trans-3,4-di-n-butyl-2,3,4,5-tetrahydrofuran (126a, 126b).

O-[1-(E-Hex-2-en-1-oxo)hex-2-yl]-O-phenylthionocarbonate (122a) (320 mg, 952 µmol) was added to a 2.3M solution of tri-n-butyltin hydride in hexane (490 µl) in a pyrex tube. A few crystals of AIBN were added, the solution degassed under vacuum during two freeze/thaw cycles, the tube sealed and heated at 80$^\circ$ overnight. Examination of the reaction mixture by analytical GC (3% SE-30 on chromosorb W (100-120 mesh)) revealed the absence of tri-n-butyltin hydride. The reaction mixture was separated by preparative GC (20% carbowax on chromosorb W (60-80 mesh)) to yield trans-3,4-di-n-butyl-2,3,4,5-tetrahydrofuran (126b) as the first major fraction.

$^1$H nmr(200): $\delta$ 3.96-4.00 (2H, m, H-2a,5b); 3.34-3.42 (2H, m, H-2b,5a); 1.05-1.83 (14H, m, H-3,4,2xCH$_2$CH$_2$CH$_2$CH$_3$); 0.86-0.92 (6H, m, 2x(CH$_2$)$_3$CH$_3$).
13C nmr: δ 73.9 (C-2,5); 45.6 (C-3,4); 32.9 (2xCH₂(CH₂)₂CH₃); 30.7 (2xCH₂CH₂CH₂CH₃); 23.0 (2x(CH₂)₂CH₂CH₃); 14.0 (2x(CH₂)₂CH₃).

MS: m/e = 183 (2%, [M-H]+); 97 (40%); 83 (48%); 69 (55%); 55 (100%).


The second major fraction proved to be cis-3,4-di-n-butyl-2,3,4,5-tetrahydrofuran (126a).

1H nmr(200): δ 3.82-3.89 (2H, m, H-2a,5a); 3.47-3.54 (2H, m, H-2b,5b); 2.05-2.18 (2H, m, H-3,4); 1.13-1.45 (12H, m, 2xCH₂CH₂CH₂CH₃); 0.87-0.93 (6H, m, 2x(CH)CH₃).

13C nmr: δ 72.5 (C-2,5); 42.0 (C-3,4); 30.8 (2xCH₂(CH₂)₂CH₃); 26.8 (2xCH₂CH₂CH₂CH₃); 23.0 (2x(CH₂)₂CH₂CH₃); 14.1 (2x(CH₂)₂CH₃).

MS: m/e = 183 (4%, [M-H]+; 97 (68%); 83 (53%); 69 (80%); 55 (100%).


29. Hexyl methanesulfonate.

Methanesulfonyl chloride (6.7g, 59.0 mmol) was added dropwise to a stirred solution of hexan-1-ol (5.0g, 49.0 mmol) and triethylamine (15 ml) in dichloromethane (60 ml). The addition proved to be highly exothermic. The mixture was stirred for 1h, poured into water (500 ml), the phases separated and the organic phase washed with 10% hydrochloric acid (4x), sat. sodium bicarbonate, water, dried (MgSO₄) and the solvent removed to give the title compound as described by Williams et al.¹⁴¹ (7.1g, 81%).

1H nmr(60): δ 4.18 (2H, t, J=6Hz, 2xH-1); 2.97 (3H, s, OSO₂CH₃); 0.87-1.95 (11H, m, R-H).


E-Hex-2-en-1-ol (500 mg, 5.0 mmol) was added to a stirred suspension of sodium hydride (130 mg, 5.5 mmol) in DME (5 ml). After the evolution of hydrogen had ceased, hexyl methanesulfonate, as prepared in part 29, (900 mg, 5.0 mmol) was added, the mixture heated at reflux for 3h and then cooled. The mixture
was poured into 10% hydrochloric acid (100 ml) and extracted with pentane (2x),
the combined extracts washed with sat. sodium bicarbonate, sat. sodium chloride,
dried (MgSO₄) and the solvent removed. The residue was separated by flash
chromatography (dichloromethane) to give a pale oil which was distilled by bulb-
bulb distillation to yield the title ether as a colourless oil (590 mg, 64%), bp-
60°/0.1mm (Kugelrohr).

νₘₕₓ: 1360, 1380, 1465, 1670 cm⁻¹.

¹H nmr(200): δ 5.49-5.76 (2H, m, H-2,3); 3.89 (2H, d, J=5.6Hz, 2xH-
1); 3.39 (2H, t, J=6.6Hz, 2xH-1'); 1.95-2.10 (2H, m, 2xH-4); 1.30-1.65 (10H, m,
2xH-5,2',3',4',5'); 0.86-0.94 (6H, m, 3xH-6,6').

¹³C nmr: δ 134.0, 126.8 (C-2,3); 71.5, 70.2 (C-1,1'); 34.5, 31.8, 29.8,
25.9, 22.6, 22.3 (C-4,5,2',3',4',5'); 14.0, 13.6 (C-6,6').

MS: m/e = 184 (57%, M⁺); 155 (9%); 141 (100%); 113 (26%).

(C₁₂H₂₄O requires: C, 78.20; H, 13.12%; M⁺ = 184.1827. Found: C,
78.10; H, 13.06%; M⁺ = 184.1827.)


1-(E-Hex-2-en-1-oxy)hexan-2-ol (123a) (390 mg, 1.95 mmol) was added to
a solution of triethylamine (400 µl) in dichloromethane (10 ml).

Methanesulfonyl chloride (270 mg, 2.34 mmol) was added and the mixture stirred
for 3h. The mixture was poured into water (50 ml) and the phases separated. The
organic phase was washed with 10% hydrochloric acid (3x), sat. sodium
bicarbonate, water, dried (MgSO₄) and the solvent removed to give 1-(E-hex-2-en-1-
oxy)hex-2-yl methanesulfonate (400 mg, 74%) in a state not requiring further
purification.

¹H nmr(60): δ 5.36-5.67 (2H, m, H-2,3'); 4.60-4.80 (1H, m, H-2); 3.80-
4.00 (2H, m, 2xH-1'); 3.82 (2H, d, J=6Hz, 2xH-1); 3.00 (3H, s, SO₂CH₃); 0.68-
2.30 (16H, m, 2xH-3,4,5,4',5':3xH-6,6').

Sodium borohydride was added portionwise to a solution of
diphenyldiselenide (250 mg) in ethanol (10 ml) until the yellow colour just
disappeared. The methanesulfonate (400 mg, 1.44 mmol) was added and the
mixture heated for 7 days under reflux. The mixture was poured into 10%
hydrochloric acid (100 ml) and extracted with pentane (2x), the combined extracts washed with sat. sodium bicarbonate, sat. sodium chloride, dried (MgSO₄) and the solvent removed. The residue was separated by flash chromatography (50% dichloromethane/pentane). The second major fraction proved to contain the title selenide as a yellow oil after removal of the solvent (110 mg, 23%).

\[ \nu_{\text{max}}: 1440, 1480, 1580, 1670 \text{ cm}^{-1} \]

\[ ^1\text{H} \text{nmr}(200): \delta 7.53-7.59 (2H, m, 2x\text{Ar-H}); 7.21-7.28 (3H, m, 3x\text{Ar-H}); 5.42-5.69 (2H, m, H-2',3'); 3.86-3.92 (2H, m, 2xH-1'); 3.46-3.61 (3H, m, 2xH-1',2'); 1.95-2.04 (2H, m, 2xH-4'); 1.24-1.69 (8H, m, 2xH-3,4,5,5'); 0.85-0.92 (6H, m, 2xH-6,6'). \]

\[ ^{13}\text{C} \text{nmr}: \delta 134.7, 129.0, 128.9, 127.3 (\text{Ar-}C); 134.5, 126.4 (\text{C-2',3'}); 73.0, 71.6 (\text{C-1,1'}); 45.1 (\text{C-2}); 34.3, 32.0, 29.9, 22.6, 22.2 (\text{C-3,4,5,4',5'}); 14.0, 13.7 (\text{C-6,6'}). \]

MS: m/e = 340 (4%, M⁺); 258 (24%); 240 (100%); 158 (35%). All quoted peaks contain the Se⁸⁰ isotope.

\[(\text{C}_{18}\text{H}_{28}\text{OSe}^{80} \text{ requires: } M^+ = 340.1305. \text{ Found: } M^+ = 340.1296.\)

32. Reaction of Z-hex-2-en-1-ol with 2-n-butyloxirane.

\[ \text{Z-Hex-2-en-1-ol} (500 \text{ mg, 5.0 mmol}) \text{ was added with stirring to a suspension of sodium hydride (130 mg, 5.4 mmol) in DME (10 ml). After the evolution of hydrogen had ceased, 2-n-butyloxirane (500 \text{ mg, 5.0 mmol}) \text{ was added and the mixture heated under reflux overnight. The mixture was poured into 10\% hydrochloric acid (50 ml) and extracted with pentane (2x), the combined extracts washed with sat. sodium bicarbonate (2x), sat. sodium chloride, dried (MgSO₄) and the solvent removed. The residue proved unable to be purified by flash chromatography or MPLC.} \]

33. 1-(Z-Hex-2-en-1-oxy)hexan-2-ol (123b).

\[ \text{Z-Hex-2-en-1-ol} (1.0g, 10.0 \text{ mmol}) \text{ was slowly added to a stirred suspension of sodium hydride (250 mg, 10.5 mmol) in DME (10 ml). When the evolution of hydrogen had ceased another equivalent of sodium hydride (250 mg, 10.5 mmol) \text{ was added followed by the dropwise addition of bromoacetic acid} \]
(1.32g, 9.5 mmol) in DME (5 ml). When the evolution of hydrogen had subsided, DMF (5 ml) was added and the mixture sonicated for 2h. The mixture was poured into 10% hydrochloric acid (100 ml), saturated with sodium chloride and extracted with dichloromethane (3x), the combined organic phases extracted with sat. sodium bicarbonate (3x), the combined alkaline phases acidified with conc. hydrochloric acid, saturated with sodium chloride and extracted with ether (5x). The combined ethereal extracts were dried (MgSO₄) and the solvent removed to give crude Z-hex-2-en-1-oxyacetic acid (125) (1.15g, 77%).

¹H nmr(60): δ 10.9 (1H, s(broad), CO$\text{H}$); 5.43-5.76 (2H, m, H-2',3'); 4.03-4.23 (4H, m, 2×H-2,1'); 1.80-2.30 (2H, m, 2×H-4'); 1.10-1.72 (2H, m, 2×H-5'); 0.70-1.10 (3H, m, 3×H-6').

The crude acid (1.15g, 7.28 mmol) was added dropwise with stirring to an ice-cold suspension of lithium aluminium hydride (500 mg, 13.2 mmol) in ether (15 ml). The mixture was heated for 4h under reflux. Ice was cautiously added until the evolution of hydrogen had ceased. The mixture was poured into 10% hydrochloric acid (75 ml) and the resultant mixture extracted with ether (3x), the combined ethereal extracts washed with sat. sodium bicarbonate (3x), sat. sodium chloride, dried (MgSO₄) and the solvent removed to give crude 2-(Z-hex-2-en-1-oxy)ethanol (650 mg, 62%) as described in part 22, with the exception that no E- isomer contaminant was present.

¹H nmr(60): δ 5.43-5.61 (2H, m, 2×H-2',3'); 4.00-4.07 (2H, m, 2×H-1'); 3.36-3.88 (4H, m, 2×H-1,2); 3.00 (1H, s(broad), OH); 1.85-2.27 (2H, m, 2×H-4'); 1.10-1.73 (2H, m, 2×H-5'); 0.76-1.10 (3H, m, 3×H-6').

DMSO (780 µl) in dichloromethane (3 ml) was added dropwise to a stirred solution of oxalyl chloride (480 µl) in dichloromethane (10 ml) cooled to -78°. After the evolution of gas had ceased the system was flushed with nitrogen, the crude alcohol (650 mg, 4.51 mmol) in dichloromethane (3.5 ml) added and the cloudy mixture stirred for 20 min at -78°. Triethylamine (3.2 ml) was added and the thick suspension left for 25 min before warming to room temperature. The mixture was poured into water (50 ml), extracted with dichloromethane (2x), the combined extracts washed with 10% hydrochloric acid and the solvent removed. The residue was dissolved in pentane (20 ml), dried (MgSO₄) and the solvent removed yielding a
yellow oil (250 mg) which was dissolved in dry ether (2 ml) and added dropwise to a solution of n-butylmagnesium bromide (prepared from butylbromide (600 mg, 4.4 mmol), magnesium (125 mg, 5.15 mmol) and a crystal of iodine in ether (5 ml)). After the addition was complete, the mixture was heated for 30 min at reflux, cautiously poured into 10% hydrochloric acid and extracted with ether (2x). The combined extracts were washed with sat. sodium chloride, dried (MgSO₄) and the solvent removed to give a pale oil identified as the title alcohol (300 mg, 16% overall) in a state not requiring further purification.

$\nu_{\text{max}}$: 1465, 1670, 3440(broad) cm⁻¹.

$^1$H nmr(200): δ 4.49-5.59 (2H, m, H-2',3'); 4.05-4.08 (2H, m, 2xH-1'); 3.66-3.72 (1H, m, H-2); 3.40-3.42 (1H, m, H-1a); 3.22-3.31 (1H, m, H-1b); 3.05 (1H, s(broad), OH); 1.98-2.09 (2H, m, 2xH-4'); 1.23-1.50 (8H, m, 2xH-3,4,5,5'); 0.87-0.94 (6H, m, 3xH-6,6').

$^{13}$C nmr: δ 133.5, 126.1 (C-2',3'); 74.7, 70.3, 66.7 (C-1,2,1'); 33.0, 29.6, 27.8, 22.8, 22.7 (C-3,4,5,4',5'); 14.0, 13.6 (C-6,6').

34. 1-(Z-Hex-2-en-1-oxy)-2-(phenylseleno)hexane (124b).

1-(Z-Hex-2-en-1-oxy)hexan-2-ol (123b) (300 mg, 1.50 mmol) was added to a solution of triethylamine (310 µl) in dichloromethane (10 ml). Methanesulfonylchloride (210 mg, 1.83 mmol) was added and the mixture stirred for 2h. The mixture was poured into water (50 ml) and the phases separated. The organic phase was washed with 10% hydrochloric acid (3x), sat. sodium bicarbonate, water, dried (MgSO₄) and the solvent removed to give 1-(Z-hex-2-en-1-oxy)hex-2-yl methanesulfonate (305 mg, 73%) in a state not requiring further purification.

$^1$H nmr(60): δ 5.37-5.66 (2H, m, H-2',3'); 4.47-4.92 (1H, m, H-2); 3.95-4.13 (2H, m, 2xH-1'); 3.43-3.54 (2H, m, 2xH-1); 3.00 (3H, s, OSO₂CH₃); 1.17-2.27 (10H, m, 2xH-3,4,5,4',5'); 0.73-1.10 (6H, m, 3xH-6,6').

Sodium borohydride was added portionwise to a stirred solution of diphenyldiselenide (1.6g, 5.4 mmol) in ethanol (20 ml) until the yellow colour just disappeared. The methanesulfonate (300 mg, 1.07 mmol) was added and the mixture heated at reflux for 60h. The mixture was poured into 10% hydrochloric
acid (100 ml) and extracted with pentane (2x), the combined extracts washed with sat. sodium chloride, dried (MgSO₄) and the solvent removed. The residue was separated by flash chromatography (50% dichloromethane/pentane). The second major fraction proved to contain the title selenide as a yellow oil after removal of the solvent (205 mg, 56%).

\[ \nu_{\text{max}}: 1475, 1580, 1660 \text{ cm}^{-1}. \]

\[^{1}H\text{ nmr}(200): \delta 7.52-7.57 (2H, m, 2xAr-H); 7.12-7.24 (3H, m, 3xAr-H); 5.49-5.53 (2H, m, H-2',3'); 3.97-4.00 (2H, m, 2xH-1'); 3.44-3.65 (2H, m, 2xH-1); 3.21-3.34 (1H, m, H-2); 1.94-2.01 (2H, m, 2xH-4'); 1.20-1.46 (8H, m, 2xH-3,4,5,5'); 0.78-0.91 (6H, m, 3xH-6,6'). \]

\[^{13}C\text{ nmr: } \delta 134.7, 129.1, 128.8, 127.3 (Ar-C); 133.4, 126.2 (C-2',3'); 73.3, 66.4 (C-1,1'); 45.1 (C-2); 32.0, 29.9, 29.6, 22.7, 22.6 (C-3,4,5,4',5'); 14.0, 13.7 (C-6,6'). \]

MS: m/e = 340 (5%, M⁺); 258 (20%); 241 (57%); 158 (49%); 83 (100%). All quoted peaks (except 83) contain the Se⁸⁰ isotope.

\((C_{18}H_{28}OSe^{80}\text{ requires: } M^+ = 340.1305. \text{ Found } M^+ = 340.1303.)\)

35. Hex-1-oxy-Z-hex-2-ene (126d).

The title ether was prepared in identical manner to the E- isomer (126c) as described in part 30, with the exception that Z-hex-2-en-1-ol (500 mg, 5.0 mmol) was used. After workup and distillation (Kugelrohr), the title compound was isolated as a colourless oil (595 mg, 65%), bp- 60°/0.1mm.

\[ \nu_{\text{max}}: 1105, 1455, 1465, 1660 \text{ cm}^{-1}. \]

\[^{1}H\text{ nmr}(200): \delta 5.23-5.57 (2H, m, H-2,3); 4.00-4.01 (2H, m, 2xH-1); 3.34-3.44 (2H, m, 2xH-1'); 1.96-2.12 (2H, m, 2xH-4); 1.29-1.67 (10H, m, 2xH-5,2',3',4',5'); 0.87-0.94 (6H, m, 3xH-6'). \]

\[^{13}C\text{ nmr: } \delta 133.0, 126.7 (C-2,3); 70.4, 66.4 (C-1,1'); 31.8, 29.8, 29.6, 25.9, 22.7, 22.6 (C-4,5,2',3',4',5'); 14.0, 13.7 (C-6,6'). \]

\((C_{12}H_{24}O \text{ requires: } C, 78.20; H, 13.12\%. \text{ Found: } C, 78.09; H, 12.97\%).\)

Hept-6-en-2-ol (152) (190 mg 1.22 mmol) was dissolved in dichloromethane (10 ml) and pyridine (360 mg) added. The system was flushed with nitrogen, phenylchlorothionocarbonate (232 mg, 1.34 mmol) added and the mixture stirred under nitrogen overnight. The mixture was poured into ethyl acetate (50 ml) and water (50 ml), the phases separated, the organic phase washed with 10% hydrochloric acid (4x), sat. sodium bicarbonate and sat. sodium chloride. The solution was dried (MgSO₄) and the solvent removed. The residue was separated by flash chromatography (5% ether/pentane) to give the title compound as a colourless oil (130 mg, 43%).

\[ \text{\( v_{\text{max}} \)}: \ 1490, \ 1590, \ 1640 \ \text{cm}^{-1}. \]

\[ ^1H \text{ nmr}(200): \ \delta \ 7.07-7.43 \ (5\text{H, m, Ar-H}); \ 5.71-5.92 \ (1\text{H, m, H-6}); \ 5.31-5.48 \ (1\text{H, m, H-2}); \ 4.94-5.06 \ (2\text{H, m, 2xH-7}); \ 2.03-2.18 \ (2\text{H, m, 2xH-5}); \ 1.40-1.92 \ (4\text{H, m, 2xH-3,4}); \ 1.40 \ (3\text{H, d, J}=6.3\text{Hz, 3xH-1}). \]

\[ ^{13}C \text{ nmr}: \ \delta \ 194.5 \ (C=S); \ 153.4 \ (Ar-C-1); \ 138.1, \ 126.3 \ (C-6,7); \ 129.4, \ 122.0, \ 115.0 \ (Ar-C); \ 82.2 \ (C-2); \ 34.9, \ 33.4, \ 24.4 \ (C-3,4,5); \ 19.1 \ (C-1). \]

(C₁₄H₁₈O₂S requires: C, 67.17; H, 7.25%. Found: C, 67.28; H, 7.25%).

37. Diethyl hex-5-en-1,1-dicarboxylate (153)

Diethyl malonate (3.0g, 18.8 mmol) was added to a solution of sodium ethoxide in ethanol (prepared by adding ethanol (20 ml) to sodium hydride (500 mg, 20.8 mmol) with vigorous stirring). 5-Bromopent-1-ene (2.9g, 19.5 mmol) was added and the mixture heated at reflux for 3h. The mixture was cooled, poured into 10% hydrochloric acid (75 ml) and extracted with ether (3x), dried (Na₂SO₄) and the solvent removed to give a brown oil which was distilled to give the title ester (2.71g, 75%), bp = 82-84°/0.5 mm (lit¹⁴²: 130-136°/14mm).

\[ \text{\( v_{\text{max}} \)}: \ 1640, \ 1735, \ 1750 \ \text{cm}^{-1}. \]

\[ ^1H \text{ nmr}(100): \ \delta \ 5.56-5.92 \ (1\text{H, m, H-5}); \ 4.88-5.16 \ (2\text{H, m, 2xH-6}); \ 4.20 \ (4\text{H, q, J}=8\text{Hz, 2xCO₂CH₂CH₃}); \ 3.33 \ (1\text{H, t, J}=7\text{Hz, H-1}); \ 1.80-2.25 \ (4\text{H, m, 2xH-2,4}); \ 1.36-1.60 \ (2\text{H, m, 2xH-3}); \ 1.27 \ (6\text{H, t, J}=8\text{Hz, 2xCO₂CH₂CH₃}). \]
38. **Diethyl l-bromohex-5-en-1,1-dicarboxylate (154).**

Diethyl hex-5-en-1,1-dicarboxylate (153) (3.0g, 13.2 mmol) was added to a suspension of sodium hydride (360 mg, 15.0 mmol) in N,N-dimethylformamide (DMF) (50 ml) and the mixture stirred under nitrogen until the evolution of hydrogen had ceased (~20 min). N-bromosuccinimide (NBS) (2.30g, 12.9 mmol) was added and the mixture stirred for 45 min. The mixture was poured into water (250 ml), extracted with ether (3x), dried (MgSO$_4$) and the solvent removed to yield a brown oil. Excess DMF was removed by filtration through a short silica column eluted with dichloromethane. After removal of the solvent, the product was distilled by bulb-bulb distillation (Kuegelrohr) to give the title ester as a colourless oil (3.10g, 78%), bp ~ 100°/0.1mm.

$\nu_{\text{max}}$: 1640, 1740, 1760 cm$^{-1}$.

$^1$H nmr(60): $\delta$ 5.40-6.16 (1H, m, H-5); 4.77-5.23 (2H, m, 2xH-6); 4.23 (4H, q, J=7Hz, 2xCO$_2$CH$_2$CH$_3$); 1.00-2.50 (6H, m, RH); 1.30 (6H, t, J=7Hz, 2xCO$_2$CH$_2$CH$_3$).

MS: m/e = 307/309 (2%, [M+H]$^+$); 181 (100%).

(C$_{12}$H$_{19}$BrO$_4$ requires: C, 46.92; H, 6.23%. Found: C, 46.98; H, 6.45%).

39. **Diethyl l-chlorohex-5-en-1,1-dicarboxylate (130)**

The title ester was prepared in identical manner to that of diethyl l-bromohex-5-en-1,1-dicarboxylate (154) as outlined in part 38, with the exception that N-chlorosuccinimide (NCS) (1.73g, 12.9 mmol) was used instead of NBS. (Yield = 2.8g, 81%), bp ~ 100°/0.1mm (Kuegelrohr).

$\nu_{\text{max}}$: 1640, 1745, 1765 cm$^{-1}$.

$^1$H nmr(60): $\delta$ 5.40-6.16 (1H, m, H-5); 4.77-5.23 (2H, m, 2xH-6); 4.23 (4H, q, J=8Hz, 2xCO$_2$CH$_2$CH$_3$); 1.00-2.50 (6H, m, RH); 1.30 (6H, t, J=8Hz, 2xCO$_2$CH$_2$CH$_3$).

MS(CI): m/e = 263/265 (74%, [M+H]$^+$); 39 (100%).

(C$_{12}$H$_{19}$ClO$_4$ requires: C, 54.86; H, 7.29%. Found: C, 54.85; H, 7.31%).
40. Diethyl cyclohexane-1,1-dicarboxylate (141)

The title compound was prepared by the method of Bergson and Biezai\footnote{120} as follows:

Sodium ethoxide was prepared by dissolving sodium (1.03g, 42.9 mmol) in ethanol (22ml). The solution was cooled and a portion of this solution (8.6ml) added to a dropping funnel. Diethyl malonate (3.6g, 22.4 mmol) was rapidly added with vigorous stirring to the remaining solution. The mixture was heated to reflux for a few minutes, cooled to room temperature and 1,5-dibromopentane (5.13g, 22.3 mmol) and the remaining sodium ethoxide solution were added simultaneously through different dropping funnels at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was heated at reflux for 2h, cooled, acidified with 10\% hydrochloric acid and extracted with ether (3x). The combined ethereal extracts were washed with sat. sodium chloride (2x), dried (MgSO\(_4\)) and the solvent removed to yield a yellow oil which was distilled to give the pure title compound as a colourless oil (1.4g, 21\%), bp = 72-75\(^\circ\)/0.2mm (lit\textsuperscript{120}: 76-80\(^\circ\)/0.1mm).

\[\nu_{\text{max}}: 1365, 1460, 1730 \text{ cm}^{-1}\]

\[^{1}\text{H nmr}(100): \delta 4.00 (4H, q, J=8Hz, 2\times\text{CO}_2\text{CH}_2\text{CH}_3); 0.94-1.96 (10H, m, \text{RH}); 1.16 (6H, t, J=8Hz, 2\times\text{CO}_2\text{CH}_2\text{CH}_3)\).

41. Diethyl 2-methylcyclopentane-1,1-dicarboxylate (157)

Diethyl 1-bromohex-5-en-1,1-dicarboxylate (154) (100 mg, 325 \(\mu\)mol) was dissolved in benzene (6 ml) and the solvent deoxygenated by bubbling argon through at a moderate rate for 10 min. Tri-n-butyltin hydride (90 \(\mu\)l, 330 \(\mu\)mol) and a few crystals of AIBN were added and the mixture heated under argon at reflux overnight. The mixture was cooled, concentrated at reduced pressure and bromine added until an excess was just evident. The mixture was filtered through a short silica column (dichloromethane as eluent) and the solvent removed to give a pale oil which was dissolved in pentane (1.0 ml) and separated by preparative GC (3\% OV-17 on GC-Q (80-100 mesh)) to give the title ester as a colourless oil which was further purified by bulb-bulb distillation, bp~ 100\(^\circ\)/8mm (lit\textsuperscript{117}: bp = 120-122\(^\circ\)/17.5mm).

\[\nu_{\text{max}}: 1250, 1460, 1730 \text{ cm}^{-1}\]
1H nmr(200): δ 4.18 (4H, m, 2xCO₂CH₂CH₃); 2.30-2.75 (1H, m, H-2); 1.25-2.10 (6H, m, RH); 1.245 (3H, t, J=6.6Hz, CO₂CH₂CH₃(a)); 1.251 (3H, t, J=6.6Hz, CO₂CH₂CH₃(b)); 0.99 (3H, d, J=7.1Hz, R-CH₃).

42. Ethyl (4-methylphenylthio)acetate (163).

Ethyl chloroacetate (10.8g, 88.2 mmol) was added to a solution of potassium hydroxide (5.2g, 92.9 mmol) and 4-methylthiophenol (10.0g, 80.6 mmol) in water (100 ml), and the mixture heated for 3h at reflux. The mixture was cooled, extracted with ether (2x), the combined extracts washed with sat. sodium bicarbonate, dried (MgSO₄) and the combined extracts removed to give a pale oil which was distilled, yielding the title compound as a colourless oil (9.0g, 53%), bp = 86-87°/0.1mm (lit143: bp = 165°/15mm).

νₘₐₓ: 1265, 1490, 1732 cm⁻¹.

1H nmr(60): δ 6.90-7.33 (4H, m, Ar-H); 4.13 (2H, q, J=7Hz, CO₂CH₂CH₃); 3.45 (2H, s, SCH₂CO₂); 2.30 (3H, s, Ar-CH₃); 1.21 (3H, t, J=7Hz, CO₂CH₂CH₃).

43. Ethyl 2-(4-methylphenylthio)hept-6-enoate (162).

Ethyl (4-methylphenylthio)acetate (163) (1.0g, 4.8 mmol) in dry DMF (3 ml) was added dropwise to a suspension of sodium hydride (120 mg, 5.0 mmol) in dry DMF (5 ml) with stirring. The system was flushed with nitrogen and stirring continued for 15 min. 5-Bromopent-1-ene (730 mg, 4.9 mmol) was added and the mixture stirred at 65° for 4h. The mixture was cautiously quenched with 10% hydrochloric acid (20 ml), extracted with ether (4x), washed with sat. sodium chloride, dried (MgSO₄) and the solvent removed to give a brown oil which was separated by flash chromatography (45% dichloromethane/hexane) and distilled by bulb-bulb distillation (Kuegelrohr) to give the title ester as a colourless oil (600 mg, 45%), bp ~ 150°/0.1mm.

νₘₐₓ: 1490, 1640, 1730 cm⁻¹.

1H nmr(200): δ 7.35 (2H, d, J=8.1Hz, 2xAr-H-2); 7.10 (2H, d, J=8.1Hz, 2xAr-H-3); 5.75 (1H, m, H-6); 4.98 (2H, m, 2xH-7); 4.11 (2H, q, J=7.1Hz, CO₂CH₂CH₃); 3.55 (1H, d:d, Jₐ=6.6Hz, Jₗ=8.1Hz, H₃-2); 2.32 (3H, s,
131.

Ar-\(\text{CH}_3\); 2.07 (2H, q, \(J=6.2\text{Hz}\), 2x\(\text{H-5}\)); 1.42-1.96 (4H, m, 2x\(\text{H-3,4}\)); 1.17 (3H, t, \(J=7.1\text{Hz}\), \(\text{CO}_2\text{CH}_2\text{CH}_3\)).

MS: \(m/e = 278\) (92%, \(M^+\)); 205 (14%); 124 (100%).

\((C_{16}H_{22}O_2\text{S})\) requires: C, 69.03; H, 7.96%. Found: C, 68.81; H, 7.98%.

44. Ethyl 2-chlorohept-6-enoate (134).

Diethyl 1-chlorohex-5-en-1,1-dicarboxylate (130) (2.5g, 9.52 mmol) was added to a stirred solution of sodium hydroxide (2.0g, 50 mmol) in ethanol (60 ml) and the mixture heated under reflux conditions for 4h, then cooled and stirred overnight. The precipitate was collected and dissolved in aqueous sodium bicarbonate (20 ml), the solution washed with ether (2x) and acidified with conc. hydrochloric acid. The mixture was extracted with ether (4x), the combined extracts dried (MgSO\(_4\)) and the solvent removed to yield the crude diacid which was heated neat at 130-140\(\circ\) until the evolution of carbon dioxide had ceased to give crude 2-chlorohept-6-enoic acid. (155a)

\(v_{\text{max}}\): 1640, 1725, 3080(broad) cm\(^{-1}\).

\(^1\text{H nmr}(60): \delta 11.3\) (1H, s(broad),\(\text{COJi}\)); 5.40-6.23 (1H, m, \(\text{H-6}\)); 4.76-5.35 (2H, m, 2x\(\text{H-7}\)); 4.35 (1H, t, \(J=6\text{Hz}\), \(\text{H-2}\)); 1.10-2.37 (6H, m, 2x\(\text{H-3,4,5}\)).

MS: \(m/e = 163/165\) (10%, [M+H]\(^+\)); 127 (100%); 122 (82%).

The crude acid was dissolved in thionyl chloride (30 ml) and the mixture heated under reflux until the evolution of gas had ceased (~1h). The excess thionyl chloride was removed at reduced pressure, ethanol (40 ml) added and reflux heating continued for 10 min. The mixture was cooled and the ethanol removed to give a brown oil which was distilled, yielding the title ester as a colourless oil (1.26g, 69%), bp ~ 100\(^\circ\)/0.2mm (Kuegelrohr).

\(v_{\text{max}}\): 1640, 1745 cm\(^{-1}\).

\(^1\text{H nmr}(60): \delta 5.40-6.13\) (1H, m, \(\text{H-6}\)); 4.73-5.20 (2H, m, 2x\(\text{H-7}\)); 3.93-4.43 (3H, m, \(\text{H-2}\): \(\text{CO}_2\text{CH}_2\text{CH}\)); 1.10-2.37 (6H, m, 2x\(\text{H-3,4,5}\)); 1.25 (3H, t, \(J=7\text{Hz}\), \(\text{CO}_2\text{CH}_2\text{CH}_3\)).

\((C_{9}H_{15}\text{ClO}_2\) requires: C, 56.59; H, 7.93%. Found: C, 56.80; H, 8.14%).
45. Ethyl 2-bromohept-6-enoate (156).

The title ester was prepared in identical manner to that of ethyl 2-chlorohept-6-enoate (134) as outlined in part 44 using diethyl 1-bromohex-5-en-1,1-dicarboxylate (154) (2.8 g, 9.1 mmol), sodium hydride (2.0 g, 50 mmol) and ethanol (40 ml), with the exception that decarboxylation was carried out at 120° for 5 h. The title ester was obtained as a colourless oil (350 mg, 16%), bp = 90°/1.0 mm (Kuegelrohr).

\[ \nu_{\text{max}}: 1445, 1460, 1640, 1740 \text{ cm}^{-1}. \]

\[ ^1\text{H nmr}(100): \delta 5.63-6.07 (1\text{H, m, H-6}); 4.92-5.20 (2\text{H, m, 2xH-7}); 4.14-4.38 (3\text{H, m, H-2: CO}_2\text{CH}_2\text{CH}_3); 1.08-2.28 (6\text{H, m, 2xH-3,4,5}); 1.29 (6\text{H, t, J}=7\text{Hz, CO}_2\text{CH}_2\text{CH}_3). \]

MS: 210 (3%); 166/168 (35%); 155 (25%); 28 (100%).

\[(\text{C}_9\text{H}_{15}\text{BrO}_2 \text{ requires: } [M-\text{Br}]^+ = 155.1072. \text{ Found: } [M-\text{Br}]^+ = 155.1072.)\]

46. Cis- and trans- ethyl 2-methylcyclopentan-1-carboxylate (158,142).

Ethyl 2-(4-methylphenylthio)hept-6-enoate (162) (200 mg, 720 µmol) and tri-n-butyltin hydride (190 µl, 710 µmol) were dissolved in benzene (190 µl). A few crystals of AIBN were added, the mixture heated overnight at reflux and then cooled. Bromine was added dropwise until the colour of bromine just persisted. The mixture was filtered through a short silica column and the solvent removed. The residual oil was dissolved in pentane (2.0 ml) and the title compounds isolated by preparative GC (3% OV-17 on GC-Q (80-100 mesh)). The isomer of lower retention time proved to be trans- ethyl 2-methylcyclopentan-1-carboxylate (142).

\[ ^1\text{H nmr}(200): \delta 4.13 (2\text{H, q, J}=7.1\text{Hz, CO}_2\text{CH}_2\text{CH}_3); 2.00-2.40 (2\text{H, m, H-1,2}); 1.50-1.95 (6\text{H, m, 2xH-3,4,5}); 1.26 (3\text{H, t, J}=7.1\text{Hz, CO}_2\text{CH}_2\text{CH}_3); 1.05 (3\text{H, d, J}=6.4\text{Hz, R-CH}_3). \]

The isomer of higher retention time proved to be cis- ethyl 2-methylcyclopentan-1-carboxylate (158).

\[ ^1\text{H nmr}(200): \delta 4.13 (2\text{H, q, J}=7.3\text{Hz, CO}_2\text{CH}_2\text{CH}_3); 2.29-2.80 (1\text{H, m, H-1}); 2.21-2.85 (1\text{H, m, H-2}); 1.50-1.95 (6\text{H, m, 2xH-3,4,5}); 1.26 (3\text{H, t, J}=7.3\text{Hz, CO}_2\text{CH}_2\text{CH}_3); 0.91 (3\text{H, d, J}=7.1\text{Hz, R-CH}_3). \]

Both isomers have previously been reported\textsuperscript{144} and the spectra are consistent with literature sources\textsuperscript{144}. 
47. Trans-2-methylcyclopentanecarboxylic acid (161).

Acetyl chloride (30.0g, 0.38 mol) was slowly added to a stirred suspension of aluminium chloride (60.0g, 0.45 mol) in cyclohexane (200 ml). The mixture was stirred vigorously for 3 days. The phases were separated and the lower phase decomposed by the portion-wise addition of ice. The brown mixture was steam distilled, the organic phase collected and fractionally distilled to give 1-acetyl-2-methylcyclopentane (160) as a yellow oil (11.0g, 23%), bp = 166-169° (lit\(^{121}\): bp = 167-168°).

\[ \nu_{\text{max}}: 1355, 1450, 1710 \text{ cm}^{-1} \]

\[^{1}\text{H nmr}(60): \delta 2.12 (3\text{H, s, C(O)CH}_3); 2.00-2.40 (1\text{H, m, H-1}); 1.40-2.00 (7\text{H, m, H-2: 2xH-3,4,5}); 1.03 (3\text{H, d, } J=5\text{Hz, R-CH}_3). \]

The spectra are consistent with literature sources\(^{145}\).

The ketone (160) (5.0g, 39 mmol) was added to a stirred solution of sodium hypobromite (prepared by adding bromine (20.4g, 0.13 mol) dropwise to an ice-cooled solution of sodium hydroxide (14.3g, 0.36 mol) in water (125 ml)). The mixture was stirred at room temperature for 2h at which time two phases were evident with the upper (aqueous) phase being colourless. The mixture was washed with ether (3x), acidified with conc. hydrochloric acid, saturated with sodium chloride and extracted with ether (3x). The combined extracts were dried (MgSO\(_4\)) and the solvent removed to give a colourless oil identified as the title acid (3.6g, 86%), bp = 118-120°/20mm (lit\(^{121}\): bp = 113°/13mm).


Trans-2-methylcyclopentanecarboxylic acid (161) (3.6g, 28.1 mmol) was dissolved in thionyl chloride (30 ml) and stirred at 40° until the evolution of gas had ceased. The solvent was removed and ethanol (30 ml) slowly added with stirring. The resultant brown solution was stirred at 40° for 30 min. The solvent was removed to give a brown oil which was distilled by bulb-bulb distillation to give the title ester as a colourless oil identical to the trans ester as described in part 46 (2.2 g, 36%), bp~ 120°/30mm.

\[ \nu_{\text{max}}: 1375, 1450, 1730 \text{ cm}^{-1}. \]

\[^{1}\text{H nmr: as described in part 46.} \]
49. Ethyl hept-6-enoate (159).

The title ester was prepared by the method of Schmidt and Ingold\textsuperscript{11d} using
diethyl hex-5-en-1,1-dicarboxylate (153) (1.08g, 5.5 mmol), sodium chloride (0.8g),
water (0.4 ml) and DMSO (11 ml). After workup, purification was achieved by
bulb-bulb distillation (Kugelrohr) to give the title ester as a colourless oil (340 mg,
46%).

\( \nu_{\text{max}} : 1370, 1640, 1735 \text{ cm}^{-1}. \)

\( ^1H \text{ nmr}(100) : \delta \ 5.64-6.08 (1H, m, H-6); 4.96-5.20 (2H, m, 2xH-7); 4.16
(2H, q, J=7Hz, CO_2CH_2CH_3); 1.40-2.42 (8H, m, 2xH-2,3,4,5); 1.12 (3H, t,
J=7Hz, CO_2CH_2CH_3). \)

50. 2,2-Dimethyloct-7-en-3-ol (165).

Trimethylacetaldehyde (920mg, 10.7 mmol) was slowly added to an ice-
cold solution of pent-4-en-1-ylmagnesium bromide (prepared from 5-bromopentene
(2.0g, 13.4 mmol), magnesium (360 mg, 15.0 mmol) and a crystal of iodine in dry
ether (20 ml)). When the addition was complete the solution was heated under
reflux for 30 min, cooled and cautiously poured into 10% hydrochloric acid (100
ml). The resultant mixture was extracted with ether (2x), the combined extracts
washed with sat. sodium bicarbonate, dried (MgSO_4) and the solvent removed to
give a pale oil which was purified by flash chromatography (10% ether/dichloromethane) to give the title alcohol as a colourless oil (680 mg, 41%).
An analytical sample was distilled by bulb-bulb distillation, bp~ 50°/0.5mm
(Kugelrohr).

\( \nu_{\text{max}} : 1360, 1480, 1640, 3380(broad) \text{ cm}^{-1}. \)

\( ^1H \text{ nmr}(200) : \delta \ 5.71-5.91 (1H, m, H-7); 4.91-5.05 (2H, m, 2xH-8); 3.10-
3.22 (1H, m, H-3); 2.20-2.13 (2H, m, 2xH-6); 1.78 (1H, s(broad), OH); 1.18-1.66
(4H, m, 2xH-4,5); 0.88 (9H, s, 9xH-1).

\( ^13C \text{ nmr} : \delta \ 138.8, 114.2 (C-7,8); 79.7 (C-3); 35.0 (C-2); 33.8, 30.9, 26.4
(C-4,5,6); 25.8 (3xC-1). \)

(C_{10}H_{20}O requires: C, 76.86; H, 12.90%. Found: C, 76.80; H, 12.63%).
51. Attempted preparation of 3-bromo-2,2-dimethyloct-7-ene (164).

2,2-Dimethyloct-7-en-3-yl methanesulfonate was prepared by the method outlined in part 29 using 2,2-dimethyloct-7-en-3-ol (165) (350 mg, 2.24 mmol) and all other reagents accordingly. After workup the methanesulfonate was isolated in a state not requiring further purification (368 mg, 70%).

The methanesulfonate (368 mg, 1.57 mmol) was dissolved in dry acetone (5 ml) and tetrabutylammonium bromide (2.5 g, 7.8 mmol) added, the solution transferred to a pyrex tube and sealed at liquid nitrogen temperature under vacuum. The solution was heated at 80° for 7 days. The tube was opened and the contents poured into water (25 ml) and extracted with ether (2x), the combined extracts dried (Na₂SO₄) and the solvent removed to yield a brown oil which proved to contain no identifiable products by ¹H nmr spectroscopy.

52. O-(2,2-Dimethyloct-7-en-3-yl)-O-phenylthionocarbonate (128).

2,2-Dimethyloct-7-en-3-ol (165) (500 mg, 3.21 mmol) was added to a solution of pyridine (940 mg) in dichloromethane (15 ml). The system was flushed with nitrogen and stirring commenced. Phenylchlorothionocarbonate (610 mg, 3.53 mmol) was added. The addition was mildly exothermic. The yellow solution was stirred under nitrogen overnight. The mixture was poured into water (50 ml) and extracted with ethyl acetate (2x), the combined organic phases washed with 10% hydrochloric acid (4x), sat. sodium bicarbonate, sat. sodium chloride and dried (MgSO₄). Removal of the solvent yielded a yellow oil which was purified by flash chromatography (8% ether/hexane) to give the title compound as a colourless oil (720 mg, 77%).

ν max: 1490, 1595, 1640 cm⁻¹.

¹H nmr(200): δ 7.05-7.42 (5H, m, Ar-H); 5.69-5.88 (1H, m, H-7); 5.34 (1H, t, J=6.4 Hz, H-3); 4.94-5.06 (2H, m, 2xH-8); 2.06-2.18 (2H, m, 2xH-6); 1.40-1.75 (4H, m, 2xH-4,5); 0.98 (9H, s, 9xH-1).

¹³C nmr: δ 195.9 (C=O); 153.4 (Ar-C-1); 138.2, 114.9 (C-7,8); 129.4, 126.3, 122.0 (Ar-C); 92.6 (C-3); 35.6 (C-2); 33.6, 29.2, 25.4 (C-4,5,6); 26.0 (3xC-1).

MS(Cl): m/e = 310 (0.23%, [M+NH₃]⁺); 293 (2%, [M+H]⁺); 237 (14% 139 (100%).
53. 7,7-Dimethyloct-1-ene (168).

O-(2,2-Dimethyloct-7-en-3-yl)-O-phenylthionocarbonate (128) (150 mg, 514 \( \mu \)mol), tri-n-butyltin hydride (165 mg, 565 \( \mu \)mol) and a few crystals of AIBN were dissolved in \( \alpha \)-butylbenzene (50 \( \mu \)l) and heated at 80\(^\circ\) overnight. Analysis of the mixture by analytical GC (25QC2/BP1) showed one major product which was isolated by preparative GC (20\% SE-30 on Chromosorb W (80-100 mesh)) to give the title olefin as a colourless oil.

\( ^1 \)H nmr(200): \( \delta \) 5.71-5.92 (1H, m, H-2); 4.89-5.05 (2H, m, 2xH-1); 2.00-2.12 (2H, m, 2xH-3); 1.15-1.35 (6H, m, 2xH-4,5,6); 0.86 (9H, s, 9xH-8).

\( ^{13} \)C nmr: \( \delta \) 138.6, 114.2 (C-1,2); 44.1 (C-3); 33.8, 30.0, 24.2 (C-4,5,6); 29.5 (3xC-8).

MS: m/e = 140 (0.51\% , M\(^+\)); 125 (1\%); 83 (15\%); 69 (27\%); 57 (100\%).

\( \text{C}_{10}\text{H}_{20} \) requires: M\(^+\) = 140.1565. Found: M\(^+\) = 140.1570.

54. Cis- and trans-1-t-butyl-2-methylcyclopentane (166,167).

O-(2,2-Dimethyloct-7-en-3-yl)-O-phenylthionocarbonate (128) (150 mg, 514 \( \mu \)mol) was added to a solution of tri-n-butyltin hydride (165 mg, 565 \( \mu \)mol) in hexane (10 ml). A few crystals of AIBN were added and the mixture heated overnight at reflux. The solution was concentrated to ca. 10 ml at reduced pressure and analysed by analytical GC (25QC2/BP1) revealing three products. Bromine was added dropwise until the orange colour just persisted. Analytical GC showed the absence of the minor of the three initial products. The sample was separated by preparative GC (20\% Carbowax on Chromosorb W (80-100 mesh)) to give as the product of lower retention time cis-1-t-butyl-2-methylcyclopentane (166) as a colourless oil.

\( ^1 \)H nmr(200): \( \delta \) 1.38-1.89 (8H, m, H-1,2: 2xH-3,4,5); 0.97 (3H, d, J=6.8Hz, C-CH\(_3\)); 0.84 (9H, s, C-C(CH\(_3\))\(_3\)).

\( ^{13} \)C nmr: \( \delta \) 57.6 (C-1); 36.3, 34.4, 32.9, 29.4, 25.6 (C-2,3,4,5: C-C(CH\(_3\))\(_3\)); 27.9 (C-C(CH\(_3\))\(_3\)); 23.8 (C-CH\(_3\)).
MS: m/e = 140 (0.12%, M+); 125 (7%); 83 (51%); 69 (37%); 57 (100%).
(C\textsubscript{10}H\textsubscript{20} requires: M\textsuperscript{+} = 140.1565. Found: M\textsuperscript{+} = 140.1569.)

The product of higher retention time proved to be trans-1-t-butyl-2-methylcyclopentane (167) which was isolated as a colourless oil.

\textsuperscript{1}H nmr(200): δ 2.12 (2H, m, H-1,2); 1.45-1.75 (6H, m, 2xH-3,4,5); 0.93 (9H, s, C-C(CH\textsubscript{3})\textsubscript{3}); 0.85 (3H, d, J=7.1Hz, C-CH\textsubscript{3}).

\textsuperscript{13}C nmr: δ 54.7 (C-1); 35.5, 34.8 (C-2,5); 29.3 (C-C(CH\textsubscript{3})\textsubscript{3}); 23.0, 21.3 (C-3,4); 16.8 (C-CH\textsubscript{3}).

MS: m/e = 140 (0.38%, M\textsuperscript{+}); 125 (7%); 83 (51%); 69 (42%); 57 (100%).
(C\textsubscript{10}H\textsubscript{20} requires: M\textsuperscript{+} = 140.1570. Found: M\textsuperscript{+} = 140.1569.)

55. 1-(Trimethylsilyloxy)cyclopentene (169).

The title ether was prepared by the method of House\textsuperscript{124} using cyclopentanone (10.5g, 125 mmol), chlorotrimethylsilane (16.3g, 150 mmol), triethylamine (30.3g, 300 mmol) and dry DMF (50 ml). The product was obtained as a colourless oil (6.7g, 34%), bp = 152-155°/720mm (lit\textsuperscript{124}: bp = 158-159°/760mm).

\textsuperscript{1}H nmr(60): δ 4.50-4.68 (1H, m, H-2); 1.63-2.47 (6H, m, 2xH-3,4,5); 0.20 (9H, s, OSi(CH\textsubscript{3})\textsubscript{3}).

56. 2-t-Butylcyclopentanone (170).

1-(Trimethylsilyloxy)cyclopentene (169) (2.34g, 15.0 mmol) and 2-chloro-2,2-dimethylpropane (1.43g, 15.5 mmol) were dissolved in dichloromethane (30 ml), the system flushed with argon and cooled to -45°. Titanium tetrachloride (2.85g, 15.0 mmol) in dichloromethane (5 ml) cooled to -45° was added under argon portionwise over a period of 2 min. After the addition was complete the mixture was stirred at -45° for 45 min. The cold solution was poured into ice/water (-250 ml) and the mixture shaken vigorously until two phases were apparent. The phases were separated, the aqueous phase extracted with dichloromethane, the combined organic extracts washed with sat. sodium bicarbonate, water, dried
(MgSO₄) and the solvent removed to yield a yellow oil which was purified by flash chromatography (10% ethyl acetate/dichloromethane) to give the title ketone as a pale oil (1.10g, 52%).

$\nu_{\text{max}}$: 1365, 1470, 1740 cm⁻¹.

$^1$H nmr(200) δ 1.66-2.37 (7H, m, H-2: 2xH-3,4,5); 0.99 (9H, s, C(CH₃)₃).

$^{13}$C nmr: δ 220.1 (C-1); 57.9 (C-2); 40.2 (C-5); 27.6 (C(CH₃)₃); 26.3, 20.2 (C-3,4).

The spectra are consistent with literature sources¹²⁵.

57. Zinc/Titanium methylenating reagent.

The reagent was prepared by the method of Lombardo¹²⁶ and stored as a thick grey slurry in tetrahydrofuran at 4°.

58. 1-Methylene-2-t-butylcyclopentane (171).

2-t-Butylcyclopentanone (170) (250 mg, 1.79 mmol) was dissolved in dichloromethane (3 ml) and the methylenating reagent, prepared as in described in part 57, added in portions until TLC indicated no further presence of the starting ketone. The mixture was poured into sat. sodium bicarbonate (50 ml) and extracted with ether (2x). The combined ethereal extracts were dried (MgSO₄) and the solvent removed to give the title olefin as a pale oil in quantitative yield. GC analysis (25QC2/BP1) indicated that the product was over 90% pure.

$\nu_{\text{max}}$: 1365, 1480, 1650 cm⁻¹.

$^1$H nmr(200): δ 4.97 (1H, m, C=CH(a)); 4.80 (1H, m, C=CH(b)); 2.10-2.32 (3H, m, H-2: 2xH-5); 1.15-1.87 (4H, m, 2xH-3,4); 0.89 (9H, s, C(CH₃)₃).

$^{13}$C nmr: δ 153.9 (C-1); 106.6 (C=CH₂); 52.2 (C-2); 35.5 (C-5); 27.7, 24.3 (C-3,4); 26.8 (C(CH₃)₃).

The compound is consistent with that reported in the literature¹⁴⁶.

1-Methylene-2-t-butylcyclopentane (171) (~100 mg) was dissolved in ethyl acetate (~1 ml) and 10% palladium on carbon (25 mg) added. The mixture was stirred under an atmosphere of hydrogen for 3h. GC analysis (25QC2/BP1) revealed the absence of starting olefin and the formation of two new compounds corresponding to cis- (95.5%) and trans-1-t-butyl-2-methylcyclopentane (4.5%) (166, 167) as prepared by the reductive cyclization of O-(2,2-dimethylct-7-en-3-yl)-O-phenylthionocarbonate (128) as described in part 54.

60. n-Butyltriphenylphosphonium iodide.

1-Bromobutane (20.0g, 0.146 mol) and triphenylphosphine (38.2g, 0.146 mol) were heated in benzene (50 ml) at reflux for 4 days. The solid was collected, washed with benzene and dried in vacuo to give the desired phosphonium salt (42.0g, 72%).


Sodium hydride (600 mg, 25.0 mmol) was stirred in dry DMSO (30 ml) until the evolution of hydrogen had ceased. n-Butyltriphenylphosphonium bromide, as prepared in part 60, (9.18g, 23.0 mmol) in DMSO (20 ml) was added and the mixture stirred at 70° for 10 min. 2-Hydroxytetrahydropyran (1.2g, 12.0 mmol) was added and the mixture stirred at 70° for 2h. The mixture was poured into ice/water (200 ml) and extracted with pentane (4x). The combined extracts were dried (MgSO₄) and the solvent removed to give a brown oil which was purified by MPLC (40% ethyl acetate/dichloromethane) to give the title alcohol (800 mg, 47%) containing ~8% E-isomer.

νmax: 1065, 1380, 1455, 3340(broad) cm⁻¹.

¹H nmr(200): δ 5.34-5.40 (2H, m, H-5,6); 3.62 (2H, t, J=6.3Hz, 2xH-1); 2.31 (1H, s(broad), OH); 1.96-2.11 (4H, m, 2xH-4,7); 1.31-1.61 (6H, m, 2xH-2,3,8); 0.90 (3H, t, J=7.6Hz, 3xH-9).

¹³C nmr: δ 130.1, 129.6 (C-5,6); 62.7 (C-1); 32.3, 29.3, 27.0, 25.9, 22.9 (C-2,3,4,7,8); 14.0 (C-9).

The spectra are consistent with literature sources¹²⁷.
62. **Z-Tridec-9-en-5-ol (173)**.

**Z-Non-5-en-1-ol (172)** (500 mg, 3.51 mmol), pyridinium dichromate (2.71 g, 7.2 mmol) and finely divided 4Å molecular sieves (2.4 g) were stirred in dichloromethane (18 ml) for 3 h. The solution was filtered through a short silica column and eluted with dichloromethane. The filtrate was collected and the solvent removed to give **crude Z-Non-5-enal** as a pale oil (210 mg, 43%).

$^1$H nmr (60) $\delta$ 9.68 (1H, d, $J=3$ Hz, H-1); 5.25-5.48 (2H, m, H-5,6); 0.73-2.57 (13H, m, R-H).

The **crude** aldehyde was added to an ice-cooled solution of n-butyllmagnesium bromide in ether (prepared from magnesium (80 mg, 3.23 mmol) and 1-bromobutane (390 mg, 2.85 mmol) in dry ether (5 ml). Initiation was achieved with a crystal of iodine.) The mixture was heated for 1 h under reflux, poured into 10% hydrochloric acid (50 ml) and extracted with ether (3x). The combined extracts were dried (MgSO$_4$) and the solvent removed. The residue was separated by MPLC (20% ethyl acetate/ dichloromethane) and further purified by bulb-bulb distillation to give the title alcohol as a colourless oil (260 mg, 92%), bp~120$^8$/1.5 mm (Kugelrohr). The oil appears to have ~8% $E$-isomer present.

$\nu_{max}$: 1380, 1465, 1650(weak), 3340 cm$^{-1}$.

$^1$H nmr (200): $\delta$ 5.33-5.39 (2H, m, H-9,10); 3.48-3.62 (1H, m, H-5); 1.94-2.10 (4H, m, 2xH-8,11); 1.84 (1H, s, OH); 1.31-1.54 (12H, m, 2xH-2,3,4,6,7,12); 0.86-0.93 (6H, m, 2xH-1,13).

$^{13}$C nmr: $\delta$ 130.1, 129.7 (C-9,10); 71.9 (C-5); 37.3, 37.1 (C-8,11); 29.4, 27.9, 27.3, 25.8, 22.9, 22.8 (C-2,3,4,6,7,12); 14.1, 13.8 (C-1,13).

(C$_{13}$H$_{26}$O requires: C, 78.72; H, 13.21%. Found: C, 78.73; H, 13.30%).

63. **O-Phenyl-O-(Z-tridec-9-en-5-yl)thionocarbonate (138)**.

**Z-Tridec-9-en-5-ol (173)** (120 mg, 610 $\mu$mol) and pyridine (180 mg) were dissolved in dichloromethane (4 ml) and the system flushed with argon. Phenylchlorothionocarbonate (123 mg, 710 $\mu$mol) was added and the mixture stirred under argon overnight. The mixture was poured into water (50 ml) and extracted with ethyl acetate (2x). The combined organic extracts were washed with 10% hydrochloric acid (4x), sat. sodium bicarbonate, sat. sodium chloride, dried
(MgSO₄) and the solvent removed. The yellow residue was separated by flash chromatography (20% dichloromethane/hexane) to give the title thionocarbonate as a pale oil (150 mg, 74%).

¹H nmr(200): δ 7.06-7.42 (5H, m, Ar-H); 5.28-5.49 (3H, m, H-5,9,10); 1.99-2.14 (4H, m, 2xH-8,11); 1.31-1.80 (12H, m, 2xH-2,3,4,6,7,12); 0.86-0.94 (6H, m, 3xH-1,13).

¹³C nmr: δ 194.9 (C=S); 153.5 (Ar-C-1); 130.4, 129.2 (C-9,10); 129.4, 126.3, 122.1 (Ar-C); 85.5 (C-5); 33.2, 33.1, 29.4, 27.3, 27.0, 25.2, 22.9, 22.6 (C-2,3,4,6,7,8,11,12); 14.0, 13.8 (C-1,13).

MS(CI): m/e = 335 (5%, [M+H]+); 248 (2%); 231 (100%); 198 (58%).

(C₂₀H₃₀O₂S requires: [M+H]+ = 335.2045. Found: [M+H]+ = 335.2046.)

64. Z-Tridec-4-ene (176).

A suspension of sodium hydride (300 mg, 12.5 mmol) in dry DMSO (25 ml) was stirred at 70° until the evolution of hydrogen had ceased. n-Butyltriphenylphosphonium bromide (4.59g, 11.5 mmol) in DMSO (10 ml) was added and the deep red solution stirred at 70° for 10 min. Nonanal (1.42g, 10.0 mmol) was added and stirring continued at 70° for 1h. The red colour disappeared immediately upon addition of the aldehyde. The mixture was poured into water (200 ml) and extracted with pentane (3x), the combined extracts washed with water (2x), dried (MgSO₄) and the solvent removed. The residue was separated by flash chromatography (hexane) to give the title alkene as a colourless oil (1.05g, 58%). A sample was distilled for analysis (bp- 100°/4mm, Kuegelrohr).

ν max': 1380, 1460 cm⁻¹.

¹H nmr(200): δ 5.30-5.38 (2H, m, H-4,5); 1.95-2.10 (4H, m, 2xH-3,6); 1.23-1.44 (14H, m, 2xH-2,7,8,9,10,11,12); 0.84-0.92 (6H, m, 3xH-1,13).

¹³C nmr: δ 130.2, 129.7 (C-4,5); 32.1, 30.0, 29.9, 29.7, 29.54, 29.48, 27.4, 23.1, 22.9 (C-2,3,6,7,8,9,10,11,12); 14.2, 13.9 (C-1,13).

(C₁₃H₂₆ requires: C, 85.63; H, 14.37%. Found: C, 85.67; H, 14.17%).
65. 4-(Cyclopenten-1-yl)morpholine (177).

Cyclopentanone (20g, 240 mmol), morpholine (33g, 380 mmol) and benzene (100 ml) were heated at reflux using a Dean-Stark water separator for 6h. The solution was cooled, the benzene removed and the residue distilled. The fore­run proved to be morpholine. The major fraction was collected and proved to be the title enamine (25g, 58%), bp = 104-106°/8mm (lit128: bp = 104-106°/12mm).

1H nmr(60): δ 4.27-4.58 (1H, m, H-2'); 3.51-3.83 (4H, m, 2xH-2,6); 2.73-3.00 (4H, m, 2xH-3,5); 1.68-2.50 (6H, m, 2xH-3',4',5').

66. 2-(But-2-en-1-yl)cyclopentanone.

4-(Cyclopent-1-yl)morpholine (177) (12.3g, 80 mmol) was dissolved in dioxan (20 ml). Crotyl bromide (5.4g, 40 mmol) was added, the mixture heated at reflux with vigorous stirring for 2h, cooled and the dioxan removed at reduced pressure. The residue was hydrolysed by addition of water (15 ml) followed by stirring for 1h. The aqueous mixture was extracted with ether (2x), the combined extracts washed with 10% hydrochloric acid (3x), water, dried (MgSO4) and the solvent removed to give a yellow oil which was purified by fractional distillation to give the title ketone as a colourless oil (3.1g, 56%), bp = 86-92°/12mm (lit139: bp = 77-83°/10mm).

νmax: 1410, 1450, 1640, 1735 cm⁻¹.

1H nmr(60): δ 4.76-5.56 (2H, m, H-2',3'); 1.53-2.45 (12H, m, H-2: 2xH-3,4,5,1': 3xH-4').

67. 2-n-Butylcyclopentanone (178).

2-(But-2-en-1-yl)cyclopentanone, prepared as described in part 66, (3.1g, 22.5 mmol) was dissolved in pentane (30 ml), 10% palladium on carbon (200 mg) added and the mixture stirred under an atmosphere of hydrogen for 1h. The solid was filtered off and the solvent removed to give the title ketone as a colourless oil (3.0g, 96%).

νmax: 1410, 1450, 1470, 1740 cm⁻¹.

1H nmr(60): δ 0.70-2.21 (16H, m, R-H).

Spectral details are consistent with literature data139.
68. 1,2-Di-n-butylcyclopentanol (179).

2-n-Butylcyclopentanone (178) (1.5g, 10.7 mmol) was added to a solution of n-butylmagnesium bromide in ether (prepared from 1-bromobutane (2.87g, 21.0 mmol), magnesium (630 mg, 26.0 mmol) and a crystal of iodine in ether (25 ml)) and the mixture heated for 30 min under reflux. The solution was cooled, poured into 10% hydrochloric acid (100 ml) and extracted with ether (2x). The combined ethereal extracts were washed with water, dried (MgSO₄) and the solvent removed. The residual oil was purified by MPLC (13% ethyl acetate/dichloromethane) to yield the title alcohol as a colourless oil (900 mg, 35%) and as predominantly one diastereoisomer.

\[ \text{v}_{\text{max}}: 1380, 1465, 3480 \text{(broad)} \text{ cm}^{-1}. \]

\[ ^1\text{H nmr}(200): \delta 1.08-2.12 (20H, m, H-2: 2xH-3,4,5: OH: 2xCH₂CH₂CH₂CH₃); 0.80-1.00 (6H, m, 2x(CH₂)₂CH₃). \]

\[ ^{13}\text{C nmr: } \delta 82.4 \text{ (C-1); 48.5 (C-2); 39.4, 38.6, 31.0, 28.3, 26.9, 23.5, 23.2, 21.1 (C-3,4,5: 2xCH₂CH₂CH₂CH₃): 14.1 (2x(CH₂)₂CH₃).} \]

MS: m/e = 198 (14%, M⁺·); 169 (33%); 156 (25%); 141 (100%); 123 (40%); 113 (88%).


69. 1,2-Di-n-butylcyclopentene (180).

1,2-Di-n-butylcyclopentanol (179) (300 mg, 1.52 mmol) was shaken with 60% hydrobromic acid for 5 min. The phases were separated, the acid phase extracted with pentane, the combined organic phases washed with water, dried (MgSO₄) and the solvent removed to give a brown oil which was separated by flash chromatography (pentane) and distilled by bulb-bulb distillation to give the title olefin as a colourless oil contaminated with ~20% other isomeric alkenes (250 mg, 91%), bp- 80°/0.1mm (Kugelrohr).

\[ \text{v}_{\text{max}}: 1380, 1470, 1645 \text{(weak)} \text{ cm}^{-1}. \]

\[ ^{13}\text{C nmr: } \delta 135.4 \text{ (C-1); 35.9, 30.6, 28.1, 22.7 (C-3,5: 2xCH₂CH₂CH₂CH₃); 21.9 (C-4); 14.0 (2x(CH₂)₂CH₃).} \]

MS: m/e = 180 (24%, M⁺·); 123 (32%); 95 (65%); 81 (100%); 79 (24%)

(C₁₃H₂₄ requires: C, 86.59; H, 13.41%. Found: C, 86.44; H, 13.60%).
70. Cis- and Trans- 1,2-Di-n-butylcyclopentane (174, 175).

1,2-Di-n-butylcyclopentene (180) (250 mg, 1.39 mmol) was dissolved in acetic acid (2 ml), 10% palladium on carbon (30 mg) added and the mixture stirred under an atmosphere of hydrogen for 48h. Ether (10 ml) was added, the solid filtered off, the filtrate washed with sat. sodium bicarbonate (3x) and dried (MgSO$_4$). Removal of the solvent gave the title compound as a colourless oil in quantitative yield. Analysis by GC (25QC2/BP1) showed that the cis/trans ratio was 4.5 : 1.

$^{13}$C nmr: δ 46.1, 35.1, 32.5, 30.9, 23.2 (C-1,2,3,5: 2xCH$_2$H$_2$CH$_3$; cis-isomer); 24.0 (C-4: cis-isomer); 14.3 (CH$_3$: cis-isomer); 42.6, 35.5, 32.3, 30.2, 29.0 (C-1,2,3,5: 2xCH$_2$H$_2$CH$_3$: trans-isomer); 26.8 (C-4: trans-isomer); 14.1 (CH$_3$: trans-isomer).

MS: m/e = 182 (M$^+$, 4%); 125 (26%); 97 (18%); 83 (67%); 69 (100%).

(C$_{13}$H$_{26}$ requires: M$^+$ = 182.2035. Found: M$^+$ = 182.2034).

71. E- and Z- 1-n-Butyl-2-butylidenecyclopentane (181).

Sodium hydride (265 mg, 11.0 mmol) was stirred in DMSO (25 ml) at 70° until the evolution of hydrogen had ceased. n-Butyltriphenylphosphonium bromide, prepared as described in part 60, (4.23g, 10.6 mmol) in DMSO (10 ml) was added and the red solution stirred at 70° before cooling to room temperature. 2-n-butylcyclopentanone (178) (1.0g, 7.1 mmol) was added and the mixture stirred at room temperature for 3h. The mixture was poured into water (300 ml), extracted with pentane (4x), the combined extracts washed with water (2x), dried (MgSO$_4$) and the solvent removed. The residue was purified by flash chromatography (pentane) to give the title olefin as a colourless oil (375 mg, 29%), bp– 80°/0.1mm (Kugelrohr). $^{13}$C nmr spectroscopy indicates a ~1:1 mixture of the geometric isomers.

ν$_{max}$: 1380, 1450, 1465, 1670(weak) cm$^{-1}$.

$^1$H nmr(200): δ 5.14-5.22 (1H, m, CCHCH$_2$); 0.80-2.58 (23H, m, RH).

$^{13}$C nmr: δ 147.3, 146.9 (C-1; both isomers); 120.7, 119.7 (CCHCH$_2$; both isomers); 44.4, 40.3, 34.9, 34.6, 33.5, 33.0, 32.1, 31.7, 31.5, 30.3, 30.2, 29.3, 24.7, 24.2, 23.1, 23.0, 14.8, 14.2, 14.0, 13.9.

MS: m/e = 180 (16%, M$^+$); 123 (45%); 95 (45%); 81 (100%).
(C_{13}H_{24} \text{ requires: C, } 86.59\% \text{; H, 13.41\%. Found: C, 86.46\%; H, 13.91\%.)}

72. **Hydrogenation of E- and Z- 1-n-Butyl-2-butylidene cyclopentane.**

The mixture of title olefins (181) (130 mg, 720 µmol) was dissolved in pentane (1.0 ml), 10% palladium on charcoal (30 mg) added and the mixture stirred under an atmosphere of hydrogen for 2h. Filtration and removal of the solvent yielded a colourless oil identified as cis-1,2-di-n-butylcyclopentane (174, 91%) and trans-1,2-di-n-butylcyclopentane (175, 9%) as indicated by $^{13}$C nmr spectroscopy and comparison with the mixture as prepared in part 70.

73. **5-Hexenal (183).**

Oxalyl chloride (2.8 ml) was dissolved in dichloromethane (60 ml) and the solution cooled to -60°. The system was flushed with nitrogen and DMSO (4.7 ml) added dropwise with stirring. When the evolution of gas had ceased, hex-5-en-1-ol (2.7g, 27.0 mmol) in dichloromethane (15 ml) was added over a 5 min period. The cloudy mixture was stirred at -60° for 20 min. Triethylamine (19.0 ml) was added and the thick suspension left at -60° for 25 min before warming to room temperature. Water (120 ml) was added and the layers separated. The aqueous phase was extracted with dichloromethane (2x), the combined organic phases washed with 10% sulfuric acid, sat. sodium chloride (2x), dried (MgSO$_4$) and the solvent removed. The residual oil was subject to bulb-bulb distillation (Kuegelrohr) to afford a colourless oil identified as the title aldehyde (2.3g, 87%), bp~ 75°/80mm (lit$^{130}$: bp = 128-129°/760mm).

$v_{\text{max}}$: 910, 995, 1640, 1720, 2720 cm$^{-1}$.

$^1$H nmr(100): $\delta$ 9.82 (1H, t, J=3Hz, H-1); 5.52-5.96 (1H, m, H-5); 4.84-5.08 (2H, m, 2xH-6); 1.40-2.48 (6H, m, 2xH-2,3,4).

74. **Reaction of 5-hexenal (183) with hydrogen chloride in methanol.**

5-Hexenal (183) (600 mg, 6.12 mmol) was mixed with methanol (210 mg, 6.5 mmol) and the mixture cooled to -30°. A steady stream of hydrogen chloride gas was passed through the solution for about 1 min. The cloudy solution was dried by the addition of finely powdered calcium chloride. The solid was removed by
filtration and the residual oil examined by \(^1\)H nmr spectroscopy, revealing an absence of unsaturation.

\(^1\)H nmr(60): \(\delta 3.42 (3H, s); 3.40-3.85 (2H, m); 1.20-2.50 (8H, m).\)

The nmr spectrum is consistent with that expected for 1-chloro-3-methoxycyclohexane (184).

75. 2-Methoxyhept-6-enoic acid (186).

Ethyl 2-bromohept-6-enoate (156) (300 mg, 1.28 mmol) was added to a solution of sodium methoxide in methanol (prepared by adding dry methanol (10 ml) to sodium hydride (180 mg, 7.5 mmol) with vigorous stirring) and the mixture heated under reflux conditions for 20h. The mixture was cooled, poured into 10% hydrochloric acid (50 ml) and the mixture extracted with ether (3x). The combined extracts were washed with sat. sodium chloride, dried (MgSO\(_4\)) and the solvent removed. The residue was purified by bulb-bulb distillation to give the title acid as a colourless oil (185 mg, 91%), bp~ 80°/0.4mm (Kuegelrohr).

\(\nu_{\text{max}}: 1440, 1460, 1640, 1720, 3080\text{ (broad) cm}^{-1} • \)

\(^1\)H nmr(200): \(\delta 10.3 (\text{CO}^{13}\text{H}); 5.69-5.90 (1H, m, H-6); 4.93-5.06 (2H, m, 2xH-7); 3.76-3.84 (1H, m, H-2); 3.43 (3H, s, OCH\(_3\)); 2.03-2.15 (2H, m, 2xH-5); 1.74-1.84 (2H, m, 2xH-3); 1.51-1.63 (2H, m, 2xH-4).

\(^1\)C nmr: \(\delta 178.0 (C-1); 138.0, 114.9 (C-6,7); 80.0 (C-2); 58.2 (OCH\(_3\)); 33.2, 31.9, 24.2 (C-3,4,5).

\((\text{C}_8\text{H}_{14}\text{O}_3\text{ requires: C, 60.74%; H, 8.92%}.\text{ Found: C, 60.70; H, 8.97%}).\)

76. 1-(2-Methoxyhept-6-enoyl)-5-methyl-(1H)-thiazolin-2-thione (136).

1-Hydroxy-5-methyl-(1H)-thiazolin-2-thione (140 mg, 950 \(\mu\)mol), 2-methoxyhept-6-enoyl chloride (prepared by stirring 2-methoxyhept-6-enoic acid (186) (140 mg, 886 \(\mu\)mol) in thionyl chloride (3 ml) at 50° until the evolution of gas had ceased followed by the removal of the solvent), pyridine (100 \(\mu\)l) and 4-dimethylaminopyridine (4 mg) were stirred in ether (5 ml) for 20 min. The precipitate was filtered off and the solvent removed. The residual green oil was separated by flash chromatography (dichloromethane) to give the title thiohydroxamic ester as a pale oil (60 mg, 24%).
147.

$^1$H nmr (200): δ 6.28 (1H, s, H-4); 5.71-5.92 (1H, m, H-6'); 4.96-5.08 (2H, m, 2xH-7'); 4.12-4.30 (1H, m, H-2'); 3.55 (3H, d, J=4.0Hz, OCH$_3$); 2.17 (3H, s, CCH$_3$); 1.90-2.20 (4H, m, 2xH-3',5'); 1.64-1.78 (2H, m, 2xH-4').

$^{13}$C nmr: δ 168.3 (C-1'); 137.8, 136.6, 115.1, 106.7 (C-4,5,6',7'); 79.1 (C-2'); 58.9 (OCH$_3$); 33.1, 32.3, 24.3 (C-3',4',5'); 13.3 (CCH$_3$).

MS: m/e = 288 (1%, [M+H]$^+$); 261 (48%); 214 (10%); 132 (100%); 81 (80%); 71 (54%).

(C$_{12}$H$_{17}$N0$_3$S$_2$ requires: [M+H]$^+$ = 288.0728. Found: [M+H]$^+$ = 288.0728.)

77. 1-Methoxyhex-5-ene (189).

Hex-5-en-1-ol (500 mg, 5.0 mmol) was added dropwise to a suspension of sodium hydride (130 mg, 5.5 mmol) in DME (5 ml). The mixture was stirred until the evolution of hydrogen had ceased. Methyl iodide (1.0 ml) was added and the mixture heated at reflux overnight. Separation was achieved by fractional distillation and the fraction (bp = 110-120°) collected. This fraction proved to contain the title ether contaminated with DME (lit$^{147}$: bp = 122°).

$^1$H nmr (200): δ 5.71-5.92 (1H, m, H-6); 4.92-5.05 (5H, m, 2xH-5); 3.60-3.69 (2H, t, J=6.4Hz, 2xH-1); 3.33 (3H, s, OCH$_3$); 2.06-2.17 (2H, m, 2xH-5); 1.44-1.68 (4H, m, 2xH-3,4).

78. 2-Methylcyclopentanol (190).

2-Methylcyclopentanone (500 mg, 5.10 mmol) was added to a suspension of lithium aluminium hydride (240 mg, 6.32 mmol) in dry ether (20 ml) at 0° and the mixture stirred at 0° for 2h and at room temperature overnight. 10% hydrochloric acid was added with stirring until the evolution of hydrogen had ceased. Further 10% hydrochloric acid (20 ml) was added, the phases separated and the aqueous phase extracted with ether. The combined extracts were washed with 10% hydrochloric acid, dried (MgSO$_4$) and the solvent removed. The residue was distilled by bulb-bulb distillation to give the title alcohol as a mixture of cis (20%) and trans (80%) isomers (495 mg, 97%), bp = 100°/100mm (Kuegelrohr). The isomer distribution is as described in the literature$^{132}$.

$\nu_{\text{max}}$: 1350, 1375, 1455, 3340(broad) cm$^{-1}$.
1 H nmr(200): $\delta$ 4.04-4.10 (0.2H, m, H-1(cis)); 3.65-3.78 (0.8H, m, H-1(trans)); 2.28 (1H, s(broad), OH); 1.45-1.93 (7H, m, H-2: 2xH-3,4,5); 1.10 (0.6H, d, J=7.3Hz, CCH$_3$(cis)); 0.96 (2.4H, d, J=7.3Hz, CCH$_3$(trans)).

13 C nmr: $\delta$ 80.4 (C-1(trans)); 76.1 (C-1(cis)); 42.6, 34.1, 31.6, 21.5 (C-2,3,4,5(trans)); 39.7, 34.6, 30.7, 22.1 (C-2,3,4,5(cis)); 18.2 (CCH$_3$(trans)); 13.6 (CCH$_3$(cis)).

79. 1-Methoxy-2-methylcyclopentane (187, 188).

Sodium hydride (115 mg, 4.8 mmol) was suspended in dry DMSO and the mixture stirred at 80° until the evolution of hydrogen had ceased. 2-Methylcyclopentanol (190) (20% cis, 80% trans) (200 mg, 2.0 mmol) and methyl iodide (1.0 ml) were added and the mixture stirred at 80° for 90 min and then at room temperature overnight. The crude reaction mixture was fractionally distilled to give as the first fraction (bp= 40-95°) mainly methyl iodide. The second fraction (bp= 95-110°) proved to contain the title ether contaminated with a little methyl iodide. The cis/trans ratio of the starting alcohol was preserved.

1 H nmr(200): $\delta$ 3.30 (4H, m, H-1: OCH$_3$); 1.51-2.00 (7H, m, H-2: 2xH-3,4,5); 0.98 (2.4H, d, 6.6Hz, CCH$_3$(trans)); 0.96 (0.6H, d, J=6.9Hz, CCH$_3$(cis)).

13 C nmr: $\delta$ 89.6 (C-1(trans)); 85.2 (C-1(cis)); 56.9 (OCH$_3$(cis)); 56.8 (OCH$_3$(trans)); 39.7, 32.2, 30.8, 22.3 (C-2,3,4,5 (trans)); 38.0, 31.2, 29.9, 21.5 (C-2,3,4,5(cis)); 19.1 (CCH$_3$(trans)); 18.1 (CCH$_3$(cis)).

MS: m/e = 114 (19%, M$^+$); 85 (25%); 71 (100%); 67 (14%).
(C$_7$H$_{14}$O requires: M$^+$ = 114.1045. Found: M$^+$ = 114.1045.)

80. 1,1,1-Trifluorohept-6-en-2-ol (191).

Ethyl trifluoroacetate (2.0g, 14.1 mmol) in dry ether (5 ml) was added dropwise to an ice-cooled, stirred solution of 4-pentenylmagnesium bromide in ether (prepared from magnesium (800 mg, 33 mmol), 5-bromopent-1-ene (4.47g, 30 mmol) and a crystal of iodine in dry ether (10 ml)). The mixture was heated at reflux for 1h, then poured into 10% hydrochloric acid (100 ml) and extracted with ether (3x). The combined organic extracts were washed with water (2x), dried (MgSO$_4$) and the solvent removed. The residue was distilled to give the title alcohol as a colourless oil (1.3g, 56%), bp = 145-147°.
\[ v_{\text{max}}: 1140, 1170, 1280, 1640, 3380 \text{(broad)} \text{ cm}^{-1}. \]

\[ ^1H \text{nmr}(60): \delta 5.43-6.17 (1H, m, H-6); 4.73-5.23 (2H, m, 2xH-7); 3.60-4.17 (1H, m, H-2); 2.36 (1H, s(broad), OH); 1.30-2.30 (6H, m, 2xH-3,4,5). \]

MS: m/e = 168 (0.2%, M+'); 150 (31%); 135 (10%); 81 (41%); 69 (56%); 54 (100%).

(C\(_7\)H\(_{11}\)F\(_3\)O requires: M+ = 168.0762. Found: M+ = 168.0761.)

81. O-Phenyl-O-(1,1,1-trifluorohept-6-en-2-yl)thionocarbonate (140).

1,1,1-Trifluorohept-6-en-2-ol (191) (500 mg, 2.98 mmol) was dissolved in dichloromethane (15 ml) and pyridine (940 mg) added. The system was flushed with argon, phenylchlorothionocarbonate (570 mg, 3.30 mmol) added and the mixture stirred under argon overnight. The mixture was poured into water (100 ml) and extracted with ethyl acetate (2x). The combined extracts were washed with 10% hydrochloric acid (4x), sat. sodium bicarbonate, sat. sodium chloride, dried (MgSO\(_4\)) and the solvent removed. The residue was separated by MPLC (40% ethyl acetate/hexane) to give the title compound as a yellow oil (610 mg, 67%).

\[ v_{\text{max}}: 1490, 1590, 1640 \text{ cm}^{-1}. \]

\[ ^1H \text{nmr}(60): \delta 6.93-7.56 (5H, m, Ar-H); 5.43-6.15 (2H, m, H-2,6); 4.78-5.23 (2H, m, 2xH-7); 1.23-2.38 (6H, m, 2xH-3,4,5). \]

\[ ^13C \text{nmr}: \delta 194.7 (\text{C-S}); 153.6 (\text{Ar-C-1}); 137.4, 126.9 (\text{C-6,7}); 129.7, 121.7, 115.7 (\text{Ar-C}); 123.6 (q, J_{CF}=283Hz, \text{C-1}); 78.9 (q, J_{CCF} = 32Hz, \text{C-2}); 33.2, 27.3, 23.6 (\text{C-3,4,5}). \]

MS: m/e = 305 (100%, [M+H]+); 223 (9%); 211 (8%); 195 (8%); 110 (38%); 94 (95%).

(C\(_{14}\)H\(_{15}\)F\(_3\)O\(_2\)S requires: [M+H]+ = 305.0823. Found: [M+H]+ = 305.0822.)

82. Trans-1-methyl-2-trifluoromethylcyclopentane (193).

Trans-2-methylcyclopentanecarboxylic acid (161) (2.0g, 15.6 mmol) was added to a 50 ml stainless-steel pressure vessel fitted with a pressure regulator and inlet/outlet valve. The vessel was sealed and cooled in liquid nitrogen. Sulfur tetrafluoride (18g) was introduced and the vessel warmed to room temperature and
then heated at 120° for 10h. The vessel was cooled to room temperature, the volatile
gases vented and the vessel opened. The residual oil was washed with sat. sodium
bicarbonate, dried (MgSO₄) and distilled to yield the title compound as a colourless
oil. GC analysis (25QC2/BP1) showed the compound to have retained the original
cis/trans ratio (ie. ~5% cis).

\[ \nu_{\text{max}}: 1100, 1160, 1270, 1390, 1450 \text{ cm}^{-1}. \]

\[ ^1H \text{ nmr}(200): \delta \ 1.45-2.16 (8H, m, H-1,2: 2xH-3,4,5); 1.10 (3H, d, J=6.3Hz, CCH}_3). \]

\[ ^{13}C \text{ nmr: } \delta \ 129.0 (q, J_{CF}=278.4Hz, CCF}_3); 50.2 (q, J_{CF}=26.4Hz, C-2); \]
\[ 35.5, 35.3, 26.9, 24.7 (C-1,3,4,5); 19.6 (CCH}_3). \]

\[ \text{MS: } m/e = 152 (2\% , M^+); 113 (16\% ); 69 (56\% ); 56 (100\%). \]

(C₇H₁₁F₃ requires: M⁺ = 152.0813. Found: M⁺ = 152.0813.)

83. (4-Carboxybutyl)triphenylphosphonium bromide.

5-Bromopentanoic acid (20g, 0.11 mol), triphenylphosphine (31.4g, 0.12 mol) and acetonitrile (80 ml) were mixed and heated at reflux overnight. The
acetonitrile was removed in vacuo. The residual oil was triturated by shaking with
2:1 benzene/methanol (~20 ml). The solid was collected, washed with benzene and
dried in vacuo to give the title compound as a pale crystalline solid (33.5g, 69%),

84. 5-Cyclohexylidenepentanol (195).

Sodium hydride (1.76g, 73.4 mmol) and dry DMSO (80 ml) were heated
at 70° with stirring until the evolution of hydrogen had ceased. (4-Carboxybutyl)-
triphenylphosphonium bromide, as prepared in part 83, (16.3g, 36.7 mmol) in
DMSO (30 ml) was added in one portion followed immediately by cyclohexanone
(3.0g, 30.6 mmol). The solution changed from red to brown. Stirring was continued
at 70° overnight. The mixture was cooled, poured into ice/water (500 ml), acidified
with conc. hydrochloric acid, extracted with ether (4x) and the combined ethereal
phases extracted with 1M sodium hydroxide (3x). The combined alkaline extracts
were washed with ether (3x), acidified with conc. hydrochloric acid, extracted with
ether (3x), the combined extracts washed with 10% hydrochloric acid, sat. sodium
chloride, dried (Na₂SO₄) and the solvent removed to give a brown oil (1.9g).
The oil was dissolved in dry ether (2 ml) and added dropwise to an ice-cooled suspension of lithium aluminium hydride (482 mg, 12.7 mmol) in dry ether (25 ml). When the evolution of hydrogen had ceased, the mixture was warmed to room temperature and stirred overnight. The mixture was cooled in ice and quenched by the dropwise addition of 10% hydrochloric acid until no further evolution of gas was apparent. Further 10% hydrochloric acid (20 ml) was added, the phases separated and the aqueous phase extracted with ether (20 ml). The combined ether extracts were washed with 10% hydrochloric acid, dried (Na₂SO₄) and the solvent removed to give a pale oil identified as the title alcohol in a state not requiring further purification (1.6 g, 31%).

\[ \text{v}_\text{max}: 1060, 1445, 1670, 3330(\text{broad}) \text{ cm}^{-1}. \]

\[ ^1\text{H} \text{nmr}(200): \delta \text{ 5.06} (1\text{H}, \text{ t}, J=7.1\text{Hz}, \text{ H-5}); 3.47 (2\text{H}, \text{ t}, J=7.0\text{Hz}, 2\times\text{H}_{-1}); 3.13 (1\text{H}, \text{s(broad), OH}); 1.95-2.08 (6\text{H}, \text{ m}, 2\times\text{H}_{4,2',6'}); 1.40-1.59 (10\text{H}, \text{ m}, 2\times\text{H}_{2,3,3',4',5'}). \]

Spectra are consistent with those previously reported⁹⁰.

85. 1-Cyclohexyl-5-cyclohexylidenepent-1-ol (196).

5-Cyclohexylidenepentan-1-ol (195) (500 mg, 2.98 mmol) was added to a stirred suspension of pyridinium dichromate (2.26 g, 6.0 mmol) and finely ground 4 molecular sieves (2.0 g) in dichloromethane (15 ml). The mixture was stirred at room temperature for 1 h. Pentane (15 ml) was added, the mixture filtered through celite, the filtrate collected and the solvent removed. The residue was passed through a short silica column and eluted with dichloromethane. The solvent was removed to give a colourless oil (360 mg).

The oil (360 mg) in ether (2 ml) was added to a solution of cyclohexylmagnesium bromide in ether (prepared from bromocyclohexane (714 mg, 4.38 mmol), magnesium (110 mg, 4.34 mmol) and a crystal of iodine in ether (15 ml)). The mixture was heated for 1 h under reflux conditions followed by stirring at room temperature for 2 h. The solution was poured into 10% hydrochloric acid (50 ml), extracted with ether (3 x), the combined extracts washed with sat. sodium chloride, dried (MgSO₄) and the solvent removed to give a yellow oil which was purified by MPLC (10% ethyl acetate/dichloromethane) and distilled by bulb-bulb
distillation to give the title alcohol as a colourless oil (340mg, 47%), bp-
170°/0.5mm.

\[ \nu_{\text{max}}: 1450, 1670(\text{weak}), 3360 \text{ cm}^{-1}. \]

$^1$H nmr(200): \( \delta \) 5.06 (1H, t, 7.3Hz, H-5); 3.26-3.37 (1H, m, H-1); 2.00-
2.23 (6H, m, 2xH-4,2',6'); 0.95-1.92 (24H, m, R-H).

(C$_{17}$H$_{30}$O requires: C, 81.54%; H, 12.07%. Found: C, 81.29%; H, 11.98%.)

86. O-[1-Cyclohexyl-5-cyclohexylidenepent-1-yl]-O-phenylthionocarbonate (132).

1-Cyclohexyl-5-cyclohexylidenepentan-1-ol (196) (255 mg, 1.02 mmol) and pyridine (300 \( \mu l \)) were dissolved in dichloromethane (10 ml). The system was flushed with argon, phenylchlorothionocarbonate (195 mg, 1.12 mmol) added and the mixture stirred under argon overnight. The mixture was poured into water (20 ml) and extracted with ethyl acetate (3x), the combined organic extracts washed with 10% hydrochloric acid (2x), sat. sodium chloride, dried (MgSO$_4$) and the solvent removed. The residue was separated by preparative TLC (10% ether/pentane). The highest band, on elution, proved to contain the title thionocarbonate which was isolated as a pale oil (280 mg, 71%).

\[ \nu_{\text{max}}: 1195, 1280, 1450, 1490, 1595, 1660(\text{weak}) \text{ cm}^{-1}. \]

$^1$H nmr(200): \( \delta \) 7.70-7.43 (5H, m, Ar-H); 5.22-5.32 (1H, m, H-1); 5.05
(1H, t, J=7.2Hz, H-5); 1.98-2.16 (6H, m, 2xH-4,2',6'); 1.10-1.83 (24H, m, R-H).

MS(Cl): m/e = 387 (100%, [M+H]$^+$); 279 (39%); 263 (53%); 250
(71%); 168 (39%).

(C$_{24}$H$_{34}$O$_2$S requires: [M+H]$^+$ = 387.2358. Found: [M+H]$^+$ = 387.2359.)

87. 1-Cyclohexyl-5-cyclohexylidenepentane (197).

1-Cyclohexyl-5-cyclohexylidenepentan-1-ol (196) (200 mg, 800 \( \mu \text{mol} \)) and triethylamine (170 \( \mu l \)) were dissolved in dichloromethane (2 ml). Methanesulfonylchloride (125 mg, 1.09 mmol) in dichloromethane (2 ml) was added and the mixture stirred at room temperature for 90 min. The solution was poured into water (20 ml), the phases separated, the aqueous phase extracted with dichloromethane (2x), the combined organic phases washed with 10% hydrochloric acid (2x), dried (MgSO$_4$) and the solvent removed to give a pale oil assigned to be 1-cyclohexyl-5-
cyclohexylidenepent-1-yl methanesulfonate (200) (260 mg, 99%).
\[ ^1\text{H nmr}(200): \delta 5.03 (1H, t, J=7.1\text{Hz}, H-5); 4.49-4.58 (1H, m, H-1); 3.00 (3H, s, \text{SO}_2\text{CH}_3); 1.90-2.12 (6H, m, 2xH-4, 2', 6'); 0.85-1.80 (21H, m, R-H). \]

The methanesulfonate (200) (100 mg, 335 \( \mu \text{mol} \)) in dry ether (1 ml) was added to a suspension of lithium aluminium hydride (22 mg, 578 \( \mu \text{mol} \)) in dry ether (1 ml) and the mixture stirred at room temperature overnight. The mixture was cautiously quenched by the dropwise addition of 10\% hydrochloric acid. When no further evolution of hydrogen was apparent, further 10\% hydrochloric acid (5 ml) was added, the phases separated and the aqueous phase extracted with ether (2x). The combined ethereal extracts were dried (\( \text{MgSO}_4 \)) and the solvent removed to give a pale oil which was distilled by bulb-bulb distillation to give the title olefin as a colourless oil (75 mg, 96\%), bp 100\%/0.5mm (Kuegelrohr).

\[ \nu_{\text{max}}: 1450, 1665(\text{weak}) \text{ cm}^{-1}. \]

\[ ^1\text{H nmr}(200): \delta 5.06 (1H, t, J=7.3\text{Hz}, H-5); 1.85-2.16 (6H, m, 2xH-4, 2', 6'); 1.08-1.75 (23H, m, R-H). \]

\[ ^{13}\text{C nmr}: \delta 139.5 (C-1'); 121.7 (C-5); 37.8, 37.6, 37.3, 33.6, 30.7, 28.9, 28.0, 27.2, 27.1, 26.9, 26.6. \]

\[ \text{MS: m/e = 234 (31\%, M^{+}); 149 (9\%); 122 (10\%); 109 (63\%); 91 (100\%); 81 (71\%).} \]

(C\(_{17}\)H\(_{30}\) requires: C, 87.10; H, 12.90\%. Found: C, 87.28; H, 12.70\%.)

88. Cis- and trans- 1,2-dicyclohexylcyclopentane (198, 199).

\[ \text{O-[1-Cyclohexyl-5-cyclohexylidenepent-1-yl]-O-phenylthionocarbonate (132) (60 mg, 155 \( \mu \text{mol} \)), tri-n-butyltin hydride (50 mg, 170 \( \mu \text{mol} \)), a few crystals of AIBN and hexane (5 ml) were heated under argon at reflux overnight. The mixture was cooled and bromine added dropwise until the orange colour just persisted. The mixture was separated by preparative-GC (2\% OV-17 on chromosorb-Q) to yield the title hydrocarbon as a mixture of cis- and trans- isomers with the trans- isomer dominating by a factor of ~2.} \]

\[ ^1\text{H nmr}(200): \delta 1.31-1.41 (0.67H, m, H-1,2: cis-isomer); 0.89-1.00 (1.33H, m, H-1,2: trans-isomer); 0.80-1.65 (28H, m, R-H). \]

\[ ^{13}\text{C nmr}: \delta 48.2 (C-1,2: cis-isomer); 47.5 (C-1,2: trans-isomer); 42.0 (2xC-1': trans-isomer); 37.8 (2xC-1': cis-isomer); 33.0, 29.1, 28.9, 27.2, 27.0, \]
26.9, 26.8 (C-3,4,5: 2xC-2',3',4',5',6': trans- isomer); 33.6, 31.1, 28.3, 28.1, 26.1, 25.7, 23.8 (C-3,4,5: 2xC-2',3',4',5',6': cis-isomer).

MS: m/e = 234 (30%, M⁺); 151 (78%); 109 (66%); 95 (100%).

(C₁₇H₃₀ requires: M⁺ = 234.2348. Found: M⁺ = 234.2346.)
Kinetic Studies using Tri-n-butyltin Hydride

General

The samples, prepared as described below, were thermolysed (T > 50°) or photolysed (T < 50°) at constant temperature for times indicated in Appendix A. Thermolysis was achieved by immersing the sample in a constant temperature oil bath, while photolysis was achieved by irradiating the sample with a 250W mercury lamp at a distance of 20 cm in a constant temperature water bath (or liquid ammonia bath for temperatures of -33°) for times as indicated in Appendix A. The sample mixtures were then analysed by gas chromatography on columns as indicated in Appendix A. Product identification was achieved by direct GC comparison with standard samples as prepared. Suitable internal standards were incorporated into trial reactions for the determination of reaction yield. Details concerning the method used as applied to each radical studied are listed in Appendix A.

Method A

Standard solutions of tri-n-butyltin hydride in the required solvent were prepared to concentrations as described in Appendix A.

A pyrex tube was charged with the required solution (100 µl), the required radical precursor (~0.1 equivalents) and a couple of crystals of AIBN added. The solution was frozen in liquid nitrogen and the tube sealed under vacuum. After the solution had thawed the tube was heated or irradiated at the required temperature and then analysed as described.

Method B

Standard solutions were prepared as described in Method A.

A vial fitted with a septum inlet was charged with the required solution (100 µl) and a couple of crystals of AIBN added. De-oxygenation was achieved by passing a stream of nitrogen through the solution for 1-2 min. The vial was immersed in the required constant temperature bath for 5 min. The required radical precursor (~0.1 equivalents) was injected. After 5-10 min a sample was removed and analysed as described.
Method C

Tri-n-butyltin hydride (1.0 equivalent) and the required radical precursor (1.05 equivalents) were dissolved in benzene and made up to concentrations as described in Appendix A.

A pyrex tube was charged with the required solution (200 µl) and a few crystals of AIBN added. The solution was frozen in liquid nitrogen under vacuum, thawed and refrozen. The tube was sealed under vacuum, thawed, heated or irradiated and then analysed as described.
APPENDIX A

Kinetic Studies of the Reaction of the Radical Precursors with Tri-n-butyltin Hydride

a) Mathematical Considerations.

Consider the cyclization reaction as depicted in Scheme A1.

It is clear that the cyclization of $R$ to give $R^1$ is a first order process. If this process is irreversible (i.e., $k_c >> k_c^{-1}$), then $R^1$ once formed will react exclusively with tri-n-butyltin hydride ($Bu_3SnH$) in a second order manner to give the cyclized product $C$. In competition with this process is the direct hydrogen abstraction by $R$ from $Bu_3SnH$ in a second order manner to give the uncyclized product $U$.

Thus:

$$\frac{d[R^1]}{dt} = k_c[R]$$

and:

$$\frac{d[U]}{dt} = k_H[R][Bu_3SnH]$$
Combining, we obtain:

\[
\frac{d[R^1]}{d[U]} = \frac{k_c}{k_H [Bu_3SnH]} \frac{1}{1}
\]

\[\text{...A2}\]

Under pseudo first-order conditions where \([Bu_3SnH] >> [R]\), then to a good approximation \([Bu_3SnH] \sim \text{constant}\), thus A2 integrates to:

\[
\frac{[C]}{[U]} = \frac{k_c}{k_H [Bu_3SnH]} \frac{1}{1}
\]

\[\text{...A3}\]

If the pseudo first-order conditions are not met, then integration of A2 leads to:

\[
[C]_f = \frac{k_c}{k_H} \ln \left( \frac{[Bu_3SnH]_o + k_c/k_H}{[Bu_3SnH]_f + k_c/k_H} \right)
\]

\[\text{...A4}\]

where the subscripts "f" and "o" denote "final" and "initial" respectively.

However, if the cyclization of \(R\) to \(R^1\) is reversible, then:

\[
\frac{d[C]}{dt} = k_H[R^1][Bu_3SnH]
\]

and:

\[
\frac{d[R^1]}{dt} = k_c[R] - k_c[R^1] - k_f[R^1][Bu_3SnH]
\]

Assuming that the equilibrium is steady state, then:

\[
\frac{d[R^1]}{dt} = 0
\]
thus:

$$[R^1] = \frac{k_c[R]}{k_c + k_H \cdot [Bu_3SnH]}$$  \(\text{...A5}\)

Combining A1 and A5 leads to:

$$\frac{d[U]}{d[C]} = \frac{k_H}{k_c} \left[ 1 - \frac{1}{K_E} \right] + \frac{k_H}{k_c} [Bu_3SnH]$$  \(\text{...A6}\)

Under pseudo first-order conditions A6 integrates to:

$$\frac{[U]}{[C]} = \frac{k_H}{k_c} \left[ 1 - \frac{1}{K_E} \right] + \frac{k_H}{k_c} [Bu_3SnH]$$  \(\text{...A7}\)

where:

$$K_E = \frac{k_c}{k_H}$$

However, if the pseudo first-order conditions are not met, integration of A6, assuming that $$[Bu_3SnH]_f = 0$$, leads to:

$$[C]_f = r \ln \left( \frac{[Bu_3SnH]_0}{r \left( 1 + \theta \right)} + 1 \right)$$  \(\text{...A8}\)

where \( r = \frac{k_c}{k_H} \) and \( \theta = 1/K_E \).

Expansion of A8 leads to the following logarithmic first-order approximation:

$$\frac{1}{[C]_f} = \frac{1 + \theta}{[Bu_3SnH]_0} + \frac{1}{2 \cdot r}$$  \(\text{...A9}\)
Thus a plot of \(1/[C]_f \text{ vs } 1/[Bu_3SnH]\) should be linear and of slope \(1 + \theta\).

It turns out that in the cases studied this relationship does hold, thus A9 is a useful approximation of A8.

Application of the above kinetic equations to the reactions studied, as outlined in the text, give values of \(k_c/k_H\), the ratio of the rate constants for cyclization to that of direct hydrogen abstraction of the radical \(R\) from \(Bu_3SnH\). Assuming the values of \(k_H\) for alkyl radicals as determined by Ingold and co-workers\(^{28c}\), the values of the cyclization rate constant \(k_c\) are readily obtained.

Variation of temperature and application of the Arrhenius equation A10 leads to values of the activation energy \(E_a\) and \(\log A\).

\[
k = A e^{-(E_a/RT)}
\]

...A10

It should be noted that each datum (\(k_c/k_H\), \(T\)) was averaged over three identical kinetic experiments and fitted to the Arrhenius equation (A10) by linear regressional analysis.

The following pages list the experimental data and the calculated kinetic parameters for the radical reactions studied, as discussed in the text.

b) Experimental data.

The experimental data presented in this section list the method employed (see experimental section) together with ratios of products as determined by the GC method described for the various reactions in this study. Unless otherwise stated, all concentrations are in moles per litre (M) and all reaction yields, as determined by direct comparison with internal standards, are in excess of 90%.

The kinetic parameters are as determined by the methods discussed in the previous section.
Hept-6-en-2-yl radical (18).

\[
\text{Br} \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad \text{cis} \quad + \quad \text{trans} \quad + \quad \text{uncyclized (U)}
\]

Experimental method used: A

Analytical GC performed with: SGE-25QC2/BP1 1.0

Reaction times: 4 - 6 h.

### Dependence of [cis]/[trans] on solvent.

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<tr>
<th>Temp (°C)</th>
<th>hexane</th>
<th>ether</th>
<th>morpholine</th>
<th>n-propanol</th>
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### Dependence of \(k_c/k_H\) on solvent.

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<th>Temp (°C)</th>
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<th>morpholine</th>
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\([C] = [\text{cis}] + [\text{trans}]\)
2,2-Dimethyloct-7-en-3-yl radical (71).

Experimental method used: **A**
Analytical GC performed with: **SGE- 25QC2/BP1 1.0**
Solvent: **Hexane**
Reaction times: **4 -6 h.**

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>( \frac{k_{cis}}{k_H} )</th>
<th>( \frac{k_{trans}}{k_H} )</th>
<th>( k_{cis}(s^{-1}) )</th>
<th>( k_{trans}(s^{-1}) )</th>
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\[
\log \left( \frac{k_{cis}}{k_H} \right) = (2.1 \pm 0.2) - \frac{(5.2 \pm 0.1)}{2.3 \ \text{RT}}
\]

\[
\log \left( \frac{k_{trans}}{k_H} \right) = (0.17 \pm 0.02) - \frac{(2.0 \pm 0.1)}{2.3 \ \text{RT}}
\]

\[
\log k_H = (8.71 \pm 0.37) - \frac{(3.47 \pm 0.49)^{28c}}{2.3 \ \text{RT}}
\]

\[
\log k_{cis} = (10.8 \pm 0.4) - \frac{(8.7 \pm 0.5)}{2.3 \ \text{RT}}
\]

\[
\log k_{trans} = (8.9 \pm 0.4) - \frac{(5.5 \pm 0.5)}{2.3 \ \text{RT}}
\]
### Dependance of [cis]/[trans] on solvent.

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</table>

### Dependance of $k_C/k_H$ on solvent.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>hexane</th>
<th>ether</th>
<th>DME</th>
<th>ethanol</th>
<th>n-propanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.041</td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>0.078</td>
<td></td>
<td></td>
<td>0.053</td>
<td>0.038</td>
</tr>
<tr>
<td>45</td>
<td>0.098</td>
<td>0.087</td>
<td>0.10</td>
<td>0.063</td>
<td>0.063</td>
</tr>
<tr>
<td>60</td>
<td>0.12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>80</td>
<td>0.14</td>
<td>0.19</td>
<td></td>
<td>0.084</td>
<td>0.085</td>
</tr>
<tr>
<td>92</td>
<td>0.18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

$[C] = [\text{cis}] + [\text{trans}]$
6-Methylenecyclodecyl radical (98b).

\[ \text{OC(S)Y} \]

\[ \text{Y} = \text{SMe, SPh, OPh.} \]

Experimental method used: A
Analytical GC performed with: SGE- 25QC2/BP1 1.0
Solvent: Benzene

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu$_3$SnH]</th>
<th>Reaction time</th>
<th>[cis]/[trans]</th>
<th>$k_{cis}/k_{trans}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.1</td>
<td>12-16h</td>
<td>3.5</td>
<td>3.5 (± 5%)</td>
</tr>
<tr>
<td>71</td>
<td>0.1</td>
<td>12-16h</td>
<td>3.3</td>
<td>3.3</td>
</tr>
<tr>
<td>80</td>
<td>0.1</td>
<td>12-16h</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>91</td>
<td>0.1</td>
<td>12-16h</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>122</td>
<td>0.1</td>
<td>12-16h</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>

The cis/trans ratios were unaffected by the variation of [Bu$_3$SnH] to 0.06 and 0.03M.

No uncyclized material was observed even in neat Bu$_3$SnH (ie: [Bu$_3$SnH] ~ 3.4M).

\[
E_a^{\text{cis}} - E_a^{\text{trans}} = -1.81 \pm 0.12 \text{ kcal mol}^{-1}
\]

\[
\log A^{\text{cis}} - \log A^{\text{trans}} = -0.63 \pm 0.06
\]

\[
\log \left( \frac{k_{cis}}{k_{trans}} \right) = (-0.63 \pm 0.06) + \frac{(1.81 \pm 0.12)}{2.3 \text{ RT}}
\]
2-(E-Hex-2-en-1-oxy)ethyl radical (113).

Experimental method used: B
Analytical GC performed with: SGE-25QC2/BP1 1.0
Solvent: Hexane
[But3SnH] = 2.87M

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[C]/[U]</th>
<th>( \frac{k_c}{k_H} )</th>
<th>( k_c(s^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>0.89</td>
<td>2.55 (± 6%)</td>
<td>9.9 x10^6</td>
</tr>
<tr>
<td>60</td>
<td>1.01</td>
<td>2.90</td>
<td>1.3 x10^7</td>
</tr>
<tr>
<td>71</td>
<td>1.10</td>
<td>3.16</td>
<td>1.7</td>
</tr>
<tr>
<td>80</td>
<td>1.21</td>
<td>3.47</td>
<td>2.2</td>
</tr>
<tr>
<td>90</td>
<td>1.36</td>
<td>3.90</td>
<td>2.8</td>
</tr>
</tbody>
</table>

\[ \log \left( \frac{k_c}{k_H} \right) = (2.1 ± 0.4) - \frac{(2.5 ± 0.2)}{2.3 RT} \]

\[ \log k_H = (9.06 ± 0.31) - \frac{(3.65 ± 0.41)}{2.3 RT} \]

\[ \log k_c = (11.2 ± 0.5) - \frac{(6.2 ± 0.5)}{2.3 RT} \]

\[ E_a = 6.2 ± 0.5 \text{ kcal mol}^{-1} \]

\[ \log A = 11.2 ± 0.5 \]
2-(Z-Hex-2-en-1-oxy)ethyl radical (114).

![Reaction Diagram]

Experimental method used: B
Analytical GC performed with: SGE-25QC2/BP1 1.0
Solvent: Hexane
$[\text{Bu}_3\text{SnH}] = 2.87\text{M}$

<table>
<thead>
<tr>
<th>Temp ($^\circ\text{C}$)</th>
<th>[C]/[U]</th>
<th>$k_c$</th>
<th>$k_c(s^{-1})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.79</td>
<td>2.27 (± 1%)</td>
<td>8.8 x 10^6</td>
</tr>
<tr>
<td>60</td>
<td>0.85</td>
<td>2.44</td>
<td>1.1 x 10^7</td>
</tr>
<tr>
<td>80</td>
<td>0.96</td>
<td>2.76</td>
<td>1.7</td>
</tr>
<tr>
<td>91</td>
<td>1.02</td>
<td>2.93</td>
<td>2.1</td>
</tr>
</tbody>
</table>

\[
\log \left( \frac{k_c}{k_H} \right) = (1.3 \pm 0.3) - \frac{(1.5 \pm 0.2)}{2.3 \text{ RT}}
\]

\[
\log k_H = (9.06 \pm 0.31) - \frac{(3.65 \pm 0.41)^{28c}}{2.3 \text{ RT}}
\]

\[
\log k_c = (10.4 \pm 0.4) - \frac{(5.2 \pm 0.5)}{2.3 \text{ RT}}
\]

$E_a = 5.2 \pm 0.5 \text{ kcal mol}^{-1}$

\[
\log A = 10.4 \pm 0.4
\]
Experimental method used: B
Analytical GC performed with: 3% SE-30 on Chromosorb W
Solvent: Hexane

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[cis]</th>
<th>[trans]</th>
<th>[C]/[U]</th>
<th>k_C/k_H</th>
<th>k_C (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-33</td>
<td>0.98</td>
<td>1.2</td>
<td></td>
<td>2.23</td>
<td>2.27 (± 73%)</td>
<td>7.9 x 10⁵</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
<td>1.2</td>
<td></td>
<td>2.16</td>
<td>2.12</td>
<td>2.0 x 10⁶</td>
</tr>
<tr>
<td>26</td>
<td>0.98</td>
<td>1.2</td>
<td></td>
<td>2.62</td>
<td>2.56</td>
<td>3.7</td>
</tr>
<tr>
<td>60</td>
<td>1.81</td>
<td>1.2</td>
<td></td>
<td>2.32</td>
<td>4.20</td>
<td>1.1 x 10⁷</td>
</tr>
<tr>
<td>90</td>
<td>1.81</td>
<td>1.2</td>
<td></td>
<td>2.59</td>
<td>4.69</td>
<td>1.9</td>
</tr>
</tbody>
</table>

[C] = [cis] + [trans]
1-((Z-Hex-2-en-1-oxy)hex-2-yl) radical (121).

Experimental method used: A, C
Analytical GC performed with: SGE-SCOT GB-30 Apiezon L
Solvent: Hexane

No reliable data was obtained due to difficulties discussed in the text.

Approximate values:

\[
\frac{[\text{cis}]}{[\text{trans}]} = 1.3 \text{ at } 25^\circ C
\]
\[
\frac{[\text{cis}]}{[\text{trans}]} = 1.5 \text{ at } 80^\circ C
\]

\[k_{\text{cis}} \simeq 4 \times 10^6 \text{ s}^{-1} \text{ at } 25^\circ C\]

No solvent effect could be detected.
1,1-Diethoxycarbonylhex-5-en-1-yl radical (129).

\[
\text{Cl} \quad \text{CO}_2\text{Et} \quad \xrightarrow{\text{Bu}_3\text{SnH}} \quad \text{CO}_2\text{Et} \quad \text{CO}_2\text{Et}
\]

\[
\begin{align*}
\text{cyclized (C)} & \quad \text{uncyclized (U)}
\end{align*}
\]

Experimental method used: A, C
Analytical GC performed with: SGE-SCOT GSD Apiezon L
Solvent: Benzene
All reactions carried out overnight.

Using method A and equation A7.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu$_3$SnH]</th>
<th>[U]/[C]</th>
<th>$k_c/k_H$</th>
<th>$k_H/k_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>0.403</td>
<td>4.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.201</td>
<td>2.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.101</td>
<td>1.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.44</td>
<td>0.090 (± 28%)</td>
<td>0.18</td>
</tr>
<tr>
<td>70</td>
<td>0.403</td>
<td>4.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.201</td>
<td>2.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.101</td>
<td>1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.60</td>
<td>0.101</td>
<td>0.32</td>
</tr>
<tr>
<td>80</td>
<td>0.403</td>
<td>3.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.201</td>
<td>1.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.101</td>
<td>1.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.48</td>
<td>0.141</td>
<td>0.32</td>
</tr>
<tr>
<td>90</td>
<td>0.403</td>
<td>2.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.101</td>
<td>1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.49</td>
<td>0.174</td>
<td>0.32</td>
</tr>
<tr>
<td>100</td>
<td>0.201</td>
<td>1.53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.101</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.050</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.025</td>
<td>0.28</td>
<td>0.183</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Using method C and equation A9.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu$_3$SnH]$_0$</th>
<th>[Cl]$_f$</th>
<th>$K_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.00</td>
<td>0.249</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.115</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.080</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.034</td>
<td>1.75</td>
</tr>
<tr>
<td>60</td>
<td>1.00</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.204</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.075</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.035</td>
<td>1.51</td>
</tr>
<tr>
<td>72</td>
<td>1.00</td>
<td>0.328</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.229</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.021</td>
<td>0.51</td>
</tr>
<tr>
<td>97</td>
<td>1.00</td>
<td>0.268</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>0.092</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.13</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.021</td>
<td>0.51</td>
</tr>
</tbody>
</table>
Calculated rate constants:

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>$k_C$ (s$^{-1}$)</th>
<th>$k_H$ (M$^{-1}$s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1.05 x 10$^5$</td>
<td>1.16 x 10$^6$</td>
</tr>
<tr>
<td>70</td>
<td>1.73</td>
<td>1.72</td>
</tr>
<tr>
<td>80</td>
<td>2.18</td>
<td>1.54</td>
</tr>
<tr>
<td>91</td>
<td>2.57</td>
<td>1.48</td>
</tr>
<tr>
<td>100</td>
<td>2.97</td>
<td>1.62</td>
</tr>
</tbody>
</table>

$E_a = 6 \pm 3$ kcal mol$^{-1}$

$\log A = 9 \pm 2$

$\log k_c = (9 \pm 2) - \frac{(6 \pm 3)}{2.3 RT}$
1-Cyclohexyl-5-cyclohexylidenpent-1-yl radical (131).

Experimental method used: A
Analytical GC performed with: SGE-25QC2/BP1 1.0
Reaction times: 4 - 6 h.

Solvent: hexane, [Bu₃SnH] = 0.087M.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[cis]</th>
<th>[trans]</th>
<th>kₜₙₐₙₕₜₜ</th>
<th>kₜₐₘₚₜₜ</th>
<th>kₜₚₐₗₙₚₜ</th>
<th>kₜₕₚₚₜ</th>
<th>[cis]ₚₚₜₚₜₜₚ</th>
<th>[trans]ₚₚₜₚₜₜₚ</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>0.13</td>
<td>0.27</td>
<td>0.011</td>
<td>0.023</td>
<td>1.3 x 10⁴</td>
<td>2.8 x 10⁴</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>0.50</td>
<td>0.79</td>
<td>0.044</td>
<td>0.069</td>
<td>9.2</td>
<td>1.4 x 10⁵</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>0.52</td>
<td>0.87</td>
<td>0.045</td>
<td>0.076</td>
<td>1.2 x 10⁵</td>
<td>2.1</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>1.23</td>
<td>2.07</td>
<td>0.107</td>
<td>0.180</td>
<td>4.0</td>
<td>6.7</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.59</td>
<td></td>
</tr>
</tbody>
</table>

Solvent: DME, [Bu₃SnH] = 0.096M.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>0.13</td>
<td>0.21</td>
<td>0.012</td>
<td>0.020</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>0.30</td>
<td>0.48</td>
<td>0.029</td>
<td>0.046</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>0.38</td>
<td>0.75</td>
<td>0.036</td>
<td>0.072</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>0.97</td>
<td>1.69</td>
<td>0.093</td>
<td>0.162</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Solvent: n-propanol, [Bu₃SnH] = 0.100M.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[cis]</th>
<th>[trans]</th>
<th>kₜₚₜₜₜₚₗₜₜ</th>
<th>kₜₗₚₜₜₜ</th>
<th>[cis]ₚₜₜₜₜₜₜ</th>
<th>[trans]ₚₜₜₜₜₜₜ</th>
<th>[cis]ₚₜₜₜₜₜₜₜ</th>
<th>[trans]ₚₜₜₜₜₜₜₜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>0.19</td>
<td>0.31</td>
<td>0.019</td>
<td>0.031</td>
<td>0.63</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61</td>
<td>0.29</td>
<td>0.51</td>
<td>0.029</td>
<td>0.051</td>
<td>0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>82</td>
<td>0.49</td>
<td>0.83</td>
<td>0.049</td>
<td>0.083</td>
<td>0.59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>102</td>
<td>0.70</td>
<td>1.17</td>
<td>0.070</td>
<td>0.117</td>
<td>0.59</td>
<td></td>
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</table>
1-Ethoxycarbonylhex-5-en-1-yl radical (133).

Experimental method used: A
Analytical GC performed with: SGE-SCOT GSC/SF96
Solvent: Benzene
All reactions carried out overnight.

Using method A and equation A7.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[U]/[cis]</th>
<th>[U]/[trans]</th>
<th>( \frac{k_{\text{cis}}}{k_{\text{trans}}} )</th>
<th>( \frac{k_{\text{trans}}}{k_{\text{cis}}} )</th>
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<tbody>
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<td>0.026 (± 11%)</td>
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<td>0.065</td>
<td>1.41</td>
<td>1.23</td>
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<td></td>
</tr>
</tbody>
</table>
\[ k_{\text{cis}} + k_{\text{trans}} = 1.4 \times 10^5 \text{ s}^{-1} \text{ at } 80^\circ \text{C} \text{ by the method of Bowry}^{107}, \]

thus, \( k_H = 1.0 \times 10^6 \text{ M}^{-1} \text{ at } 80^\circ \text{C}. \)

(cf: \( k_H = 3.6 \times 10^6 \text{ at } 80^\circ \text{C} \) for secondary alkyl radicals\textsuperscript{28c}.)

\[ E_{a}^{\text{cis}} = 2.7 \pm 0.1 \text{ kcal mol}^{-1} \]

\[ E_{a}^{\text{trans}} = 2.5 \pm 0.1 \text{ kcal mol}^{-1} \]

\[ \log A^{\text{cis}} - \log A^{H} = 0.49 \pm 0.05 \]

\[ \log A^{\text{trans}} - \log A^{H} = 0.42 \pm 0.04 \]

\[ \log \left( \frac{k_{\text{cis}}}{k_H} \right) = \left( 0.49 \pm 0.05 \right) \cdot \frac{2.7 \pm 0.1}{2.3 \text{ RT}} \]

\[ \log \left( \frac{k_{\text{trans}}}{k_H} \right) = \left( 0.42 \pm 0.04 \right) \cdot \frac{2.5 \pm 0.1}{2.3 \text{ RT}} \]
1-Methoxyhex-5-en-1-yl radical (135).

![Chemical Structure]

Experimental method used: A
Analytical GC performed with: SGE-25QC2/BP1 1.0
Reaction times: 1 - 2 h.

Solvent: n-propanol.

<table>
<thead>
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<th>Temp (°C)</th>
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<th>[trans] [U]</th>
<th>k_{cis} \left/ k_H \right.</th>
<th>k_{trans} \left/ k_H \right.</th>
<th>[cis] [trans]</th>
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<td>0.20</td>
<td>0.035 (± 6%)</td>
<td>0.039 (± 6%)</td>
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<td>0.032</td>
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<td>0.089</td>
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<td>0.95</td>
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<tr>
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<td>0.71</td>
<td>0.75</td>
<td>0.137</td>
<td>0.145</td>
<td>0.95</td>
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<tr>
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Solvent: DME.

<table>
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<tr>
<th>Temp (°C)</th>
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<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>k_{cis} \left/ k_H \right.</th>
<th>k_{trans} \left/ k_H \right.</th>
<th>[cis] [trans]</th>
</tr>
</thead>
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<tr>
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<td>0.166</td>
<td>0.65</td>
<td>0.68</td>
<td>0.108 (± 5%)</td>
<td>0.113 (± 5%)</td>
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</tr>
<tr>
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<td>0.092</td>
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<td>0.119</td>
<td>0.125</td>
<td>0.96</td>
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<tr>
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</table>
Solvent: benzene.

<table>
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<th>[trans] [U]</th>
<th>$k_{cis}$</th>
<th>$k_{trans}$</th>
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<td>0.80</td>
<td>0.83</td>
<td>0.145  (± 6%)</td>
<td>0.150  (± 6%)</td>
<td>0.97</td>
</tr>
<tr>
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<td>0.101</td>
<td>1.35</td>
<td>1.39</td>
<td>0.136</td>
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<td>1.02</td>
<td>1.10</td>
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<td>0.199</td>
<td>0.93</td>
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<td>2.10</td>
<td>0.199</td>
<td>0.212</td>
<td>0.94</td>
</tr>
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<td>45</td>
<td>0.181</td>
<td>1.50</td>
<td>1.65</td>
<td>0.272</td>
<td>0.299</td>
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<td>2.84</td>
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<td>0.287</td>
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</tbody>
</table>

In benzene:

\[
\log \left( \frac{k_{cis}}{k_H} \right) = (1.5 \pm 0.2) - \frac{(3.0 \pm 0.1)}{2.3 \, RT}
\]

\[
\log \left( \frac{k_{trans}}{k_H} \right) = (1.7 \pm 0.3) - \frac{(3.3 \pm 0.1)}{2.3 \, RT}
\]
Z-Tridec-9-en-5-yl radical (137).

Experimental method used: A
Analytical GC performed with: SGE- 25QC2/BP1 1.0
Reaction times: 4 -6h

Solvent: **hexane**

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>( \frac{k_{\text{cis}}}{k_{\text{H}}} ) (± 25%)</th>
<th>( \frac{k_{\text{trans}}}{k_{\text{H}}} ) (± 9%)</th>
<th>[cis] [trans]</th>
<th>( k_{\text{cis}}(s^{-1}) )</th>
<th>( k_{\text{trans}}(s^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.21</td>
<td>0.16</td>
<td>0.29</td>
<td>0.034</td>
<td>0.061</td>
<td>0.53</td>
<td>3.1 x10⁴</td>
<td>5.6 x10⁴</td>
</tr>
<tr>
<td>25</td>
<td>0.23</td>
<td>0.42</td>
<td>0.080</td>
<td>0.048</td>
<td>0.088</td>
<td>0.57</td>
<td>7.1</td>
<td>1.3 x10⁵</td>
</tr>
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<td>0.61</td>
<td>0.103</td>
<td>0.046</td>
<td>0.128</td>
<td>0.63</td>
<td>1.7 x10⁵</td>
<td>2.7</td>
</tr>
<tr>
<td>59</td>
<td>0.49</td>
<td>0.75</td>
<td>0.150</td>
<td>0.088</td>
<td>0.158</td>
<td>0.67</td>
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<td>4.2</td>
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<td>81</td>
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<td>0.210</td>
<td>0.72</td>
<td>5.5</td>
<td>7.6</td>
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</table>

Solvent: **DME**

<table>
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<tr>
<th>Temp (°C)</th>
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<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>( \frac{k_{\text{cis}}}{k_{\text{H}}} ) (± 11%)</th>
<th>( \frac{k_{\text{trans}}}{k_{\text{H}}} ) (± 8%)</th>
<th>[cis] [trans]</th>
<th>( k_{\text{cis}}(s^{-1}) )</th>
<th>( k_{\text{trans}}(s^{-1}) )</th>
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<td>0.070</td>
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<td>0.102</td>
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<td>0.176</td>
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<td>0.66</td>
<td>0.124</td>
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<td>0.67</td>
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</tr>
<tr>
<td>81</td>
<td>0.62</td>
<td>0.88</td>
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<td>0.27</td>
<td>0.73</td>
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Solvent: **n-propanol**

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>( \frac{k_{\text{cis}}}{k_{\text{H}}} ) (± 7%)</th>
<th>( \frac{k_{\text{trans}}}{k_{\text{H}}} ) (± 5%)</th>
<th>[cis] [trans]</th>
<th>( k_{\text{cis}}(s^{-1}) )</th>
<th>( k_{\text{trans}}(s^{-1}) )</th>
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<td>0.10</td>
<td>0.20</td>
<td>0.020</td>
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<td>0.040</td>
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<td>0.034</td>
<td>0.060</td>
<td>0.082</td>
<td>0.082</td>
<td>0.57</td>
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<tr>
<td>45</td>
<td>0.26</td>
<td>0.41</td>
<td>0.052</td>
<td>0.082</td>
<td>0.104</td>
<td>0.104</td>
<td>0.62</td>
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<tr>
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<td>0.49</td>
<td>0.066</td>
<td>0.098</td>
<td>0.126</td>
<td>0.126</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td>0.46</td>
<td>0.63</td>
<td>0.092</td>
<td>0.126</td>
<td>0.158</td>
<td>0.158</td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>
In hexane:

$$\log \left( \frac{k_{\text{cis}}}{k_H} \right) = (1.5 \pm 0.2) - \frac{(3.8 \pm 0.1)}{2.3 \, \text{RT}}$$

$$\log \left( \frac{k_{\text{trans}}}{k_H} \right) = (1.3 \pm 0.1) - \frac{(3.1 \pm 0.1)}{2.3 \, \text{RT}}$$

$$\log k_H = (8.71 \pm 0.37) - \frac{(3.47 \pm 0.49)^{28c}}{2.3 \, \text{RT}}$$

$$\log k_{\text{cis}} = (10.2 \pm 0.4) - \frac{(7.3 \pm 0.5)}{2.3 \, \text{RT}}$$

$$\log k_{\text{trans}} = (10.0 \pm 0.4) - \frac{(6.6 \pm 0.5)}{2.3 \, \text{RT}}$$
1,1,1-Trifluorohex-6-en-2-yl radical (139).

![Chemical structure and reaction](image)

Experimental method used: A
Analytical GC performed with: SGE- 25QC2/BP1 1.0
Reaction times: 4 -6 h.

Solvent: hexane, [Bu₃SnH] = 0.203M.

<table>
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<th>k_{trans} (k_H) (± 8%)</th>
<th>k_{cis} (s⁻¹)</th>
<th>k_{trans} (s⁻¹)</th>
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</thead>
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<td>3</td>
<td>0.32</td>
<td>0.24</td>
<td>0.065</td>
<td>0.049</td>
<td>5.9 (\times 10^4)</td>
<td>4.4 (\times 10^4)</td>
</tr>
<tr>
<td>25</td>
<td>0.42</td>
<td>0.37</td>
<td>0.085</td>
<td>0.075</td>
<td>1.3 (\times 10^5)</td>
<td>1.1 (\times 10^5)</td>
</tr>
<tr>
<td>61</td>
<td>0.68</td>
<td>0.61</td>
<td>0.138</td>
<td>0.124</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>80</td>
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<td>0.167</td>
<td>0.152</td>
<td>6.0</td>
<td>5.5</td>
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</table>

Solvent: DME, [Bu₃SnH] = 0.194M.

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<th>[trans] [U]</th>
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<th>k_{trans} (k_H) (± 11%)</th>
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<td>0.53</td>
<td>0.26</td>
<td>0.103</td>
<td>0.050 (± 11%)</td>
<td>2.05</td>
</tr>
<tr>
<td>25</td>
<td>0.72</td>
<td>0.39</td>
<td>0.140</td>
<td>0.076</td>
<td>1.86</td>
</tr>
<tr>
<td>61</td>
<td>1.07</td>
<td>0.75</td>
<td>0.207</td>
<td>0.146</td>
<td>1.54</td>
</tr>
<tr>
<td>80</td>
<td>1.39</td>
<td>1.92</td>
<td>0.270</td>
<td>0.179</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Solvent: n-propanol, [Bu₃SnH] = 0.100M.

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>[Bu₃SnH]</th>
<th>[cis] [U]</th>
<th>[trans] [U]</th>
<th>k_{cis} (k_H) (± 30%)</th>
<th>k_{trans} (k_H) (± 30%)</th>
<th>[cis] [trans]</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.193</td>
<td>0.60</td>
<td>0.31</td>
<td>0.116</td>
<td>0.059 (± 30%)</td>
<td>1.94</td>
</tr>
<tr>
<td>25</td>
<td>0.214</td>
<td>0.86</td>
<td>0.51</td>
<td>0.184</td>
<td>0.109</td>
<td>1.70</td>
</tr>
<tr>
<td>45</td>
<td>0.193</td>
<td>1.18</td>
<td>0.76</td>
<td>0.228</td>
<td>0.147</td>
<td>1.56</td>
</tr>
<tr>
<td>60</td>
<td>0.214</td>
<td>1.66</td>
<td>1.17</td>
<td>0.355</td>
<td>0.250</td>
<td>1.43</td>
</tr>
<tr>
<td>79</td>
<td>0.193</td>
<td>2.17</td>
<td>1.61</td>
<td>0.419</td>
<td>0.311</td>
<td>1.32</td>
</tr>
</tbody>
</table>
In hexane:

\[
\log \left( \frac{k_{\text{cis}}}{k_H} \right) = (0.7 \pm 0.1) - \frac{(2.4 \pm 0.1)}{2.3 \, RT}
\]

\[
\log \left( \frac{k_{\text{trans}}}{k_H} \right) = (0.9 \pm 0.1) - \frac{(2.8 \pm 0.1)}{2.3 \, RT}
\]

\[
\log k_H = (8.71 \pm 0.37) - \frac{(3.47 \pm 0.49)}{2.3 \, RT}
\]

\[
\log k_{\text{cis}} = (9.4 \pm 0.4) - \frac{(5.9 \pm 0.5)}{2.3 \, RT}
\]

\[
\log k_{\text{trans}} = (9.6 \pm 0.4) - \frac{(6.3 \pm 0.5)}{2.3 \, RT}
\]
Consider a set of \( N \) data points \((x_i, y_i)\) distributed normally about the line of best fit, given by:

\[
y = mx + c
\]

...\( B1 \)

The average value of each co-ordinate \( \zeta_i \) is defined by:

\[
\bar{\zeta} = \frac{1}{N} \sum_{i} \zeta_i
\]

...\( B2 \)

and the standard deviation \( \sigma_{\zeta} \) about the overall mean value \( \bar{\zeta} \) is defined by:

\[
\sigma_{\zeta}^2 = \frac{1}{N} \sum_{i} (\zeta_i - \bar{\zeta})^2
\]

...\( B3 \)

The slope, \( m \), and intercept, \( c \), of the line of best fit are given by:

\[
m = \frac{N \sum x_i y_i - \sum x_i \sum y_i}{N \sum x_i^2 - (\sum x_i)^2}
\]

...\( B4 \)

and

\[
c = \frac{y \sum x_i^2 - \sum x_i \sum x_i y_i}{N \sum x_i^2 - (\sum x_i)^2}
\]

...\( B5 \)
Thus; the standard deviation in the slope of the line of best fit, \( \sigma_m \), is given by:

\[
\sigma_m^2 = \frac{N \sigma^2}{\sum x_i^2 - (\sum x_i)^2}
\]

...B6

and the standard deviation in the intercept, \( \sigma_c \), is given by:

\[
\sigma_c^2 = \frac{\sigma^2 \sum x_i^2}{N \sum x_i^2 - (\sum x_i)^2}
\]

...B7

where:

\[
\sigma^2 = \frac{1}{N-2} \sum (y_i - c - mx_i)^2
\]

...B8

The covariance, \( \mu \), of \( x_i \) on \( y_i \) is defined by:

\[
\mu = \frac{1}{N} \sum (x_i - \bar{x})(y_i - \bar{y})
\]

...B9

and the correlation coefficient, \( r \), is defined by:

\[
r = \frac{\mu}{\sigma_x \sigma_y}
\]

...B10
It can be shown\textsuperscript{149a} that the mean standard deviation of the $y$ values from their estimates, $S_y$, is given by:

$$S_y = \sigma_y \left( 1 - r^2 \right)^{1/2}$$

...B11

Thus, the mean error, $E_y$, in the values of $y_i$ over the values of $x_i$ is given by:

$$E_y = 2 S_y \quad (95\% \text{ confidence})$$

...B12

In the work described in Chapters 3 and 4, rate constants, $k$, are correlated in logarithmic form with reciprocal temperature ($1/T$) and are fitted to the logarithmic form of the Arrhenius equation (A10):

$$\log k = \log A - \frac{E_a}{2.3 RT}$$

...B13

Application of equations B1 ... B12 to the data being fitted to B13 gives rise to estimates in the errors of the calculated values of $E_a$, $\log A$ and $\log k$.

If the relative error in $\log k$ is small, then the error in the rate constant, $k$, can be approximated by:

$$\Delta k \approx 2.3 k \Delta (\log k)$$

...B14

where $\Delta (\log k)$ is the error in $\log k$. 

NOTES AND REFERENCES


184.


51. See references 29b and 29c.


71. Thanks to Prof. N.V. Riggs, formerly of the University of New England, Armidale, N.S.W. and currently at The Research School of Chemistry, A.N.U. for kindly supplying the ab initio data at STO-3G, 3-21G and 6-31G* levels.


84. We thank Dr. H.D. Beckhaus for providing these parameters.


88. See also references in ref. 87.


94. See reference 61b.


96. Abeywickrema, A.N., private communication.


107. Bowry, V.W., private communication.


112. Unpublished work in these laboratories have on occasion suggested E- and Z- isomer rate differences.


119. Authentic samples of 148 and 149 were available from the Chemical Sample Co., Columbus, Ohio, USA., while 150 was purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, USA.


