Radical Ring Opening Reactions of the Cyclopropylcarbinyl System.

A Thesis Presented by

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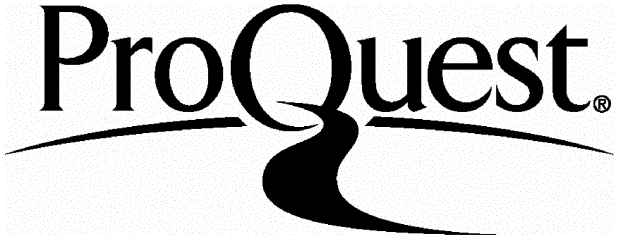

Abstract

This thesis is divided into six chapters. Chapter one commences with a brief discussion of the physical organic chemistry of the monocyclic cyclopropylcarbinyl system, this is followed by an investigation of the regioselectivity observed in ring opening as a function of substituent on the cyclopropane moiety. This is succeeded by the application of the cyclopropylcarbinyl radical as a probe in establishing the reaction mechanism in enzyme catalysed reactions. This section concludes with a brief survey of the synthetic utility of such systems. In a similar fashion, chapter two discusses the ring-opening of bicyclo[n.1.0]alk-2-yl radicals.

Chapter three is prefaced by a brief consideration of the previous work on the generation and synthetic utility of ketyl radicals, concentrating in particular, on the reductive ring opening reactions of the cyclopropylcarbinyl system with lithium in liquid ammmonia. This is followed by a brief review of the reduction of the carbonyl group by samarium(II) iodide before presenting a critical analysis of our own results using this reagent towards the studies of the reductive ring opening of both *cis*- and *trans*- cyclopropyl ketone substrates. Samarium(II) iodide ring opening of both the former and the latter gave, in each case the product of thermodynamic control arising from cleavage of the more substituted bond. This chapter finally concludes with the attempted formation of enolate derivatives under these reaction conditions.

Chapter four introduces the development of a novel alkylidenecyclopropylcarbinyl rearrangement by taking advantage of a variety of radical triggers. The major part of this section concentrates on the generation of radical anions from the corresponding ketones specifically by lithium in liquid ammonia. By varying the substitution pattern on the ring, ring opened alcohol products, as well as the expected ketones were observed.

Chapter five elaborates this methodology further by investigating the mode of ring-opening of a relatively simple bicyclic analogue under the same reaction conditions. Lithium in liquid ammonia ring opening of 7-methylenebicyclo[4.1.0]heptan-2-one gave products arising from cleavage of the exocyclic bond as a result of stereoelectronic control. However, cleavage of the endocyclic bond was also seen to occur, leading to cycloheptyl derivatives *via* the lower energy allylic radical. Finally, the adaptation of this methodology to a bicyclic system which incorporates a tandem cyclopropylcarbinyl rearrangement/cyclisation on route to bicyclic structures is presented.

Chapter six provides a formal description of the experimental results and procedures.

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Abbreviations

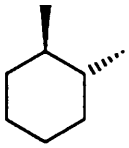
Ac	Acetyl
AIBN	α,α'-Azoisobutyronitrile
Ar	Unspecified aromatic group
b.pt.	Boiling point
br	Broad
Bu	Butyl
Bz	Benzyl
cat	Catalytic
CoA	Coenzyme A
d	Doublet
DCM	Dichloromethane
de	Diastereomeric excess
DHP	Dihydropyran
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DBM	Dibenzoylmethido
DME	1,2-Dimethoxyethane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
DTBP	Di-*tert*-butylperoxide
dy	Days
ee	Enantiomeric excess
ESR	Electron Spin Resonance
Et	Ethyl
Ether	Diethyl ether
EtOAc	Ethyl Acetate
FAD	Flavin adenine dinucleotide

FMO	Frontier molecular orbital
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
hr(s)	Hour(s)
Im	Imidazole
ir	Infra-red
lit	Literature
LUMO	Lowest occupied molecular orbital
m	Multiplet
M	Unspecified metal
Me	Methyl
min(s)	Minute(s)
MO	Molecular orbital
m.pt.	Melting point
NMP	*N*-methylpyrrolidone
nmr	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
p	Para
PDC	Pyridinium dichromate
Petrol	40-60°C petrol
Ph	Phenyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PTFA	Pyridinium trifluoroacetate
PTSA	*p*-toluenesulfonic acid
q	Quartet
R	Unspecified carbon-centred group, usually alkyl

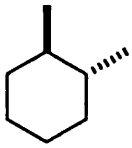
r.t.	Room temperature
s	Singlet
sept	Septet
SOMO	Singly occupied molecular orbital
t	Triplet
TBDMS	Tertiarybutyldimethylsilyl
TBS	Tributylsilyl
TCI	1,1'-Thiocarbonyldiimidazole
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
tlc	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
UV	Ultra Violet

Stereochemical Notation.

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr*. Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.



Single Enantiomer



Racemic

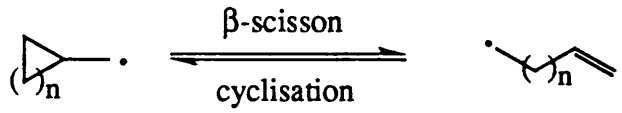
*H. Maehr, *J. Chem. Ed,.* 1985, **62**, 114.

Chapter One

1.1 INTRODUCTION.

The work described in this thesis is concerned with the regioselectivity and stereoselectivity involved in the ring opening of (a) monocyclic cyclopropylcarbinyl systems, and (b) their bicyclic congeners. In order to set our own studies into proper perspective, sections 1.2 through to 1.6 of this introductory chapter will at the outset, briefly discuss the physical organic chemistry of monocyclic systems followed by variations in ring opening as a function of the substituent on the cyclopropane ring. The penultimate section will be concerned with the application of the cyclopropylcarbinyl radical in the study of enzyme mechanisms, and finally the chapter will be concluded with a survey of the synthetic utility of these systems. Chapter 2 will take a similar form, but from the point of view of the bicyclic congener.

One of the conspicuous features of the recent chemical literature is the speed with which the area of free radical cyclisation is being developed by synthetic organic chemists.[1,2,3] By way of contrast, the synthetic possibilities of the reverse process, namely radical ring opening (scheme 1.1), have received far less attention. These reactions have been studied by physical organic chemists[4] in considerable detail and have often been used as mechanistic probes and chronometric devices (radical clocks)[5] (*vide infra*) for the examination and detection of radical intermediates.

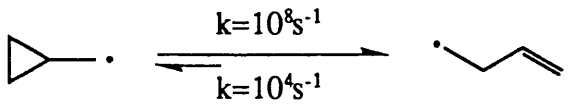


scheme 1.1

1.2 CHARACTERISTICS OF THE CYCLOPROPYCARBINYL-HOMOALLYL REARRANGEMENT.

Since the discovery[6,7] of the cyclopropylcarbinyl-homoallyl radical rearrangement in 1951, a substantial amount of work by many groups around the world has been published on its mechanistic, synthetic, theoretical and biological importance

(scheme 1.2).



scheme 1.2

Ring opening of the cyclopropylmethyl radical gives the but-3-enyl radical with a rate constant of $1x10^8s^{-1}$ at 300K.[8,9] The formally acute angles (60°) are an obvious source of ring strain, being considerably less than that associated with ideal sp^3 hybridisation (109.5°). In addition, torsional strain arises from the eclipsed nature of the carbon-hydrogen bonds. Hence, the thermodynamic driving force for ring opening is inherently great.

Many descriptions for the bonding in the "parent" cyclopropanes exist, the most widely accepted models being (a) the valence bond treatment, more commonly referred to as the "bent" or "banana" Coulson Moffatt[10] approach and (b) one involving increased π-character arising from the overlap of the centrally pointing p-orbitals as proposed by Walsh[11] (figure 1.1).

Coulson Moffatt Model
C-C bonds 20% s, 80% p
C-H bonds 30% s, 70% p

Walsh Model
C-C bonds formed using p-orbitals
C-H bonds formed using sp^2 hybrid orbitals

figure 1.1

The cyclopropyl group exerts a small but significant stabilising effect on the adjacent radical centre. The C-H bond dissociation energy for methyl cyclopropane ($412kJmol^{-1}$) is slightly less than that of the C_2H_5-H bond dissociation energy ($420kJmol^{-1}$), i.e. there is a small but significant interaction between the SOMO of

the radical and the low lying LUMO of the ring. This in turn arises from the considerable π-character of the cyclopropane bonds. Beckwith[12] has postulated that the ring opening proceeds *via* a dipolar transition state (1) (figure 1.2), thus, substituents which increase this dipolar character would in turn be expected to increase the rate of ring opening, and *vice versa*.

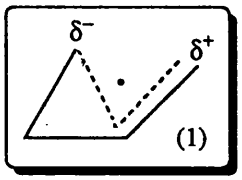


figure 1.2

Finally, EPR studies by Kochi,[13] and more recently by Walton[14] have shown not only that the cyclopropylcarbinyl and allylcarbinyl moieties are discrete free radicals, but that the titled rearrangement and that of related radicals occur at temperatures higher than -120°C. These workers have further shown that the plane of the CH_2 group bisects the cyclopropane ring plane (figure 1.3).

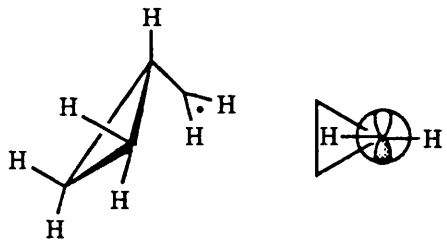


figure 1.3

1.3 FRONTIER MOLECULAR ORBITAL THEORY OF BONDING.

Inspection of the molecular orbitals for the cyclopropylcarbinyl radical rearrangement, reveals that a greater deal of stabilisation is derived from the interaction of the carbinyl radical SOMO and the cyclopropane LUMO than from the interaction of the SOMO-HOMO pair (figure 1.4). Therefore, any substituents on the ring will of course interact with the cyclopropane ring orbitals, lifting the degeneracy

of these orbitals, and hence, the SOMO may interact more strongly with orbitals of one of these bonds than the other as we shall see shortly.

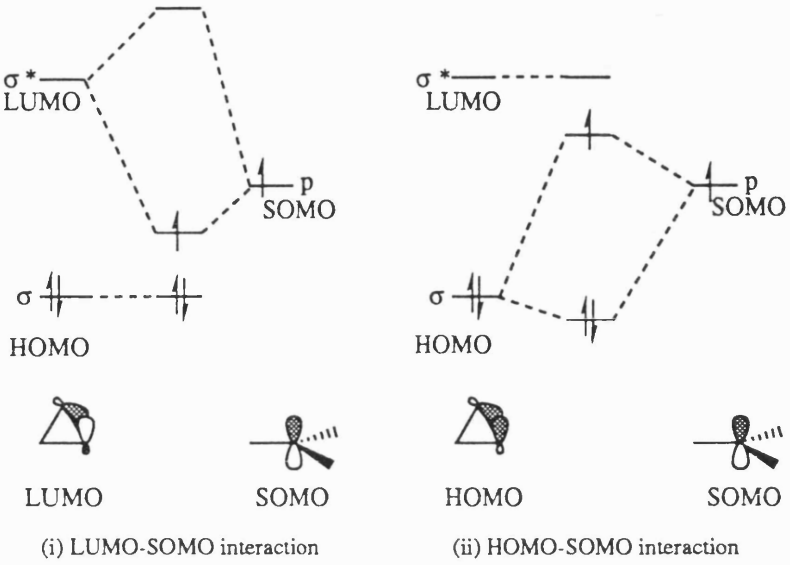
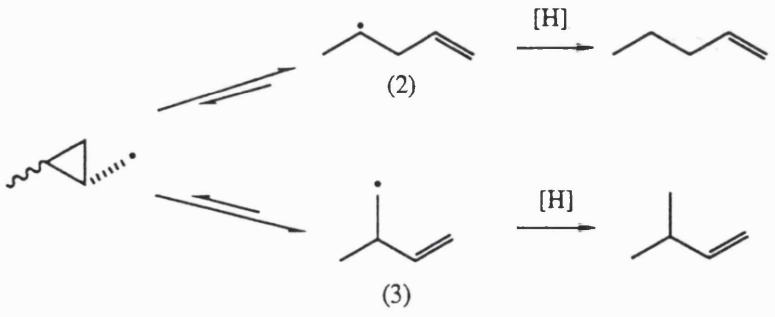


figure 1.4

1.4 REGIOSELECTIVITY OF RING OPENING.

1.4.1 Substituent Effects.

Davies and Pereyre[15] performed a series of experiments on the regioselectivity of the ring opening of both *cis*- and *trans*- methylcyclopropylcarbinyl radicals over a range of temperatures. Mechanistic consideration reveal that cleavage of the less substituted cyclopropane bond will result in the formation of the primary radical (3), whereas cleavage of the more substituted bond results in the formation of the lower energy secondary radical (2) (scheme 1.3).



scheme 1.3

Thus, on thermodynamic grounds, cleavage to the secondary radical would be expected. These workers found that the *cis-* substituted radical did indeed preferentially open to the thermodynamically more stable secondary radical under kinetic control, as a result of radical alignment minimising the steric interaction thus encountered (figure 1.5).

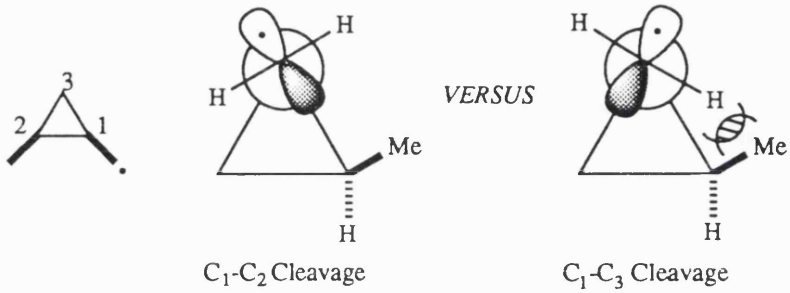
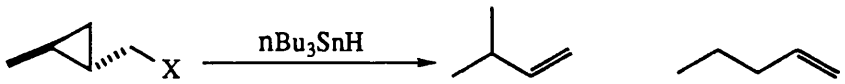


figure 1.5

To their surprise, however, at lower temperatures, the *trans-* system displayed a curious kinetic preference for formation of the higher energy primary radical (a ratio of 4:1 primary : secondary), despite the absence of any obvious steric restrictions on conformational alignment (table 1.1). An interesting, but at the same time puzzling element of Davies' work as previously stated, was that under the same conditions, the *trans-* cyclopropylcarbinyl radicals generated from the bromide and chloride substrate showed similar but not identical regioselectivities.



X	METHOD	PRODUCT DISTRIBUTION
Br	NEAT/UV/25°C	66 : 34
Cl	NEAT/UV/25°C	59 : 41
Br	NEAT/AIBN/UV/45°C	53 : 47
Cl	NEAT/AIBN/UV/45°C	47 : 53
Br	0.2MPhH/AIBN/UV/45°C	26 : 74
Cl	0.2MPhH/AIBN/UV/45°C	22 : 78
Br	0.02MPhH/AIBN/UV/45°C	8 : 92
Cl	0.02MPhH/AIBN/UV/45°C	4 : 96

table 1.1

This is surprising since cyclopropylcarbinyl radicals, once formed, should be indistinguishable and not betray their origins by some form of "memory effect". The data shows that the first formed radical is the "less stable" one, which is trapped more easily at higher concentrations of reducing agent. On dilution, the reduction tends to give mainly the product arising from the thermodynamically more stable secondary radical, assuming that the hydrogen transfer step under such conditions is slow enough to allow equilibration through ring reclosure and re-opening[16,17] (scheme 1.4).

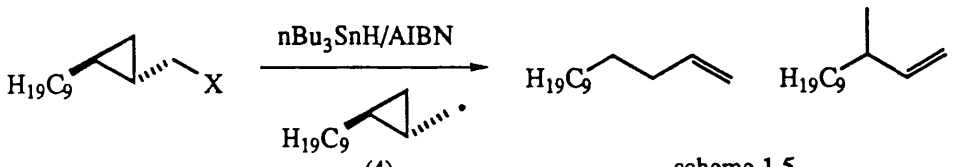
scheme 1.4

The product distribution was accounted for on the basis that reduction of the bromides, often exothermic, is much easier than that of the corresponding chlorides.[18] The reaction of the bromides has already taken place to some extent in the period between the preparation of the mixture of reagents (at low temperature)

and the commencement of heating.

Over a decade later, Motherwell,[19,20] being intrigued both by the selectivity obtained at lower temperatures and even moreso by the dependence on the nature of the radical trigger found by Davies and Pereyre, deemed it necessary to extend these studies (table 1.2).

Reduction of the substituted cyclopropanes to ring opened products proceeds *via* the common cyclopropylcarbinyl radical (4), which can fragment to give either the product derived from the lower energy secondary radical or the primary radical (scheme 1.5).



(4) scheme 1.5

METHOD	X	YIELD	PRODUCT DISTRIBUTION
A	Br	23	98 : 2
A	Cl	89	96 : 4
B	Br	81	66 : 34
B	Cl	73	67 : 33
B	OCSSMe	63	73 : 27
C	Br	72	62 : 38
C	Cl	28	56 : 44
C	SePh	82	60 : 40
D	Br	70	60 : 40
D	Cl	76	62 : 38
D	SePh	80	63 : 37
D	OCSSMe	GC	58 : 42
E	Br	GC	51 : 49
E	Cl	GC	49 : 51
E	SePh	GC	47 : 53
E	OCSSMe	GC	52 : 48

METHOD A:slow addition of nBu_3SnH to a refluxing PhH solution of the substrate. METHOD B:slow addition of the substrate to a refluxing PhH of nBu_3SnH. METHOD C:neat substrate and nBu_3SnH (45°C). METHOD D:slow addition of the substrate to a concentrated reluxing nBu_3SnH in PhH. METHOD E: solution of the substrate and nBu_3SnH with hexaphenylditin/hv as initiator (-78°C to r.t.).

table 1.2

As expected, a preparatively useful procedure for maximising the thermodynamic product was obtained (Method A, this is consistent with Davies observations). However, a complementary method for the non-thermodynamic product was not established even under high stannane concentrations, at best a 1:1 mixture of

products was obtained. More importantly, however, in contrast to Davies results, the nature of the radical trigger *did not* have a significant effect on the outcome of the reaction.

Following these initial studies by Davies and Pereyre, and as a result of the advent of more accurate trapping techniques, a wide range of data on the ring opening of cyclopropylcarbinyl radicals has emerged,[8,21,22,23] which on the whole, agrees with earlier findings. No exception to this rule of regioselectivity appears to be known except in the case of radical stabilising groups such as phenyl where the secondary radical is formed, however, this is presumed to be due to benzylic stabilisation.[24,25]

A FMO approach very conveniently explains the regioselectivity observed in ring opening.[26,27,28] Electron release by an alkyl group raises the energy of the σ and σ^* orbitals of the C(1)-C(2) bond above that of the C(1)-C(3) (likewise for the HOMO) (figure 1.6). Hence, the reasons for the anomalous ring opening of *trans*-2-methylcyclopropyl radicals now becomes very obvious. The dominant interaction in the transition state will be between the SOMO and low lying σ^* i.e. that of the C(1)-C(3) bond, leading to the formation of the thermodynamically less stable primary radical.

However, in the case of the *cis*- derivative, any such effect is overridden by steric interferences between the two *cis*- substituents in the conformation that leads to C(1)-C(3) cleavage[29,30] (figure 1.7).

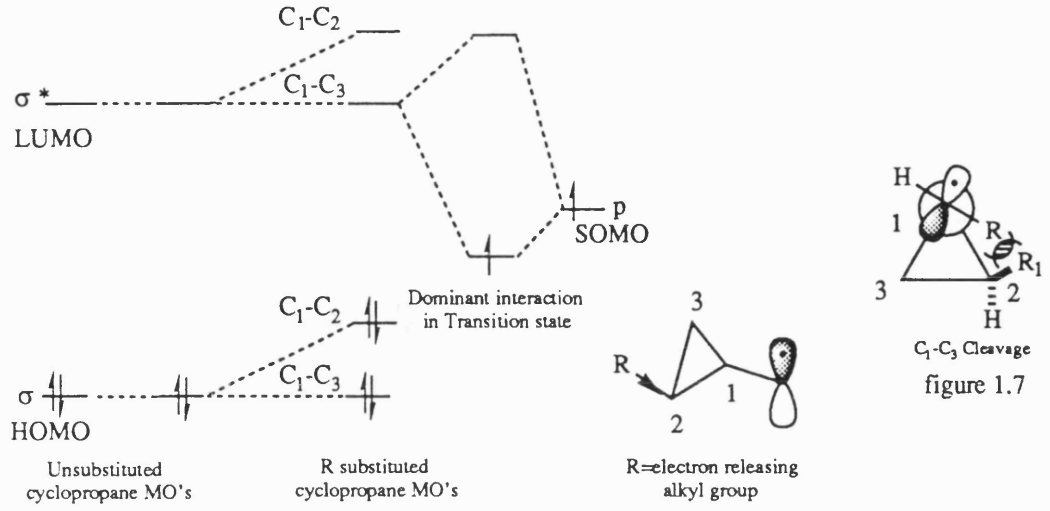
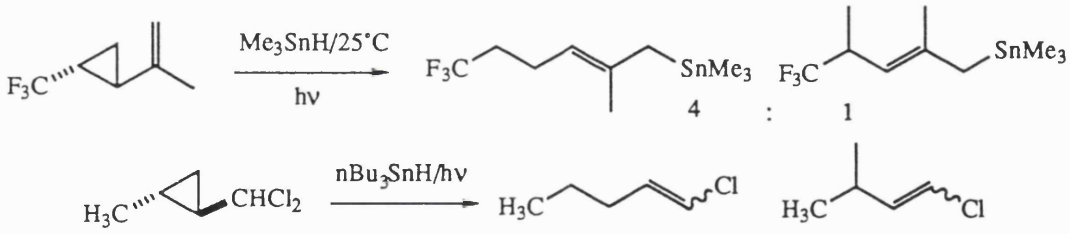


figure 1.7

figure 1.6

This model is further capable of accommodating the regioselectivity observed when the radical centre or substituents on the ring are rendered electronegative. Thus, replacement of a *trans*- alkyl group with a trifluoromethyl group changes the regioselectivity such that the secondary radical is now favoured (scheme 1.6).



25°C	74	:	26
-25°C	63	:	37
-80°C	40	:	25

scheme 1.6

Electron withdrawing groups, such as the trifluoromethyl, place the energy of the C(1)-C(2) σ* orbital below that of the C(1)-C(3), hence, the SOMO-C(1)-C(2) σ* interaction becomes dominant, leading to the product derived from the secondary radical, *via* cleavage of the C(1)-C(2) bond (figure 1.8).

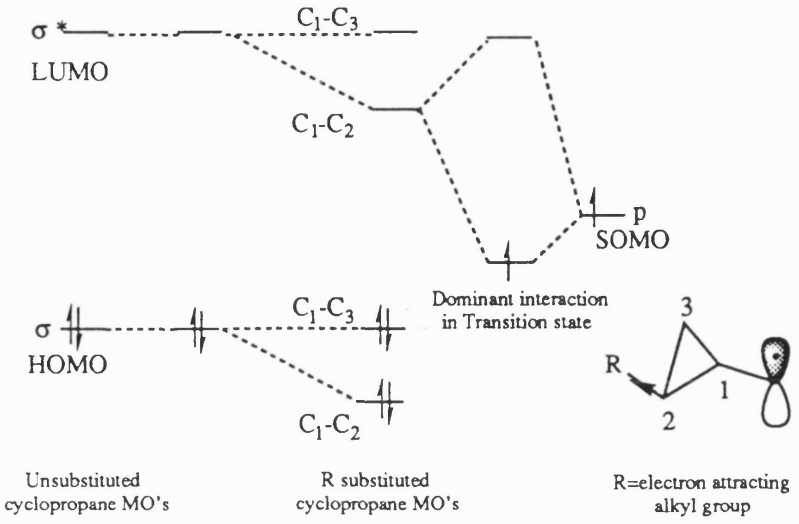
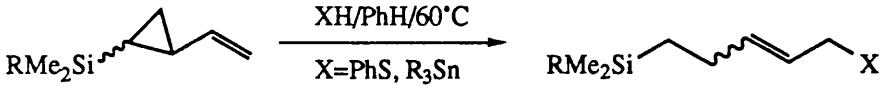


figure 1.8

Likewise, a similar conclusion can be drawn if chloro groups are introduced at the radical centre while substitution on the ring is kept constant. Preferential formation of the secondary radical is again evident (scheme 1.6). From a study of the ionisation potentials and Mulliken electronegativites,[31] it may be assumed that chlorination at the radical centre lowers the energy of the SOMO and thus, the major interaction is with the C(1)-C(2) σ orbital leading to the formation of the secondary radical. In contrast, a hydroxyl group reduces the electronegativity at the radical centre by conjugate electron release and the dominant interaction is now with the C(1)-C(3) σ* orbital. However, these authors[28] in their concluding remarks, stress that such a model is highly qualitative and its limitations should be recognised, namely (i) quantitative knowledge of the energy levels is not fully understood, (ii) only energy levels are considered, proper treatment would also take into consideration the coefficients of the atomic orbitals involved, and (iii) ring opening in the presence of electronegative substituents was found to be relatively slow.

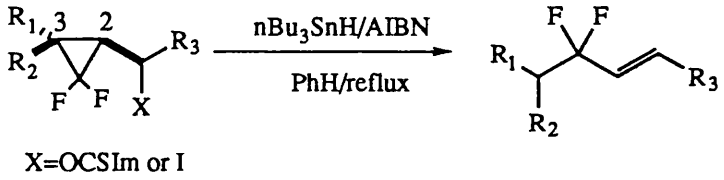
An interesting study of radical additions to silyl-substituted vinyl cyclopropanes revealed that the silyl groups substantially stabilise free radicals[32] (scheme 1.7). Only the homoallylic silane was observed when the ring was free of substituents and

the products obtained were found to be independent of the stereochemistry of the starting cyclopropane. The vacant d-orbitals of the silicon atom are presumably responsible, and in some way lower the adjacent carbon-carbon cyclopropane LUMO energies.



scheme 1.7

Kobayashi[33] has studied the tin mediated radical ring opening of gem-difluorocyclopropanes *via* deiodination and deoxygenation of the corresponding iodides and O-thiocarbonylimidazolide derivatives respectively (scheme 1.8).



scheme 1.8

Under standard tributylstannane conditions, the reaction is both regio- and stereospecific and only the *(E)*-difluoro allylic system was obtained (table 1.3). Again, in contrast to the previous work, it appears that the stereochemistry of the difluorocyclopropane does not influence that of the product.

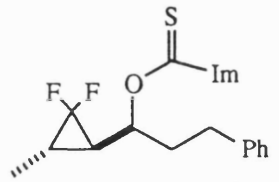
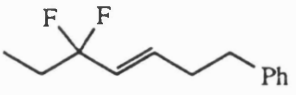
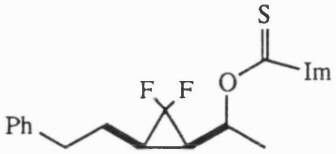
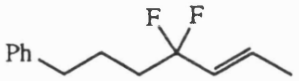
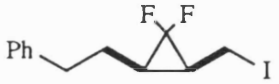
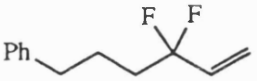
DIFLUOROCYCLOPROPANE	PRODUCT	YIELD%
		83
		77
		89

table 1.3

Thus, in contrast to the work previously discussed concerning the regiochemical complexity involved in the ring opening of non-fluorinated *cis*- and*trans*-cyclopropanes, a gemdifluoro group exhibits a remarkable effect on the regioselectivity of ring cleavage. Neither substitution on C_3 (alkyl or aryl), nor the stereochemical relationship of the substituents on C_2 or C_3 effect the regioselectivity. The stereoselectivity can be rationalised by a consideration of the transition state geometries (figure 1.9), that leading to the *cis*- isomer is clearly disfavoured. Whether or not these reactions are occurring under thermodynamic control, however, is not clearly understood.

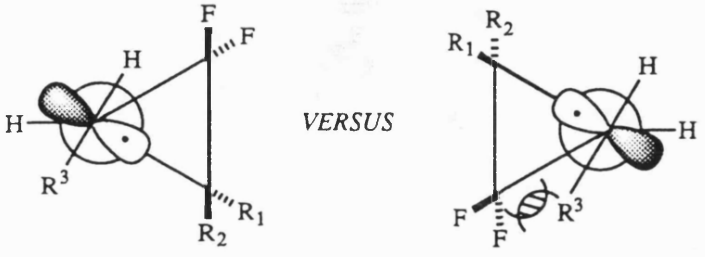
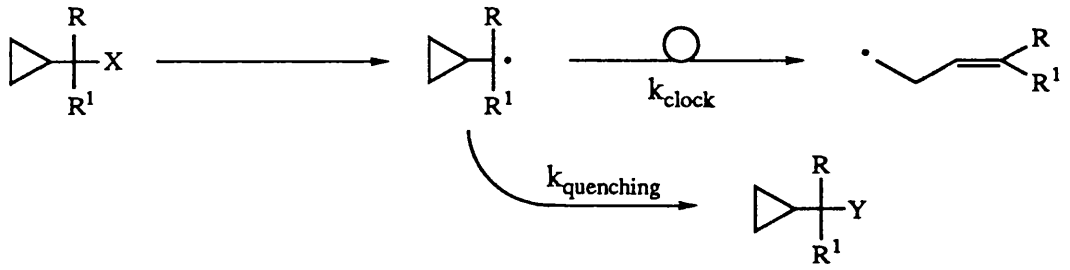


figure 1.9

1.5 FREE RADICAL CLOCKS.

Since the pioneering studies of Ingold,[5] suitably substituted cyclopropanes have been increasingly used as mechanistic and kinetic probes for chemical and, far more importantly, biochemical transformations[34] (*vide infra*). The clean production of ring opened products from a cyclopropylcarbinyl substrate is generally accepted as evidence for the formation of a discrete free radical with its centre adjacent to the cyclopropane ring. The ratio of ring-closed to ring opened products can be used as a measure of how rapidly the initially formed radical undergoes intermolecular reactions ("quenching") in competition with ring opening - the so called "clock reaction" (scheme 1.9).



scheme 1.9

A full explanation of the clock reaction concept requires, that for each group of radical types, there should be available a collection of calibrated clock reactions which cover a wide range of time scales. Ingold and Griller,[5] in a seminal review of this subject, suggested that such a collection be called a *"horlogerie"*, which in French denotes a small store where clocks can be obtained. Very recently Beckwith and Bowry[35] further elaborated this horlogerie by studying the ring opening of α-substituted cyclopropanes in the presence of a nitroxide radical trap. As expected, α-substituted cyclopropylcarbinyl radicals underwent ring opening slower than their unsubstituted counterparts; likewise, the presence of radical stabilising groups retard ring opening (table 1.4).

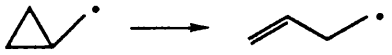
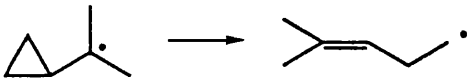
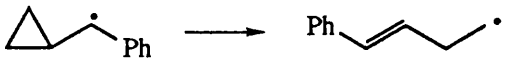
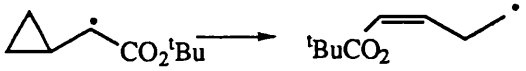
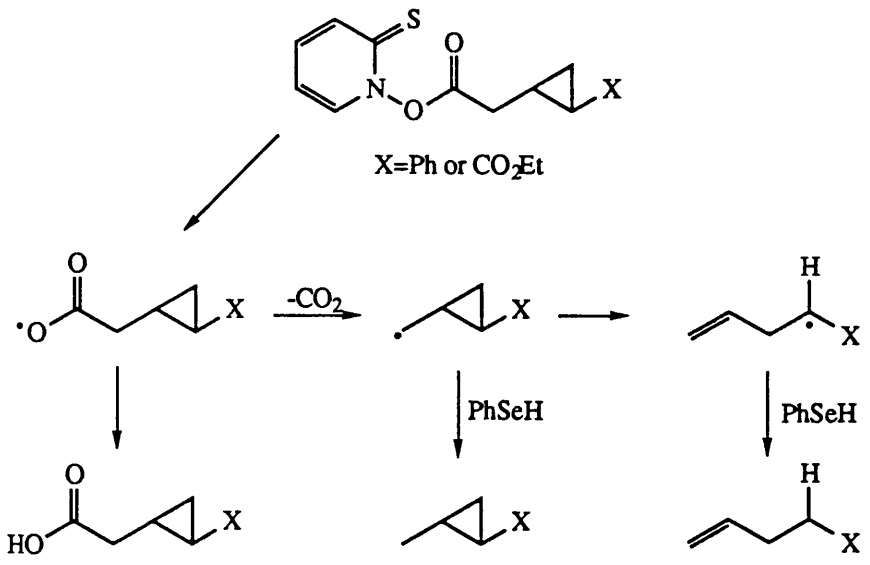
REACTION	$k_T^{80°C}(10^7 s^{-1})$	E_{act} (k_{cal} / mol)
	61	7.05
	36	8.3
	2.8	12.6
	1.2	12.4

table 1.4

Newcomb has also examined the kinetics of phenyl[36] and ethoxycarbonyl[37] substituted cyclopropanes by the adaptation of Barton's[38] PTOC ester method (scheme 1.10). Rearrangements of the phenyl substituted cyclopropylcarbinyl radicals were found to be accelerated by more than three orders of magnitude (3-5x$10^{11}s^{-1}$) over that of the parent system.



scheme 1.10

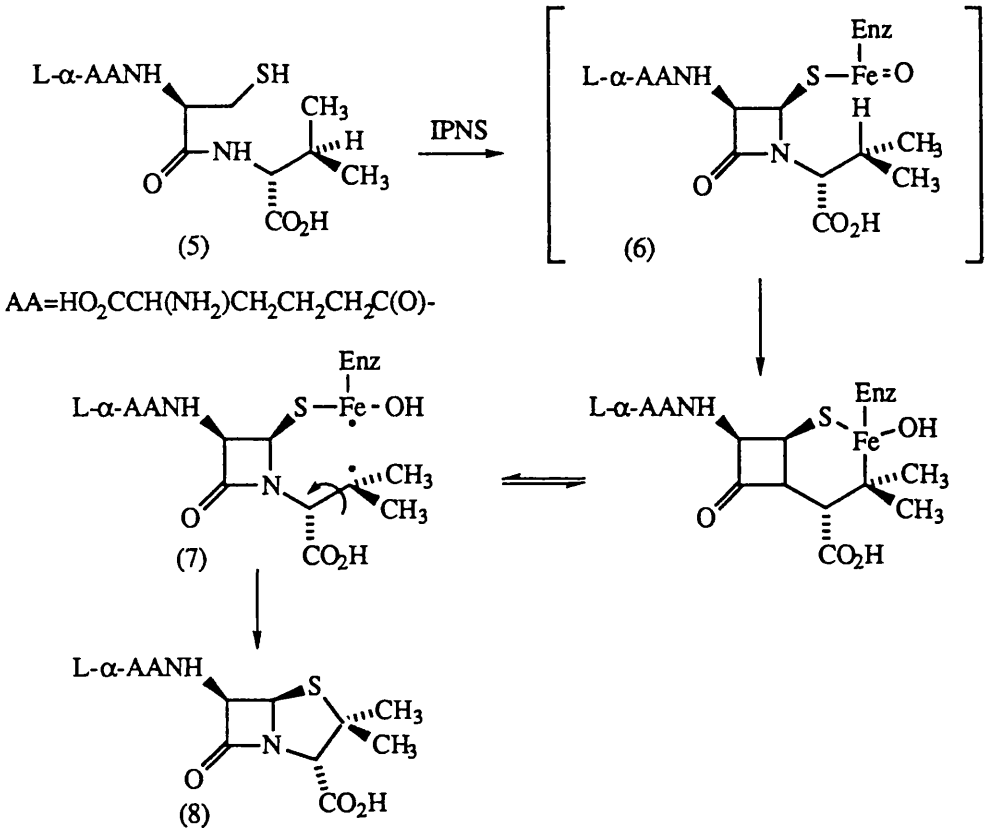
Hence, it is clear that over the last few years, the top end of the radical clock scale has jumped to greater than $1x10^{11}s^{-1}$ at 25°C, which means that radical clocks now exist for the entire range of radical kinetics that are of interest.

1.6 MONOCYCLIC CYCLOPROPYLMETHYL RADICALS AS PROBES OF REACTION MECHANISMS IN ENZYME CATALYSED REACTIONS.

The ring opening of the cyclopropylcarbinyl radical holds a position of distinction in mechanistic studies involving "mechanistic probes". Numerous studies have employed potential precursors of this radical and its analogues in attempts to implicate radical intermediates in both enzymatic and non-enzymatic reactions.[34] From the following discussion it is hoped that the reader will get a feel for the breadth of this methodology.

1.6.1 The Mechanism of Penicillin Biosynthesis.

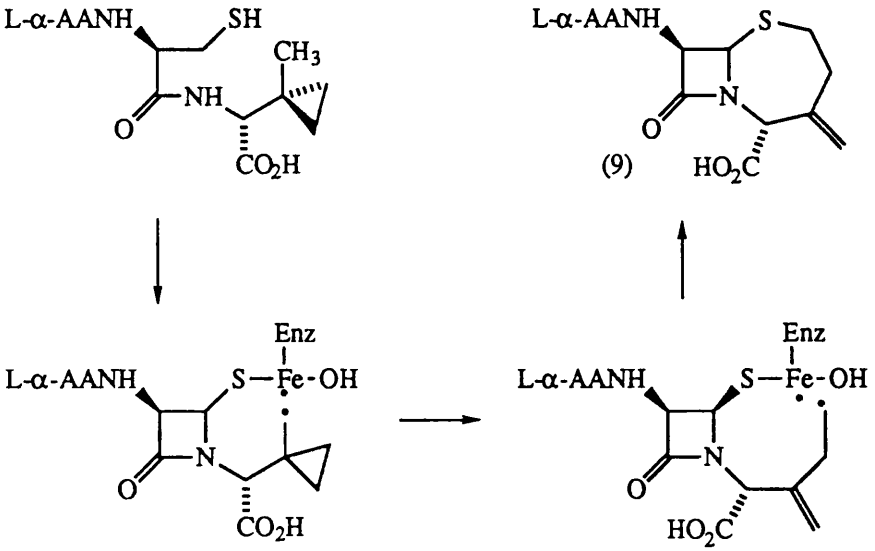
A stepwise mechanism[39,40] has been proposed for the action of isopenicillin N synthase (IPNS), which is responsible for the desaturative ring closure of an acyclic tripeptide, LLD-ACV (5), into isopenicillin N (8) (scheme 1.11).



scheme 1.11

The first step involves the formation of an enzyme-bound iron oxene species (6) which inserts stereospecifically into a C-H bond forming a iron-carbon bond. This is followed by reversible homolytic dissociation to the diradical species (7) which in turn couples at sulfur in an S_H2 fashion to give the penicillin.

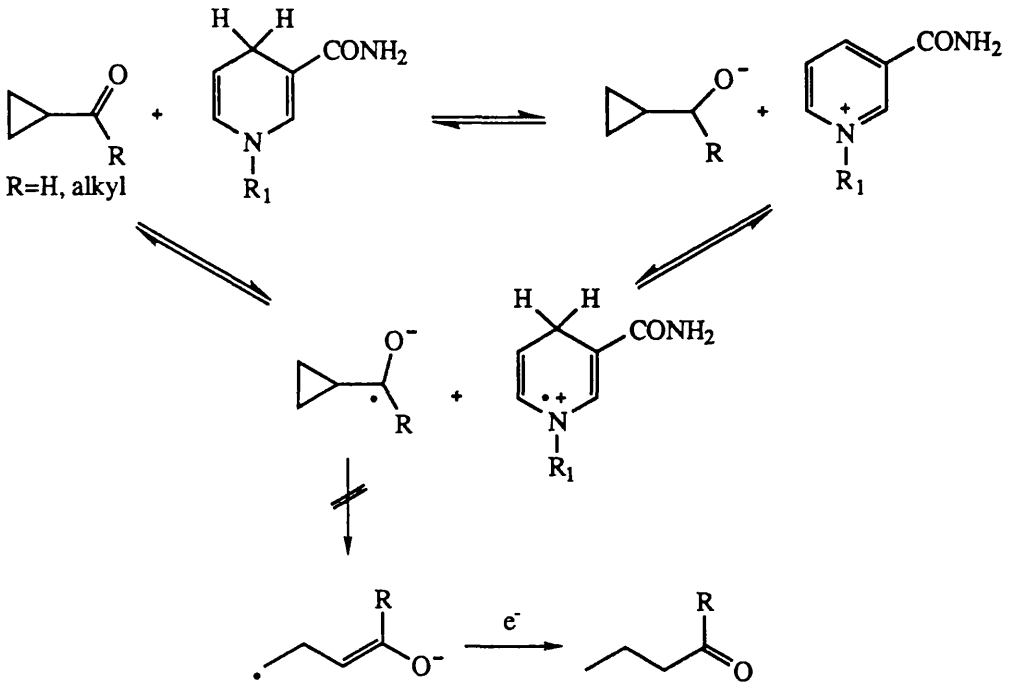
Formation of the ring enlarged product (9) in the enzymatic reaction is in accord with the intermediacy, during C-S bond formation, of a cyclopropylcarbinyl species, and hence, evidence for radical intermediates in such reactions (scheme 1.12). Also significant is the absence of any cyclobutane containing products, which discounts the involvement of cyclopropylcarbinyl cation intermediates.



scheme 1.12

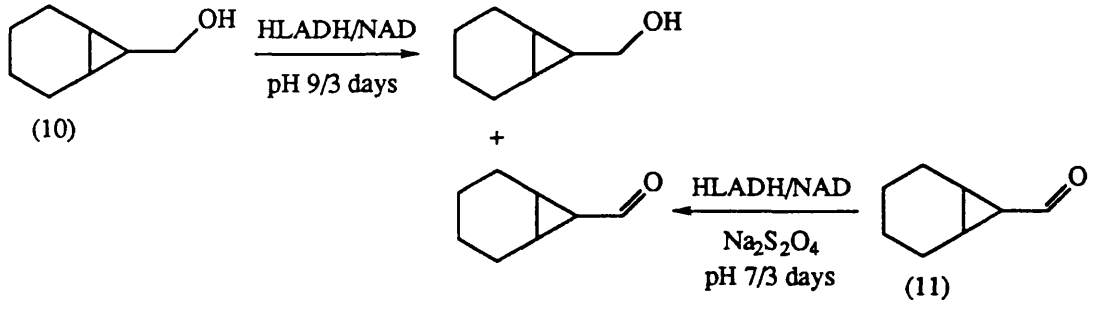
1.6.2 Are Radical Intermediates Really Involved in the Hydrogen Transfer by Nicotinamide Co-Enzyme ?

The question of the mechanism by which hydrogen is transferred by nicotinamide co-enzyme has been a subject of continuous debate. Pioneering work by Westheimer[41] in the late 1950's favoured a hydride-like mechanism. However, fifteen years later, Hamilton[42] raised the question of the involvement of radical intermediates, thus stimulating a resurgence of interest in this area.[43,44,45,46] The mechanism has been probed by studying the oxidation of cyclopropylmethanols (scheme 1.13). Such a probe is applicable since ring opening of the unsubtituted radical occurs at a rate approximately 10^6 times faster than hydrogen transfer by HLADH (horse liver alcohol dehydrogenase) (in the range of 30-100s^{-1}).[47,48]



scheme 1.13

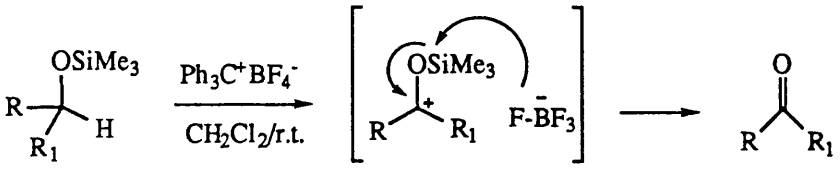
Thus, if radical intermediates were involved, ring opened products would be detected. Initial work by Suckling[45] using HLADH with the alcohol (10) and the corresponding aldehyde (11) resulted in no ring opened products being detected (scheme 1.14).



scheme 1.14

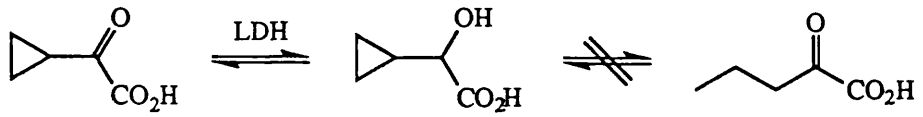
Model studies served to confirm that the substrates of choice would undergo redox reactions under both hydride transfer and radical pathways. Reduction of the aldehyde (11) under tributyltin hydride conditions resulted in ring opened products, giving cyclohexane-ethanol but oxidation of the trimethylsilyl ether of alcohol (10)

with triphenylmethyl tetrafluoroborate yielded no such product, giving only the corresponding aldehyde (11) in quantitative yield (scheme 1.15).



scheme 1.15

This thereby demonstrates that ring opening would take place if the reaction proceeded *via* a radical but not a cationic intermediate. Hence, it seems improbable that a radical intermediate is involved in the HLADH mediated hydrogen transfer reactions. Extension of this work to the oxidation of cyclopropaneglycolic acid (12)[43] with lactate dehydrogenase (LDH) was also investigated. HLADH contains zinc cations at its active site and since it has been argued that metal cations favour single electron transfer,[49] a dehydrogenase which did not employ a metal ion was chosen. Again, ring opened products were not seen (scheme 1.16), suggesting that it is improbable that hydrogen transfer occurs *via* a radical process.



(12)

scheme 1.16

However, a radical intermediate cannot be ruled out for certain since the radical species involved is a capto-dative[50] stabilised radical, and an analogous radical (13) has been shown not to rearrange even at temperatures as high as 100°C (scheme 1.17).

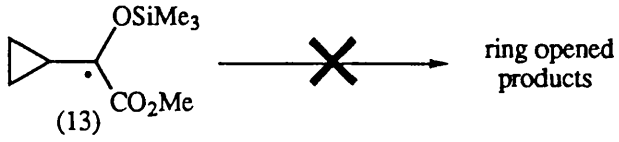
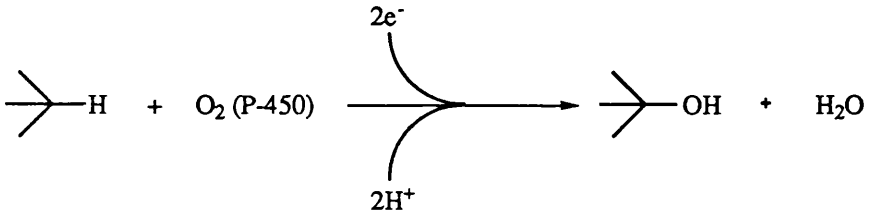


figure 1.17

Thus, the general consensus at the present time is that these redox reactions should be regarded as "hydride like".

1.6.3 Cytochrome P-450 Hydroxylation of Alkanes.

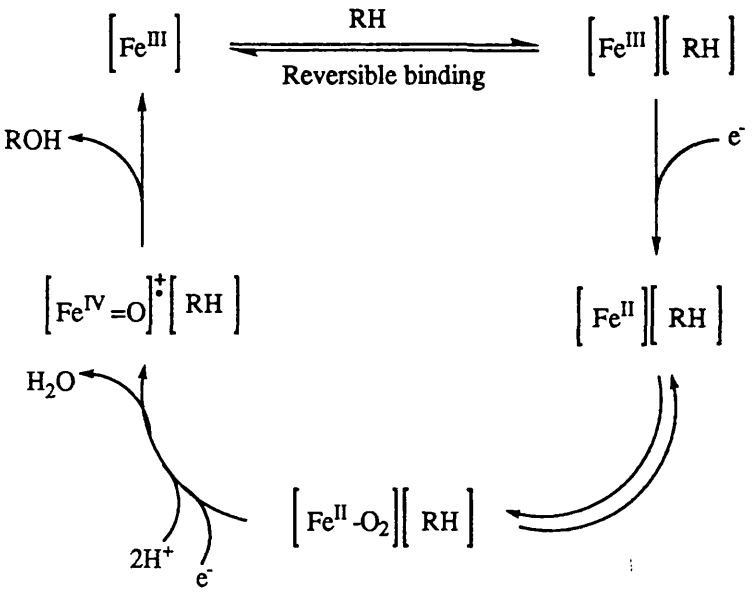
The term cytochrome P-450 refers to a family of membrane-bound iron porphyrin containing monooxygenases which catalyse the incorporation of molecular oxygen into unactivated molecules in a selective manner. Undoubtedly, one of the most intriguing of such oxidations has to be the hydroxylation of alkanes (scheme 1.18).

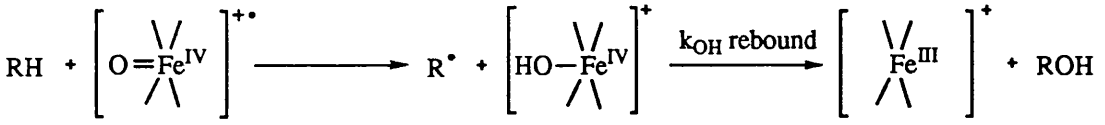


scheme 1.18

These reactions were first thought to occur *via* a concerted *oxene insertion* but recently evidence has come to light favouring a non-concerted mechanism. Insertion of oxygen into the C-H bond has been proposed to involve hydrogen abstraction from the C-H bond, followed by transfer of an "iron-bound" hydroxyl radical to the resulting alkyl radical (scheme 1.19).

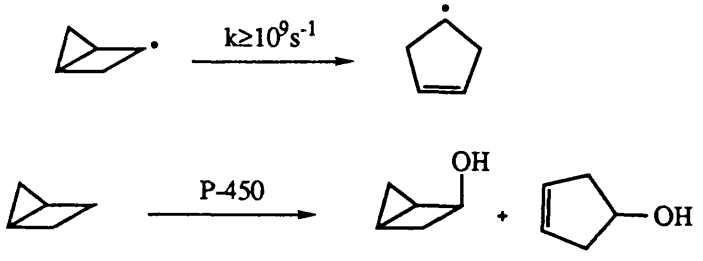
In 1987, Ortiz de Montellano and Stearns[51] found that under such conditions the cyclopropylmethyl radical yielded only cyclopropylmethanol, implying either that radical intermediates were not involved, or that the hydroxyl radical transfer was so rapid that the radical had insufficient time to ring open.





scheme 1.19

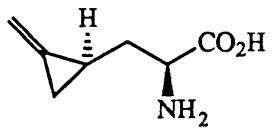
The bicyclo[2.1.0]pent-2-yl radical rearranges far more rapidly than the cyclopropylmethyl radical and proves to be an ideal candidate to answer the above question.[51,52] The cytochrome P-450 hydroxylation of this substrate gave a 7:1 mixture of *endo*-bicyclo[2.1.0]pentan-2-ol and the 3-cyclopenten-1-ol, indicating that some ring opening had occurred in the mode expected for free radical intermediates (scheme 1.20).



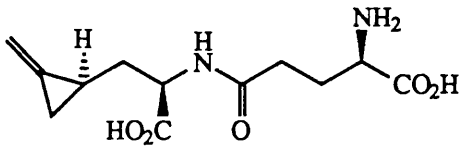
scheme 1.20

1.6.4 Jamaican Vomiting Sickness.

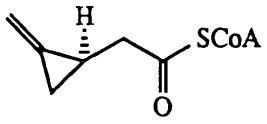
Hypoglycin (A) together with its γ-glutamyl conjugate, hypoglycin (B) (figure 1.10), were first isolated by Hassal and Reyle[53] from the seeds of the unripe ackee *(Blighia Sapida)*. While the ripe ackee fruit serves as a dietary staple in Jamaica, ingestion of amino acids hypoglycin (A) or (B) from the unripe fruit is responsible for Jamaican vomiting sickness, which led to a mortality rate of over 80% before the introduction of a glucose infusion treatment in the mid 1950's.



HYPOGLYCIN (A)



HYPOGLYCIN (B)



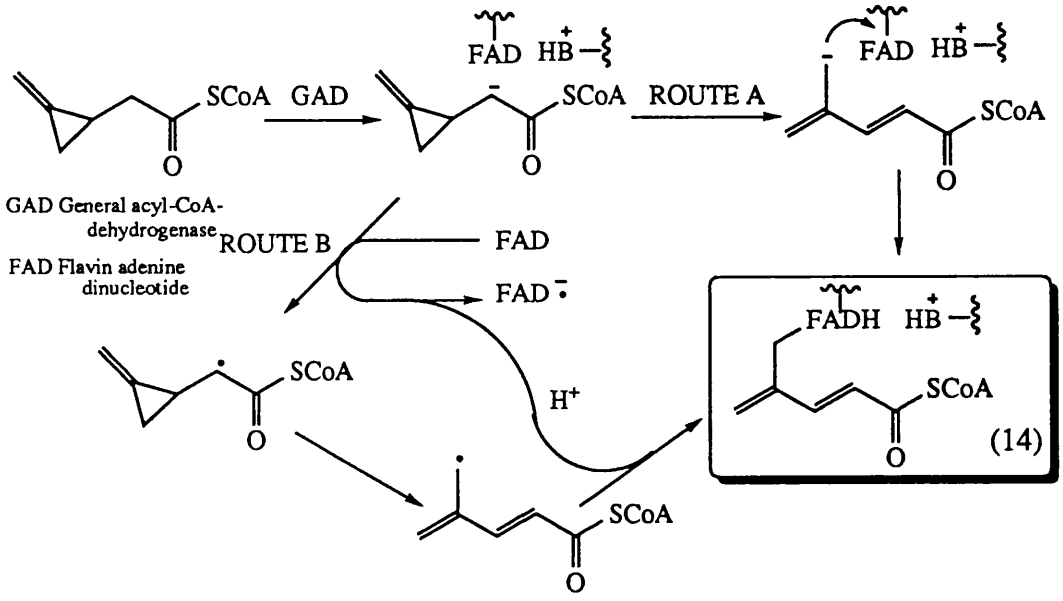
MCPA-CoA

figure 1.10

The ingested hypoglycin (A) is metabolised *in vivo*, to (1R)-[(methylenecyclopropyl)acetyl]-CoA (MCPA-CoA)[54,55,56] (figure 1.10), the actual causative agent of the Jamaican vomiting sickness. Despite the fact that this disease has been studied for several years, the question of whether its mechanism of action on the flavin dependent enzyme, General acyl-CoA dehydrogenase occurs through a radical or ionic process has never been fully addressed. Recently, however, new evidence supporting a radical mechanism for the deactivation has been brought to light.[57,58]

When GAD is exposed to MCPA-CoA, time dependent inactivation ensues with concomitant bleaching of the active FAD site. The molecular course of the inhibition is widely believed to proceed *via* α-proton abstraction followed by ring

fragmentation and covalent modification of the flavin co-enzyme (14). However, Liu[59] has found this inactivation to be non-stereospecific, and thus, proposed a single electron oxidation pathway (route B) *via* the thermodynamically more stable allyl radical, as opposed to the anion induced cleavage (route A) (scheme 1.21).



scheme 1.21

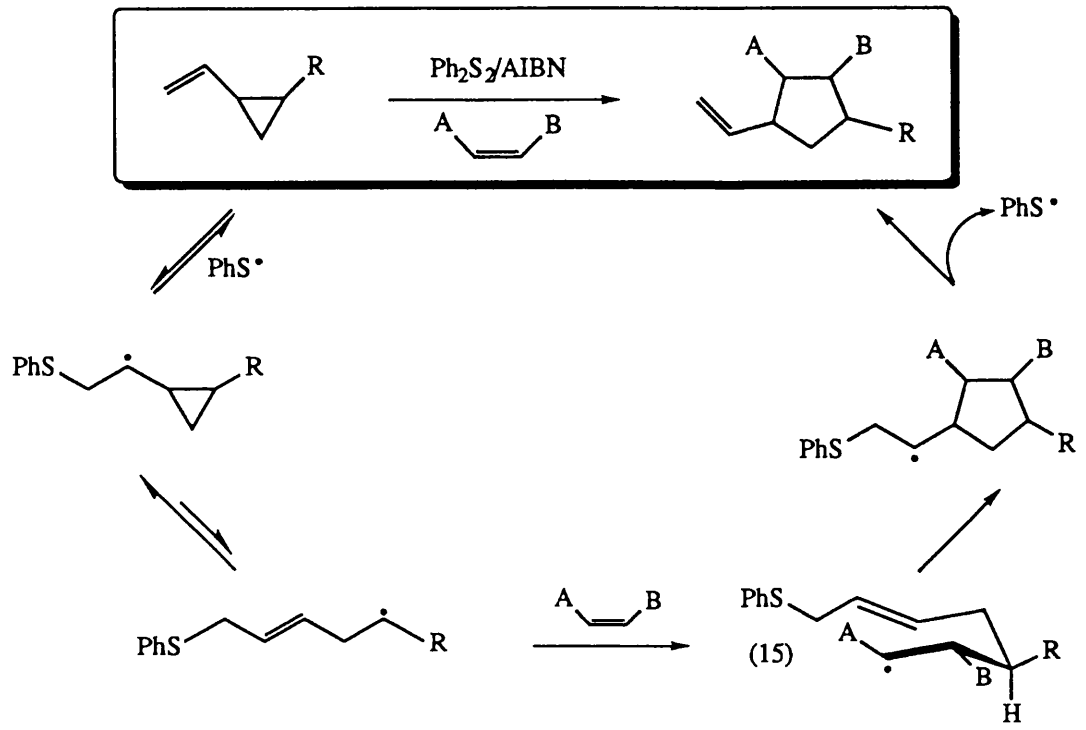
1.7 THE USE OF CYCLOPROPYLCARBINYL RADICALS IN SYNTHESIS.

1.7.1 Vinylcyclopropanes in [3+2] Addition Reactions.

1.7.1.1 Cyclopentane / Cyclopentene Synthesis.

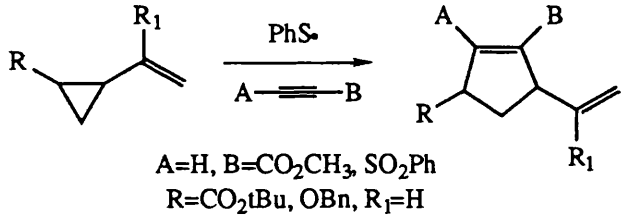
Feldman's[60,61] approach to free radical based cyclopentanoid synthesis relies on the phenylthio radical catalysed combination of substituted vinylcyclopropanes with functionalised alkenes to afford vinylcyclopentane derivatives (scheme 1.22). Although this reaction proceeds through a complex multistep mechanism, the product stereochemistry is set in a single step, namely the cyclisation of the 5-hexenyl radical (15). Initiation occurs by the addition of the phenylthio radical to the vinylcyclopropane followed by ring opening to the homoallylic species, which, after addition to the alkene, cyclises with subsequent ejection of the catalytic phenylthio

radical to generate the vinylcyclopentane.



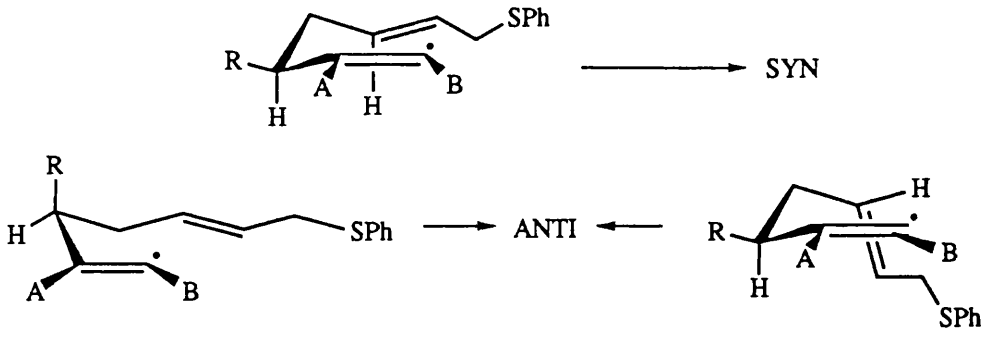
scheme 1.22

Likewise, Feldman[62] has extended this methodology to the synthesis of functionalised cyclopentenes *via* the incorporation of alkynes (scheme 1.23).



scheme 1.23

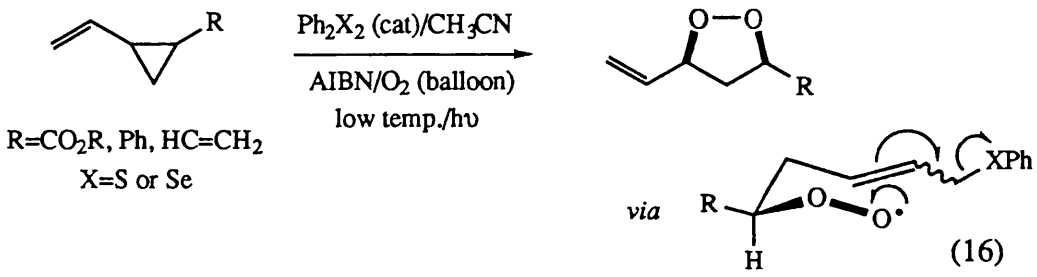
A mechanism analogous to that for the formation of the cyclopentane products can be envisioned. The more modest yields (30-50%) in contrast to the cyclopentanes (50-90%), and lower stereoselectivity results from the diminished reactivity of alkynes relative to alkenes. Product stereoselectivity is set during the 5-hexadienyl ring closure as before (scheme 1.24).



scheme 1.24

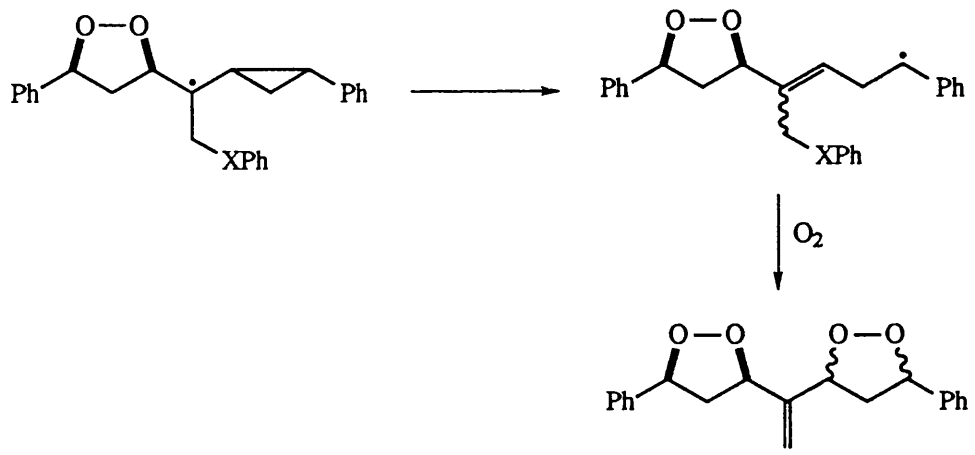
1.7.1.2 Synthesis of Dioxolanes.

Using the same strategy, Feldman[63,64] has designed a useful route to *syn*-dioxolanes by trapping of the intermediate homoallyl radical with dioxygen (scheme 1.25).



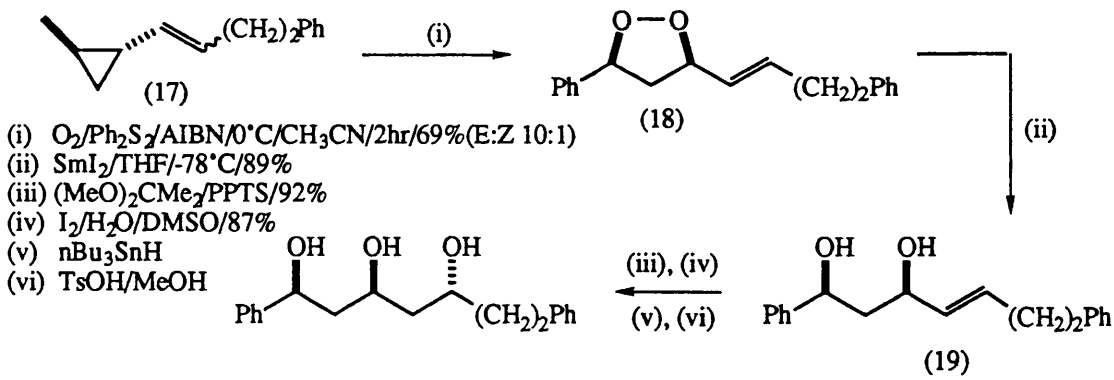
scheme 1.25

In this case, the stereochemistry arises *via* the lowest energy chair-like transition state (16) in which R is pseudo equatorial. Incorporation of a second cyclopropyl substituent has shown to divert the reaction from that illustrated above towards the formation of *bis*- and *tris*-(1,2-dioxolanes)[65] by ring cleavage and a second oxygenation sequence (scheme 1.26).



scheme 1.26

Interest in these polyoxygenated hydrocarbons stems from the fact that the corresponding 1,3-diol unit is common to many polyacetate derived natural products, for example (±)-yashabushitriol.[66] Phenylthiyl radical catalysed reaction of the either the *(E)* or *(Z)* vinylcyclopropane (17) led to the *syn-(E)*-1,2-dioxolane (18). Smooth cleavage of the latter with samarium(II) iodide in THF led to the diol (19) in high yield. Conversion to the natural product was then achieved in four steps (scheme 1.27).

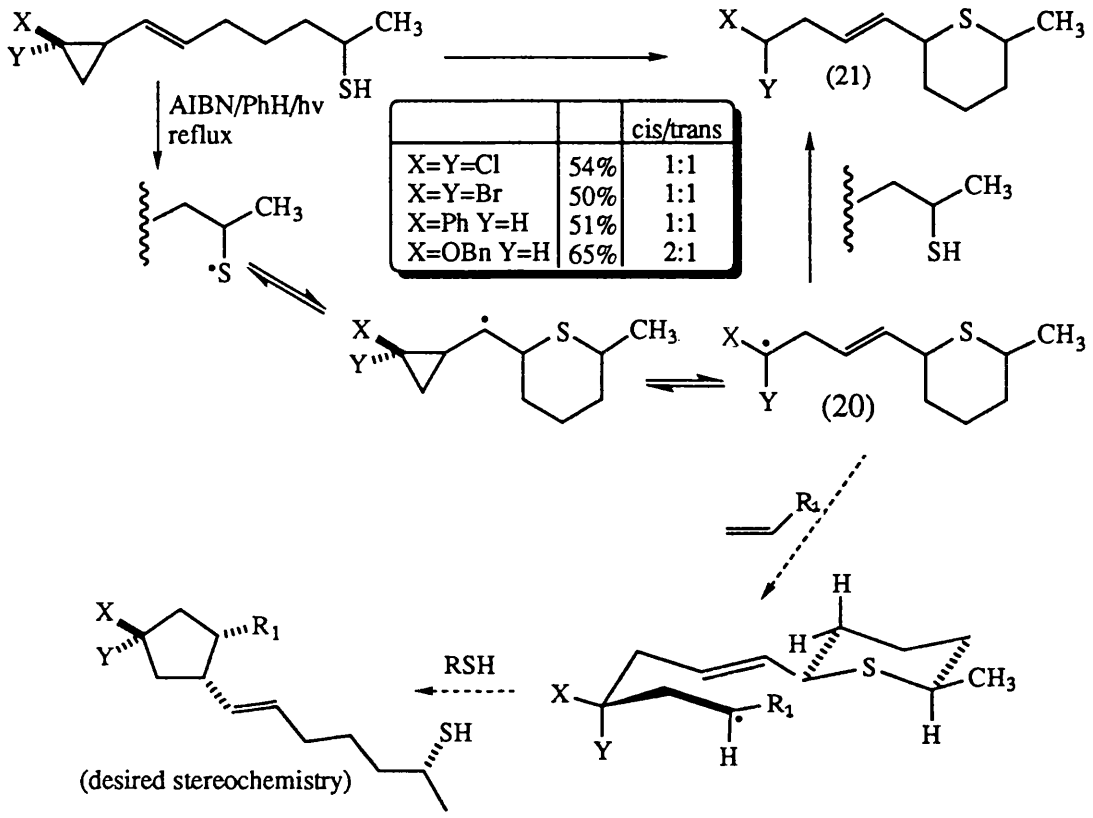


scheme 1.27

1.7.1.3 Thiopyran Formation.

More recently, Feldman[67] has been looking into the cyclisation of 2-thiyl-6-heptenyl radicals onto vinylcyclopropanes in an intramolecular sense, with the intention of trapping the homoallylic radical (20) in future work (shown by the dotted arrows)

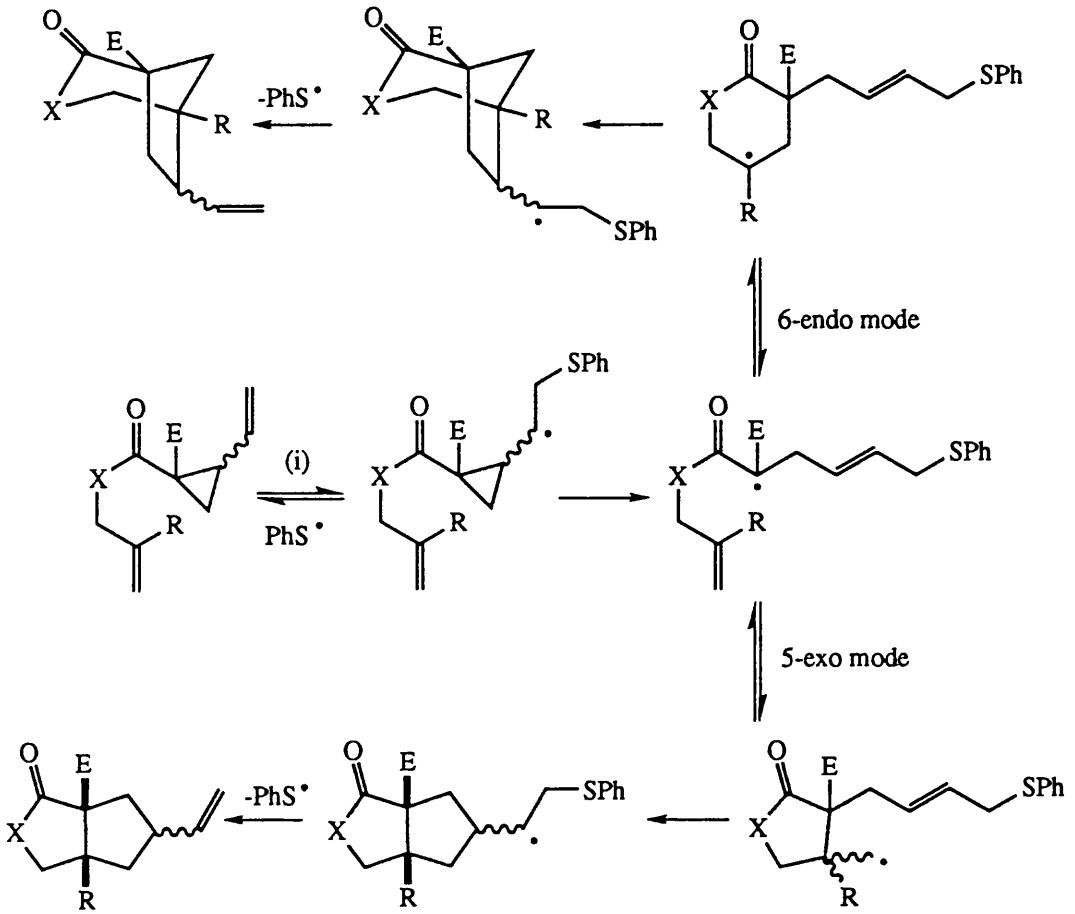
(scheme 1.28). These workers wished to explore the hypothesis that delivery of the thiyl radical, maybe *via* an intermediate thiopyran, leads to formation of (21). Indeed, ring opened products were obtained in moderate yield, albeit with no discernible stereochemical preference.



scheme 1.28

1.7.1.4 Vinylcyclopropanes en Route to Lactones / Lactams and Ketones.

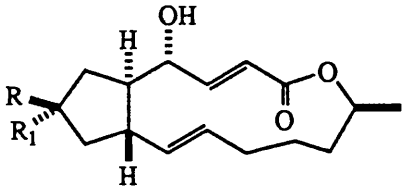
Another similar intramolecular approach by a group of French workers[68] demonstrates that the radical involved rearrangement of vinylcyclopropanes, derived from the activated esters and amides, are potential precursors to bridged and fused bicyclic compounds (scheme 1.29).



scheme 1.29

1.7.1.5 Entry into the Brefeldin Ring System.

A common feature of the brefeldin family of antibiotics is their 1,3,4-trisubstituted vinylcyclopentane moiety (figure 1.11).

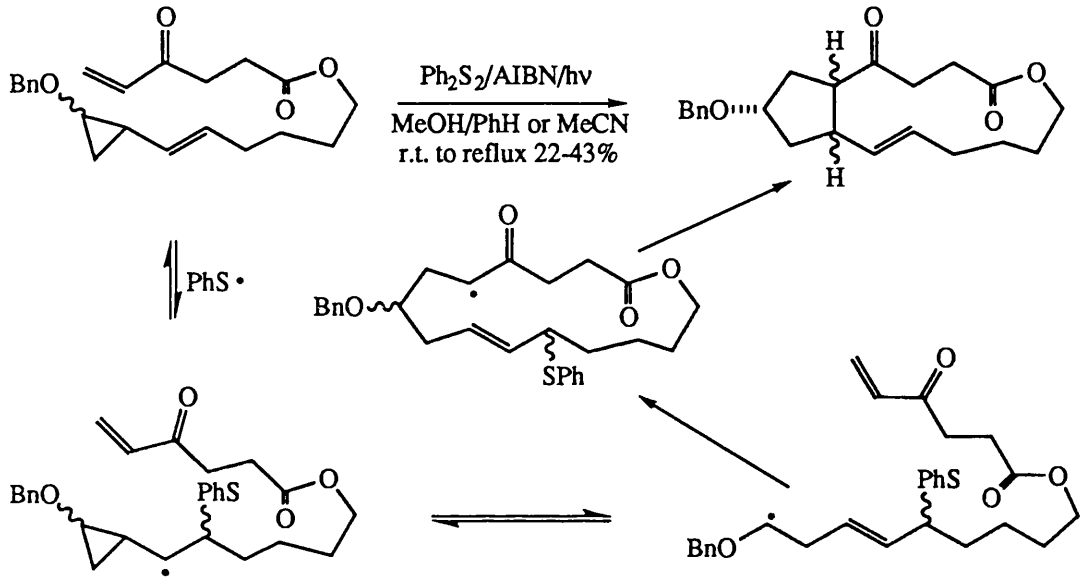


R=H R_1=OH BREFELDIN A
R=R_1=H BREFELDIN C

figure 1.11

Feldman[69] demonstrated that an intramolecular macrocyclisation variant of his

radical mediated addition of substituted vinylcyclopropanes with activated alkenes, proceeds in good yield to provide bicyclic products (scheme 1.30). Although construction of the brefeldin skeleton was achieved, the stereochemical control in the macrocyclisation step was unsatisfactory, hence, additional efforts directed towards the synthesis of the natural product have been abandoned.



scheme 1.20

1.7.2 Towards the Synthesis of (±)-Rocaglamide.

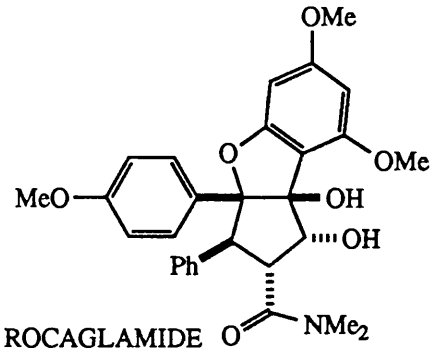
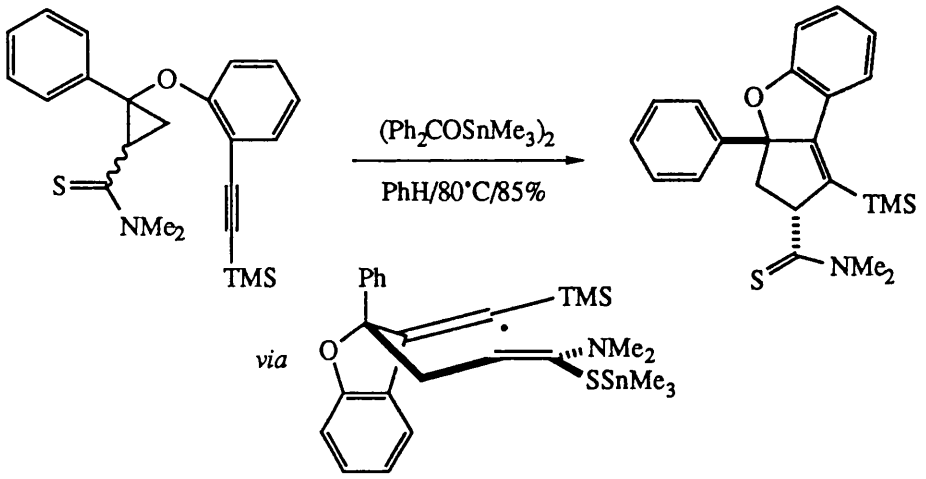


figure 1.12

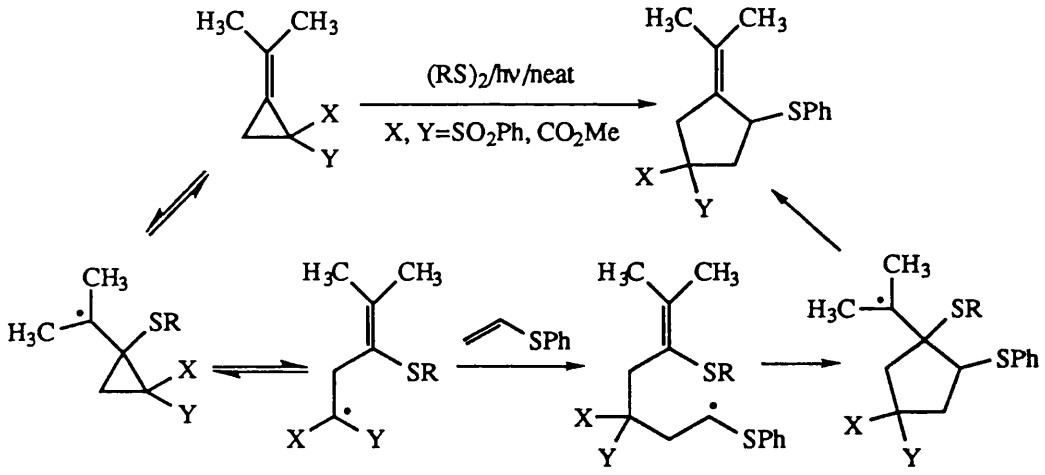
A further application of Feldman's[70] radical mediated [3+2] addition methodology is found in the synthesis of the rocaglamide skeleton (figure 1.12), a class of antileukemic natural products, *via* cyclopropyl thioamides (scheme 1.31).



scheme 1.31

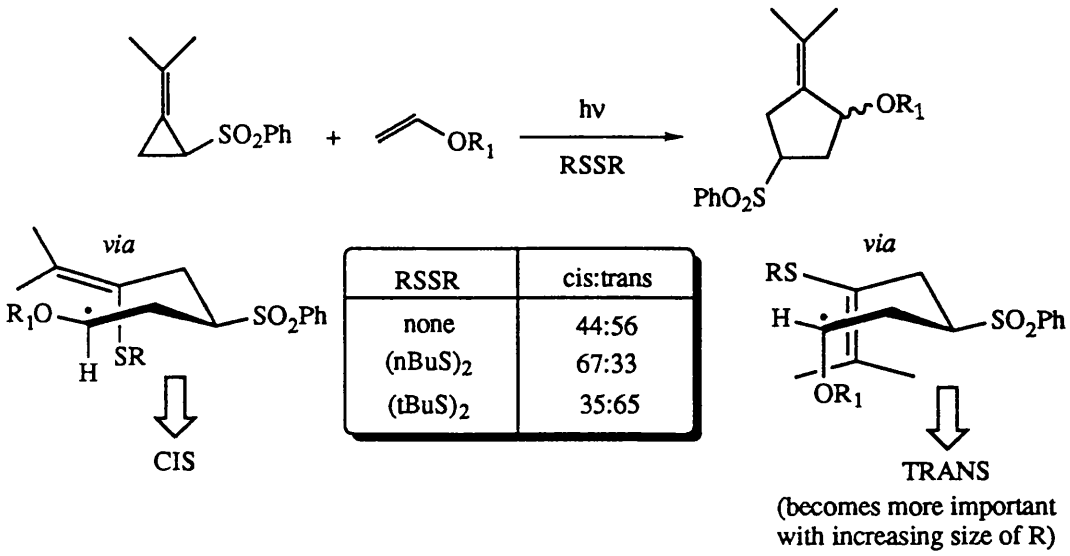
1.7.3 Methylenecyclopropanes in [3+2] Addition Reactions.

1.7.3.1 Synthesis of Methylenecyclopentanes.



scheme 1.32

In contrast to Feldmans vinylcyclopentene synthesis, Singleton[71,72] has applied a similar concept to methylenecyclopropanes (scheme 1.32). The mechanism is envisioned as being analogous to that proposed by Feldman, the stereochemistry being dictated by the 5-*exo*-trig ring closure, which in turn is influenced by the steric bulk of the radical catalyst (scheme 1.33).

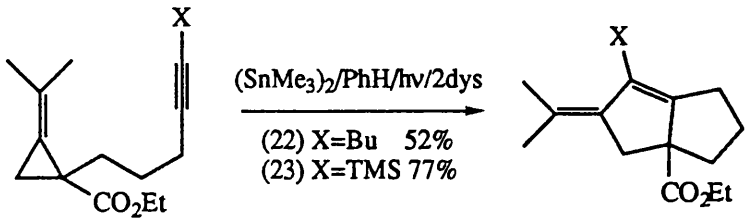


scheme 1.33

1.7.3.2 Diquinane Synthesis.

An intramolecular variant of the [3+2] methylenecyclopropane annulation led Singleton[73] to report a quick and efficient synthesis of diquinanes (scheme 1.34).

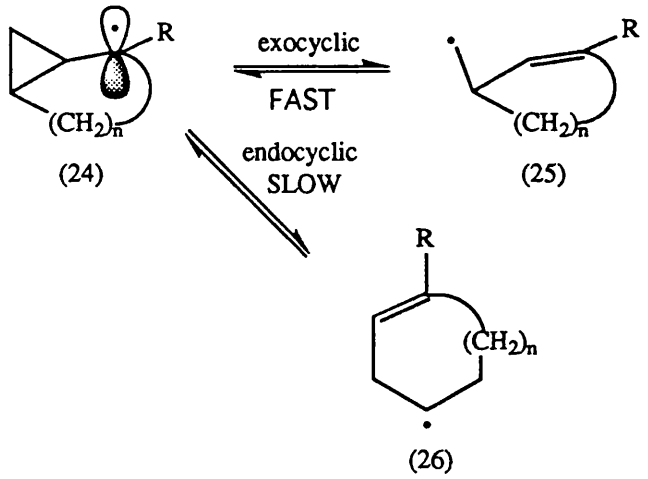
An intriguing aspect of this reaction is that under conditions successful in previous intermolecular reactions, no cyclised products were obtained. However, irradiation of a benzene solution of the substituted methylenecyclopropane in the presence of 20% hexamethylditin led to the desired diquinanes.



scheme 1.34

Chapter Two

2.1 RING OPENING OF BICYCLO[n.1.0]ALK-2-YL SYSTEMS.



scheme 2.1

The regiochemical outcome in systems where the cyclopropane is fused to a second ring is also of interest. In principle, the bicyclo[n.1.0] radical (24) can ring open to give the thermodynamically more stable cycloalkyl-3-enyl radical (26), *via* endocyclic bond cleavage. Thus, ring opening in this mode would be favourable under conditions of thermodynamic control, for example, in the presence of strategically positioned radical stabilising substituents, or if the transition state is product like. Conversely, exocyclic cleavage may occur to give the higher energy primary cycloalkyl-2-enylmethyl radical (25) (scheme 2.1). However, it is the latter which is favoured on stereoelectronic grounds since the σ^* orbitals of the external bond overlap more efficiently with the adjacent p-orbitals of the radical SOMO (figure 2.1).

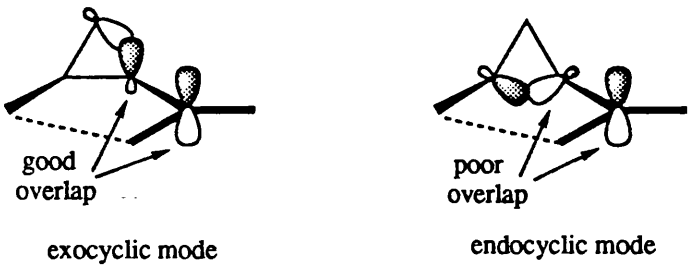
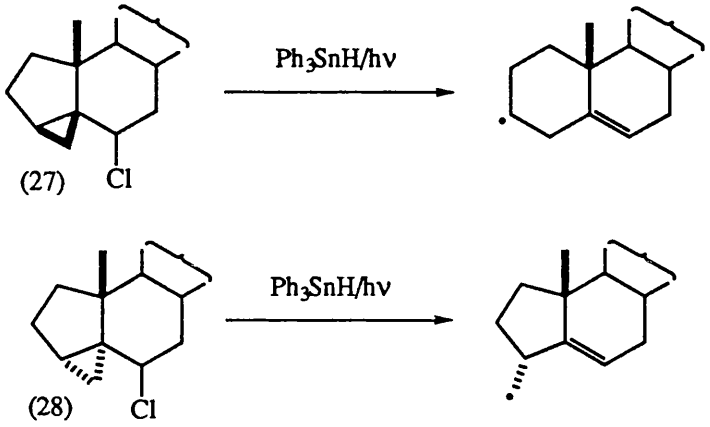


figure 2.1

As expected, the rate of ring opening of these systems when compared to their monocyclic counterparts is inherently faster due to the greater release of strain on cleavage.

This overlap "rule" is particularly well demonstrated in the steroidal work of Beckwith and Phillipou[74] (scheme 2.2).



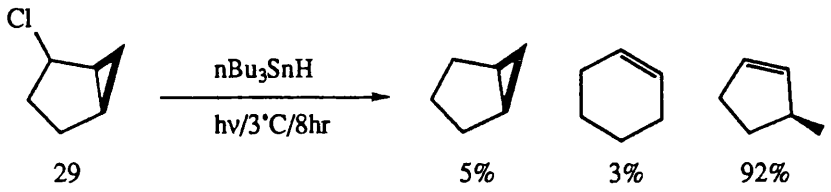
scheme 2.2

Examination of models containing the B ring in a chair conformation reveals that the plane of the p-orbital in (27) is aligned with that of the internal bond, while in the analogous (28), favourable overlap occurs with the external bond. It has previously been shown[75] that (28) undergoes regiospecific rupture of the 3-5 bond. Similarly, Beckwith concluded that stereoelectronic effects are the overriding feature in determining the direction of bond fission in (27).

In order to examine this phenomenon in greater detail, Freidrich and Holmstead[76] investigated the radical rearrangements of bicyclo[3.1.0] and [4.1.0]heptyl systems.

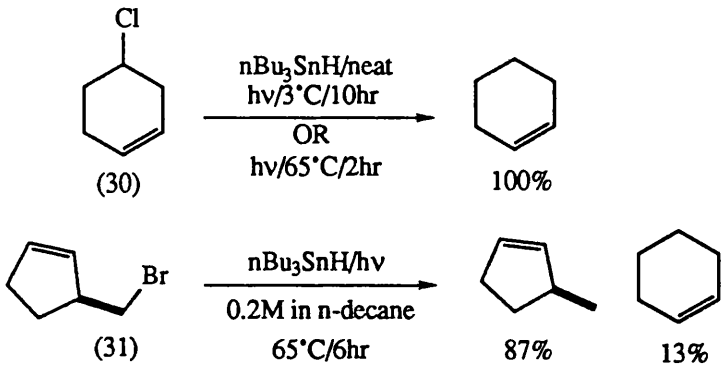
2.1.1 The [3.1.0] Hexyl System.

In the absence of solvent, reduction of the appropriate bicyclo[3.1.0] halide (29) gave predominantly the product derived from cleavage of the external bond, i.e. formed under stereoelectronic control (scheme 2.3).



scheme 2.3

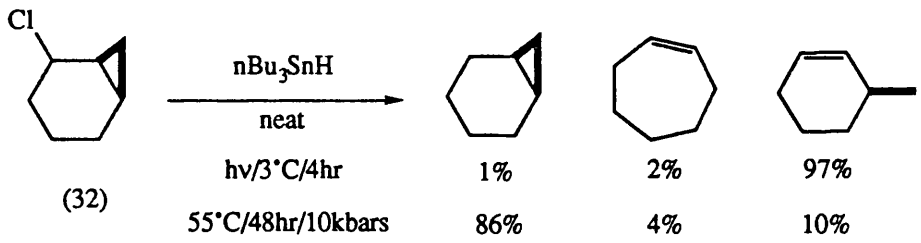
In order to determine whether any bicyclo[3.1.0]hexane is formed *via* ring closure to the cyclopropylcarbinyl radical, tributylstannane reductions were conducted on 4-chlorocyclohexene (30) (scheme 2.4). Cyclohexene was the sole product in this reaction, eliminating the possibility of rapid interconversion *via* the corresponding cyclopropylcarbinyl radical. A similar study was conducted with the 3-cyclopentylmethyl radical derived from (31). No products involving ring closure of the homoallylic radical were observed under neat tributylstannane conditions. However, under more dilute conditions at elevated temperatures, cyclohexene was detected. Therefore, ring closure to the cyclopropylcarbinyl radical, although relatively slow, does occur (scheme 2.4).



scheme 2.4

2.1.2 [4.1.0]Heptyl System.

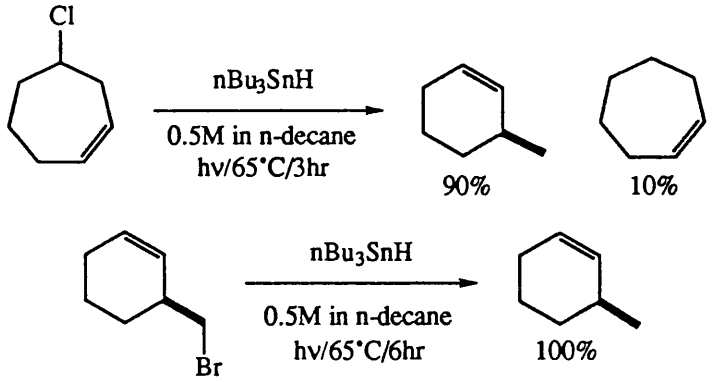
Reduction of 2-chlorobicyclo[4.1.0]heptane (32), in accord with stereoelectronic preference, gave the expected 3-methylcyclohexene (scheme 2.5).



scheme 2.5

However, Pereyre[27] found that under a high pressure environment in the presence of an equimolar amount of tributylstannane, the composition of the mixture was surprisingly different with ring opening essentially halted.

In contrast to the lack of rearrangement of the 4-cyclohexenyl radical, parallel studies with the 4-cycloheptenyl radical at elevated temperatures led to relatively slow isomerization, however, ring closure of the 3-cyclohexenylmethyl radical did not occur (scheme 2.6).



scheme 2.6

As an extension of the work by Friedrich, Walton[77] carried out ESR studies of his own *via* hydrogen abstraction of *t*-butyloxy radicals from bicyclo[n.1.0]alkanes. He found the main site of attack to be C(2), giving bicyclo[n.1.0]alkyl-2-yl radicals (24, n=3-6) which then under went rearrangement. As expected, for n=3-6, preferential rupture of the outer bond resulted in the formation of the cycloalkenylmethyl radical (25). Models for n=4-6, indicate that the SOMO can overlap with the internal bond when the ring adopts a boat conformation. However, such conformations are unlikely

to be important. Hence, stereoelectronic factors lead to the formation of the product derived from the less stable primary radical.

Estimated values for the relief of ring strain involved in the two modes of ring cleavage have been made based on the corresponding hydrocarbons (table 2.1).

n	Endocyclic Cleavge ($kJmol^{-1}$)	Exocyclic Cleavge ($kJmol^{-1}$)
3	131	112
4	98	115
5	99	101
6	89	105

RELIEF OF RING STRAIN ON RING OPENING FOR BICYCLIC[n.1.0] SYSTEMS

table 2.1

As can be seen, fission of either the endocyclic or exocyclic bond leads to a large relief of strain. For n=4-6, both stereoelectronic effects and ring strain (thermodynamic) favour rapture of the outer bond. Surprisingly, for the n=3 system, at first glance, the endocyclic mode is the preferred pathway (by approximately 20 $kJmol^{-1}$). However, this does not outweigh the favourable stereoelectronics.

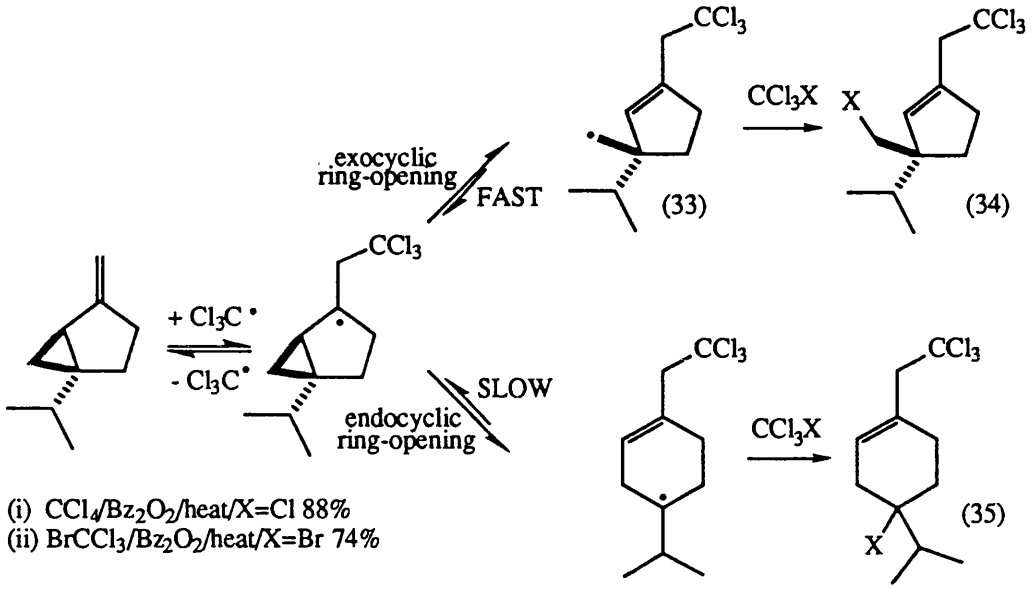
2.2 WORK IN THESE LABORATORIES.

2.2.1 Trichloromethyl Radical Addition to [n.1.0] Vinylcyclopropanes.

Motherwell and Harling[78] were so intrigued by the original observations made by Davies[79] in 1970, involving the radical addition of trichloromethyl radicals to sabinene, that in the first instance they verified the original findings (scheme 2.7).

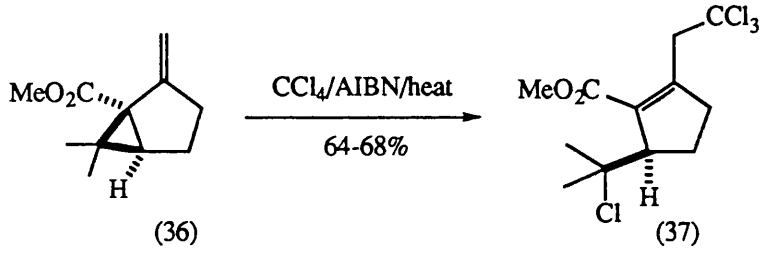
Davies observed exclusive formation of the six membered ring adduct (35), which is the product of endocyclic ring opening and not the expected product from a stereoelectronically controlled ring opening. These initial observations were confirmed with Motherwell proposing that slower abstraction of the more tightly bound chlorine atom from the solvent permits reversible ring reclosure of (33) to occur, thus allowing the alternative endocyclic ring opening to give the thermodynamically favoured product. With bromotrichloromethane, however, only

the five membered ring adduct was isolated as a result of kinetically controlled *exo* ring cleavage. In this case, rapid bromine atom abstraction from the solvent, which has a relatively weak carbon-bromine bond, renders the formation of (33) essentially irreversible.



scheme 2.7

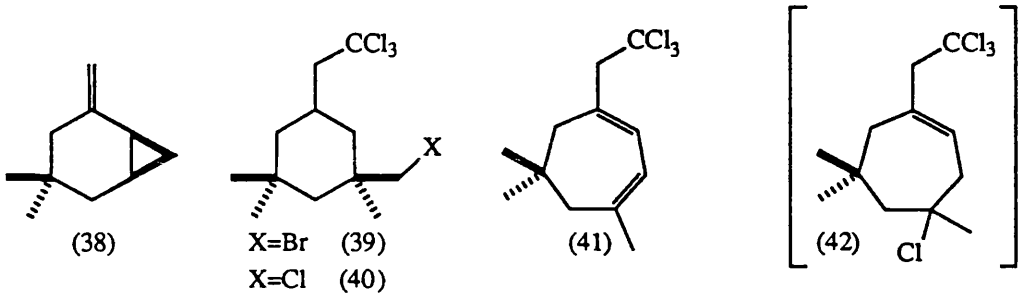
In contrast to the argument laid out above, Paquette[80] showed that the sole product arising as a result of tetrachloromethane addition to (36) was the 5-membered ring adduct (37) (scheme 2.8).



scheme 2.8

However, closer examination reveals that the initially formed ring opened radical is a tertiary radical. Moreover, reclosure of the tertiary radical to the ester bearing carbon of the acrylate double bond maybe significantly slower in this case and is certainly disfavoured in electronic terms.

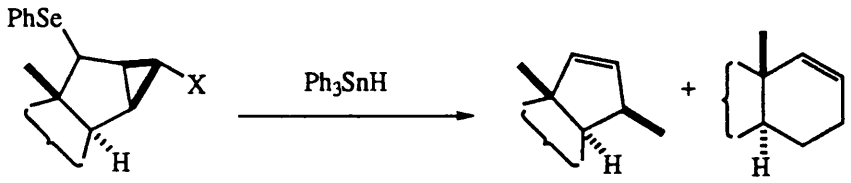
As an extension to this work, Motherwell and Batey[78] applied the same principle to the analogous bicyclo[4.1.0] congener (38). Treatment with bromotrichloromethane under the same experimental conditions gave, as expected, the six membered ring adduct (39) as the sole product, whereas reaction in tetrachloromethane afforded both the chloro analogue (40) and the cycloheptadiene (41) in a ratio of 1:2 respectively, the latter as a result of elimination of hydrogen chloride from the initially formed seven membered ring adduct (42) (scheme 2.9).



scheme 2.9

2.3 MISCELLANEOUS

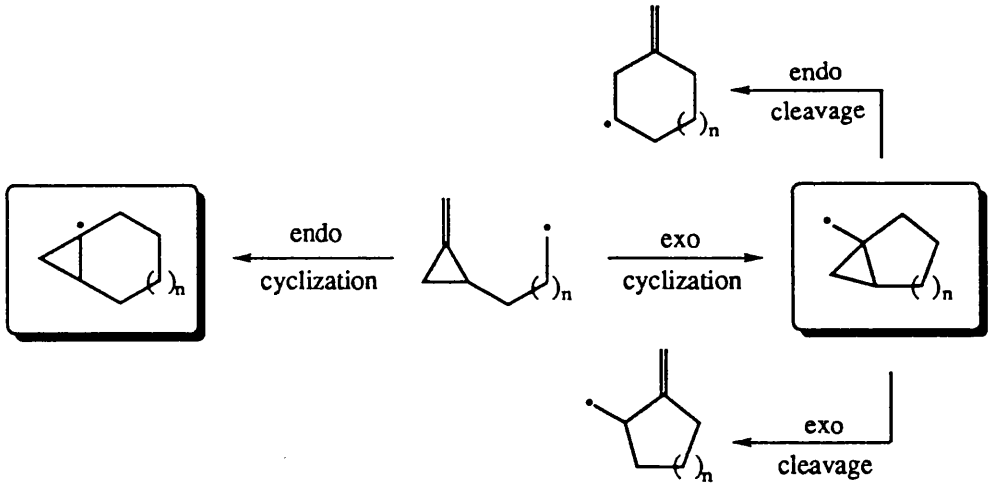
A study by Clive,[81,82] using an identical strategy to that introduced within our group one year earlier (see section 3.1.1) utilised a range of cyclopropylselenides as the radical precursors to generate alkyl substituted cyclic structures. In the absence of a substituent on the non-bridgehead position, products arising from ring expansion were detected, with low temperatures being used to suppress this undesired pathway. In the presence of strategically positioned electron withdrawing groups, however, the reactions were found to be more selective, since, ring opening was facilitated as a result of the enhanced stability of the ring opened radical (scheme 2.10).



X=H	hv/(sunlamp)/-30°C	84%	16%
	AIBN/PhH/reflux	78%	22%
$X=CO_2Et$	nBu_3SnH/AIBN PhH/reflux	90%	

scheme 2.10

In comparison to Singleton's[71,72] work, Kilburn[83] has developed a similar strategy involving the 5-*exo* cyclisation of an alkyl radical to an alkylidenecyclopropane in an intramolecular sense (scheme 2.11).

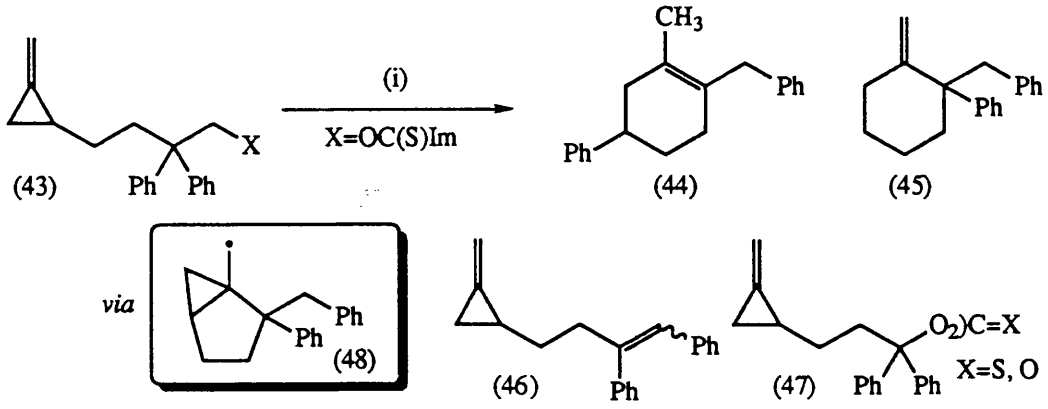


scheme 2.11

Initial *endo* cyclisation might be favoured as this pathway encounters less steric hindrance, and would lead to a relatively stable cyclopropyl radical. Alternatively, *exo* cyclisation would also lead to an intermediate cyclopropylmethyl radical, that would be expected to open rapidly, to give products arising from cleavage of both the internal and external bonds, since free rotation can occur to line up the SOMO p-orbital with either the exocyclic or the endocyclic bond.

Initial studies concentrated on the 3-(methylenecyclopropyl)butyl radical derived

from the deoxygenation of (43), the reaction gave a mixture of largely unexpected products (scheme 2.12).



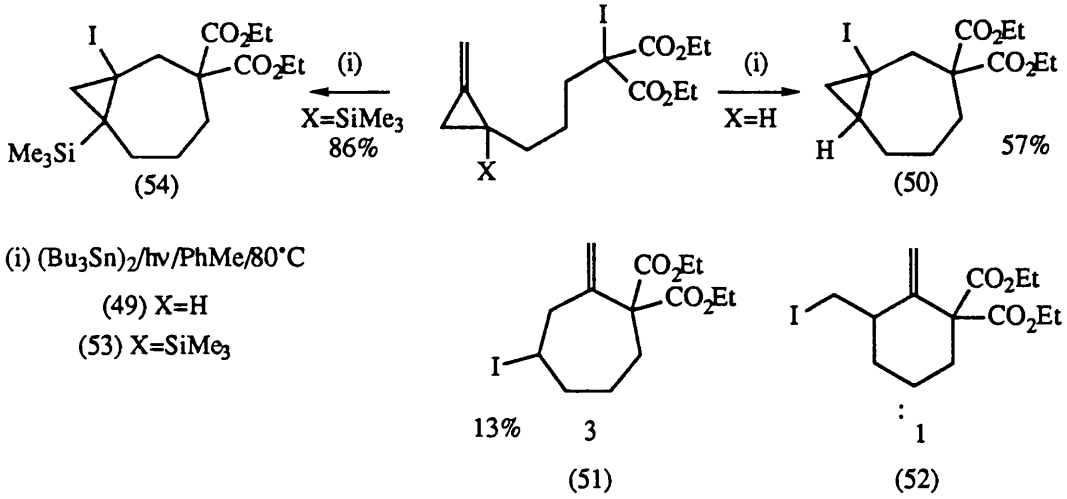
(i) nBu_3SnH/AIBN/xylene/reflux

scheme 2.12

Diene (46) is presumably formed by a simple 1,2-phenyl migration elimination process, and although the mechanism for the formation of (47) is not entirely clear, however, it is not thought to involve the intermediacy of the initial radical generated from the thiocarbonylimidalozide precursor. This primary radical undergoes a 1,2-phenyl migration to give the more stable benzylic radical, and then cyclises in a 5-*exo* fashion to give the radical intermediate (48). It appears that *endo* ring cleavage is the preferred mode of cleavage under these high dilution conditions, and since the opening is reversible and thus, under thermodynamic control, preferential formation of the 6-membered product is seen. Transannular 1,4 -phenyl migration to give the tertiary allylic radical, from the parent radical of (45), followed by reduction at the sterically more accessible allylic position leads to (44).

Cyclisation of similar methylenecyclopropyl derived malonate radicals was also investigated (scheme 2.13). Malonate (49, X=H) predominately gave the product of 7-*endo* cyclisation (50), along with an inseparable mixture of compounds arising from initial 6-*exo* cyclisation, followed by both *endo* and *exo* ring opening to give (51) and (52) respectively. Cyclisation of systems such as (53 X=SiMe3), however, gave the bicyclo[5.1.0]nonane (54), the product of 7-*endo* cyclisation, as the only

isolable product.

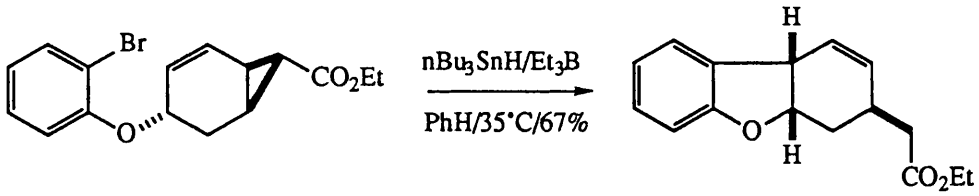


scheme 2.13

2.4 SYNTHETIC APPLICATIONS.

2.4.1 Benzofuran Derivatives.

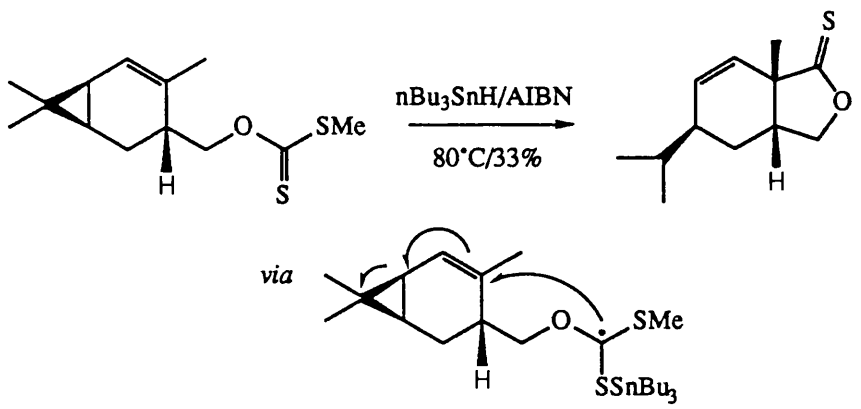
An intramolecular variant of the tandem cyclopropylcarbinyl radical opening/cyclisation strategy has been used by Clive[84] in the preparation of benzofuran derivatives (scheme 2.14).



scheme 2.14

2.4.2 Synthesis of Thionolactones.

In a similar fashion, another intramolecular approach has been developed by a group of Japanese[85] workers *en* route to the synthesis of thionolactones from homo allylic xanthates (scheme 2.15).



scheme 2.15

2.5 CONCLUSION

The foregoing introduction has hopefully demonstrated the versatility of the cyclopropylcarbinyl rearrangement, from its use as a mechanistic probe to its application in the synthesis of natural products.

In summary, therefore, while in monocyclic systems, the *cis*- cyclopropylcarbinyl radical rearranged, *via* cleavage of the more substituted bond as a result of a steric interaction, in contrast, the regioselectivity observed in the *trans* congener is uncomplicated by the existence of such a steric effect. Nevertheless, under controlled conditions, the product arising from cleavage of the more substituted bond can be obtained. However, it is also evident that such systems display a curious kinetic preference for the formation of the product arising from the cleavage of the less substituted cyclopropane bond. Finally, in bicyclic systems, the rigidity is such that orbital overlap with the radical SOMO and the exocyclic bond is favoured on stereoelectronic grounds, and hence, formation of the product derived from the higher energy primary radical is observed.

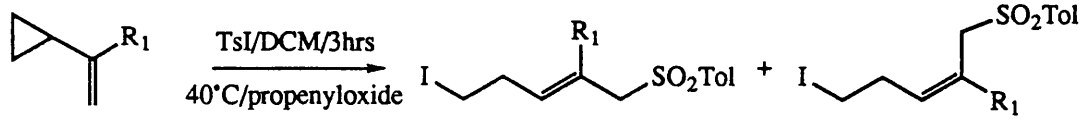
Results and Discussion

Chapter Three

3.1 INTRODUCTION.

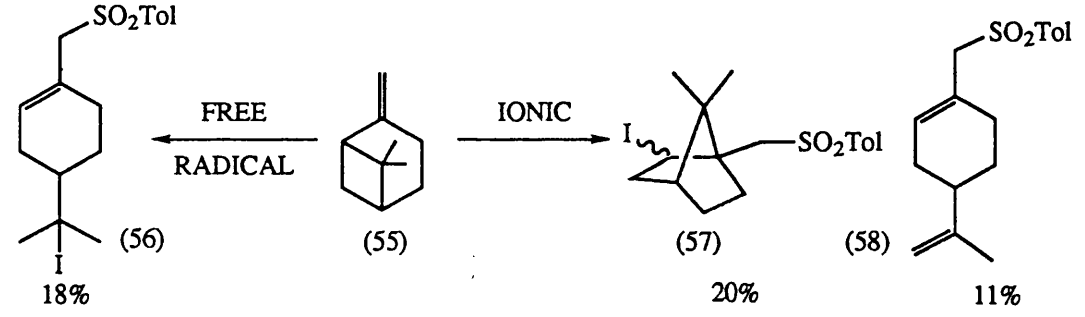
3.1.1 Previous Work Within the Group.

Since this present thesis is concerned primarily with the cyclopropylcarbinyl rearrangement, it is only appropriate to dicuss previous work within our laboratories on the cyclopropylcarbinyl system This has concentrated mainly on three areas, the first being the ring opening of vinyl cyclopropanes with *p*-toluenesulfonyl iodide[86] (scheme 3.1).



scheme 3.1

From a mechanistic stand point, this reaction was originally conceived as a free radical chain process, featuring addition of the *p*-toluenesulfonyl radical to the olefin followed by cyclopropylcarbinyl radical rearrangement and finally capture of the resultant open chain radical by tosyl iodide. To further investigate this point, β-pinene (55) was reacted with tosyl iodide and found to give not only (56) arising from the free radical chain reaction, but also the bicyclo[2.2.1] derivative (57) originating from intermediate carbocation formation followed by Wagner-Meerwein rearrangement, together with the elimination product (58) (scheme 3.2).

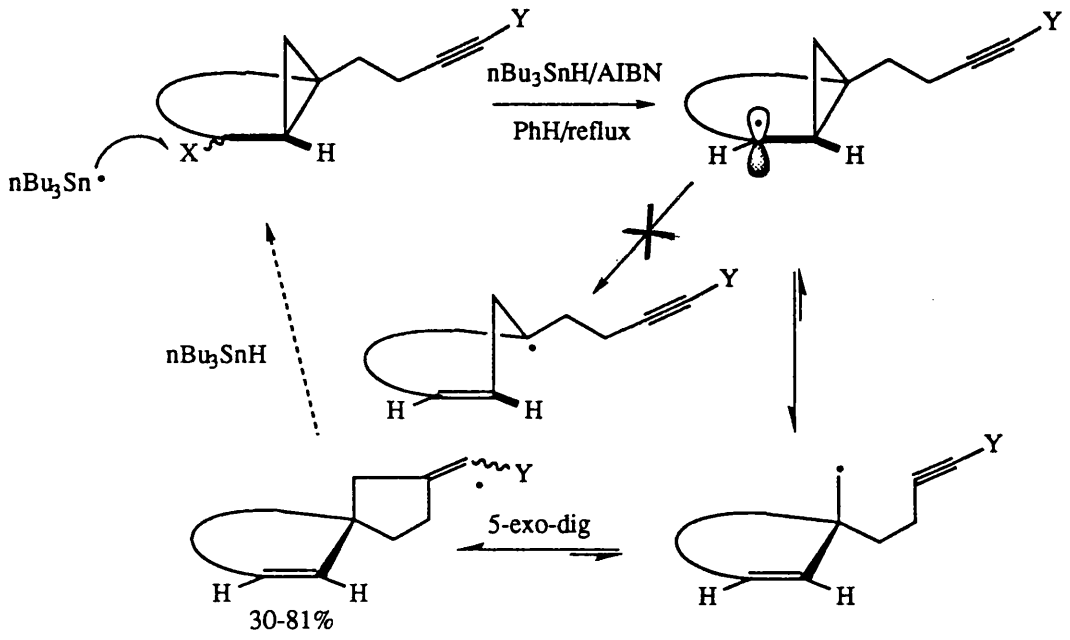


scheme 3.2

Thus, it appears that tosyl iodide can be tuned to display the characteristics of both a free radical and an ionic reagent, since irradiation with a tungsten lamp in petrol at

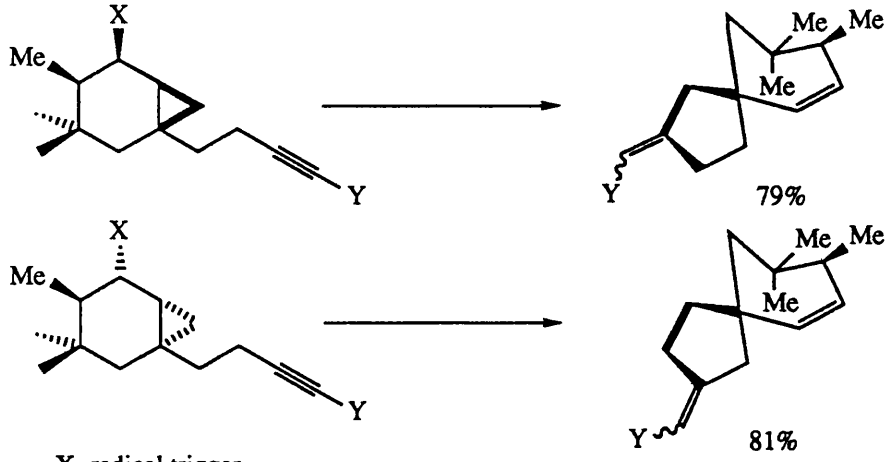
low temperature gave the product arising from the free radical pathway, while in the more polar 1,2-dimethoxyethane and hydroquinone, effective quenching of the radical component of the reaction was found to occur.

Interest also focussed on the development of a tandem cyclopropylcarbinyl rearrangement-5-*exo*-dig-cyclisation strategy towards the stereospecific synthesis of spirocycles[19] (scheme 3.3).



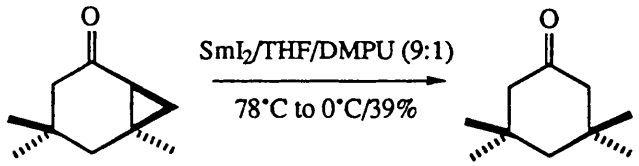
scheme 3.3

In this study, introduction of a stereochemical marker illustrates that reversible ring expansion to seven membered rings did not occur under such reaction conditions (scheme 3.4).



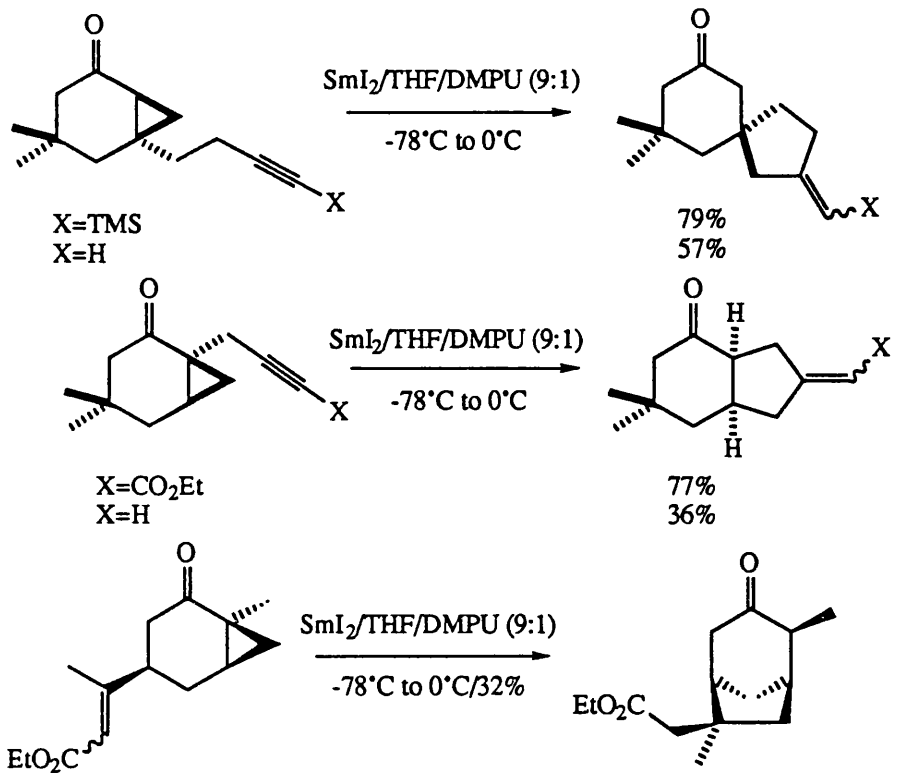
scheme 3.4

More recently, however, Batey and Motherwell[87] have further enhanced this strategy by using a tandem cyclopropyl ketone rearrangement-cyclisation strategy *en* route to the synthesis of spirocycles and bicycles. Samarium(II) iodide was found to be the most effective single electron transfer reagent for the addition to the carbonyl group. Simple bicyclo[4.1.0] systems proceeded as anticipated to give the kinetic product as a result of stereoelectronic control (scheme 3.5).



scheme 3.5

Elaboration of this methodology by the judicious introduction of an appropriately positioned side chain, led to the formation of a variety of bridged bicyclic compounds, as well as spirocycles and hydrindane systems (scheme 3.6).



scheme 3.6

It is clear that the overall process occurs through some form of samarium enolate, and this provides obvious opportunity for subsequent reaction with electrophilies other than simple protons. This aspect will be discussed in greater detail in due course.

The work in this thesis is primarily concerned with the extension and further understanding of the ring opening reactions of both monocyclic and bicyclic cyclopropyl ketone substrates of the type shown below (figure 3.1).

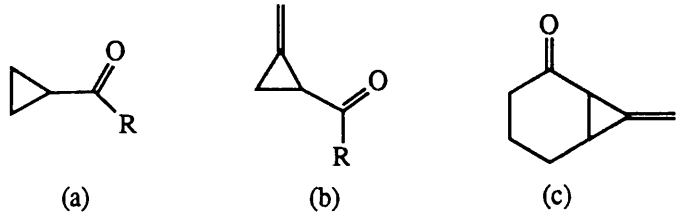
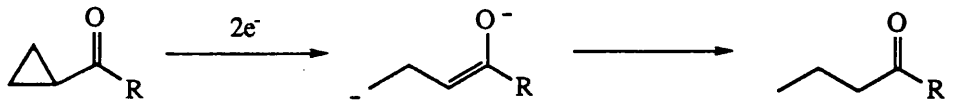


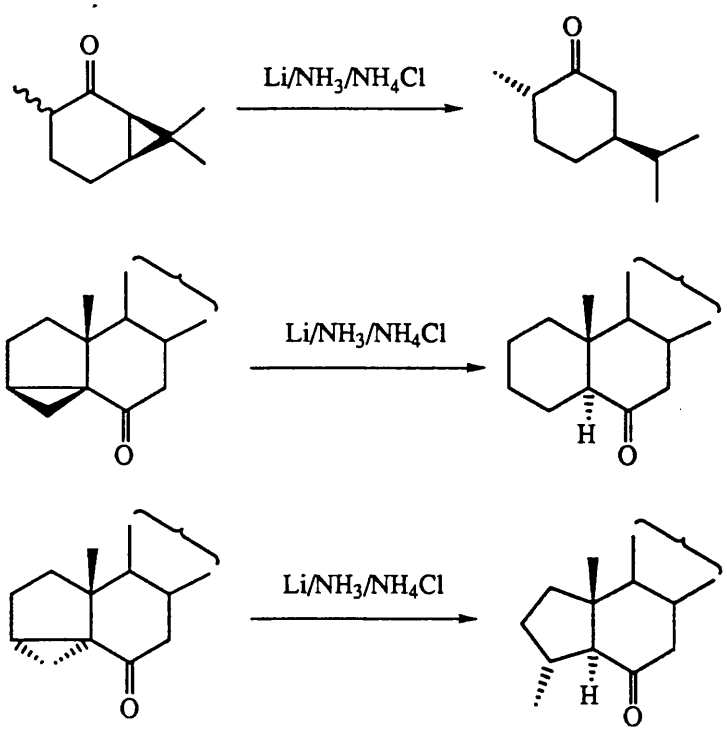
figure 3.1

Firstly, however, it is important to summarise relevant work in this area on the ring opening of systems of type (a) as demonstrated by Dauben over a quarter of a century ago. Cyclopropyl ketones are known to be reduced by M/NH3 systems in an overall two electron process (scheme 3.7).



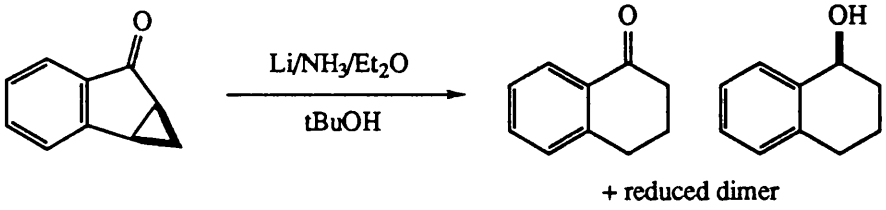
scheme 3.7

If such a process were controlled by thermodynamic considerations, reduction should break the cyclopropane bond leading to the more stable carbanion. Dauben and Norin have illustrated, in some classical work, that in bicyclo[3.1.0] and [4.1.0] ketones, the resultant ring-opening is subject to stereoelectronic rather than thermodynamic control.[88,89] Thus, the bond that best overlaps with the adjacent carbonyl π-system is usually the one that is broken (see section 2.1) (scheme 3.8).



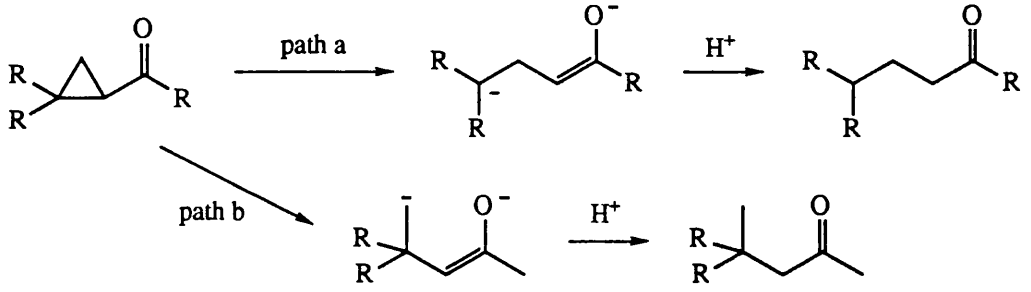
scheme 3.8

In exceptional circumstances, however, electronic factors may override orbital overlap factors, such as when an adjacent aromatic group weakens the endocyclic bond[90] (scheme 3.9).



scheme 3.9

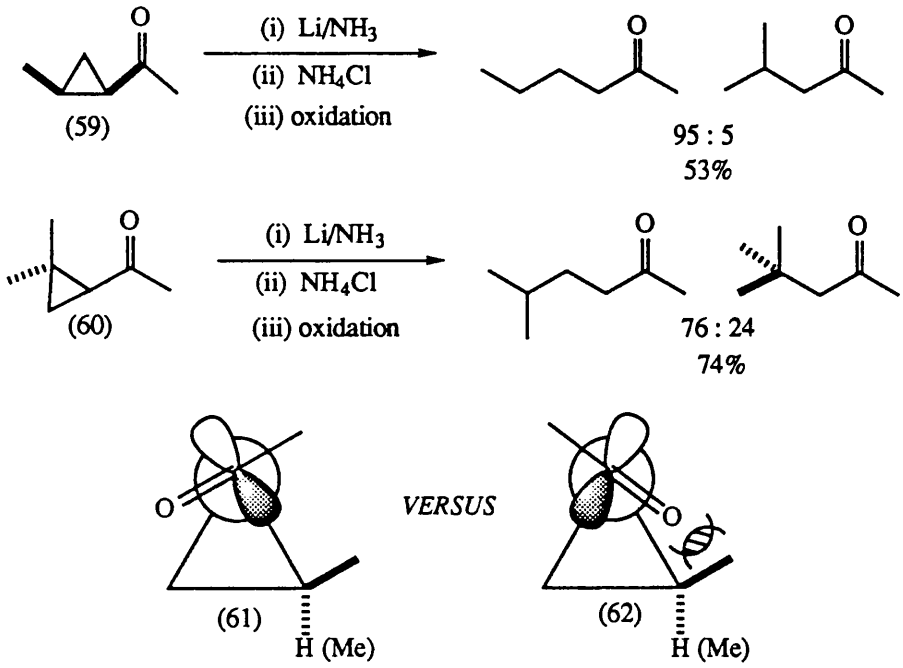
In monocyclic ketones, however, the situation is more intriguing and complex, as might be expected from the earlier discussion (see section 1.4), since both bonds of the cyclopropyl ring, by virtue of free rotation, are free to overlap with the carbonyl π-system. The lithium in liquid ammonia reduction of an unsymmetrically substituted moncyclic cyclopropyl ketone can lead to two different ring opened products (scheme 3.10), either *via* the less stable secondary or tertiary carbanions (path a), or conversely *via* the more stable primary carbanion (path b). Thus, under considerations of simple thermodynamic stability of the dianionic intermediates, the latter should lead to the predominant product.



scheme 3.10

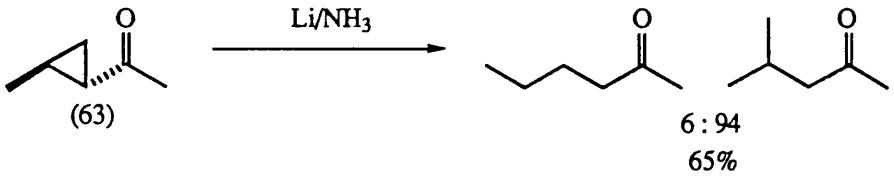
Reduction of the *cis*-substituted ketone (59) and the dimethyl substituted ketone (60) results in preferential opening of the more substituted bond.[91,92] This situation is similar to that of the simple radical induced ring opening of *cis*-cyclopropanes, i.e. cleavage is controlled by stereoelectronic factors, *via* the less hindered conformer

(61) (scheme 3.11).



scheme

Reduction of the corresponding *trans*-substituted ketone (63) is of more interest in that it is relatively independent of any steric or conformational preferences, and should, therefore, be controlled by electronic factors alone. Thus, reduction of (63) gave almost exclusive cleavage of the less substituted bond[91] (scheme 3.12), this has been rationalised in terms of the stability of the intermediate carbanions.

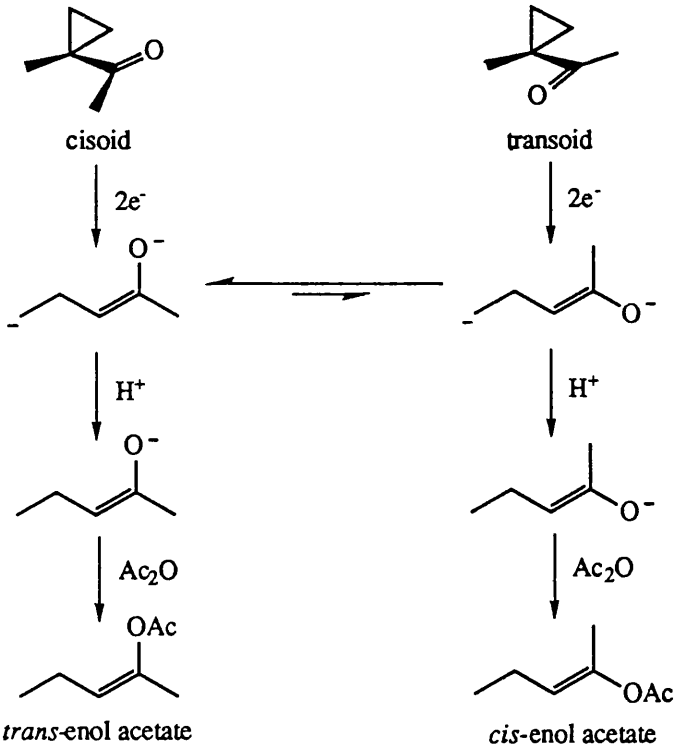


scheme 3.12

Dauben did not elaborate on the exact nature of the mechanism, and merely stated that the data was "consistent with developing carbanion character on the cyclopropyl carbon".

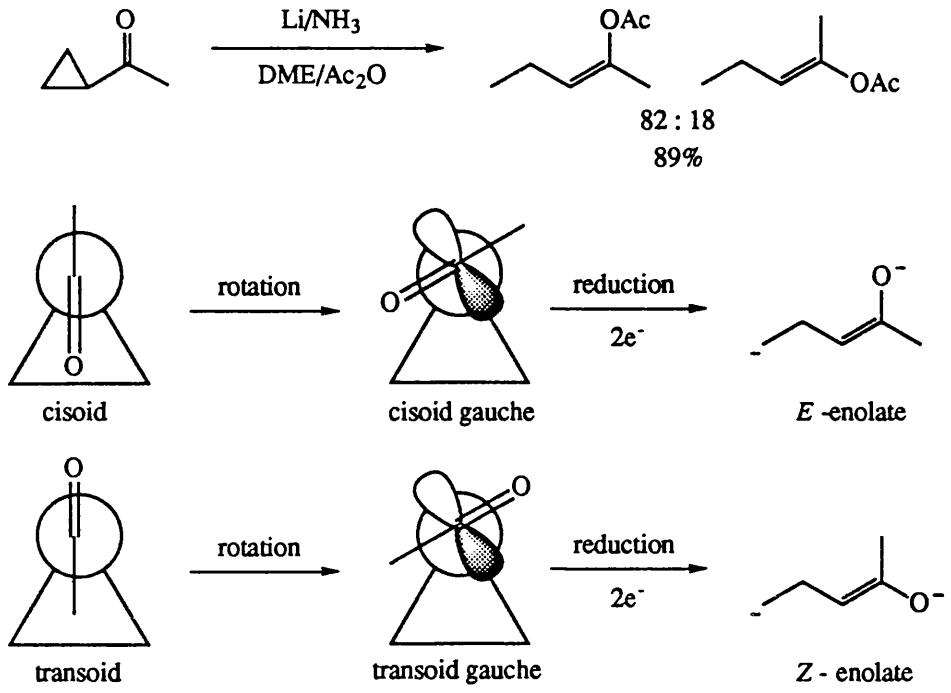
As explained earlier, the lithium in liquid ammonia reduction of conjugated

cyclopropyl ketones can be viewed as an overall two electron process to give a carbanion-enolate intermediate; the dianion generated is sufficiently basic to abstract a proton from ammonia, but the enolate that remains is not basic enough to abstract a second proton from ammonia. It will, therefore, remain until a proton source is added or it is trapped by a second electrophilic reagent such as acetic anhydride. The geometry of the lithium enolate thus formed will be related to the original conformer of the cyclopropylmethyl ketone at the time of ring opening provided that no equilibration of the lithium enolate takes place during the trapping process (scheme 3.13).



scheme 3.13

Dauben and Wolf[93] showed by enolate trapping experiments that the cisoid conformation was reduced in preference to the transoid (scheme 3.14). This is therefore a reflection of the preference for cyclopropylmethyl ketones to exist mainly in such a conformation. We propose that the transoid conformer has associated with it unfavourable steric interactions between the alkyl group of the ketone and the substituents on the cyclopropyl carbons thus, discouraging its existence.

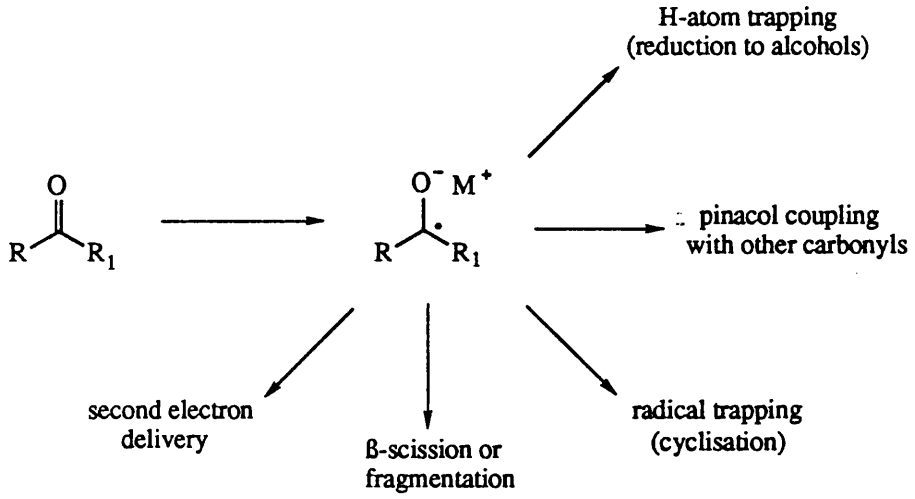


scheme 3.14

Whereas the ring opening reactions of monocyclic cyclopropyl ketones under lithium in liquid ammonia conditions has been extensively studied, no information exists on the analogous reactions using samarium(II) iodide. We felt therefore, that this avenue warranted further investigation. However, before embarking on the analysis of our results in this area, it is appropriate to discuss briefly the generation and fate of ketyl radical anions, and to survey the reduction of the carbonyl group by samarium(II) iodide. These facets can be essentially divided into two somewhat disparate parts.

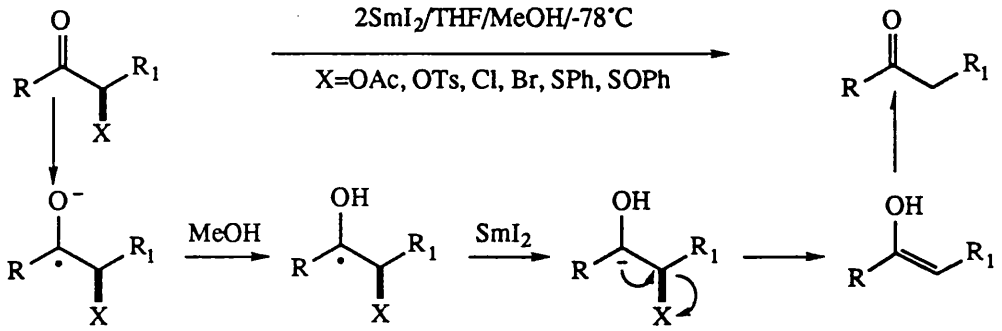
3.2 THE SYNTHETIC UTILITY OF KETYL RADICALS: AN OVERVIEW.

Electron transfer to a carbonyl group (or radical addition) results in the formation of a ketyl radical[94] which can, as a function of its mode of generation and reaction conditions, be subject to a variety of different fates (scheme 3.15).



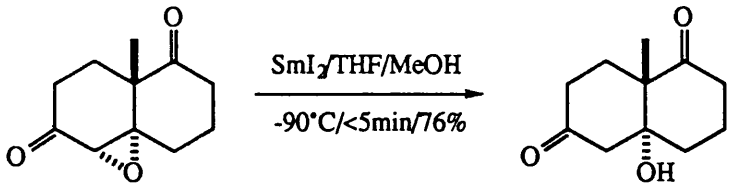
scheme 3.15

The simplest of these is hydrogen atom trapping at the carbon atom usually from the solvent, resulting in overall reduction to the alcohol. Alternatively, the radical centre can undergo pinacol coupling or be trapped by other unsaturated centres, such as an alkene or alkyne, either in an intermolecular or intramolecular fashion (*vide infra*). If the ketyl radical anion has an adjacent leaving group, then the latter can be eliminated, i.e. β-scission. This may be a neighbouring heteroatom or group[95] (scheme 3.16).



scheme 3.16

Alternatively, adjacent carbo- or heterocyclic rings, such as in cyclopropyl or epoxy ketone[96] reductions, can intervene (scheme 3.17).



scheme 3.17

From both a mechanistic and preparative viewpoint, such electron transfer reactions are often complicated by the possibility of delivering a second electron. In this eventuality a ketyl dianion equivalent is formed, thus accessing the manifold of carbanionic reactions. The ketyl radical anion can also react through the oxygen atom, such as in a protonation step; the resultant hydroxy alkyl derivatives are of course still radical in character, but have different properties from their precursor radical anions.

Esr studies of aliphatic ketyl radical anions suggest that approximately 70% of the unpaired spin density is centred on the carbon atom. In resonance terms, this means that the resonance form (64) is a greater contributor than (65) because oxygen is more electronegative than carbon[97] (figure 3.2).

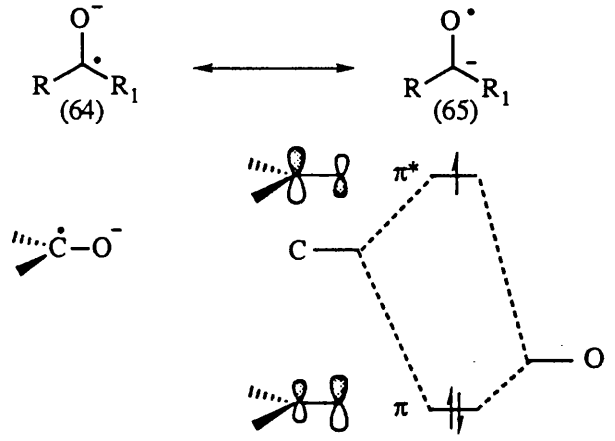


figure 3.2

Using molecular orbital theory, this is just as readily understood in terms of a doubly occupied bonding orbital (π) and a singly occupied *anti*-bonding molecular orbital

(π^*) in which the former has a greater orbital coefficient on the oxygen. Note, however, that the situation is still overall bonding in character, and in the presence of powerful reductants formation of a ketyl will be an energetically favourable process.

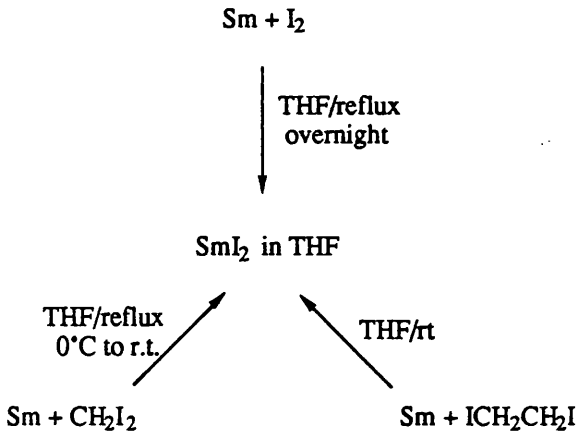
The general principles pertaining to dissolving metal reductions have been outlined in a classic text by House.[94] At that time, lithium and sodium in liquid ammonia were among the most commonly employed systems. Much of the work which will be described in due course will focus in particular on such a reagent system, in addition to the results obtained when samarium(II) iodide was used. The latter reagent is perhaps considered to be the most interesting and important method for ketyl radical anion generation at the present moment in time.

3.3 SAMARIUM(II) IODIDE AS A ONE ELECTRON REDUCTANT.

It is clear from the foregoing introduction, that our interest in the chemistry of the lanthanide reagent samarium(II) iodide stems from the success of previous work carried out within our laboratories on the reduction of bicyclic[4.1.0] ketones. The use of samarium(II) iodide in organic synthesis has been well documented,[98,99,100] and we have therefore restricted our comments in this section to the reduction of the carbonyl functionality.

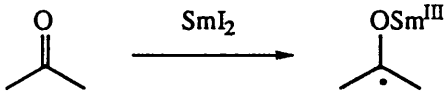
The publication of Kagans's[101] seminal paper in 1980 marked the birth of samarium(II) chemistry for the modern day chemist. The samarium(II) oxidation state is a relatively powerful reductant (Sm^{2+}/Sm^{3+}= -1.55V in aqueous solution),[102] and moreover, it is soluble in THF and is stable so long as it is protected from aerobic oxidation or water. Three methods are important for its synthesis (scheme 3.18); the reaction of samarium metal with 1,2-diiodoethane[102] or diiodomethane,[103] and the reaction of samarium and molecular iodine.[104] The presence of THF is sometimes found to have detrimental results, hence the use of alternative solvents such as acetonitrile,[105] a mixture of benzene and HMPA[106] and

finally tetrahydropyran.[107]



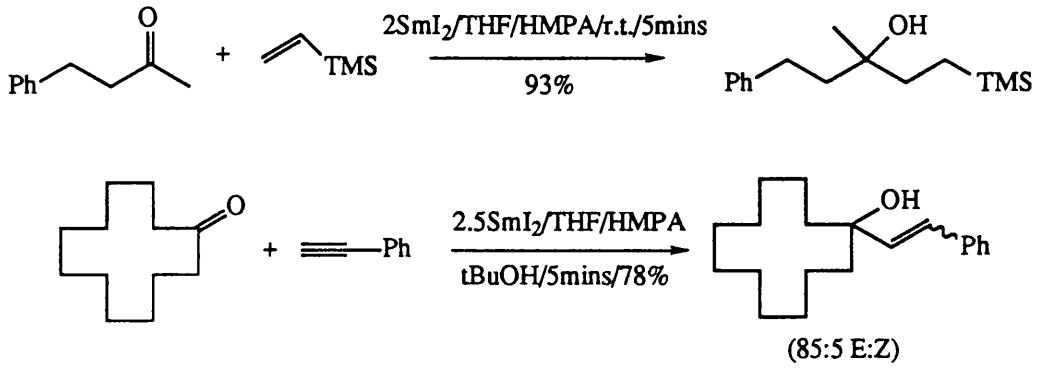
scheme 3.18

Samarium is highly oxophilic and the reduction of carbonyl groups, therefore, proceeds *via* the generation of a samarium(III) ketyl species (scheme 3.19).



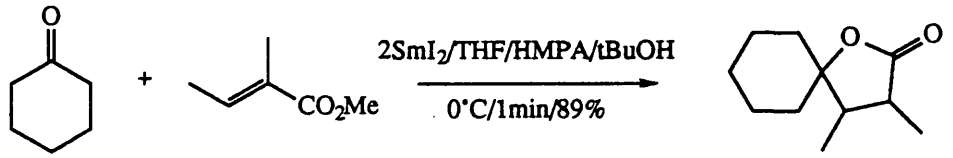
scheme 3.19

Samarium ketyls prepared by the reduction of ketones with samarium(II) iodide, apart from simple reduction to alcohols, can couple intermolecularly with alkenes[108] and alkynes,[109] as demonstrated by Inanaga to give the coupled products in excellent yields (scheme 3.20).



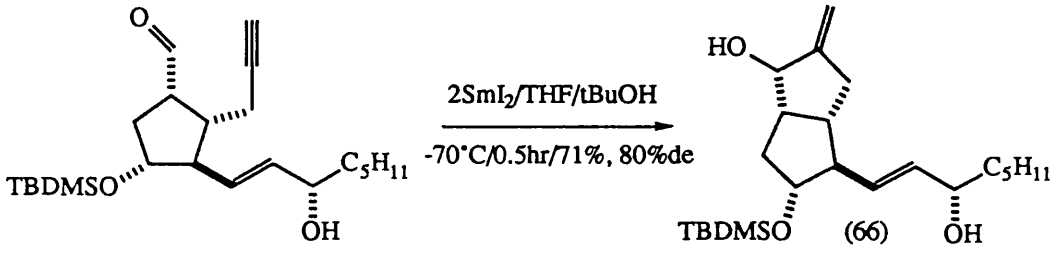
scheme 3.20

Likewise, coupling with α,β -unsaturated esters has led to the synthesis of butyrolactones. The use of HMPA was found to greatly enhance the rates and yields of such reactions[110] (scheme 3.21), although the use of two equivalents of samarium(II) iodide might imply nucleophilic attack of a carbanion on the unsaturated ester.



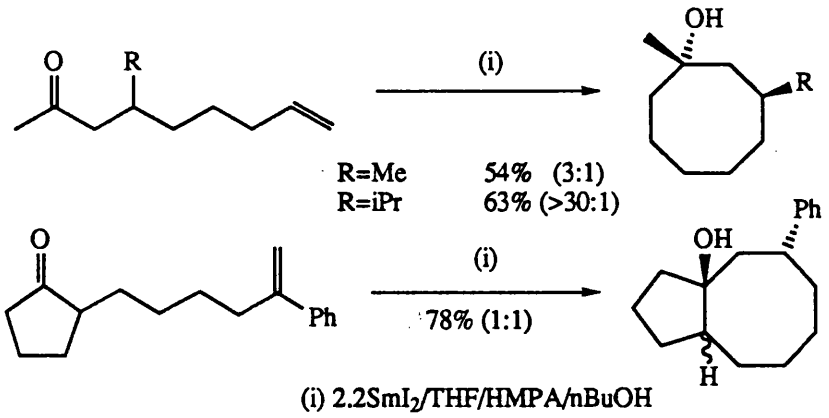
scheme 3.21

This protocol has been used in an intramolecular sense in the synthesis of isocarbacyclin[111] (66) (scheme 3.22).



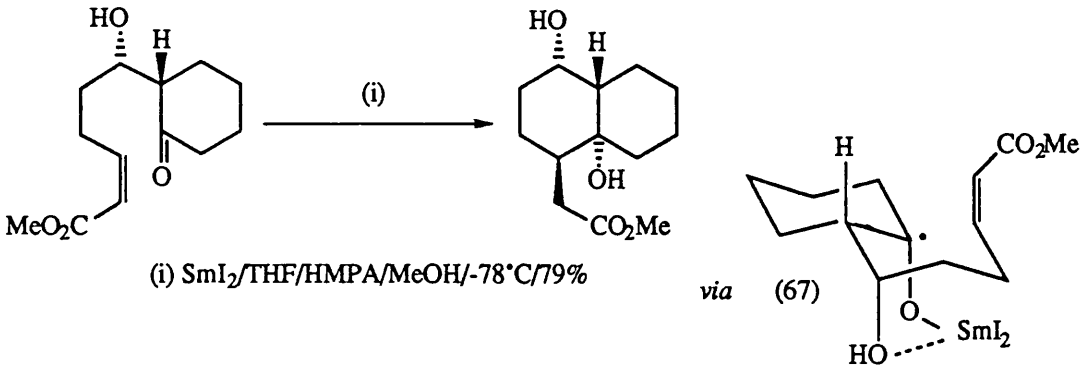
scheme 3.22

Continuing with this intramolecular theme, Molander[112] has very recently reported the synthesis of substituted cyclooctanols by a samarium(II) iodide promoted 8-*endo* radical cyclisation to proceed in good yield (scheme 3.23).



scheme 3.23

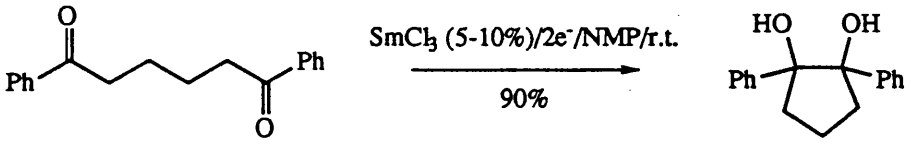
Finally, a group of Japanese[113] workers have reported the formation of the decalin skeleton *via* a hydroxy group directed cyclisation (scheme 3.24). These workers suggest that chelation of the samarium(III) species to the hydroxyl group leads to a six membered intermediate (67) which then adds to the olefin. Since reaction of the *tert*-butyldimethylsilyloxy ketone led to complete recovery of starting material, the chelation plays an important role both in electron delivery and in the cyclisation reaction (scheme 3.24).



scheme 3.24

Samarium(II) iodide has also been shown to be a particularly mild reagent for both intermolecular and intramolecular pinacolic coupling. These reactions require the use of a stoichiometric amount of samarium(II) which is transformed into samarium(III)

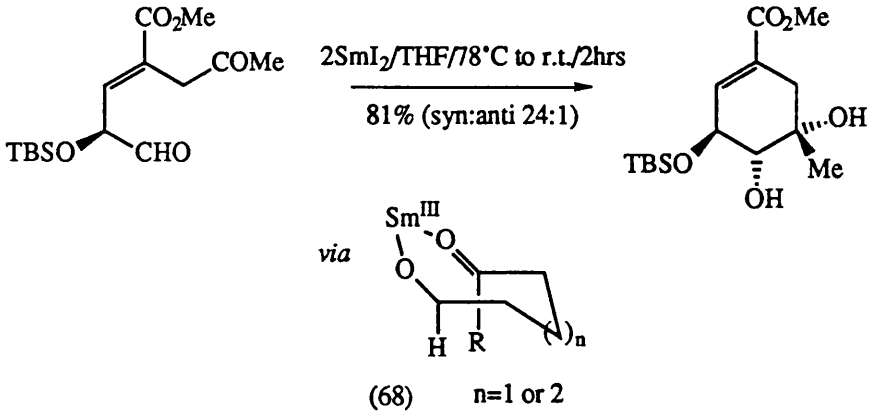
with no further recycling of the latter. Dañach,[114] however, has reported a samarium(III)-catalysed electrochemical dimerization of carbonyl compounds. In the catalytic cycle, $SmCl_3$ (a stable, commercially available compound) is postulated to be electrochemically reduced to a samarium(II) species, which then serves as the active electron transfer reagent (scheme 3.25).



scheme 3.25

This brings to light an intriguing advance in this field, since the preparation of the air and water sensitive samarium(II) iodide is no longer necessary and more importantly, an efficient catalytic procedure has been developed.

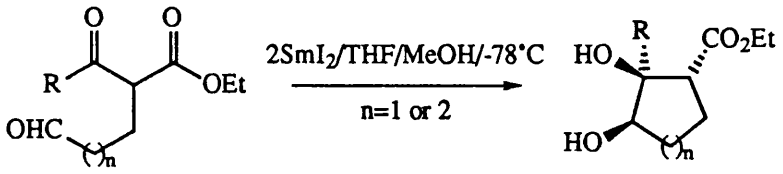
Hanessian[115] has shown that, in intramolecular couplings with SmI_2/THF/tBuOH, near exclusive formation of the *syn*-substituted 1,2-diols is seen as a result of samarium chelation in the transition state (68) (scheme 3.26).



(68) n=1 or 2

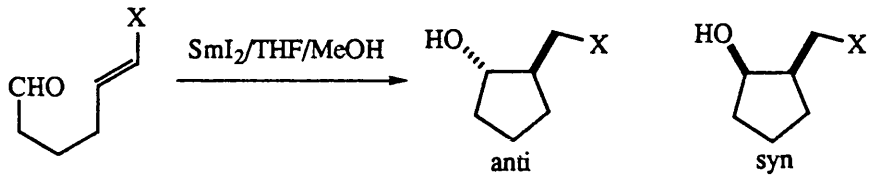
scheme 3.26

Molander[116] has utilised a similar approach, achieving very high levels of diastereoselectivity with β-keto esters and amides (scheme 3.27). Again the formation of the diol proceeds *via* a chelated ketyl-samarium-carbonyl species *via* electron transfer to the most readily reduced functional group, namely the aldehyde.



scheme 3.27

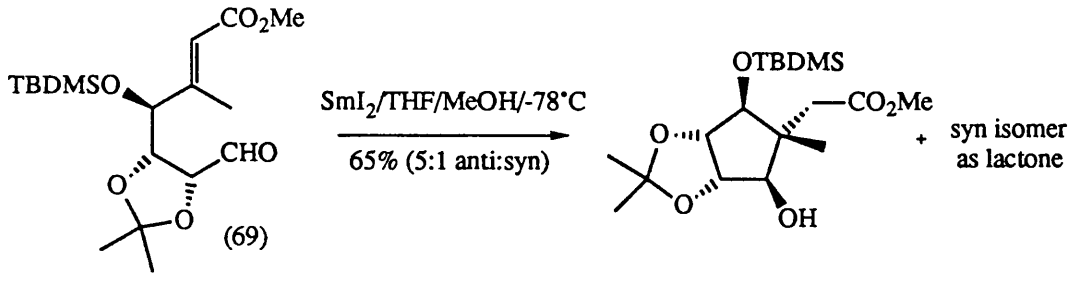
Generally, activated double bonds have proven to be extremely good in 5-*exo* trig samarium ketyl cyclisations[110,117,118] (scheme 3.28).



X=CO_2Et	69%	3.1	1
X=Ph	73%	2.5	1
X=CN	72%	2.7	1
X=H	0%		pinacol dimer

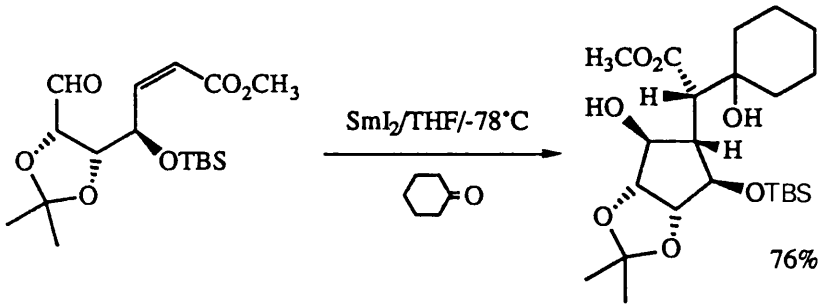
scheme 3.28

Enholm has utilised this aspect in the enantiospecific synthesis of a fragment of the trichothecene anguidine.[119] The aldehyde (69), synthesised from L-(+)-arabinose, when subjected to samarium(II) iodide reduction in the presence of a proton donor, resulted in the formation of a 5:1 mixture of *anti/syn* cyclised products (scheme 3.29).



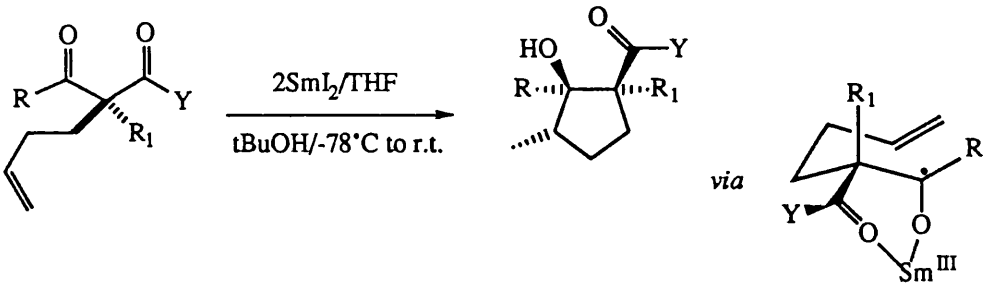
scheme 3.29

More recently, Enholm[120] has elaborated this technology further by the incorporation of a second electrophile to trap the samarium enolate (scheme 3.30).



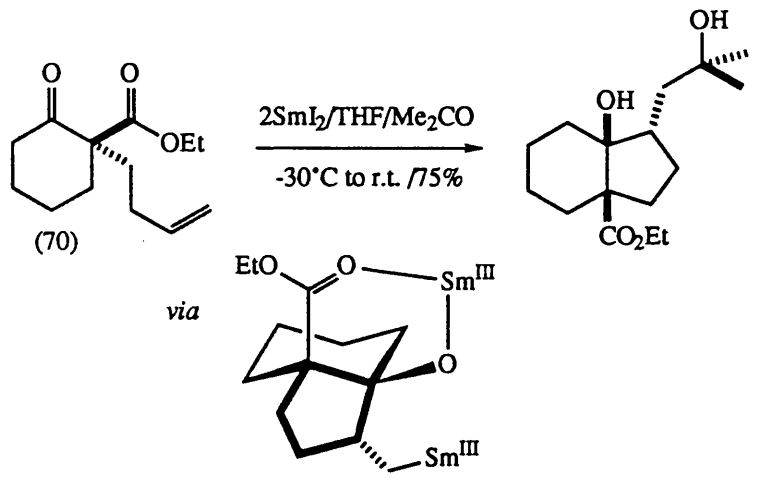
scheme 3.30

Molander and co-workers have reported several elegant examples of intramolecular keto-alkene coupling using their β-keto ester and amide technology, the advantage being that Sm^{3+} chelation results in highly ordered transition states leading to very high diastereoselectivities.[121,122,123] Highly functionalised carbocyclic products are obtained, and in addition, unactivated olefins are sufficiently good radical traps, in contrast to the examples previously discussed (scheme 3.31).



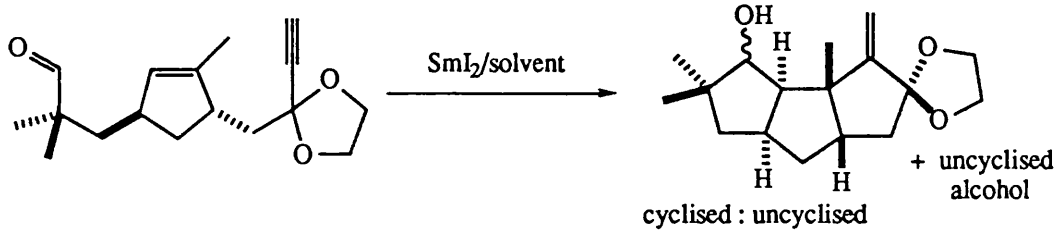
scheme 3.31

Thus, reduction of precursors of the type (70) leads to the formation of cyclised products with excellent stereocontrol over three contiguous centres. Practically, these reductions are carried out by adding the substrate to samarium(II) iodide in the presence of a proton donor. The transient organosamarium intermediates can also be trapped by suitable electrophilies (scheme 3.32).



scheme 3.32

Curran[124] has demonstrated the synthetic ability of samarium(II) iodide promoted ketyl-olefin cyclisations in the syntheses of (±)-hypnophilin and (±)-coriolin (scheme 3.33). The use of HMPA or DMPU as additives was essential for the success of the tandem cyclisation. Although these additives have repeatedly been shown to enhance reaction rates and selectivities, the exact nature of their effect remains a mystery. The entire process requires approximately 1.3 equivalents of samarium(II) iodide, suggesting that the cyclisation is a one electron process.

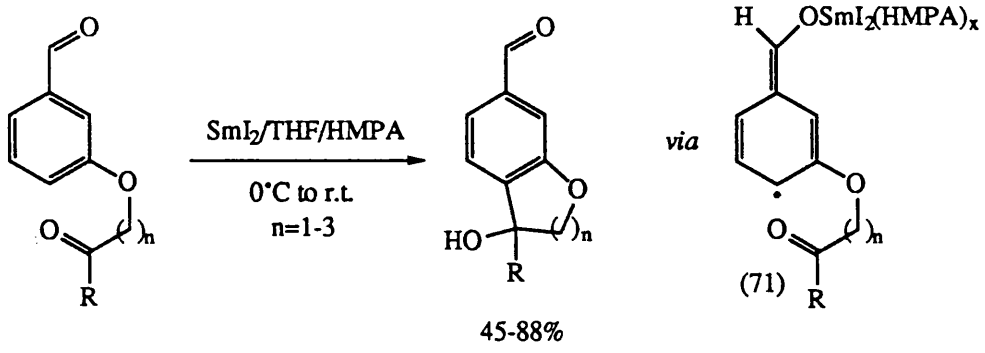


cyclised : uncyclised

THF / HMPA	20 : 1	63%	91 : 9
THF / DMPU	20 : 1	69%	96 : 4

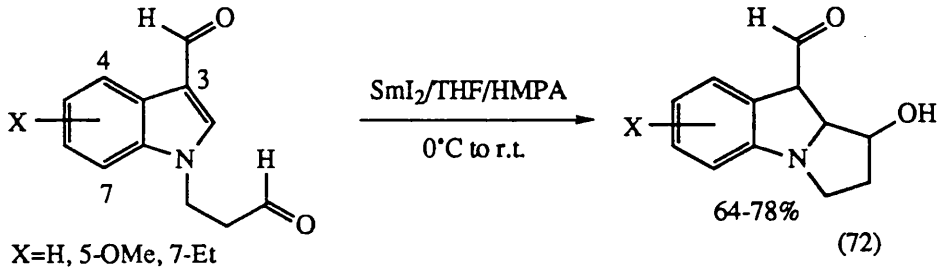
scheme 3.33

A novel intramolecular coupling reaction of *meta*-substituted benzaldehydes has recently been reported to generate substituted benzofurans in excellent yields[125] (scheme 3.34). The initially formed "ketyl radical" (71) is prevented from taking up hydrogen or proceeding to a subsequent pinacol coupled product by the presence of HMPA molecules, and hence, attack occurs at the *para* position.

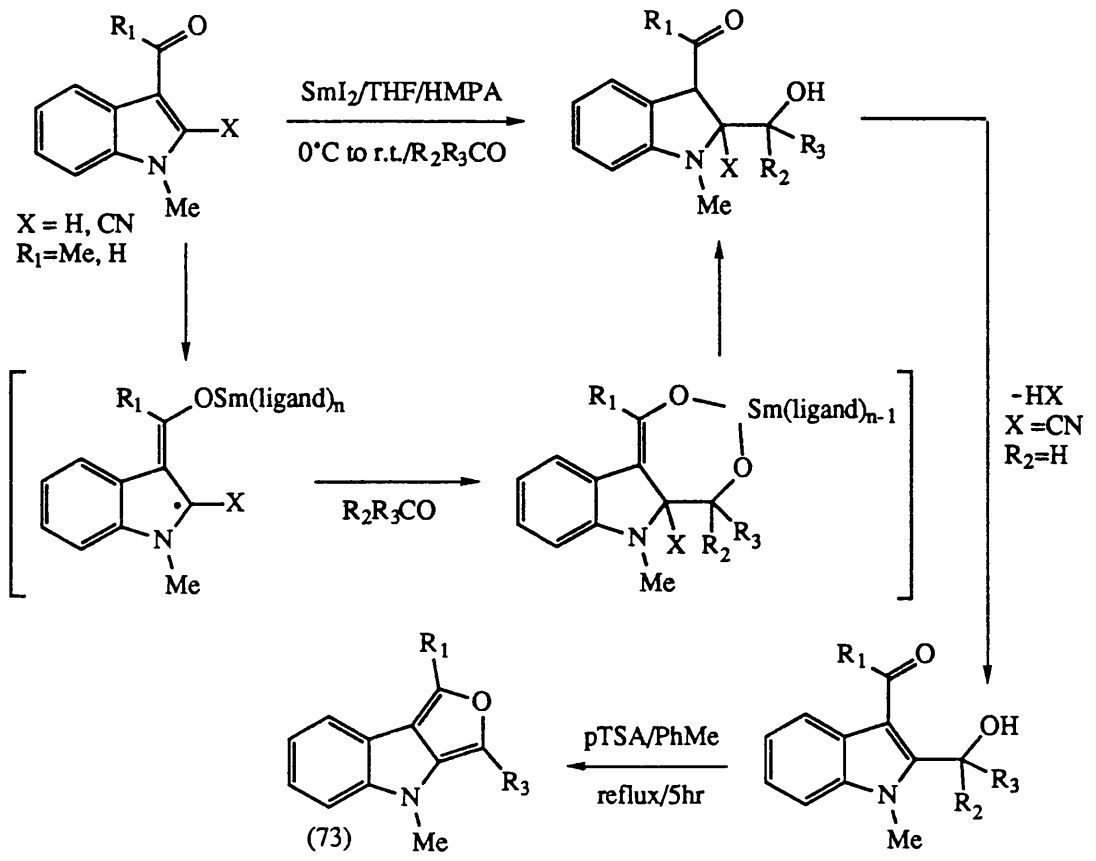


scheme 3.34

A more creative contribution by this group has led to the syntheses of pyrrolidinoindoles (72) (scheme 3.35) and to furoindoles (73) (scheme 3.36).[126]

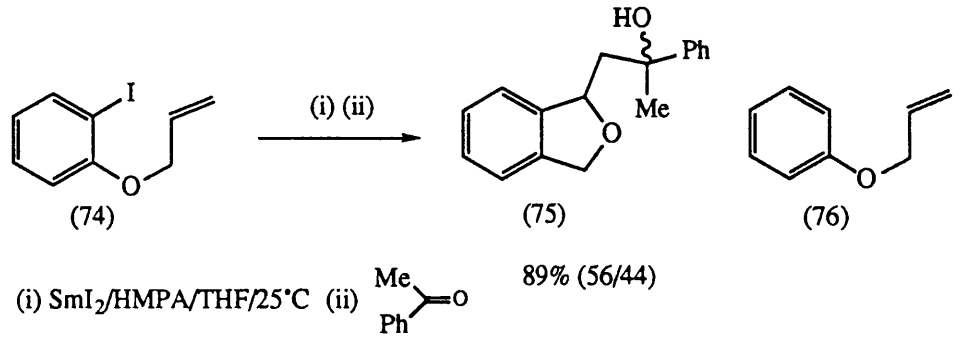


scheme 3.35



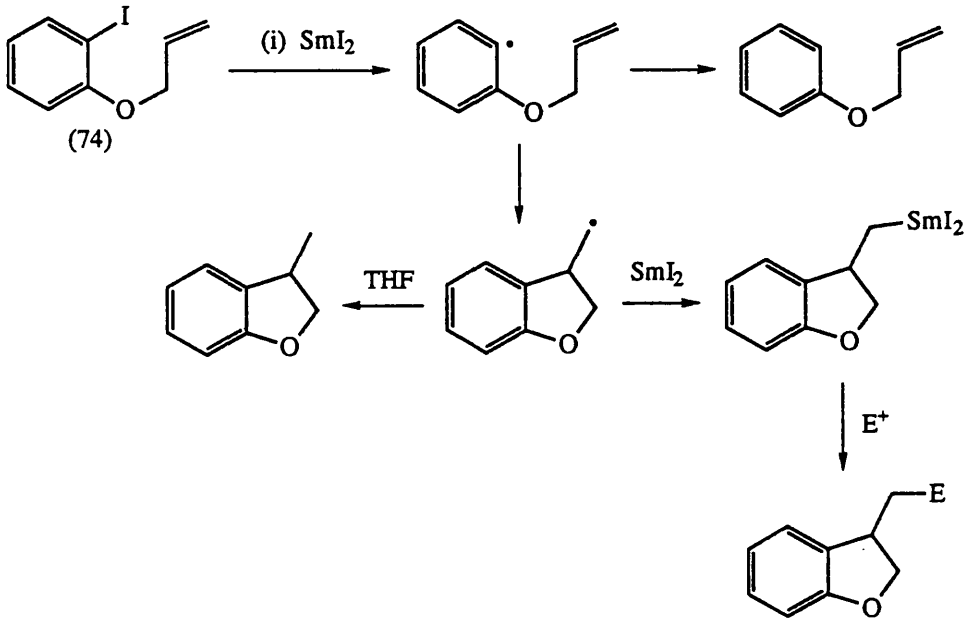
scheme 3.36

The samarium(II) iodide mediated Barbier reaction has received much attention over the last decade. Studies by Curran,[127] in particular have demonstrated that organosamarium intermediates are indeed involved. Reduction of 1-allyl-2-iodophenol (74) with excess samarium(II) iodide proceeded in the presence of HMPA to generate the expected cyclised product (75) as well as trace amounts of the reduced product (76) (scheme 3.37).



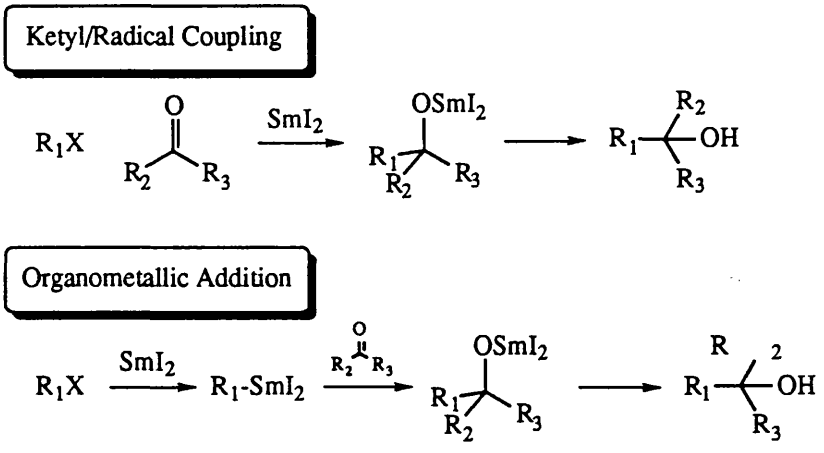
scheme 3.37

The mechanism proposed below suggests the intermediacy of organosamarium intermediates following radical cyclisation (scheme 3.38).



scheme 3.38

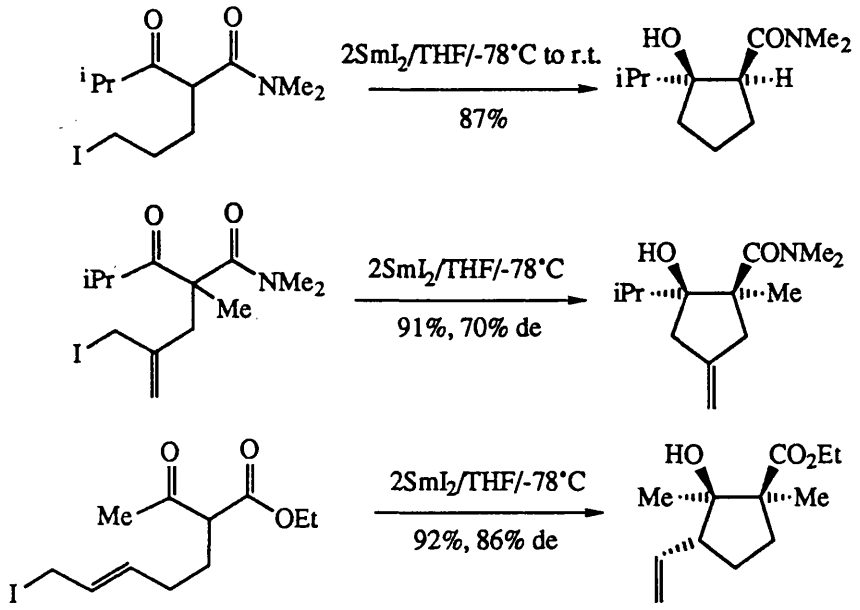
Control experiments indicated that (74) was completely consumed prior to addition of the electrophile (aldehyde or ketone), thus (75) could not possibly arise from the ketyl/radical coupling mechanism (scheme 3.39).



scheme 3.39

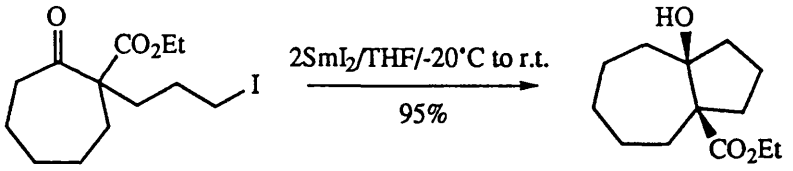
Likewise, Molander[128] has utilised both β-keto esters and amides *en* route to highly functionalised and stereodefined carbocyclic ring systems (scheme 3.40). As

expected, the high oxophilicity of the samarium allows both carbonyl groups to coordinate, forming a six membered template which in turn directs the coupling, as we have seen previously.



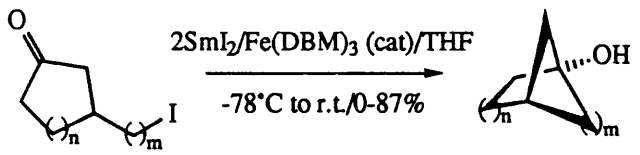
scheme 3.40

Molander[129] has also shown that samarium(II) iodide can be utilised in the annulation of 5 and 6 membered ring products (scheme 3.41). The reactions were found to proceed with considerable diastereoselectivity when substituents were placed at the α-position of the cycloalkanone.



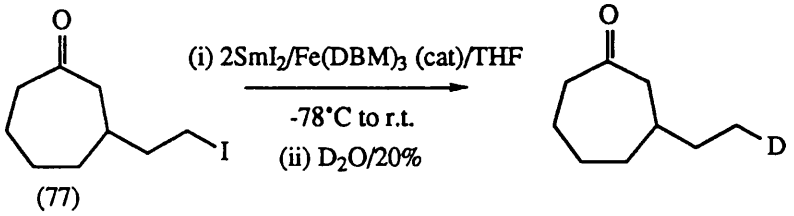
scheme 3.41

Molander and McKie[130] have shown that by the slow addition of iodoketones to samarium(II) iodide (0.015M in THF) in the presence of a tris-(dibenzoylmethido)iron(III) catalyst, the formation of bicyclo[n.m.1]alkan-1-ols and even highly strained [2.1.0] systems is possible (scheme 3.42).



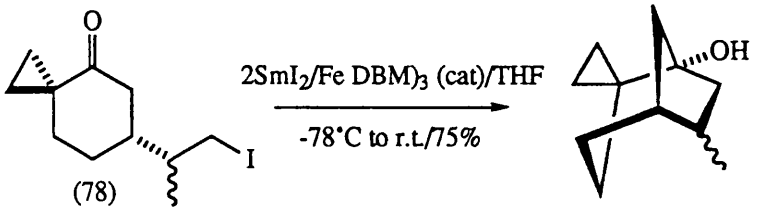
scheme 3.42

The intermediacy of an organosamarium species, formed *via* initial electron transfer to the carbon-iodine bond, was proposed on the grounds that when 3-(2-iodoethyl)cycloheptanone (77) was treated with samarium(II) iodide, followed by a D_2O quench, 3-ethylcycloheptanone was isolated with >90% deuterium incorporation (scheme 3.43).



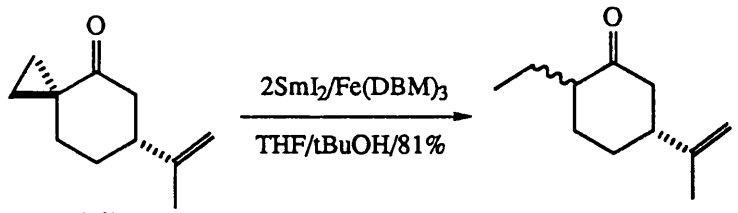
scheme 3.43

The involvement of intermediate ketyl radicals was further discounted since the reduction of the spirocyclic cyclopropyl iodoketone (78) under the above conditions occurred without ring opening (scheme 3.44).



scheme 3.44

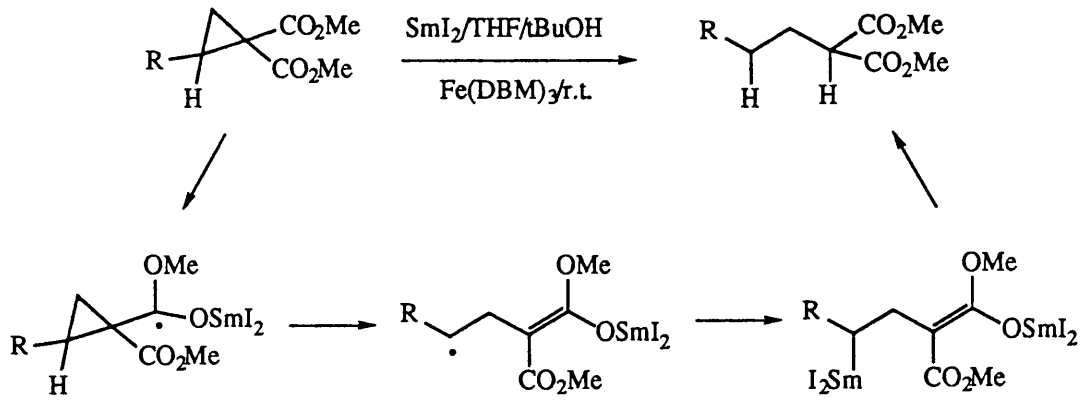
In the absence of the more reactive alkyl iodide, a ketyl was generated and hence,ring opening of the spirocyclic cyclopropyl ketone (79) was seen (scheme 3.45). This single mechanistic example was carried out in the presence of *tert*-butanol as a proton donor, thus,making any samarium enolate chemistry impossible.



(79)

scheme 3.45

Finally before we present our own findings in this area, a recent publication by Imamoto[131] which appeared at a late stage during our own work is worthy of comment. These Japanese workers examined the reductive ring opening of a series of cyclopropane carboxylic esters. Surprisingly, HMPA was not effective as an additive. However, use of a catalytic amount of Fe(DBM)3 resulted in excellent yields and short reaction times (scheme 3.46). The reaction proceeds *via* prior electron transfer to one of the otherwise inert ester groupings. Even when R=Me, only one regioisomer was obtained, namely dimethyl propylmalonate, the product arising from thermodynamic control. As we shall see in due course, this is in accord with our own findings.

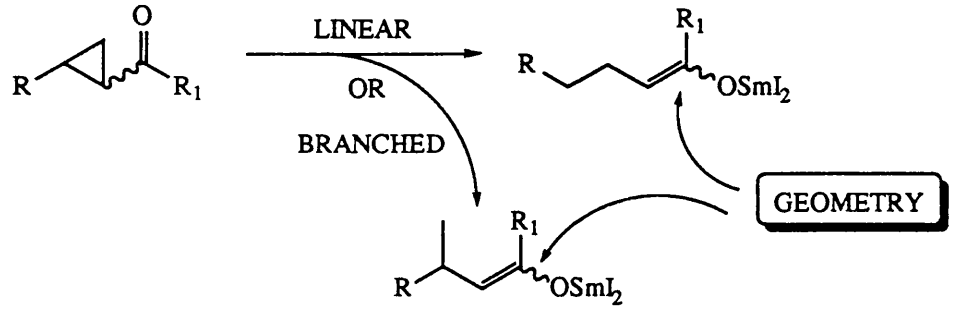


scheme 3.46

3.4 SYNTHETIC STUDIES

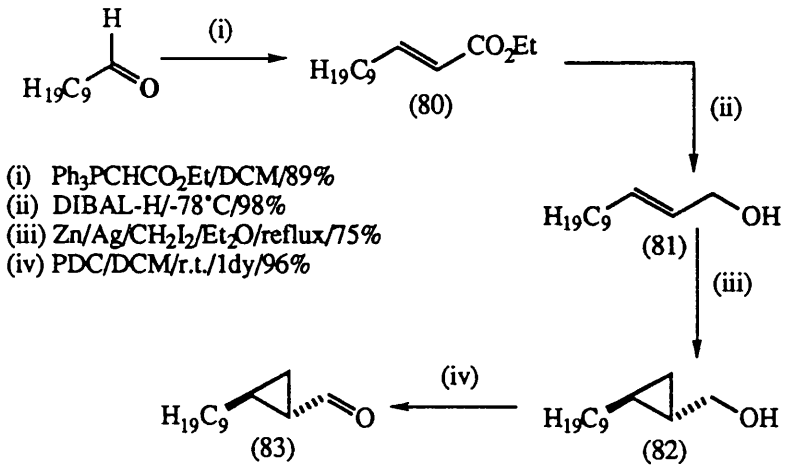
From the foregoing overview, it is apparent that samarium(II) iodide is able to mediate a large spectrum of reactions, and hence we thought it to be the reagent of

choice for our study. The factors of particular interest to us concerning the ring opening of cyclopropyl ketones are summarised below (scheme 3.47). Our initial goal was to examine how the stereochemistry and nature of the substituents around the starting ketone influenced the ring opening, and concomitantly, to see how the resultant enolate geometry varied as a function of the presumably preferred conformation of the ketone.



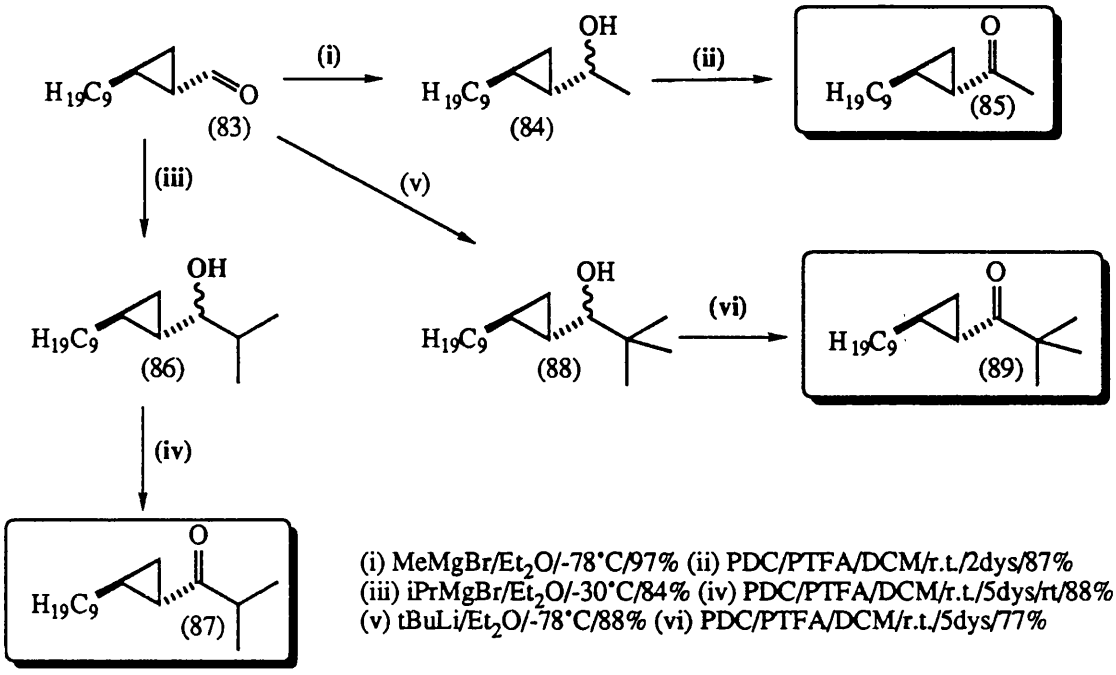
scheme 3.47

In the first instance we elected to study the ring opening of a series of *cis*- and *trans*-substituted monocyclic cyclopropyl ketones. The requisite *trans*- precursors were readily constructed using standard methodology from the cyclopropyl aldehyde (83), which in turn was prepared in four steps from decanal (scheme 3.48). Thus, Wittig reaction of decanal with the stabilised (carboethoxymethylene)triphenylphosphorane ylid gave the α,β-unsaturated ester (80) in 89% yield as an approximately 95:5 mixture of E/Z isomers. Diisobutylaluminium hydride (DIBAL-H) reduction then gave the allylic alcohol (81) in 98% yield. A hydroxyl-directed Simmons-Smith cyclopropanation of the latter using a modified zinc-silver couple,[132] which has been reported to give improved yields and shorter reaction times, then gave the cyclopropylcarbinol (82) in 75% yield. Finally, pyridinium dichromate (PDC) oxidation provided the key intermediary aldehyde (83) in 96% yield.



scheme 3.48

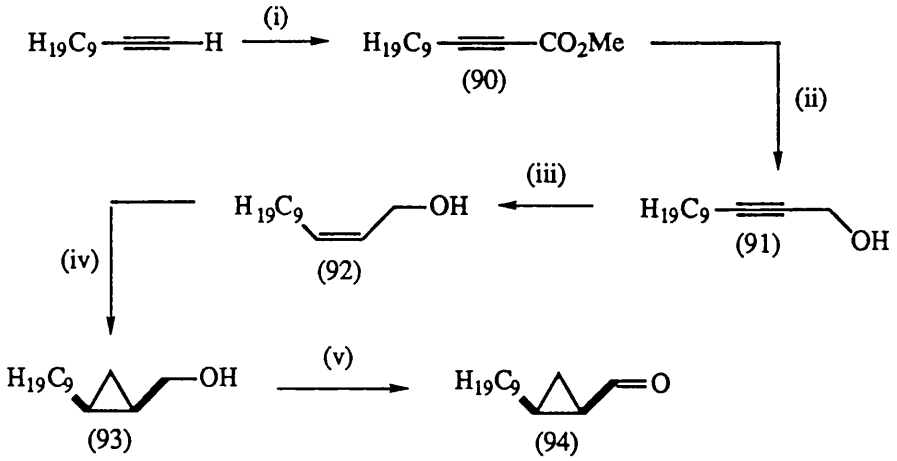
Dropwise addition of methylmagnesium bromide to a solution of the aldehyde (83) at -78°C afforded the desired secondary alcohol (84) as a mixture of diastereomers in a combined yield of 97%. PDC oxidation on this occasion was carried out in the presence of pyridinium trifluoracetate (PTFA).[133] The use of a small amount of this reagent allows for the use of a minimal quantity of PDC, and maintains a satisfactory reaction rate as the oxidation nears completion. In this fashion, the desired *trans*-derivative (85) was obtained in 87% yield. The corresponding *iso*-propyl and *tert*-butyl congeners were synthesised in similar fashion. Thus, inverse addition of the aldehyde to *iso*-propylmagnesium chloride at -30°C yielded the corresponding alcohol (86) as a separable mixture of diastereomers in 84% yield and subsequent oxidation over a 5 day period gave the desired ketone (87) in 79% yield. *tert*-Butyllithium addition to the aldehyde at -78°C afforded the desired alcohol (88) as a separable mixture of diastereomers in 88% yield and again PDC/PTFA oxidation gave the *tert*-butyl ketone (89) in 77% yield (scheme 3.49).



(i) MeMgBr/Et_2O/-78°C/97% (ii) PDC/PTFA/DCM/r.t./2dys/87%
(iii) iPrMgBr/Et_2O/-30°C/84% (iv) PDC/PTFA/DCM/r.t./5dys/rt/88%
(v) tBuLi/Et_2O/-78°C/88% (vi) PDC/PTFA/DCM/r.t./5dys/77%

scheme 3.49

Likewise, the requisite *cis*-precursors were constructed from the analogous *cis*-cyclopropyl aldehyde (94) which was prepared as outlined below (scheme 3.50).

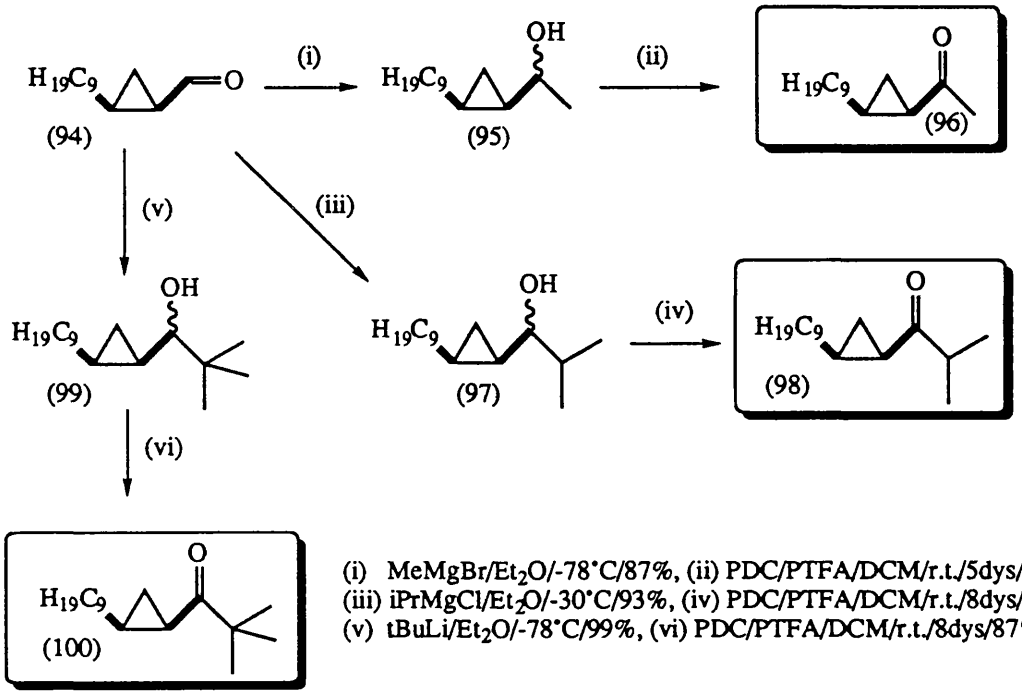


(i) nBuLi/MeOCOCl/-78°C/100% (ii) DIBAL-H/r.t./PhMe/92%
(iii) Pd/C/quinoline/H_2/-20°C/PETROL/100% (iv) Zn/Ag/CH_2I_2/Et_2O/reflux/42%
(v) PDC/DCM/r.t./1dy/96%

scheme 3.50

Thus, deprotonation of undecyne by *n*-butyllithium at -78°C followed by quenching with methylchloroformate yielded the alkynoate ester (90) in quantitative yield. DIBAL-H reduction under the usual conditions gave the propargylic alcohol (91) in

92% yield. The latter, upon Lindlar hydrogenation was quantitatively converted to the *(Z)*-alkene (92). Hydroxyl directed Simmons-Smith cyclopropanation gave the cyclopropylcarbinol (93) in 42% yield, and in a similar fashion to the *trans*-isomer above, PDC oxidation gave the desired aldehyde (94) in 96% yield. An identical strategy was then used for the construction of the ketonic *cis*- counterparts (scheme 3.51).



(i) MeMgBr/Et_2O/-78°C/87%, (ii) PDC/PTFA/DCM/r.t./5dys/99%
(iii) iPrMgCl/Et_2O/-30°C/93%, (iv) PDC/PTFA/DCM/r.t./8dys/87%
(v) tBuLi/Et_2O/-78°C/99%, (vi) PDC/PTFA/DCM/r.t./8dys/87%

scheme 3.51

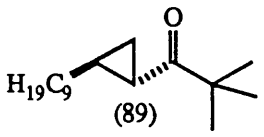
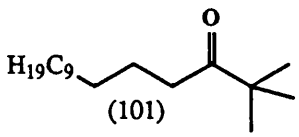
With our precursors in hand we were ready to begin a study of their radical ring-opening reactions with samarium(II) iodide. The experimental protocol followed throughout this investigation involved the dropwise addition of a solution of samarium(II) iodide (0.1M solution in THF, commercially available from Aldrich chemicals) to a solution of the cyclopropyl ketone in THF/DMPU (9:1) at room temperature under argon until a permanent mauve/purple colouration was obtained (i.e. titration). Throughout these studies variable quantities of samarium(II) iodide were often required for complete reaction and the end point was often difficult to pin-point, since the formation of the mauve/purple colouration was not sharp. Moreover,

even though a permanent colouration formed, sometimes tlc examination at this stage showed that starting material remained. The reactions were always performed as carefully as possible, under a positive flow of argon with oven-dried glassware.

This method is essentially based on that described by Curran.[124] It should be noted, that while samarium(II) iodide in THF is a dark-blue coloured, air and water sensitive solution, addition of THF/DMPU leads to a heterogeneous mauve-purple coloured reagent mixture. The exact nature of this solution is still unknown, but presumably some form of samarium(II) iodide-DMPU complex is the active species. We opted to use DMPU as opposed to the more commonly used HMPA, because of the carcinogenic nature of the latter. HMPA[134,135] ligated to samarium(II) iodide has been shown to be a powerful reductant, and it is well known that electron donating ligands increase the reduction potential of low valent metals. The co-ordination sphere of samarium can accommodate many ligands, thus the use of HMPA leads to an acceleration of these reactions. DMPU,[136] similarly to HMPA, acts as mediator for electron transfer and also as an efficient dipolar aprotic cation solvator.

3.4.1 Samarium(II) Iodide Induced Ring Opening of the Trans Series.

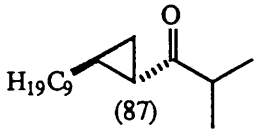
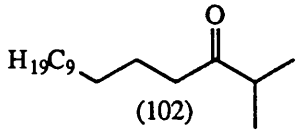
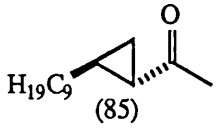
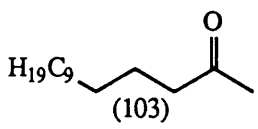
We initiated our studies by investigating the ring opening of the most hindered *tert*-butyl substituted derivative (89), in order to probe what effect, if any, the bulk of the substituent on the carbonyl carbon would have on the outcome of the reaction. Thus, it was found that samarium(II) iodide induced ring opening of the system in question gave the linear ketone (101) as the sole isomer to be isolated in 79% yield (table 3.1).

KETONE	PRODUCT	YIELD%
 (89)	 (101)	79

SmI_2/THF/DMPU (9:1) /r.t./5mins

table 3.1

In due course, we turned our attention to the sterically less demanding *iso*-propyl (87) and methyl (85) substituted systems. Reduction under the usual conditions, namely dropwise addition of a solution of samarium(II) iodide to the substrate in THF/DMPU at room temperature under argon, also gave only the straight chain ketones (102) and (103) in 77% and 62% yield respectively (table 3.2).

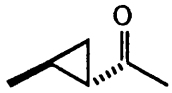
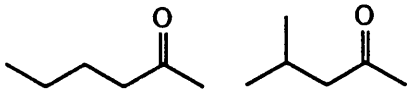
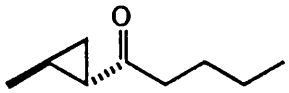
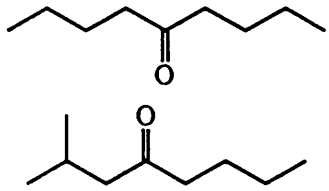
KETONE	PRODUCT	YIELD%
 (87)	 (102)	77
 (85)	 (103)	62

SmI_2/THF/DMPU (9:1) /r.t./5mins

table 3.2

These results were initially a source of some puzzlement, since they differed markedly from those obtained with similar *trans*-cyclopropyl ketones using such varied systems as lithium in liquid ammonia[91] (*vide supra* scheme 3.12), tributylstannane[137] and zinc-chlorotrimethylsilane.[20] In contrast to our findings, Dauben[91] has found that the lithium in liquid ammonia reduction of *trans*- 2-methylcyclopropyl alkyl ketones proceeded *via* cleavage of the less substituted bond

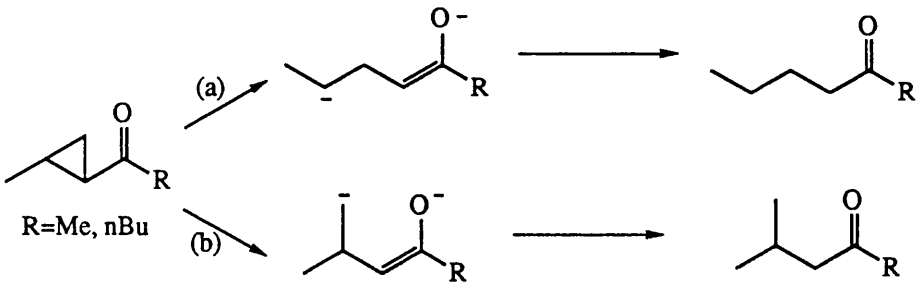
(table 3.3).

KETONE	PRODUCT	RATIO
		6 : 94
		12 : 88

(i) Li/NH_3 (ii) NH_4Cl

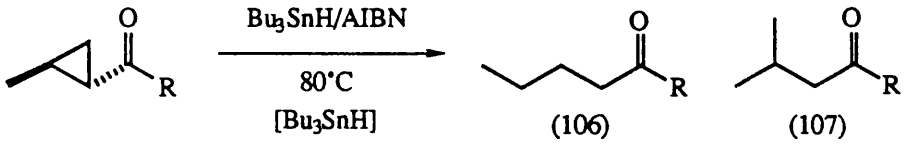
table 3.3

Since free rotation of the carbonyl group permits "equal" π–overlap to either of the cyclopropane bonds, the predominant influence here appears to be the relative thermodynamic stability of the carbanionic intermediates generated. In other words, the reaction proceeds *via* formation of the primary carbanion (path b) (scheme 3.51).



scheme 3.51

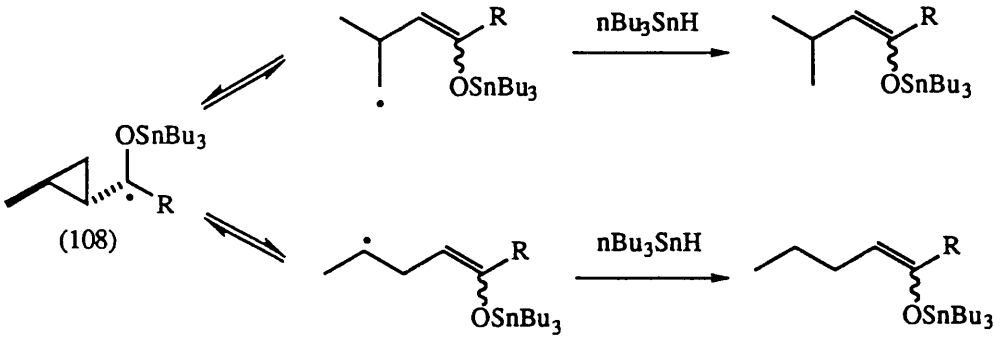
Likewise, in contrast to our findings, addition of tributylstannane to similar *trans*-substituted systems at 80°C, also led to predominant formation of the branched ketones (scheme 3.52). However, concentration was found to be an important factor here.



(104) R=Me	Neat	25%	75%
(105) R=iBu	0.1M	42%	58%
(105) R=iBu	0.2M	76%	24%

scheme 3.52

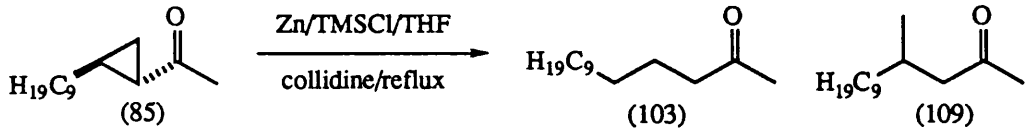
The dependence upon stereochemistry of the reactant is in accord with the discussion of section 1.4, i.e. *trans-* (104), which is free from any conformational bias, opened mainly *via* the less substituted bond, to give a primary radical which was rapidly trapped to give ketone (107, R=Me). Reduction of *trans-* (105) in benzene, however, gave the ring opened products, the proportion of which were dependent upon the concentration of the stannane. At high concentration, primary radicals are rapidly trapped, at relatively low concentrations, however, the radical escapes capture for long enough to approach equilibration by reversible ring closing and ring opening through a cyclopropylcarbinyl radical such as (108) (scheme 3.53). Hence, a reversal of regioselectivity is evident (scheme 3.52).



scheme 3.53

Finally, before discussing our results, work carried out in our laboratories on the ring-opening of a similar system with zinc-chlorotrimethyl silane deserves attention. Reduction of (85) gave approximately a 1:1 mixture of the ring opened ketones (103) and (109) in a combined yield of 62% (scheme 3.54). However, the lack of selectivity observed here was somewhat disappointing and hence, halted further

investigation with this reagent.



scheme 3.54

In summary, it is, therefore, apparent that our results are in conflict with those documented in the literature. As explained for the tributylstannane case, frontier molecular orbital arguments (see section 1.4) suggest that opening of the less substituted bond should predominate on either anion or radical induced cleavage of (110) under kinetically controlled conditions (figure 3.3). It, therefore, appears that reduction with samarium(II) iodide is occurring under "thermodynamic" control.

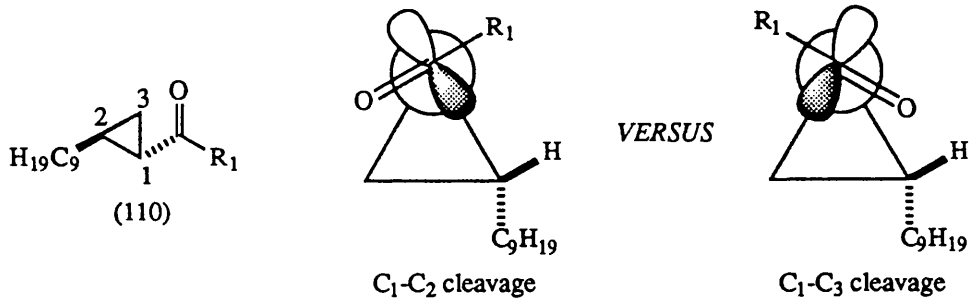
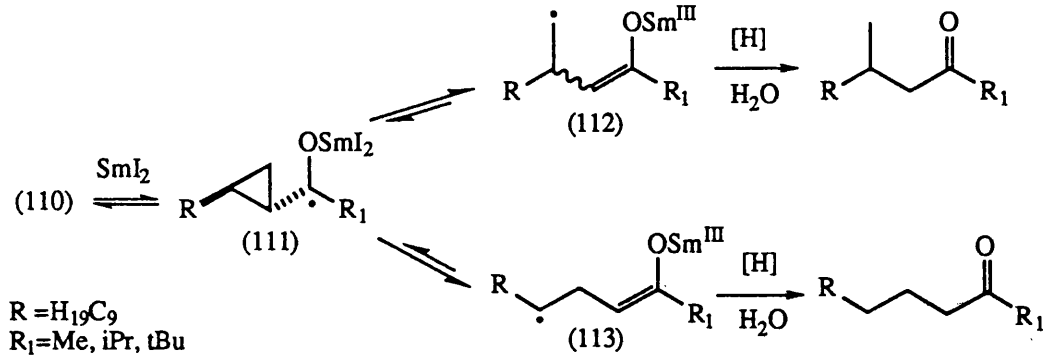


figure 3.3

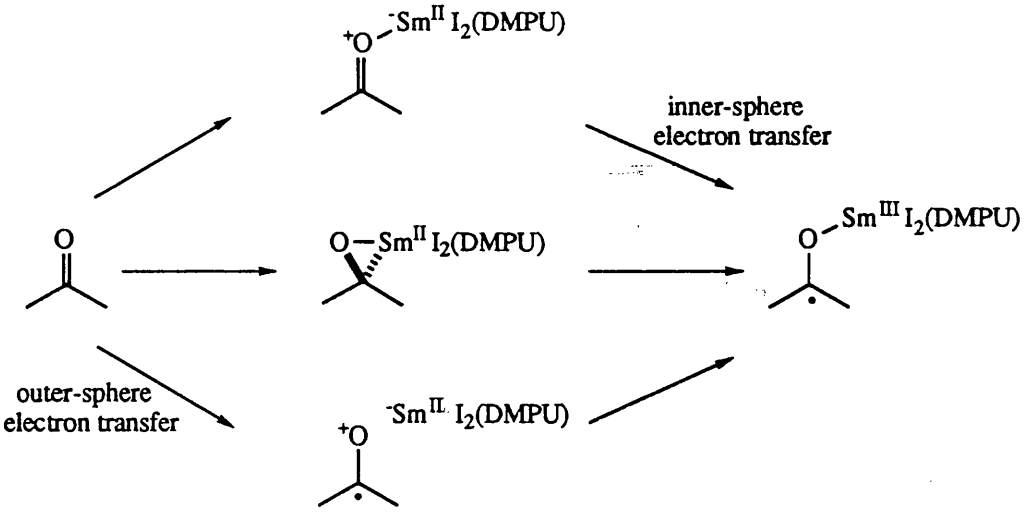
A proposed mechanism for the reduction is detailed below (scheme 3.55). While electron transfer to give the samarium ketyl radical (111) may or may not be a reversible process, the subsequent ring opening step involving cleavage of either of the two bonds should be rapid. As suggested above, however, ring opening to (112) should be faster than to (113), and assuming these radicals can equilibrate *via* reclosure to (111) and ring opening, formation of the lower energy secondary radical (113) will ultimately be favoured.



scheme 3.55

This would not of course be the case with the anion, since primary carbanions are known to be more stable[138]; furthermore, equilibration is less likely at the dianion stage (i.e. after second electron delivery), since the required 3-*exo*-cyclization would have to occur onto the electron-rich double bond of the samarium enolate. Given that the ring closure of the parent homoallylic radical to the cyclopropylcarbinyl radical is relatively slow ($K=10^3 s^{-1}$), it seems surprising that equilibration of the radicals (112) and (113) is possible, and therefore, this must be faster than either H-atom trapping from the solvent (the rate of hydrogen atom abstraction from THF by alkyl radicals is reported to be in the order of $10^3 mol^{-1}s^{-1}$),[139] or a second electron delivery to the anion. Thus, it is the product arising from (113) rather than that from (112) that is isolated after hydrolytic work-up.

It is viable to invoke the presence of both samarium bound radicals or organosamarium intermediates in these reactions, since the active existence of such species is widely speculated (*vide infra*). In our case, however, since the samarium(II) iodide is always in a very low concentration, the formation of stable diorganosamarium species is likely to be discouraged. Nevertheless, we can safely say that samarium ketyls are involved, and three pathways for their formation can be envisaged (scheme 3.56).



scheme 3.56

By analogy with "inner sphere" electron transfer, a samarium(II)-oxygen bond would initially form with the corresponding loss of a solvent molecule from the co-ordination sphere of samarium, followed by electron transfer "across" the bound oxygen atom. Alternatively, but less likely, a 3-membered heterocyclic (-C-O-Sm-) species could form (with the corresponding loss of two solvent molecules), followed by radical cleavage of the carbon-samarium bond. Finally, with "outer sphere" electron transfer, no such strong Sm(II)-O bond occurs and electron transfer precedes full samarium(III)-oxygen bond formation. In each of these mechanisms, an initial π-co-ordinated carbonyl-SmI_2 complex could also be involved. Unfortunately, at present, no firm evidence to distinguish between these pathways is available. It is also interesting to speculate on the possibility of cyclic organosamarium intermediates (figure 3.4) participating in the reaction.

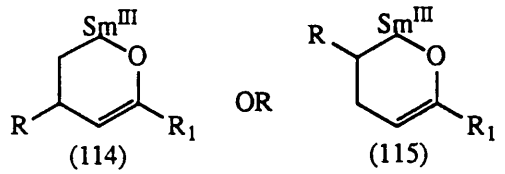


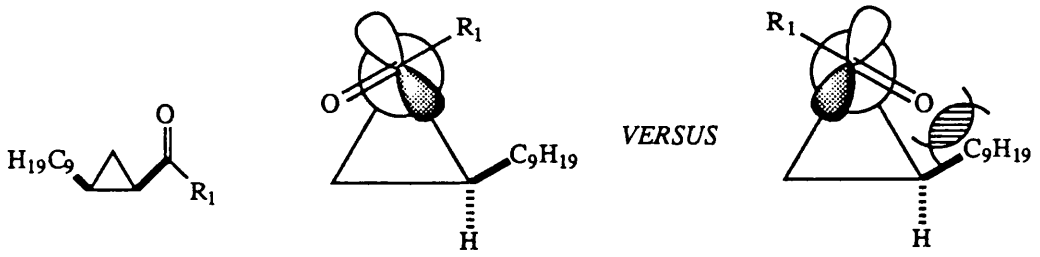
figure 3.4

The presence of a species such as (114), however, suggests that equilibration to (113)

(scheme 3.55) would be very slow, and hypothetically speaking formation of the product arising from the primary radical should be observed.

3.4.2 Samarium(II) Iodide Induced Ring Opening of the Cis Series.

Experimental evidence has shown that *cis*- substituted cyclopropylcarbinyl radicals do indeed preferentially open *via* cleavage of the more substituted bond, to give the thermodynamically more stable product, arising from the secondary radical under kinetic control (see section 1.4). This is explained on the basis that stereoelectronic alignment minimises the steric interaction encountered between the alkyl chain and the carbonyl group (figure 3.5).

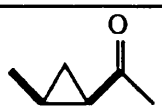
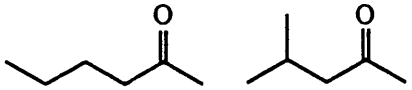
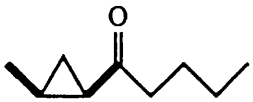
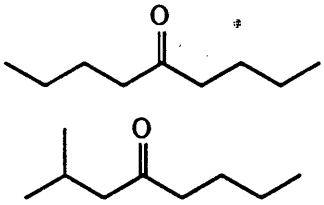


C_1-C_2 cleavage favoured

C_1-C_3 cleavage disfavoured

figure 3.5

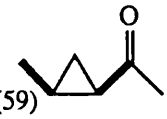
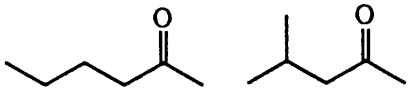
Before presenting our own work in this area, it is appropriate to comment on the results of Dauben and other workers. Dauben[91] has shown that the lithium in liquid ammonia reduction of *cis*- systems gave the product of thermodynamic control, implying that the steric effect is far more important than the relative stability of the intermediate anions (table 3.4).

KETONE	PRODUCT	RATIOS
		95 : 5
		91
		9

(i) Li/NH_3 (ii) NH_4Cl

table 3.4

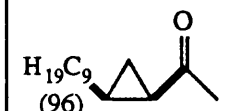
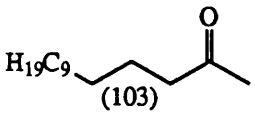
Likewise, returning to the work of Pereyre,[137] again the linear ketone was found predominate when the dimethyl substituted ketone (59) was subjected to ring opening under tributylstannane conditions (table 3.5).

KETONE	PRODUCT	RATIOS
 (59)		90 : 10

nBu_3SnH (neat)/AIBN/80°C

table 3.5

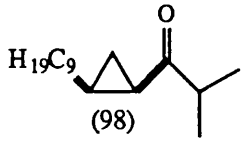
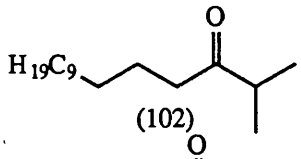
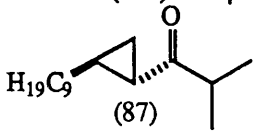
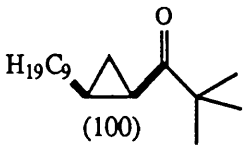
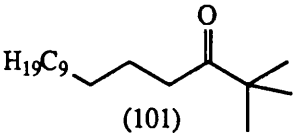
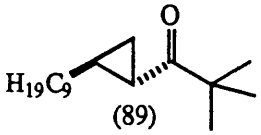
It is clearly evident, that although the results obtained with our *trans*- cyclopropyl ketones conflicted with literature precedent, those of the corresponding *cis*- counterparts agreed favourably (*vide infra*). Thus, ring opening of the *cis*- substituted cyclopropylmethyl ketone (96) gave, as expected, only one product, namely tetradecan-2-one (103) in 62% (table 3.6).

KETONE	PRODUCT	YIELD%
 (96)	 (103)	62

SmI_2/THF/DMPU/ (9:1)/ r.t./ 5min

table 3.6

The Newman projections depicted above (figure 3.5) clearly illustrate that cleavage of the alternative bond (C_1-C_3) does not occur. Similarly, reduction of the sterically more demanding *iso*-butyl and *tert*-butyl ketones (98) and (100), gave 2-methylpentadecan-3-one (102) in 59% yield and 2,2-dimethylpentadecan-3-one (101) in 70% yield as expected on the basis of the above analysis (table 3.7).

KETONE	PRODUCT	YIELD%
 (98)	 (102)  (87)	59 14
 (100)	 (101)  (89)	70 17

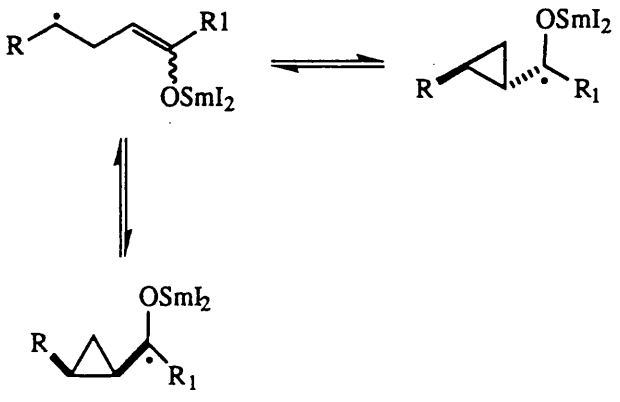
SmI_2/THF/DMPU/ (9:1)/ r.t./ 5min

table 3.7

In both cases we were intrigued by the isolation of the cyclopropyl ketones (87) and

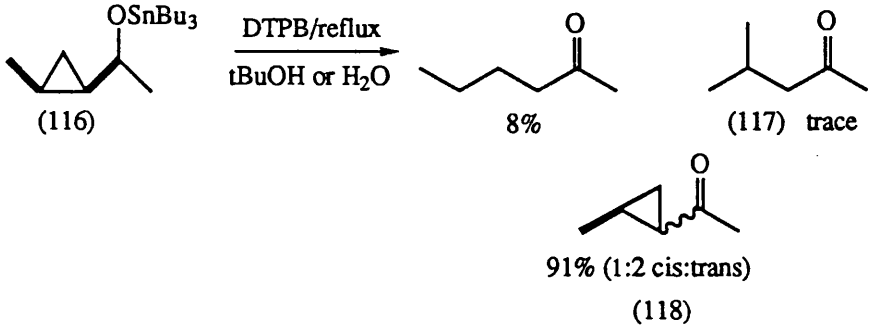
(89) respectively. Identification of these entities was not immediately apparent. Although these mysterious products were ketonic in nature (ir spectra 1696 and 1692cm^{-1} respectively), it was apparent that they were not the branched isomer arising from cleavage of the less substituted bond. Since tlc analysis of the reaction mixture showed that all the starting ketone (100) had been consuned, the multiplet signal at 0.69ppm in the proton nmr spectrum strongly suggested that some kind of isomeric cyclopropyl ketone derivative had been formed. This was confirmed by the presence of a molecular ion identical to that of the starting ketone in the mass spectrum. In the event, we finally reasoned that the product was the *trans*-isomer (89). This was further confirmed by comparison with an authentic sample, which we had made previously, and of course it was possible to verify that this material was not present in our starting *cis*-cyclopropyl ketone (100). Similarly, the *iso*-propyl cyclopropyl ketone (98) gave its *trans*- congener (87) in 14% yield.

The isolation of the *trans*-cyclopropyl ketones (87) and (89) from the reaction of the corresponding *cis*- isomers, was of course fortuitous, inasmuch as they could have undergone subsequent ring-opening as we have previously seen. Nevertheless, it is a highly significant observation and emphasises, yet again, that the 3-*exo* reclosure of the homoallylic radical on to the samarium enolate is certainly occurring at a sufficiently fast rate to be a competitive process during these reactions (scheme 3.57).



scheme 3.57

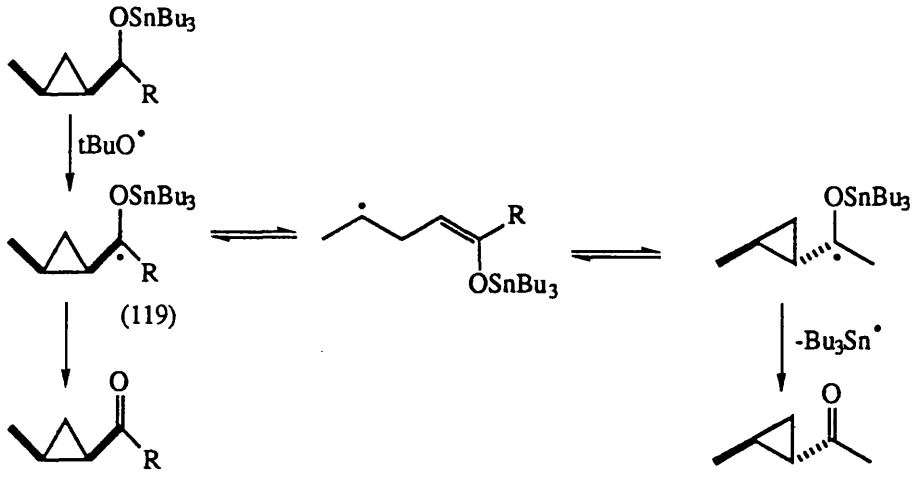
From a preparative standpoint, these observations are somewhat disappointing and suggest, as we have in fact found, that "thermodynamic" ring-opening will always be the favoured process, irrespective of substrate selection. From a mechanistic standpoint it was interesting to note that a similar phenomenon has been reported by Pereyre[140] during the oxidation of cyclopropyltin alkoxides with di-*tert*-butyl peroxide. Thus, reaction of (116) with di-*tert*-butyl peroxide yielded not only the expected linear ketone, but also trace amounts of the "unexpected" branched ketone (117), however, predominant formation the isomeric cyclopropyl ketone (118) was seen (scheme 3.58).



scheme 3.58

This isomerization is favoured because of the poor hydrogen donor ability of the solvent and by virtue of the fact that the radical (119) is in equilibration with the linear ring opened radical (scheme 3.59).

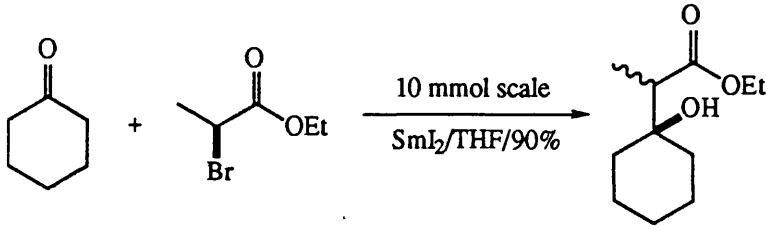
Clearly far more detailed studies are required in order to gain an insight into the surprising interconversion involved in the ring-opening of the cyclopropylcarbinyl system involving samarium as a metalloalkoxyalkyl radical trigger.



scheme 3.59

3.5 SAMARIUM ENOLATE STUDIES

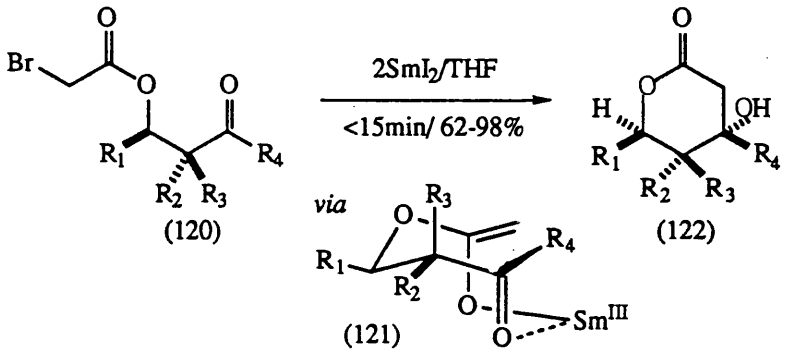
The next objective in our studies was to extend the versatility of this method further by intercepting the intermediate samarium enolate species with diverse electrophiles other than by simple protonation to give ketones. Surprisingly, despite the popularity of samarium(II) iodide as a reductant, the potential of samarium enolate chemistry has yet to be fully realised. In their seminal paper, Kagan, Girard and Namy[101] reported a high yielding intermolecular Reformatsky reaction (scheme 3.60). The carbon-carbon bond forming step could be considered to occur either by a radical-type process or through a samarium(III) ester enolate reacting with the cyclohexanone.



scheme 3.60

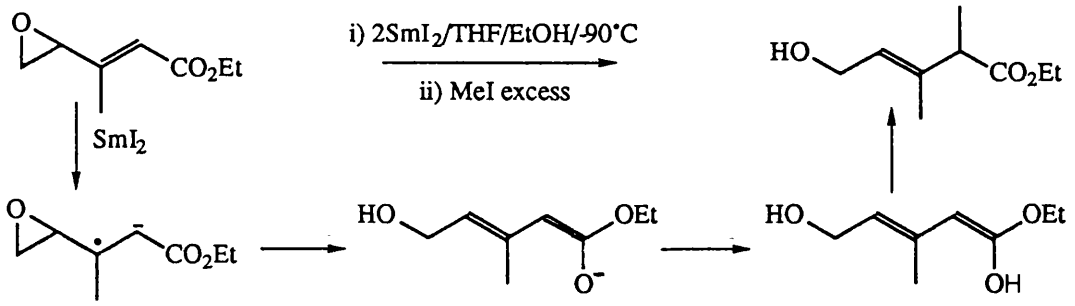
Work on ester enolates seems to have been more widely studied. Thus, Molander[141] has postulated the reduction of α-bromoesters of the type (120) to proceed *via* a

samarium(III) ester enolate, which cyclises through the highly organised rigid transition state (121) to form the lactones (122) as a single diastereomer (scheme 3.61).



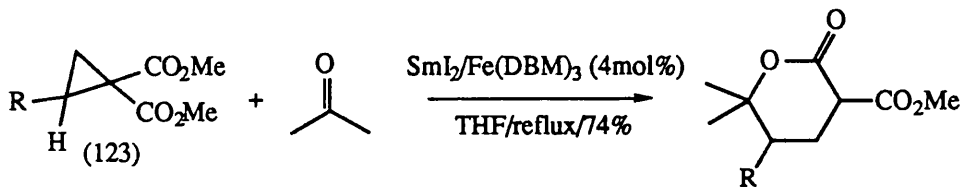
scheme 3.61

Molander has also successfully alkylated a samarium ester enolate formed with concomitant epoxide cleavage[142]; under these conditions alkylation was kinetically controlled (scheme 3.62).



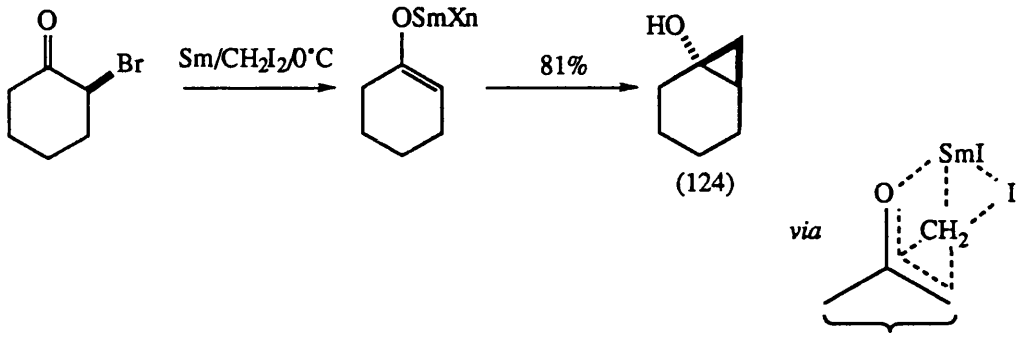
scheme 3.62

Imamoto's[131] most recent contribution to this domain is based on the synthesis of pentanolides, formed from the trapping of the intermediate samarium enolate resulting from the ring opening of the cyclopropane carboxylic ester (123) (scheme 3.63).



scheme 3.63

The use of α-haloketones as precursors for samarium enolates, has led Imamoto[143] to a novel synthesis of cyclopropanols (scheme 3.64).



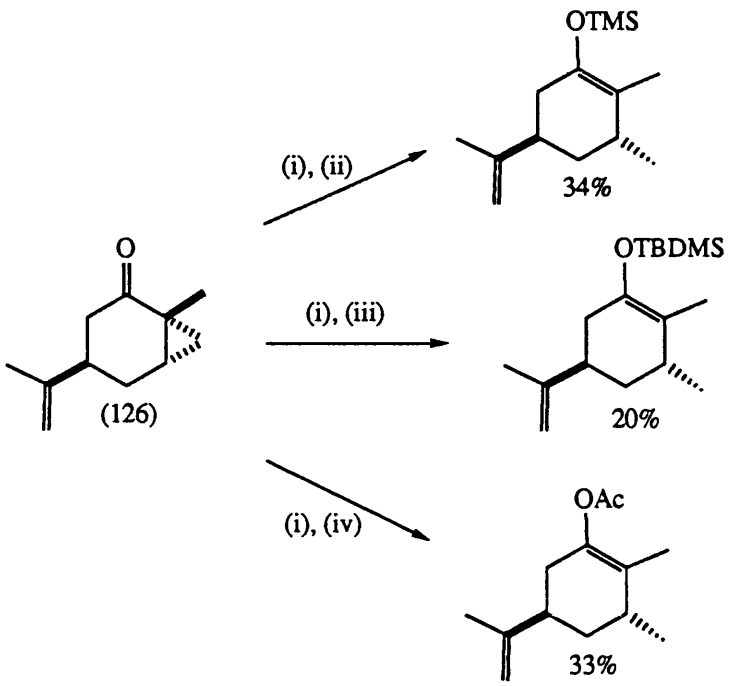
scheme 3.64

Treatment of 2-bromocyclohexanone for instance with samarium and diiodomethane furnished the cyclopropanol (124) presumably *via* cyclopropanation of an intermediate samarium enolate. This result was derived through utilisation of the samarium carbenoid (125) implied as an intermediate in the generation of samarium(II) iodide (scheme 3.65).

$$Sm + CH_2I_2 \longrightarrow \underset{(125)}{[ICH_2SmI]} \longrightarrow SmI_2 + CH_2{=}CH_2$$

scheme 3.65

As an extension to their ring opening studies, Motherwell and Batey[87] also explored the chemistry of the intermediate samarium enolate. Thus, reduction of (126) and subsequent trapping with a variety of electrophilies led to the first reported products derived from samarium enolate trapping on oxygen in somewhat modest yields (scheme 3.66).



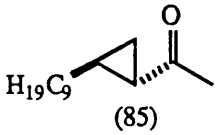
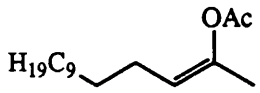
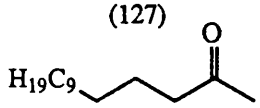
(i) SmI_2/THF/DMPU/r.t. (ii) TMSCl/2,6-Lutidine/-78°C to r.t.
(iii) TBDMSOTf/2,6-Lutidine/-78°C to r.t. (iv) AcCl/-78°C to r.t.

scheme 3.66

As a continuation of our studies in this area we therefore wished to explore the *E/Z* selectivity of the samarium enolate arising from our model cyclopropyl ketone substrates. It should be noted, however, that at this stage we were unaware of the potential for conversion of the *cis*-substituted cyclopropyl ketones into their *trans*-isomers via samarium ketyls.

The experimental protocol followed again involved the dropwise addition of samarium(II) iodide to the ketone until a permanent mauve/purple colouration was obtained and persisted for 5 minutes. The reaction vessel was then immediately cooled to -78°C and an excess of the electrophile rapidly added. Stirring was continued at this temperature for 0.5-1hour, and the solution was then warmed to room temperature over a further 0.5-1hour and quenched in the usual manner. To our disappointment, however, the enolate trapping experiments proved somewhat unsatisfactory and isolation of enol acetates was only achieved in two cases, in very poor yield.

We initiated our studies using acetyl chloride as the electrophilic trap and after several attempts managed to isolate the desired enol acetate (127) from the *trans*-cyclopropyl methyl ketone derivative (85) albeit in a very poor yield. This was accompanied by the ring opened ketone (103) in 53% yield (table 3.8).

KETONE	PRODUCT	YIELD%
 (85)	 (127)	16
	 (103)	53

(i) SmI_2/THF/DMPU (9:1) (ii) AcCl/-78°C

table 3.8

The stereochemistry of the enol acetate (127) was confirmed by nOe experiments. Irradiation of the vinylic methyl protons produced a reasonably strong response from H_3 (8%) (figure 3.6). Conversely, irradiation of the acetate methyl led to no enhancement of the proton in question.

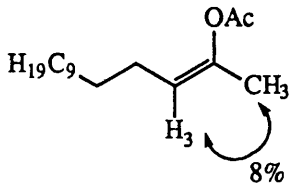
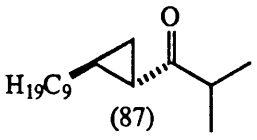
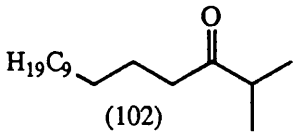
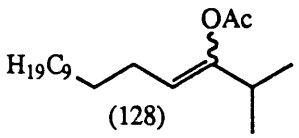


figure 3.6

The presence of THF was proving to be somewhat detrimental in these reactions, since in addition to the enol acetates and ring opened ketone products, the by-product arising from the ring opening reaction of THF by acetyl chloride was always present in significant quantities. This reaction was further facilitated by the presence of samarium(III) iodide, which has been reported to catalyse the reaction of THF with acid chlorides.[144] About this time a paper by Ruder[105] claimed to prepare

samarium(II) iodide in acetonitrile in an analogous way to the Sm/CH_2I_2/r.t. method. In our hands, however, we were unable to reproduce the preparation of this reagent in acetonitrile despite the fact that the diiodoethane was purification immediately prior to use, and deoxygenation using free thaw techniques were employed. Unfortunately, sincethe completion of our work, an article by Kagan and Namy[107] studying the reducing properties of samarium(II) iodide in tetrahydropyran has appeared in the literature. No product derived from the ring opening could be detected in this solvent even in the presence of acid chlorides. Unfortunately, we were unable to adopt this observation, and our alternative approach had been to use acetic anhydride, since reactions with the latter would not be complicated by products arising from reaction with the solvent. However, the use of acetic anhydride, whist eliminating the formation of the by-product did in no way promote the formation of the desired enol acetates.

Samarium(II) iodide reduction of the *trans*-isopropyl substituted cyclopropyl ketone (87) in the usual fashion with samarium(II) iodide followed by quenching with acetic anhydride yielded an inseparable mixture of two products. Inspection of the ^1H nmr spectrum revealed a triplet at 5.00ppm together with a sharp singlet at 2.16ppm. This led us to speculate that we had indeed generated the enol acetate.

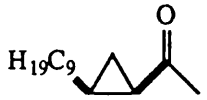
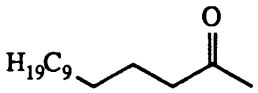
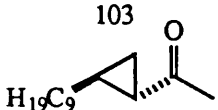
KETONE	PRODUCT	YIELD%
 (87)	 (102)  (128)	77 (102):(128) (2:1)

(i) SmI_2/THF/DMPU (9:1) (ii) Ac_2O/-78°C to r.t.

table 3.9

Further justification came from analysis of the mass spectrum, which showed the expected peak under chemical ionisation conditions. In addition, further confirmation was obtained from analysis of the ir spectrum which showed the ester stretch at 1766cm^{-1} corresponding to the desired product (128) as well as the 1715cm^{-1} stretch of the carbonyl compound (102) (table 3.9).

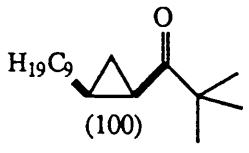
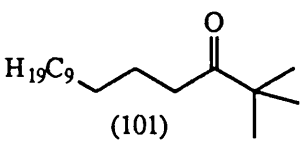
Contrastingly, however, subjection of the*cis*-cyclopropyl methyl ketone (98) to the same reaction conditions did not furnish the desired enol acetate. The products isolated were tetradecan-2-one (103) in 33% yield, the isomerized product (85) in 11% yield and recovered starting material in 30% yield (table 3.10).

KETONE	PRODUCT	YIELD%
 (98)	 103  (85)	33 11

(i) SmI_2/THF/DMPU (9:1) (ii) Ac_2O/-78°C to r.t.

table 3.10

In a similar fashion, the adventitious proton precluded our attempted acylation of (100) which afforded only the "hydrolysed" product (101) in 72% yield (table 3.11).

KETONE	PRODUCT	YIELD%
 (100)	 (101)	72

(i) SmI_2/THF/DMPU (9:1) (ii) Ac_2O/-78°C to r.t.

table 3.11

This led us to believe that maybe approach of the acetic anhydride might be sterically

disfavoured by the *tert*- butyl group (figure 3.7).

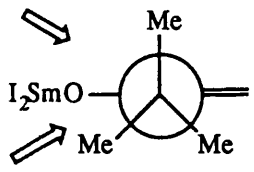
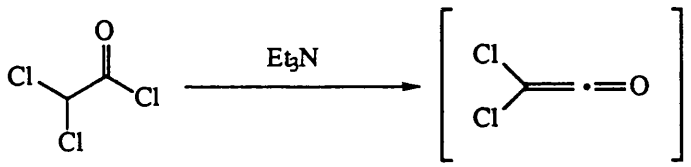


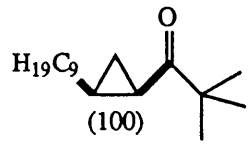
figure 3.7

Hence we turned our attention to a linear equivalent, namely the ketene[145] generated from dichloroacetylchloride with triethylamine (scheme 3.67).



scheme 3.67

Thus, samarium(II) iodide was added dropwise to a solution of the ketone (100) and the purple solution was immediately cooled to -78°C, prior to the addition of triethylamine followed by dichloroacetyl chloride (table 3.12).

KETONE	PRODUCT
 (100)	?

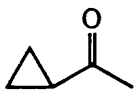
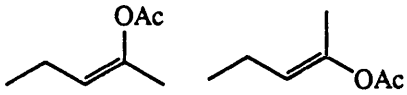
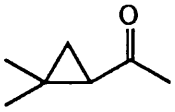
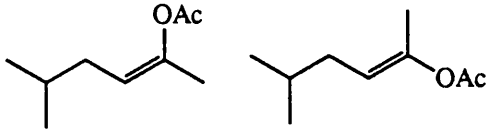
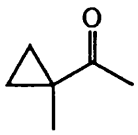
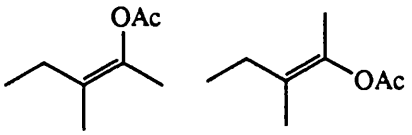
(i) SmI_2/THF/DMPU (9:1) (ii) $ClCOCHCl_2/Et_3N$/-78°C to r.t.

table 3.12

Alas, formation of the desired product was not observed; furthermore, the only isolated products involved formation of an unidentified dicarbonyl species bearing surprisingly only a single chlorine atom. The diketo functionality was evident from

^{13}C nmr (209 and 211ppm) and from analysis of the ir spectrum (1705cm^{-1}) a strong stretch was evident at 1705cm^{-1}, while the mass spectrum showed an isotope pattern consistent with the presence of only one chlorine.

In contrast to these results, Dauben's[93] enolate traping experiments proved far more fruitful. Comparison, however, maybe somewhat misleading, since his examples involve simpler substrates than those studied by us (table 3.13).

KETONE	PRODUCT	RATIOS
		82 : 18
		88 : 12
		70 : 30

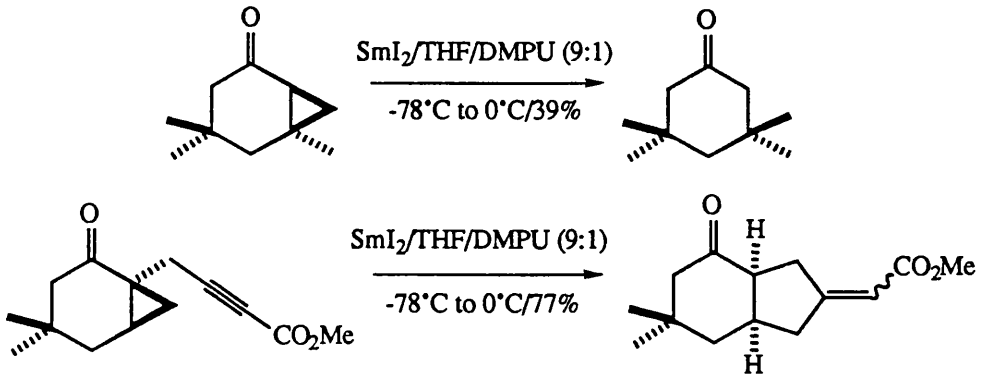
(i) Li/NH_3 (ii) Ac_2O/DME

table 3.13

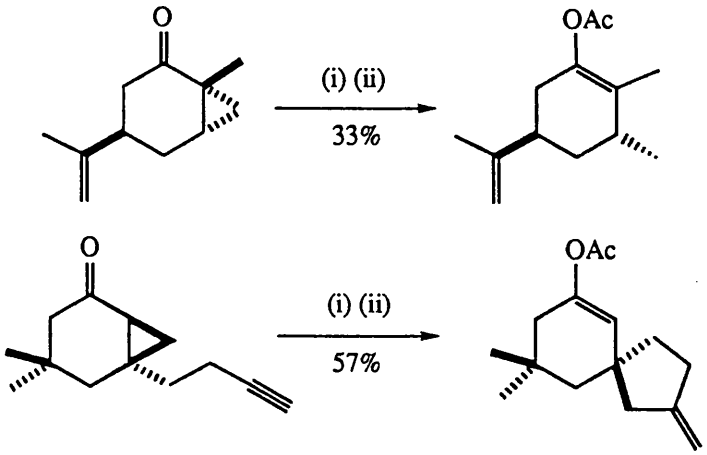
At first glance it is interesting to note that the disubstituted methyl derivative (entry 2) gave enol acetates arising from cleavage of the more substituted bond, whereas simple reductive ring opening gave products arising from cleavage of both bonds (scheme 3.11). However, due to the multiplicity of this product mixture the presence of products arising from cleavage of the alternative bond could not be ruled out.

3.6 CONCLUSION

Throughout our studies on the ring opening of cyclopropyl ketones using samarium(II) iodide, we have been constantly perplexed by the fact that the isolated yields of products, whether derived from protic work-up or electrophilic quench, are highly dependent on the substrate structure. It would often seem that the more complex bicyclic precursors, bearing strategically placed pendant chains,[87] were more effective than the parent monocyclic models from which they should in theory be derived under protic conditions (scheme 3.68) as well as on enol acetate formation (scheme 3.69).



scheme 3.68



(i) SmI_2/THF/DMPU/rt (ii) AcCl/-78°C to r.t.

scheme 3.69

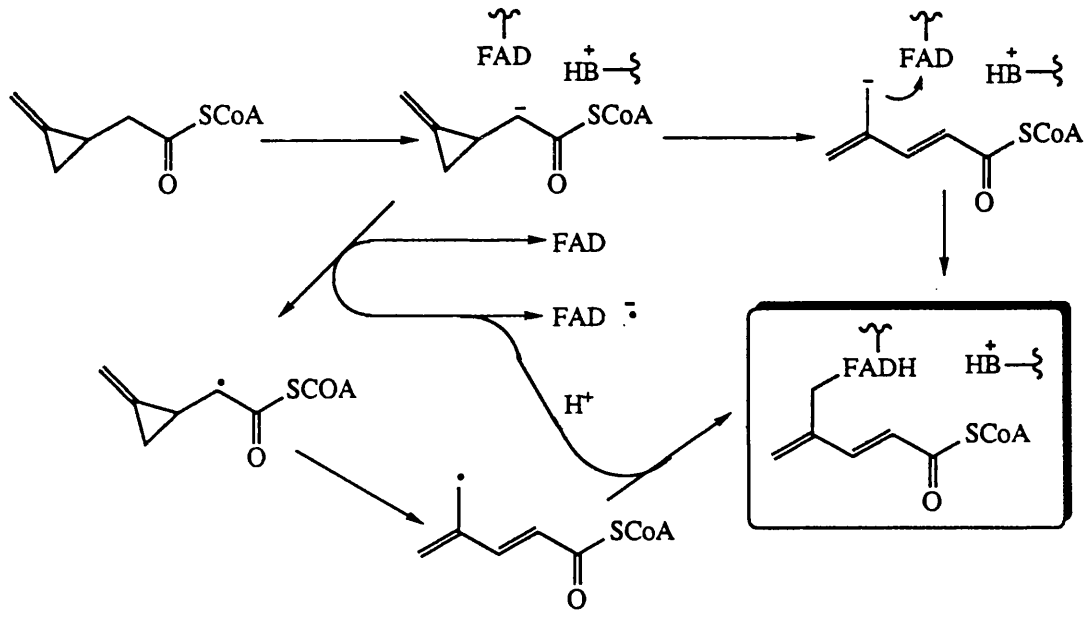
Nevertheless, we have demonstrated that samarium(II) iodide is a useful reagent for the ring opening of simple monocyclic cyclopropyl systems. Reductions can conveniently be carried out on small scale, using short reaction times at ambient temperatures and under very mild conditions. In comparison with other reductive ring-opening methods, several features of mechanistic interest are apparent. In particular, it is interesting to note that while the more traditional reductive systems can be biased to give products arising from cleavage of either bond of the cyclopropane ring as a function of the initial geometry, no such effect was observed using the more modern samarium(II) iodide reagent. Irrespective of the geometry of the substitutents around the cyclopropyl ketone, it would appear that the samarium(II) iodide induced ring opening will favour formation of the thermodynamic product, i.e. that arising from cleavage of the more substituted cyclopropyl bond. Most peculiar of all, however, and totally unexpected, was the appearance of the isomerized cyclopropyl products which would imply, in sharp contrast to other electron transfer induced reductions, that ring opening and reclosure of the intermediate homo-allylic radical is relatively fast.

Chapter Four

4.1 THE METHYLENE CYCLOPROPYLCARBINYL SYSTEM

4.1.1 Generation of Carbon Centred Radicals

Our initial interest in this area stemmed from the mode of action of the actual causative agent of Jamaican Vomiting Sickness (JVS) (see section 1.6.4). Despite the fact that JVS has been studied for many years, the question of whether the reaction proceeds *via* a radical mediated reaction as shown in scheme 4.1 has never been fully addressed.



scheme 4.1

Before proceeding with a critical analysis of our own work in this area, we shall set our objectives into perspective namely: (a) why is such a system of interest ? (b) how does it differ from systems which we have previously discussed ? and finally (c) how do we anticipate the reaction to proceed ?

The methylenecyclopropylcarbinyl moiety differs from its cyclopropylcarbinyl cousin principally by the inclusion of the sp^2 centre of the *exo*methylene double bond. From a quantitative point of view, as expected this results in an increase in the C_1-C_2-C_3 angle, and a lengthening, and hence weakening of the C_1-C_3 bond[146] (figure 4.1).

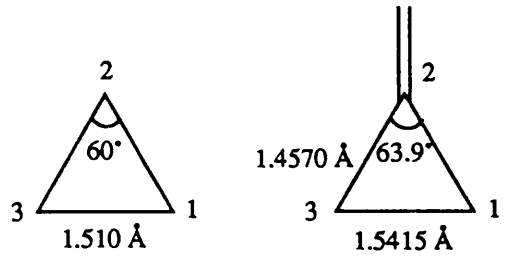
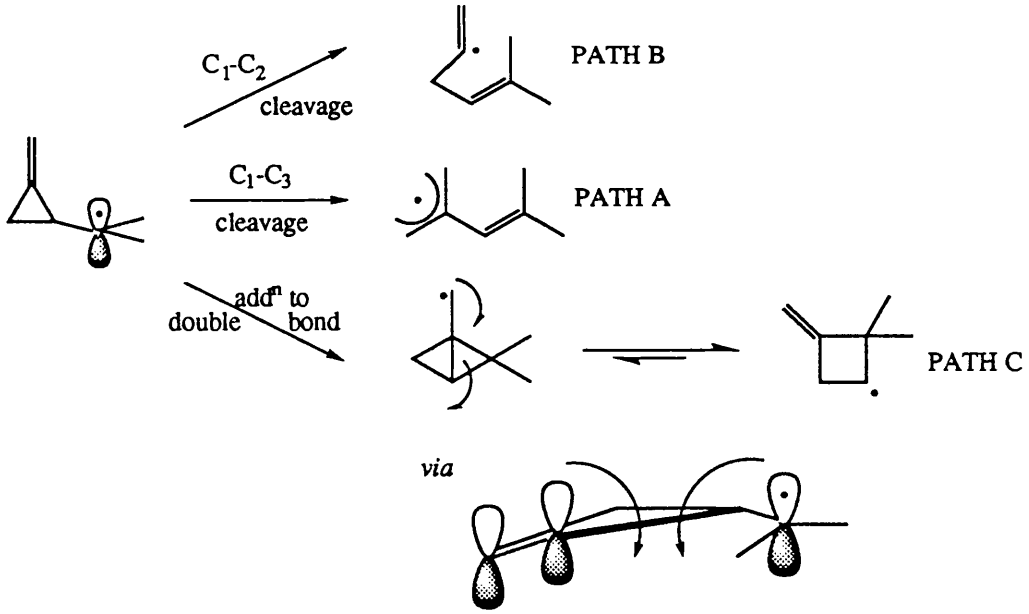


figure 4.1

Thus, as in the ring opening of the cyclopropylcarbinyl system, ring opening of an equivalent alkylidene system will no doubt be rapid, since as well as ring strain arising from the formally acute angles, additional relief is associated with the bringing about of the correct geometry of the sp^2 centre at C_2. Consequently, such a system would appear to be an ideal candidate for ring cleavage reactions. From a formal analytical standpoint, radical induced cleavage can be perceived to occur as depicted in scheme 4.2.

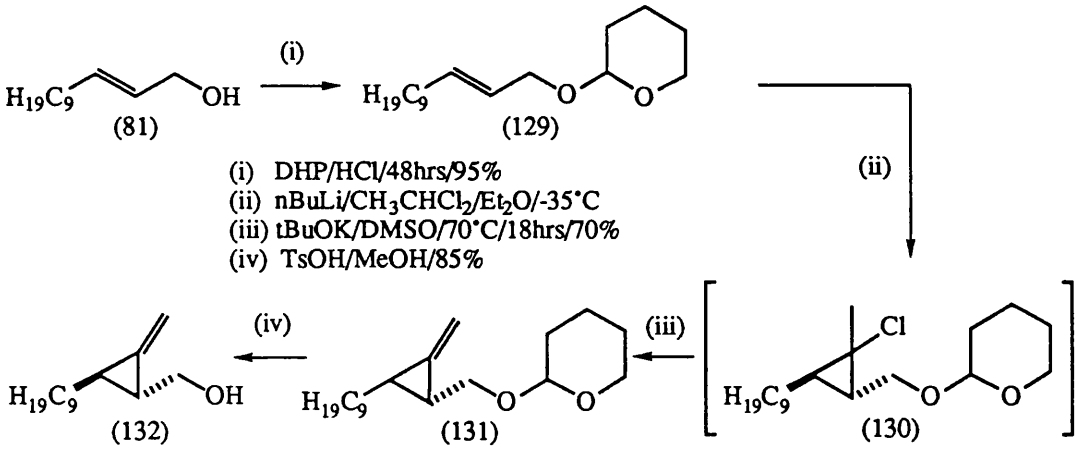


scheme 4.2

Of the three possibilities shown, given that free rotation can occur in such systems, ring opening to produce the allylic radical which also forms part of conjugated diene system (Path A) would seem to be overwhelmingly favoured. Path B, resulting in

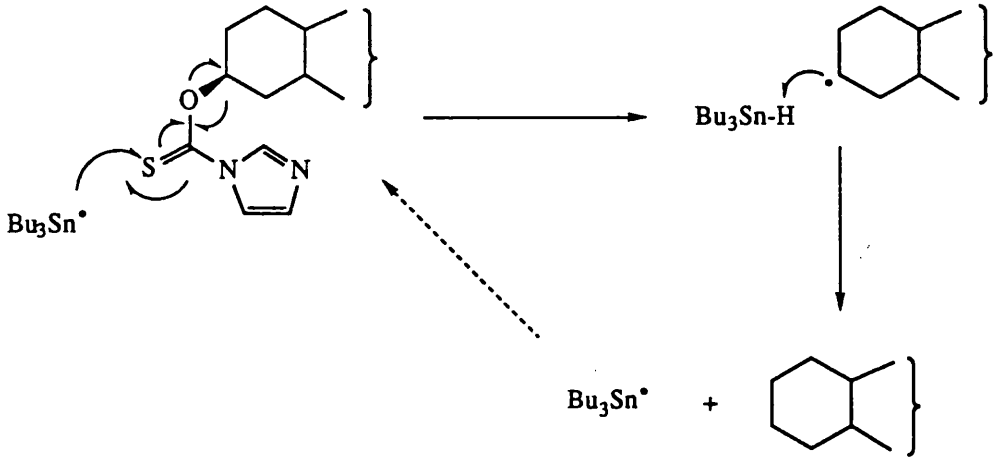
formation of the higher energy vinylic radical has no intrinsic stereoelectronic advantage, and path C which leads to an even more highly strained bicyclo[1.1.0] intermediate also appears to have unfavourable orbital overlap.

We, therefore, focussed our attention on the study of model methylenecyclopropylcarbinyl radical systems and accordingly, set out to synthesise a suitable precursor. Protection of the allylic alcohol (81) with dihydropyran gave the THP ether (129) in 95% yield. Treatment of (129) with methyl chlorocarbene,[147] generated from 1,1-dichloroethane and *n*-butyllithium at -35°C, gave the cyclopropyl derivative (130). Introduction of the *exo*methylene double bond was achieved by dehydrohalogenation using potassium *tert*-butoxide in dimethylsulfoxide, generating the methylene cyclopropane (131) in 70% yield. Subsequent removal of the hydroxyl protecting group using *p*-toluenesulfonic acid gave the desired alcohol (132) in 85% yield (scheme 4.3).



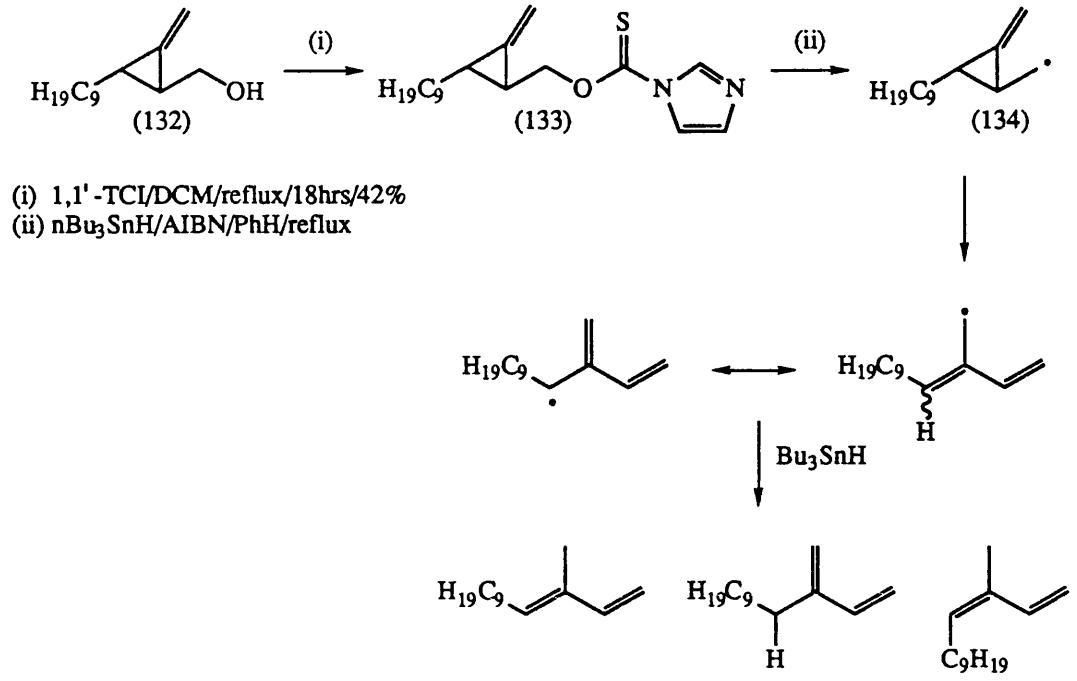
scheme 4.3

All that now remained was to replace the hydroxyl group of (132) with a group from which a radical could be generated at the cyclopropylcarbinyl centre. Thiocarbonylimidazole derivatives, which can be formed directly from alcohols under neutral conditions,[148] have been shown to react with tin radicals and collapse as shown in an overall chain process, and were, therefore, the derivatives of choice (scheme 4.4).



scheme 4.4

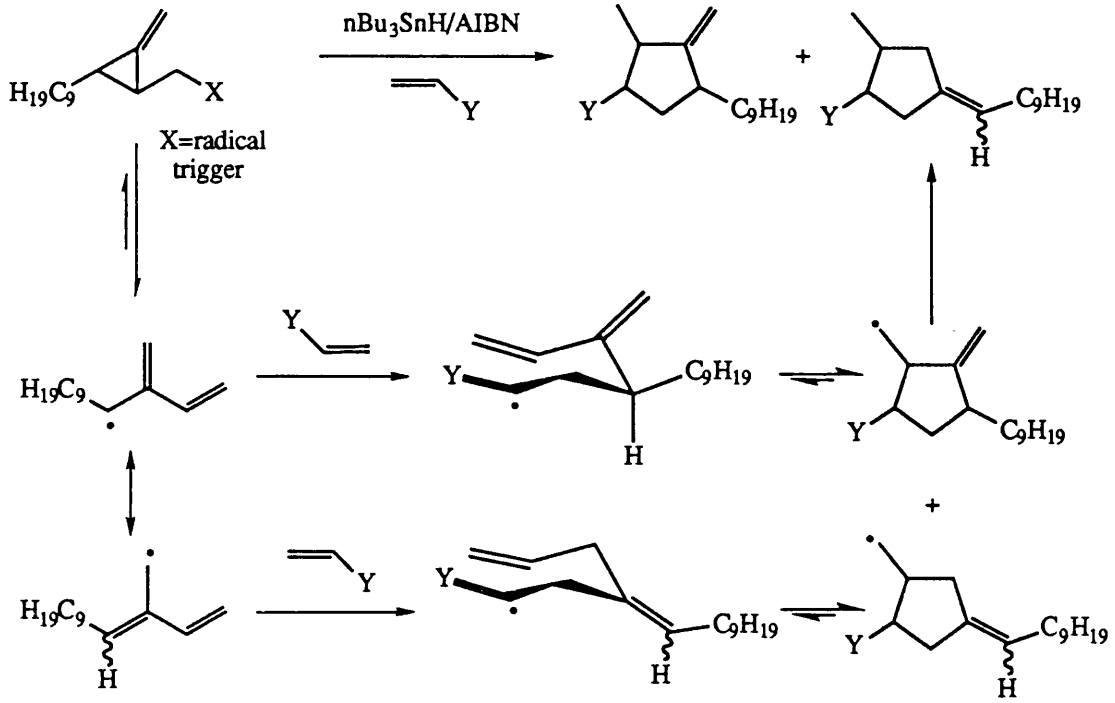
Hence, the methylenecyclopropyl alcohol (132) was refluxed in dichloromethane for 18 hours with 1,1'-thiocarbonyldiimidazole to provide the requisite trigger in a modest 42% yield. The radical reaction was subsequently performed by the dropwise addition of the stannane and AIBN to a thoroughly degassed solution of the thiocarbonylimidazolide (133) in refluxing benzene over a 30 minute period. These reaction conditions provide a low tri-*n*-butyltin hydride concentration at any given time so that the initially formed cyclopropylmethyl radical (134) is given maximum opportunity to open (scheme 4.5).



scheme 4.5

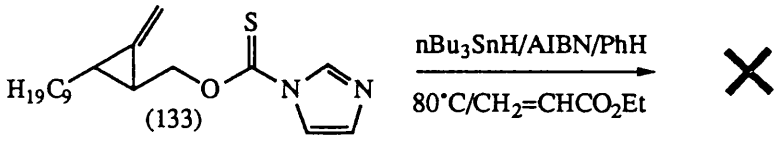
Tlc analysis of the crude reaction mixture revealed that a complex product mixture had been produced. Consequently, even though we had anticipated that a mixture of dienes would be produced, we were unable to isolate any products after silica gel chromatography. It can be assumed that the carbinyl radical (134) was formed, and in turn underwent rapid ring opening for the reasons stated previously and as was observed with the saturated congener. Thus it appears that the resultant dienes are far too unstable and/or reactive under the reaction conditions. We reasoned, therefore, that it may be possible to trap the radical intermediates *insitu* with suitable alkenes. We envisaged that such rearrangement could, therefore, be used in a tandem radical cyclisation *en* route to cyclopentanoids similar to Feldman's vinylcyclopropane addition approach[60, 61] (see section 1.7) (scheme 4.6).

Thus, the reaction can be perceived to proceed *via* formation of the cyclopropylcarbinyl radical, which rapidly ring opens to give a mixture of dienes. Addition of the alkene would then produce the 5-hexenyl radical, which would eventually lead to the methylenecyclopentanes *via* a prior 5-*exo* ring closure process.



scheme 4.6

The radical reaction was performed under analogous conditions to that described previously, namely dropwise addition of a solution of tri-*n*-butylstannane and AIBN to a refluxing benzene solution comprising of the thiocarbonylimidazolide derivative (133) together with ethyl acrylate as the radical trap (scheme 4.7).

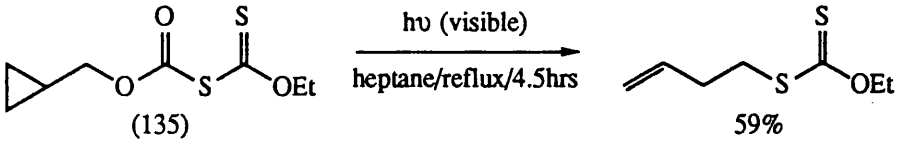


scheme 4.7

Although tlc analysis of the brown oil isolated upon work-up showed that all the starting material had been consumed, formation of any new products was not detected and only very polar base line material was present. Likewise, no conclusion could be drawn from analysis of the ^{1}H nmr spectrum of the reaction mixture. These observations lead us to speculate that such dienes appear to polymerise faster than undergoing a clean tandem process.

In the intervening time we were encouraged by Zard's[149] *S*-alkoxycarbonyl xanthate

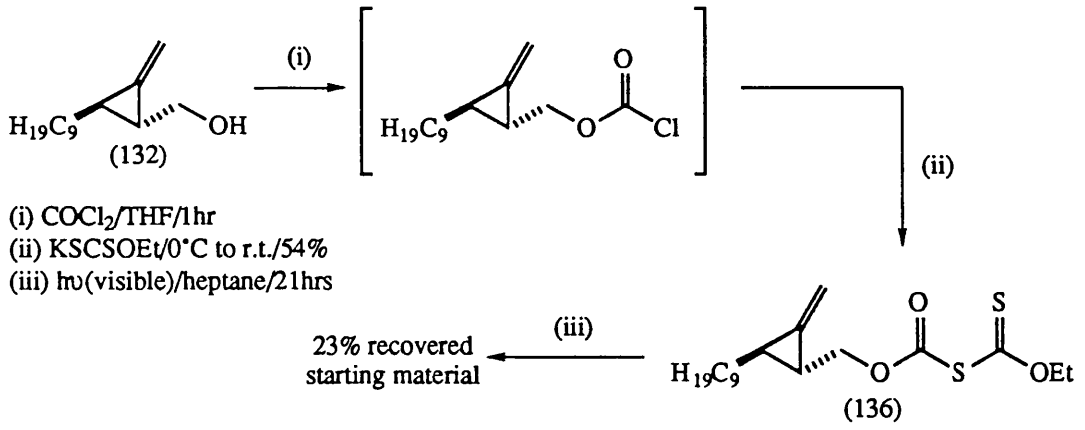
chemistry. Irradiation of the cyclopropyl xanthate derivative (135) with visible light in refluxing heptane gave the*S*-3-butenyl-O-ethyl xanthate in a 59% yield, as a result of decarboxylation of an alkoxycarbonyl radical generating the corresponding alkyl radical (scheme 4.8).



(135) 59%

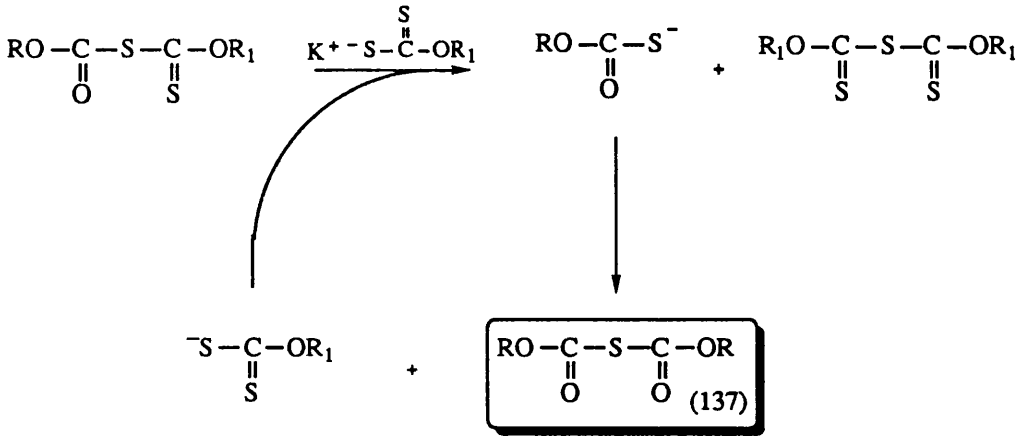
scheme 4.8

In its simplest form, this process converts an alcohol into the corresponding *S*-xanthate through a radical chain mechanism, hence we decided to subject our methylenecyclopropyl alcohol (132) to these conditions. Thus, the chloroformate arising from exposure of a solution of (132) to phosgene was treated with potassium-*S*-ethyl xanthate, which in turn afforded the requisite *S*-alkoxycarbonyl xanthate (136) in 54% yield (scheme 4.9).



scheme 4.9

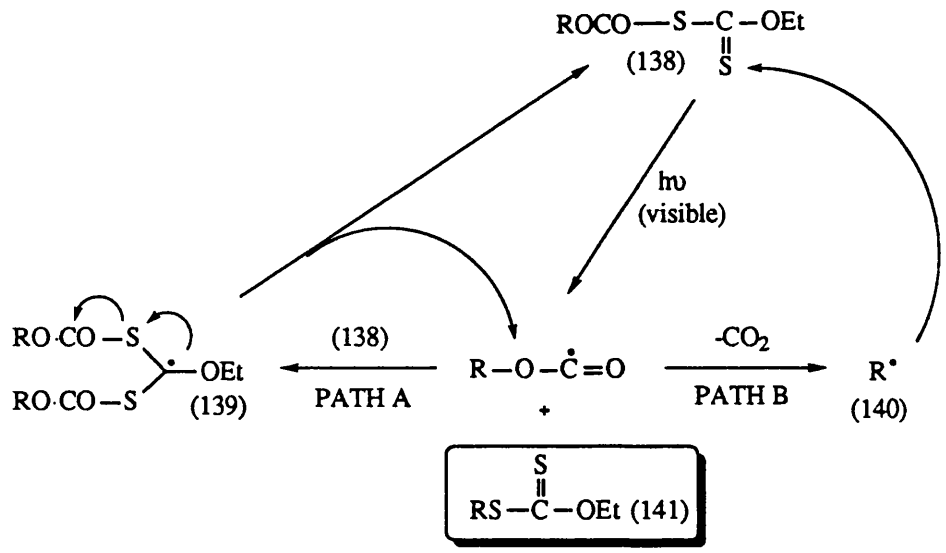
We were careful not to use an excess of the potassium ethyl xanthate as this would lead to the decomposition of the product by an ionic chain mechanism resulting in the formation of a thioanhydride species (137) (scheme 4.10).



scheme 4.10

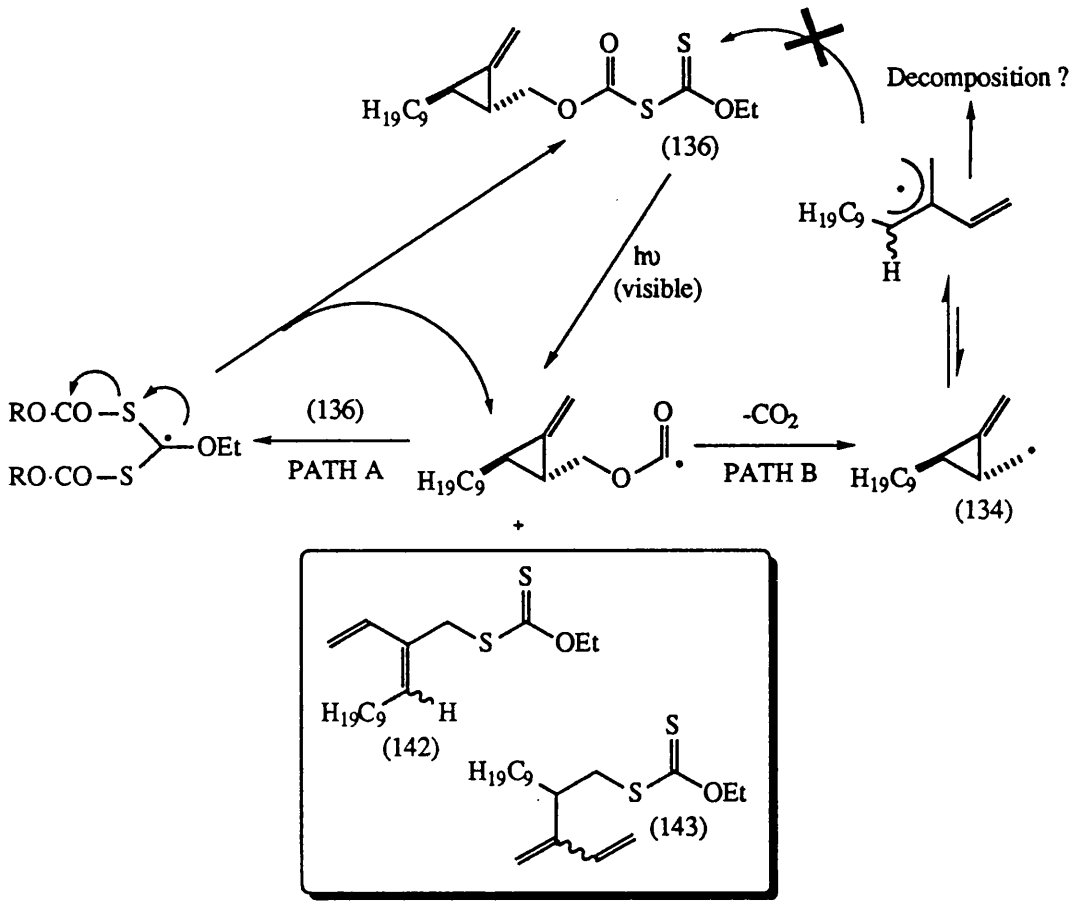
Irradiation of the anhydride in heptane with a 500W tungsten filament lamp for 21 hours, gave the starting xanthate in 23% as the only recognisable product (scheme 4.9).

Zard proposes that the reaction proceeds as depicted in scheme 4.11. Irradiation of *S*-alkoxycarbonyl xanthate derivatives leads to the corresponding alkoxycarbonyl radical, reaction of this with its precursor (138) (path A) is reversible and degenerate, since the resulting *symmetrical* intermediate (139) can only collapse to give the same alkoxycarbonyl radical and (138) the parent xanthate (fragmentation by rupture of the strong OEt bond is highly unlikely). This reaction does, therefore, not compete with the expulsion of carbon dioxide (path B), which results in the generation of the alkyl radical (140) which in turn reacts with its precursor to give the *S*-xanthate (141).



scheme 4.11

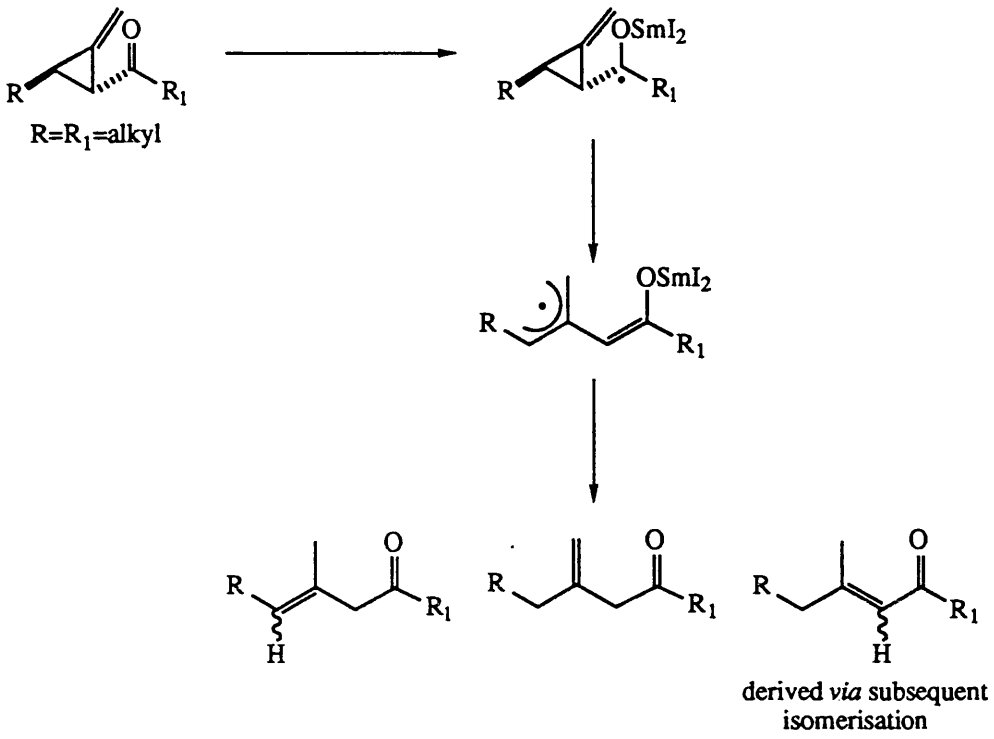
Thus, recovery of starting material upon irradiation of (136) may be as a result of the regeneration of the latter by the virtue of the cycle, and not purely as a result of unreacted starting material. It is viable to conclude that irradiation is followed by expulsion of carbon dioxide to generate the alkyl radical (134) which undoubtedly undergoes rapid ring opening (path B) (scheme 4.12). Rearrangement and/or decomposition of this species, however, appears to be faster than reaction with precursor (136). Concomitantly, reaction of the alkoxy carbonyl radical with the starting xanthate (136) (path A) may be favoured over carbon dioxide expulsion, the latter being to slow to be of importance. Hence reaction with (136), followed by expulsion of ROCO• would regenerate the starting alkylidene cyclopropyl species. It is clear that path A leads to regeneration of the of the starting *S*-alkoxycarbonyl xanthate, and may, thus, account for the isolation of (136) as opposed to the expected dienes (142) and (143).



scheme 4.12

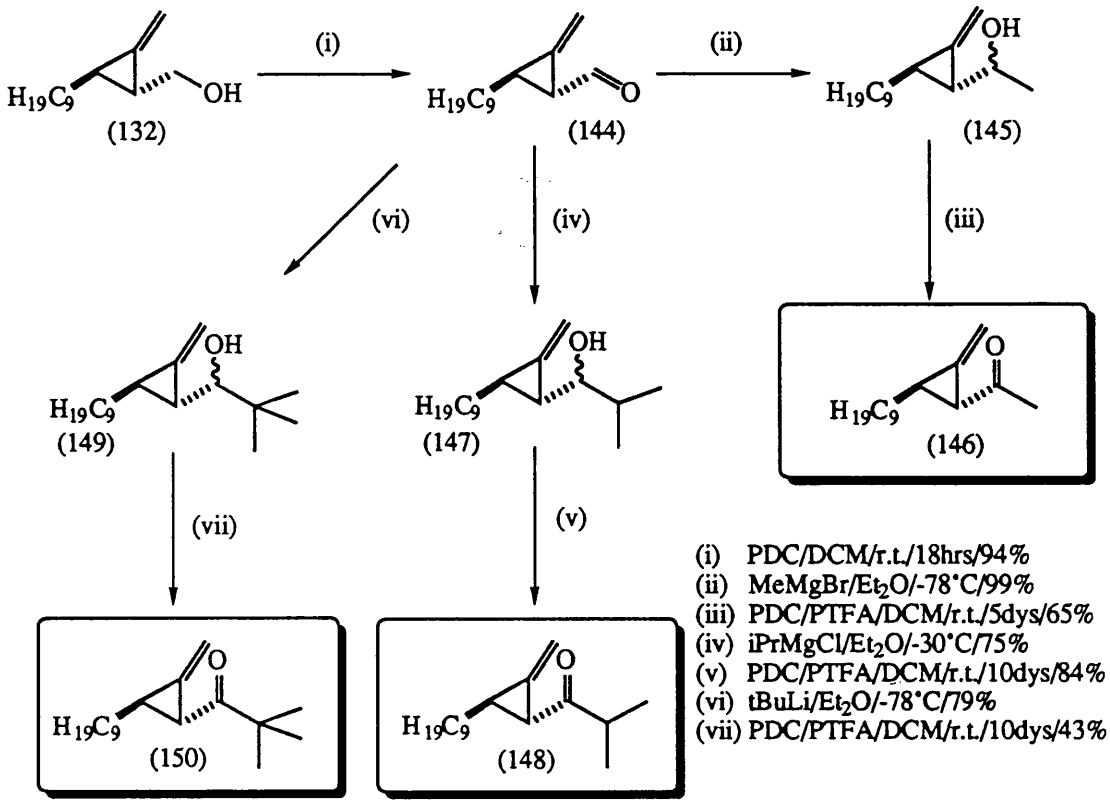
4.1.2 Radical Anion Generation by Samarium(II) Iodide.

The minimal success achieved in attempting to generate carbon centred radicals promoted us pursue other channels, and thus, we decided to probe the generation of radical anions from the corresponding methylenecyclopropyl ketones. Hypothetically speaking, ring cleavage can be envisaged to occur as shown below, leading to the formation of α,β and or β,γ-unsaturated ketones (scheme 4.13).



scheme 4.13

With the alcohol (132) in hand, we set out to synthesise appropriately substituted alkylidenecyclopropyl ketone derivatives in an analogous manner to that described previously and thus, investigate the generation of radical anions from the respective ketone substrates (146), (148) and (150) (scheme 4.14).



scheme 4.14

In the first instance, exposure of the ketones to the usual experimental conditions, namely dropwise addition of a 0.1M solution of samarium(II) iodide to a solution of the substrate in a (9:1) mixture of THF/DMPU, led in all three cases, to a complex mixture of products. We felt that, as a result of the allylic assistance to bond breaking, ring opening was prehaps too rapid at room temperature. Thus, addition of samarium(II) iodide was preformed at -78°C, but this was to no avail. It was intriguing to speculate whether an added proton source, which could protonate the basic organometallic intermediates (samarium ketyls, alkoxides or enolates or alkylsamarium) would make a difference. Thus, reaction of (148) was again repaeted by addition of the reductant at low temperature, but this time in the presence of an added proton source, namely methanol. Unfortunately, however, a complex mixture of products was again obtained and no solid conclusion could be drawn. A possible explanation for the absence of the desired products as depicted in scheme 4.13, may stem from the association of the exomethylene double bond of the

methylenecyclopropyl ketone with a samarium species, since this is the major difference between the cyclopropylketones studied previously and those in question.

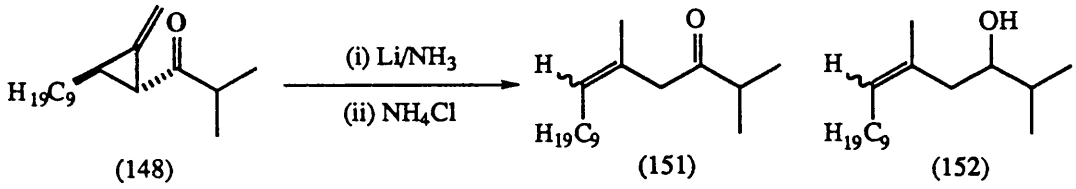
Unfortunately, as a result of the inherent reactivity associated with the radicals generated in this study, we decided that it was inappropriate to pursue this avenue of research further. In all probability, with hindsight, the generation of a conjugated dienes capable of undergoing extremely facile radical polymerisation may well be responsible for our failure to isolate simple low molecular weight products. Consequently, we turned to consider a more traditional and far more established reducing system for the generation of ketyl radical anions, lithium in liquid ammonia.

4.1.3 Radical Anion Generation by Lithium in Liquid Ammonia.

Hence, we set forth on an analogous study employing the methylenecyclopropyl ketones (146), (148) and (150). The experimental protocol followed throughout this investigation involved the dropwise addition of a solution of the ketone in ether to a solution of lithium in liquid ammonia, and the blue ammoniacal solution was then allowed to reflux for 40 minutes. Care was taken to ensure that the ammonia was thoroughly dried. This was achieved by stirring the latter for a period of 30 minutes over sodium followed by distillation into the reaction vessel and stirring for a further 30 minutes over lithium metal. This process is important since ammonia cylinders are known to contain traces of iron which invariably contaminates commercial sources of the gas and can hence lead to the production of the metal-amide. Portionwise addition of an excess of solid ammonium chloride to destroy the excess lithium, neutralise the lithium amide formed and to protonate the organolithium enolate, was followed by evaporation of the ammonia and work-up in the normal manner.

Gratifyingly, and in contrast to our studies using samarium(II) iodide, subjection of the alkylidenecyclopropyl derivative (148) to the conditions specified above led to

the isolation of an isomeric mixture of ketones (151) and to our initial surprise, the isomeric alcohols (152) (scheme 4.15).

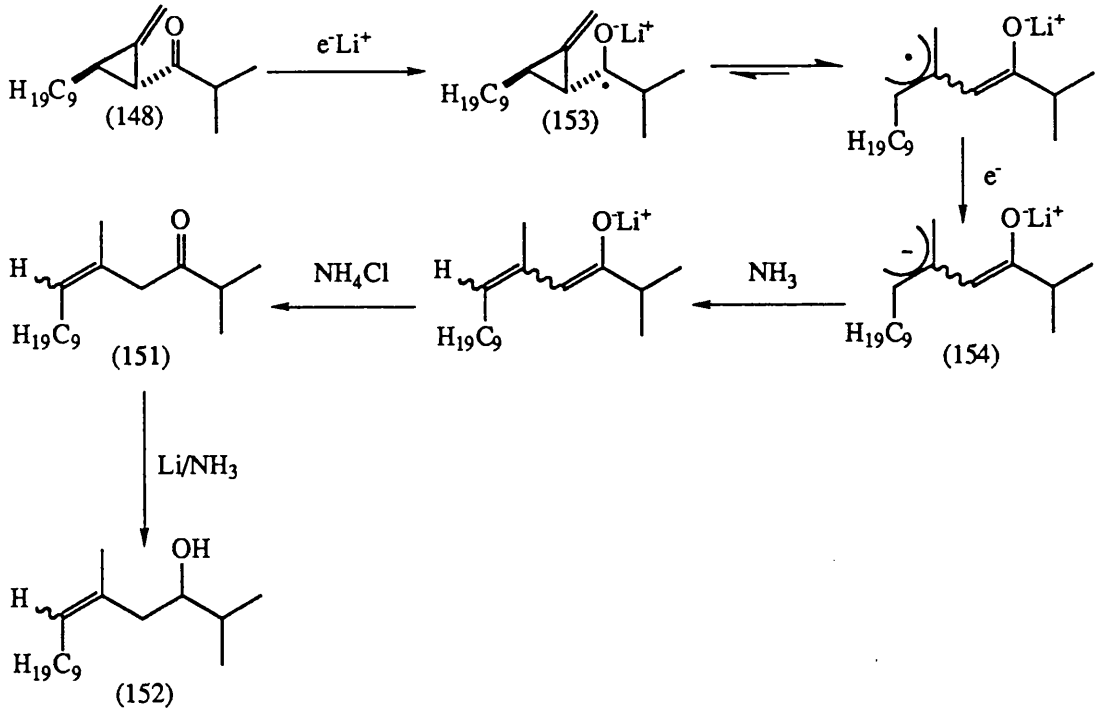


(148) (151) (152)

Addition time 10 mins	48%	22%
60 mins	41%	41%

scheme 4.15

The overall sequence of electron transfer and protonation can hence, be summarised as shown in scheme 4.16. Thus, electron transfer to the ketone proceeds *via* the ketyl radical anion (153) which then ring opens *via* cleavage of the C_1-C_3 bond.

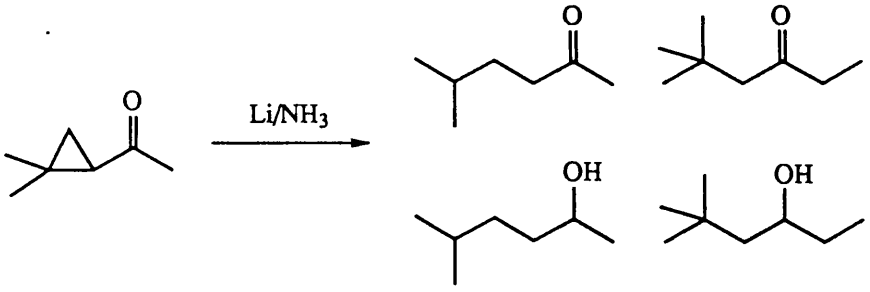


scheme 4.16

A second electron delivery then leads to the dianionic species (154) which, as a result of kinetic control, is apparently quenched in a regiospecific fashion by the ammonia to give an isomeric mixture of the ketones (151) arising from the more

stable primary carbanion. The derived alcohols (152) were then presumably formed during the workup by further reduction and protonation.

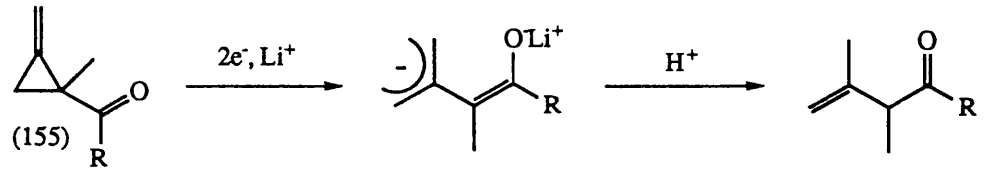
Closer inspection of the literature revealed that this phenomenon of over reduction was known to occur especially with cyclopropyl derivatives (see below), and we found this feature plagued many of our forthcoming reactions. In his work concerning the reduction of conjugated cyclopropyl ketones with lithium in liquid ammonia, Norin[89] only mentions that a further oxidation step was required in order to transform small amounts of alcohols present in the reaction mixture to the corresponding ketones. Following this disclosure, Dauben[91] also reported the formation of alcohols in the reduction of 2,2-dimethylcyclopropyl methyl ketone, again an oxidation step was conveniently employed to oxidise the alcohols to the corresponding ketones (scheme 4.17). It is interesting to note that no further explanation pertaining to the formation of the alcohols was advanced.



scheme 4.17

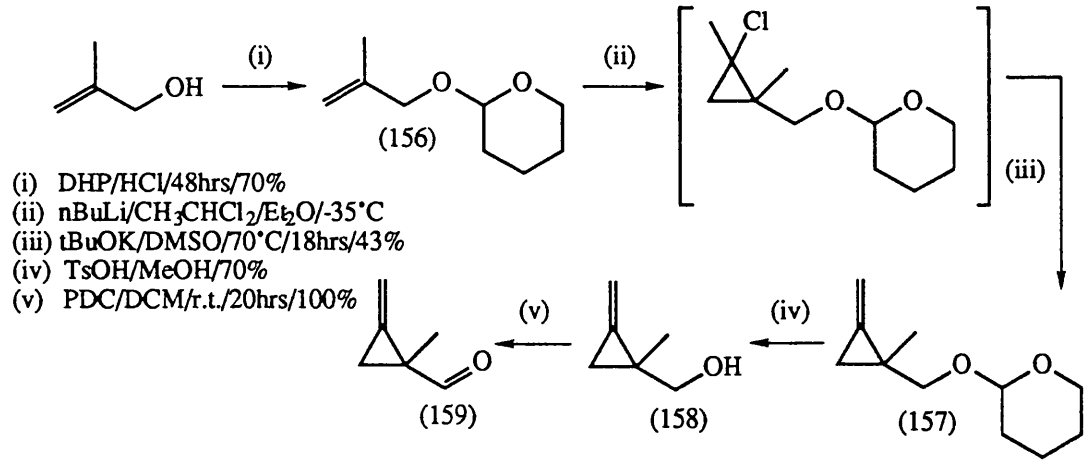
Throughout our studies, the blue colour of the lithium in liquid ammonia solution persisted till the time of quenching, implying that free electrons were still present in solution. Addition of solid ammonium chloride resulted in protonation affording the ketones, which were then rapidly reduced before the colour disappeared to produce the alcoholic products.

At this stage, we turned our attention to the construction of the modified derivative (155), which, self evidently, would not be complicated by the formation of isomeric products on ring cleavage (scheme 4.18).



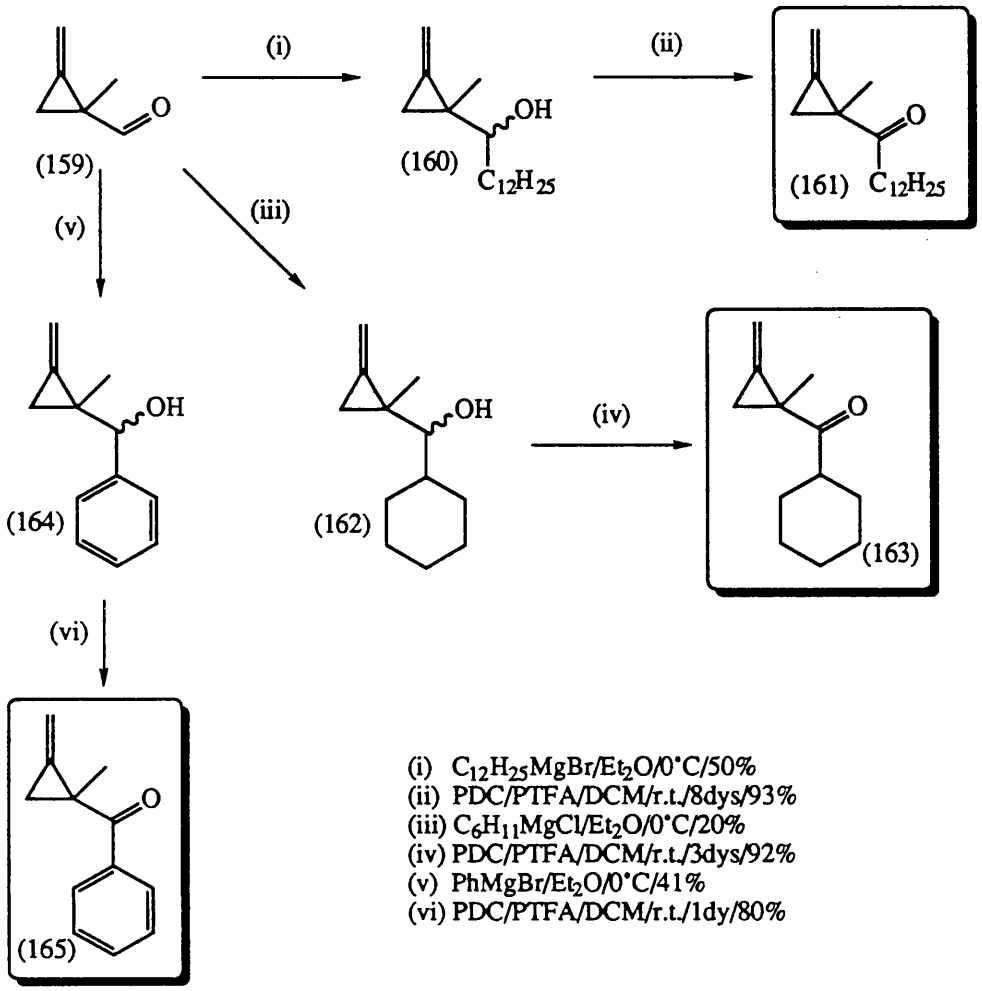
scheme 4.18

The methodology employed in the synthesis of the desired precursor was similar to that described previously. Protection of 2-methyl-2-propen-1-ol as its THP ether proceeded to give (156) in 70% yield. Methyl chlorocarbene addition followed by dehydrohalogenation under the standard conditions, gave the protected methylenecyclopropyl derivative (157) in 43% over the two steps. Subsequent removal of the hydroxyl protecting group afforded the alcohol (158) in 70% yield, and PDC oxidation yielded the requisite aldehyde (159) quantitatively (scheme 4.19).



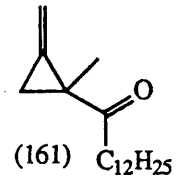
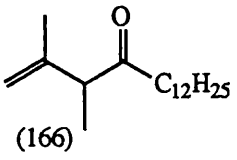
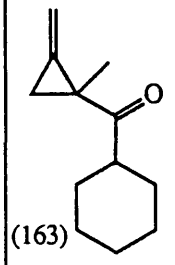
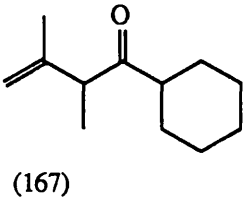
scheme 4.19

Subsequent reaction of (159) with the respective Grignard reagents, followed by oxidation, afforded the requisite cyclopropyl ketones (161), (163) and (165) in excellent yields (scheme 4.20).



scheme 4.20

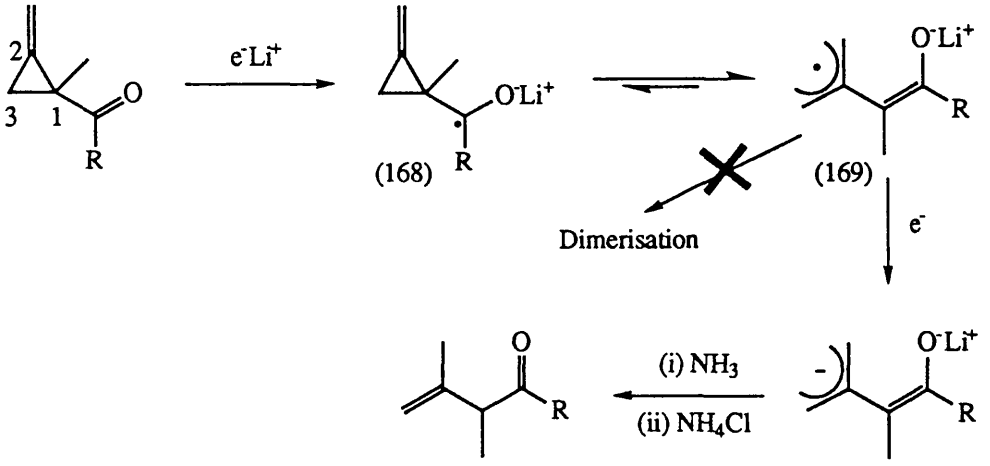
Subjection of (161) to the standard lithium in liquid ammonia conditions led to the β,γ-unsaturated ketone (166) in very good yield. Likewise, reduction of the cyclohexyl derivative (163) gave the ring opened product (167) in 63% yield (table 4.1).

KETONE	PRODUCT	YIELD%
 (161)	 (166)	78
 (163)	 (167)	63

(i) Li/NH_3/ (ii) NH_4Cl

table 4.1

In both of these examples, we can envisage the reaction to proceed *via* initial electron transfer to the carbonyl group generating the ketyl species (168). This in turn undergoes rapid ring opening with exclusive cleavage of the C_1-C_3 bond to give the primary radical intermediate (169) faster than reduction to the dianion species (scheme 4.21).

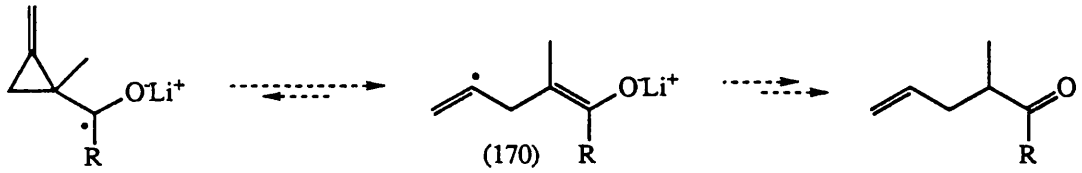


scheme 4.21

The formation of the former is probably due to the inherent allylic assistance to bond breaking, coupled with the extra stabilisation attained from the resulting conjugated

system thus produced.

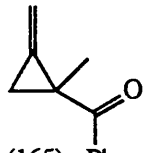
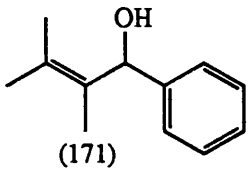
Cleavage of the alternative C_1-C_2 bond can also formally be envisaged, but this would give the higher energy vinylic radical species (170) (scheme 4.22). The radical in question is in an orbital perpendicular to that of the π-system and hence, the stabilisation present in (169) is obviously absent, thus disfavouring its formation.



scheme 4.22

Although the intermediacy of radical anions suggest that dimerization may compete with simple reduction, the high concentration of electrons in solution favours the probability of (169) accepting a second electron faster than dimerisation. The resultant dianion being highly basic, is capable of abstracting a proton from ammonia to form a simple enolate, and subsequent addition of ammonium chloride can than lead to protonation of this species to generate the observed ketonic products (166) and (167).

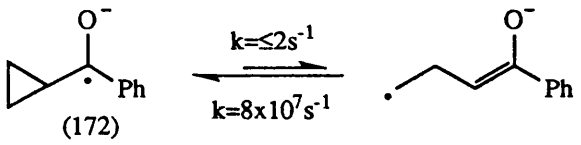
Subjection of the phenyl substituted methylene cyclopropyl ketone (165) to the standard conditions afforded to our surprise, the alcohol derivative (171) in 48% yield (table 4.2).

KETONE	PRODUCT	YIELD%
 (165) Ph	 (171)	48

(i) Li/NH_3 (ii) NH_4Cl

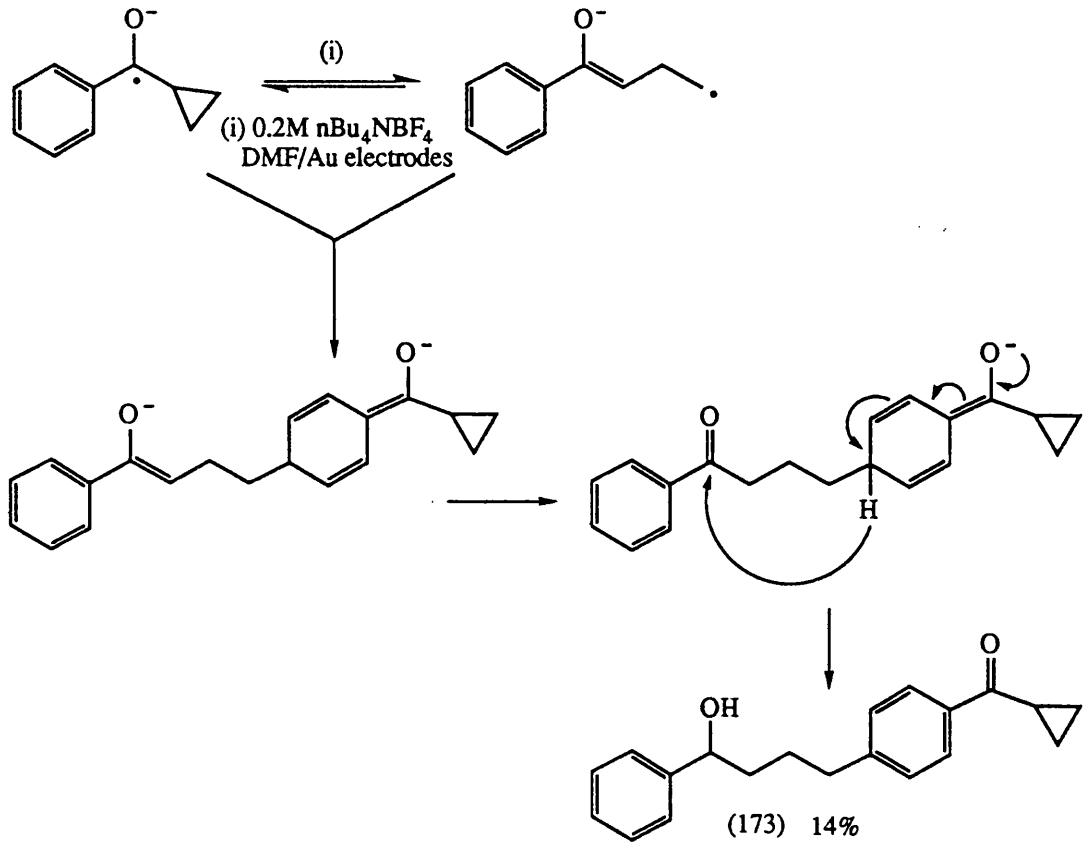
table 4.2

Tanko[150] has proved false the assumption that the use of the ring opening reaction of cyclopropylcarbinyl radicals as a mechanistic probe can be extended to cyclopropyl ketyls such as (172). He has further shown that the ring opening is reversible, with an equilibrium constant for the ring opening of (172) being $2x10^{-8}$, which overwhelmingly favours the ring closed form (scheme 4.23).



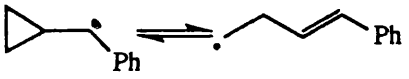
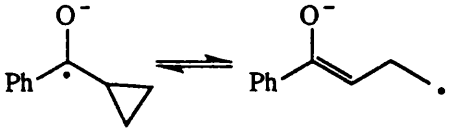
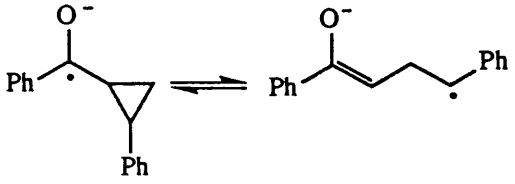
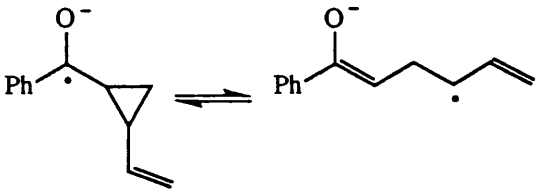
scheme 4.23

Hence, ketyls can be present in solution without ring opening being observed. This observation is attributed, as expected to the conjugative stabilisation arising from the presence of the neighbouring phenyl group. Further investigation has shown that the principle product isolated when phenylcyclopropyl ketone is subjected to bulk electrolytic reduction is the alcohol (173), arising from the coupling of the ring opened and ring closed forms, followed by an intramolecular hydride transfer (scheme 4.24).



scheme 4.24

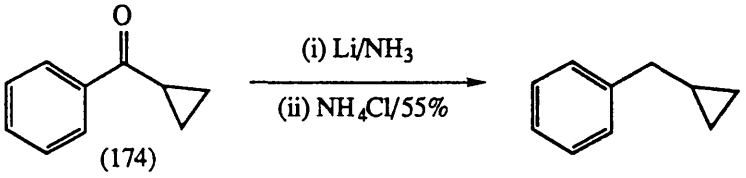
More recently, these workers have expanded on this theme by examining how the placement of radical stabilising substituents on the cyclopropyl ring facilitate ring opening.[151] Their results are summarised below together those of Ingold[152] and Beckwith[12] for comparison (table 4.3).

REACTION	k_1/s	k_{-1}/s
	$1.2x10^8$	$5x10^3$
	$1x10^6$	$1.2x10^7$
	≤ 2	$8x10^7$
	$1x10^7$	-
	$\geq 5x10^5$	-

k_1=rate of ring opening, k_{-1}=rate of ring closure

table 4.3

Finally, in contrast to our system, it is also interesting to note that some 20 years ago a group of American workers[153] reported the absence of any ring opened products in the lithium in liquid ammonia reduction of (174) (scheme 4.25).



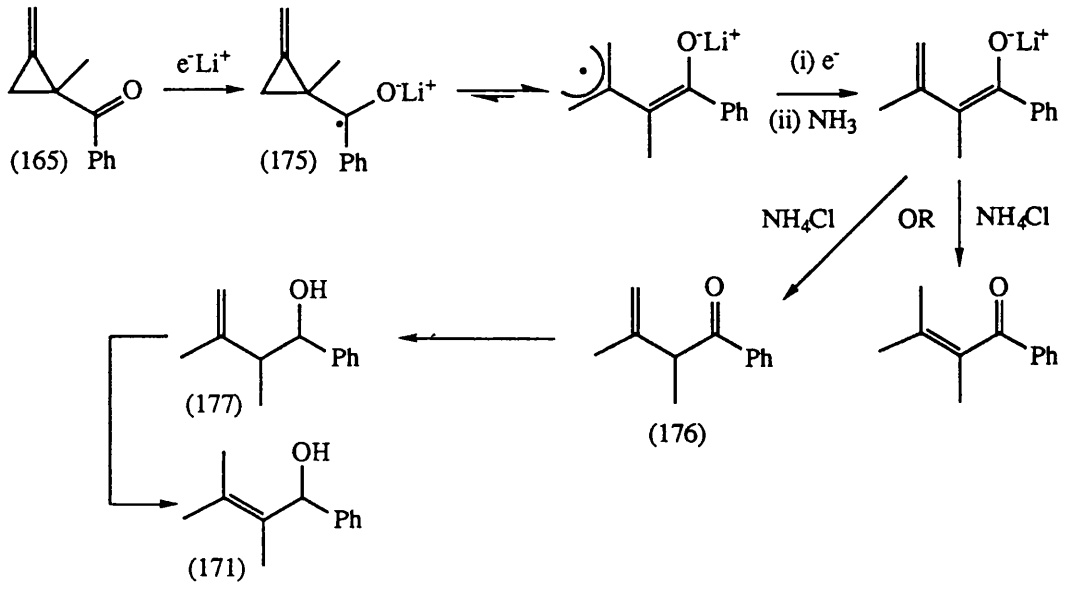
(174)

scheme 4.25

They explained this phenomenon by suggesting that the stabilisation effect by delocalisation into the neighbouring phenyl ring must be principle reason why cleavage was not observed, and as a consequence, (174) reduces as an aromatic ketone rather than as a cyclopropyl ketone.

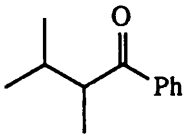
Thus, in comparison, we would expect the loss of resonance energy associated with ring opening in our system, not to be compensated by relief of ring strain. This is obviously not the case and other factors have to be considered. It appears that the exomethylene unit, as a result of allylic assistance, facilitates the ring opening process in a similar fashion to that observed with entry 5 (table 4.3). Thus, by virtue of the resultant allylic radical, reclosure to the ketyl radical anion is comparatively slow relative to the addition of the second electron to give the low energy enolate-allylic dianion. It is possible that partial compensation for the loss of resonance energy arises from stabilisation of the radical (or anion) portion of the ring opened radical anion (or dianion) *via* resonance, making the reaction both kinetically and thermodynamically more favourable.

From a mechanistic point of view, ring opening of (165) follows a similar sequence to that described for the reduction of the alkyl substituted congeners. Conversion of the aromatic ketone (165) to the ketyl radical anion (175) is followed by ring opening, subsequent addition of ammonium chloride generates the enone derivative (176) which in turn is further reduced to the alcohol before the excess lithium is destroyed (scheme 4.26).



scheme 4.26

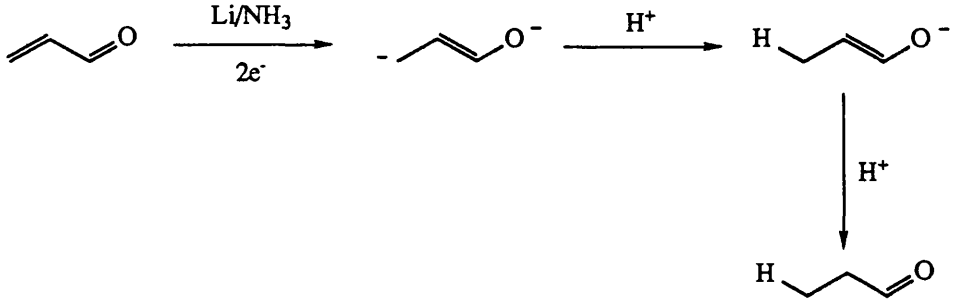
The isolation of the allylic alcohol (171) rather than the homoallylic alcohol (177) or the fully reduced ketone (178) (figure 4.2) is also surprising since the normal fate of enone reduction by dissolving metals is to give the saturated ketone product (scheme 4.27).



(178)

figure 4.2

The presence of the aromatic grouping may, however, in this instance encourage an anomalous protonation. At this moment in time, however, we have no clear mechanistic rationale for the isolation of (171) rather than (176) or (178).

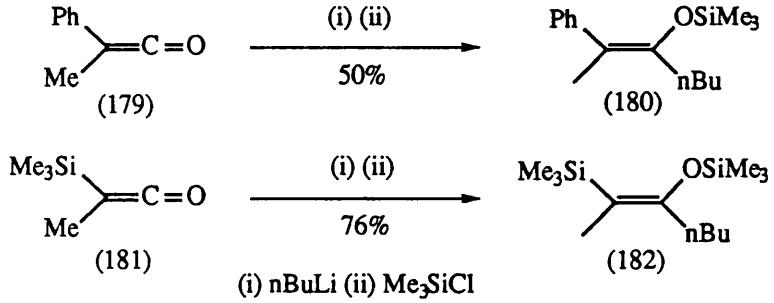


scheme 4.27

4.2 LITHIUM ENOLATE STUDIES.

With this preliminary success, the opportunity to study the possibility of trapping the intermediate lithium enolates with electrophilies other than protons became too important to reject. Both examples chosen for this study should, hypothetically speaking, lead to tetrasubstituted enolates, which are difficult to control in terms of stereospecificity. Moreover, we anticipated that the latter entities would be far more amenable to trapping than those generated under samarium(II) iodide conditions.
The direct stereocontrolled formation of tetrasubstituted enolates is one of the facets

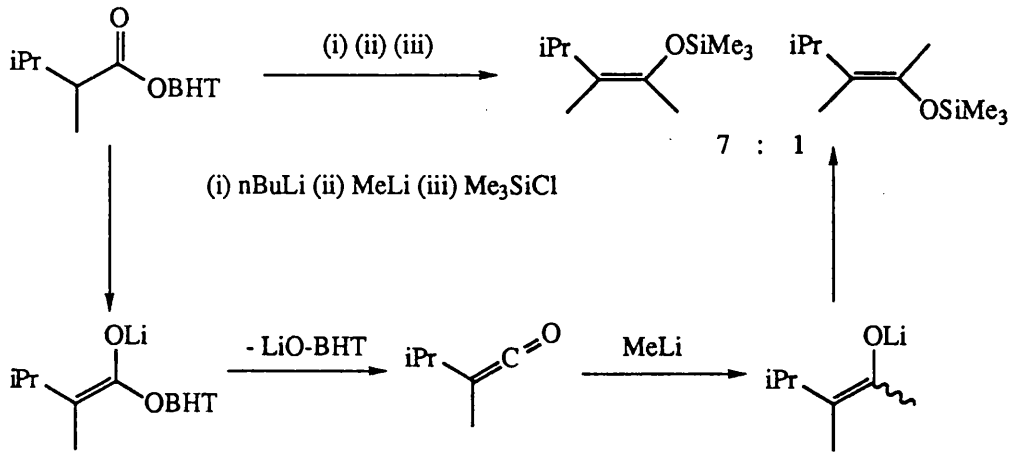
of enolate chemistry where recourse to the chemistry of the carbonyl group fails to provide a satisfactory synthetic method. The only controlled method which has been utilised to generate tetrasubstituted enolates is the addition of organolithium reagents to ketenes[154] (scheme 4.28).



scheme 4.28

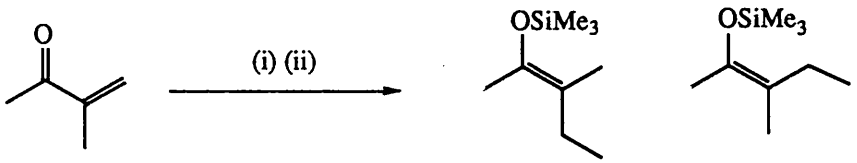
Tidwell found that *n*-butyllithium attacked from the least hindered face of the ketenes (179) and (181) to afford the silyl enol ethers (180) and (182) as the sole isomer to be isolated (scheme 4.28).

Clearly, however, the synthesis and lability of the precursor ketenes is a major drawback to this approach, and in work published simultaneously, Seebach[155] prepared ketenes *insitu via* the decomposition of 2,6-di(*t*-butyl)-4-methylphenyl (BHT) ester enolates. Addition of organolithium reagents again occurred stereoselectively as indicated below (scheme 4.29).



scheme 4.29

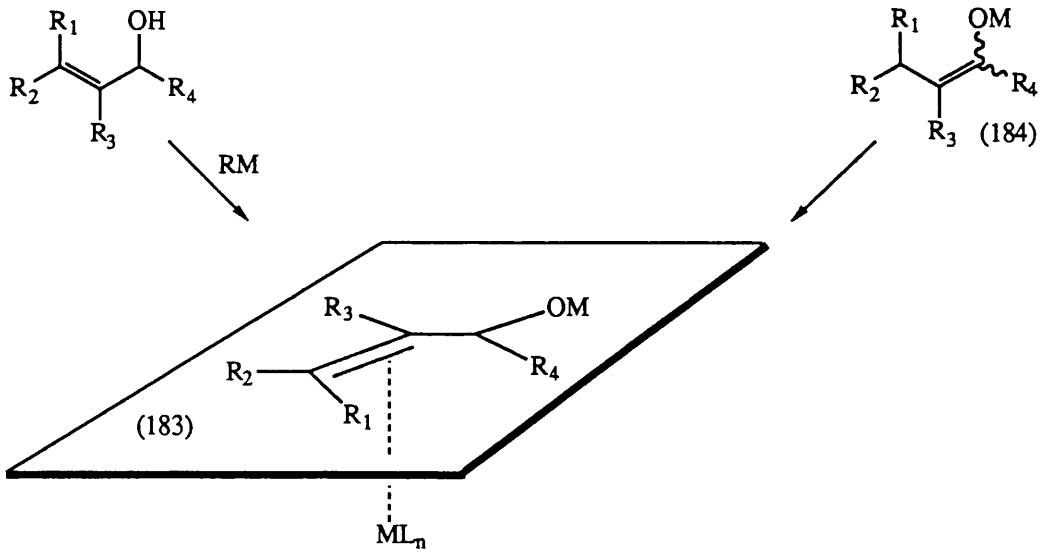
Nakamura[156] has shown that enolate generation *via* conjugate addition of organocopper reagents is possible in acyclic systems, however, the level of control of enolate geometry is only moderate (scheme 4.30).



(i) Me_2CuLi/THF (ii) Me_3SiCl/HMPA 2.6 : 1

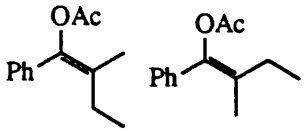
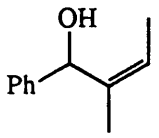
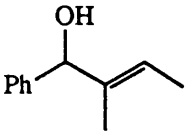
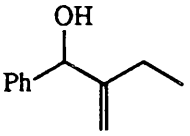
scheme 4.30

These examples clearly illustrate the need for a more general method for tetrasubstituted enolate formation under stereocontrolled conditions, this issue has also been addressed within our own laboratories[157] utilising allylic alcohols. The reaction proceeds *via* formation of an alkoxide species (183) in the presence of *n*-butyllithium, followed by catalytic isomerization of the double bond by the transition metal complex to generate the enolate (184) (scheme 4.31).



scheme 4.31

Subsequent low temperature quenching delivers the enol acetates in good to excellent yields, but again with only moderate stereoselectivity (table 4.4).

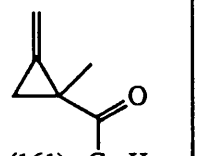
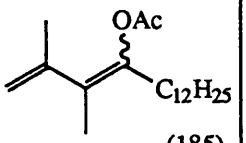
ALLYLIC ALCOHOL		YIELD%
	4 : 1	37
	3 : 1	75
	3.2 : 1	49

(i) nBuLi/THF (ii) $(Cy_3P)_2NiCl_2$ (10 mol%)/reflux (iii) AcCl/-78°C

table 4.4

Thus, on inspection, ketones (161) and (163) respectively appear to be ideal candidates for the generation of both regio and stereospecific tetrasubstituted enolates. The experimental protocol followed was similar to that described by Dauben and Wolf.[93] A solution of the ketone in ether was added dropwise to the blue ammoniacal solution as before, and reflux continued for 40 minutes. After evaporation of the ammonia the milky white residue was taken up in ether and added dropwise to ice-cold acetic anhydride and stirring continued overnight.

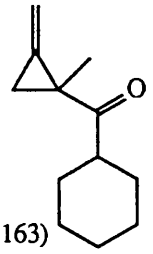
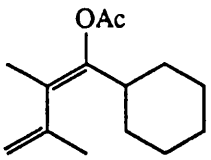
Thus, reduction of ketone (161) and subsequent trapping with acetic anhydride gave the desired enol acetate (185) in a modest 26% yield (table 4.5) Unfortunately, nOe experiments were inconclusive in establishing the true stereochemical outcome of the resulting acetate.

KETONE	PRODUCT	YIELD%
 (161) $C_{12}H_{25}$	 (185)	26

(i) Li/NH_3 (ii) $Ac_2O/0°C$ to r.t./18hrs

table 4.5

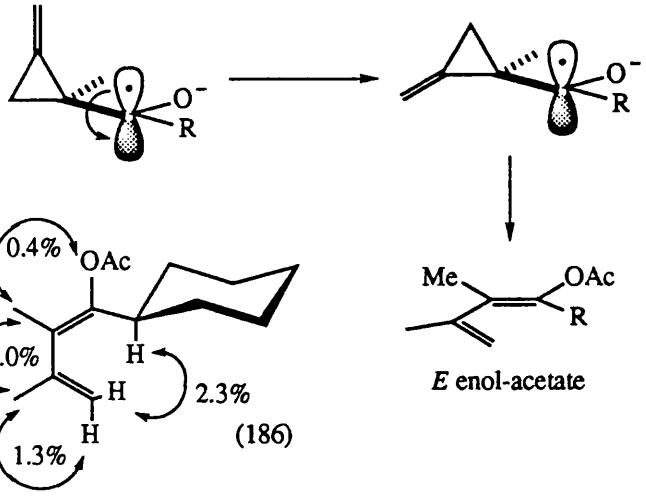
Sequential reduction of the cyclohexyl substituted methylenecyclopropyl ketone (163) and trapping with acetic anhydride gave the acetylated product (186) in a somewhat more pleasing 35% yield (table 4.6).

KETONE	PRODUCT	YIELD%
 (163)	 (186)	35

(i) Li/NH_3 (ii) $Ac_2O/0°C$ to r.t./18hrs

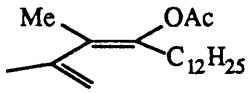
table 4.6

In this case, however, nOe experiments revealed a *cis* relationship between the C3-methyl group and the acetoxy functionality, and irradiation of the olefinic protons resulted in a positive response from the proton on the cyclohexyl ring. On closer inspection of (163), it becomes clear that it is set up to deliver only the *E* isomer (scheme 4.32).



scheme 4.32

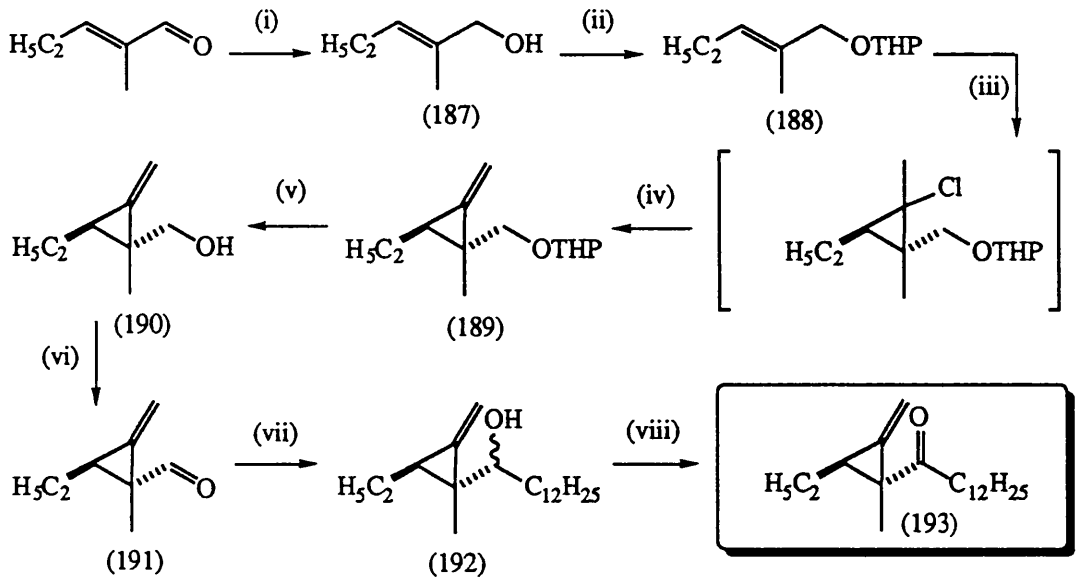
Likewise, we can also conclude that (161) most probably also adopts a similar geometry (figure 4.3).



E enol-acetate
(161)

figure 4.3

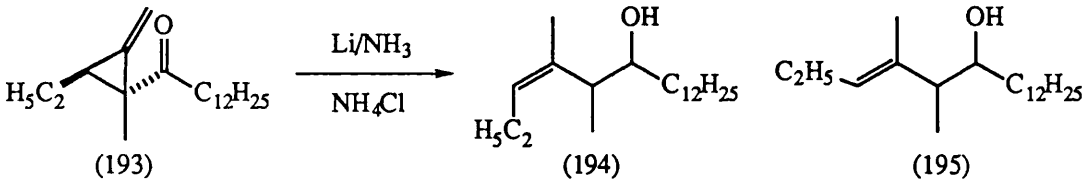
In our eagerness to probe further into this otherwise uncharted territory, concurrent with the previous studies, we set forth on the synthesis of yet another modified system by utilising the methodology previously described. DIBAL-H reduction of 2-methyl-2-pentenal led quantitatively to the allylic alcohol (187). Protection as before proceeded to give (188) in 89% yield and introduction of the methylenecyclopropyl moiety gave the desired cyclopropyl species (189) in 70% yield. Deprotection, followed by PDC oxidation, and Grignard addition of dodecylmagnesium bromide delivered the alcohol (192) in excellent yield. Further oxidation led to us to the requisite precursor (193) in 54% yield (scheme 4.33).



(i) DIBAL-H/PhMe/-78°C/98% (ii) DHP/HCl/48hrs/89%
(iii) nBuLi/CH_3CHCl_2/Et_2O/-35°C (iv) tBuOK/DMSO/70°C/18hrs/70%
(v) TsOH/MeOH/89% (vi) PDC/DCM/r.t./20hrs/71%
(vii) $C_{12}H_{25}MgBr$/Et_2O/0°C/99% (viii) PDC/PTFA/DCM/r.t./3dys/54%

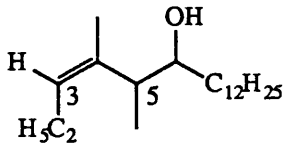
scheme 4.33

Subjection of (193) to the standard reduction conditions yielded two isomeric alcohols, the less polar (194) in 16% yield and the more polar (195) in 46% yield, unfortunately, no ketonic products were observed.



scheme 4.34

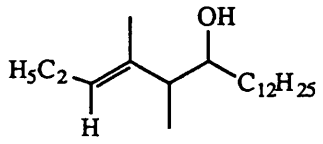
In order to elucidate the structure of the two products, nOe experiments were conducted. These were particularly useful in confirming the stereochemistry about the double bond. Irradiation of the alkenic proton of the less polar product caused an enhancement of the allylic methyl group and *vice versa* (table 4.7).



Irradiated	nOe Enhancement	
H_3	C_4-CH_3	0.5%
	C_5-CH_3	0.6%
	H_5/H_2	4.3%
C_4-CH_3	H_3	2.1%

table 4.7

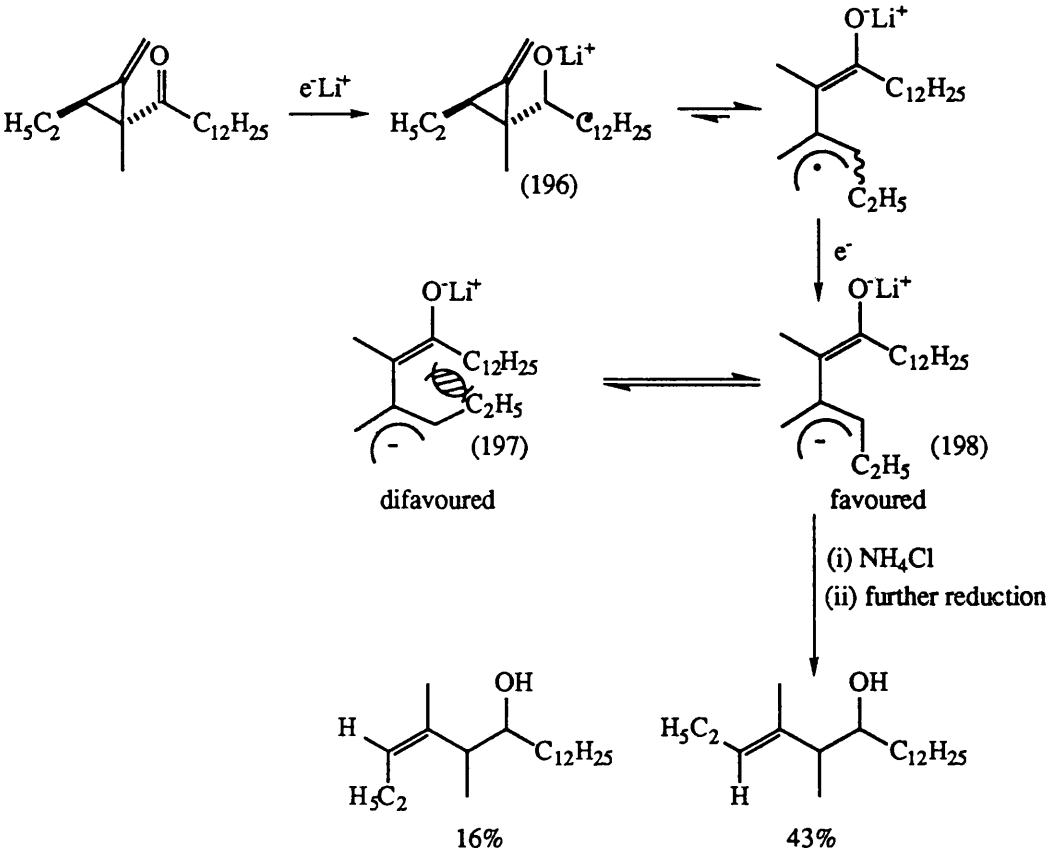
Likewise, irradiation of the olefinic proton of the more polar resulted in no nOe enhancement between the C_4-methyl and this proton, however, a small differentiated signal was evident, indicating that a through bond coupling effect was operating between these two groups (table 4.8).



Irradiated	nOe Enhancement	
H_3	C_5-CH_3	1.2%
	C_2-CH_3	2.4%
	H_5	4.0%

table 4.8

Predominance of the product displaying the *trans* geometry was not totally unexpected. Initial electron transfer to the ketone generated the ketyl radical anion (196), which subsequently ring opened to give (197) and (198). Thus, the unfortunate steric interaction associated with (197), between the ethyl grouping and the alkyl chain, disfavours formation of the *Z* geometric isomer of the allylic alcohol unit (scheme 4.35).



scheme 4.35

4.3 CONCLUSION.

In summary, therefore, systems of type (a) led to mixtures of alcoholic and ketonic products, whereas type (b) gave exclusively the ketone products, and those of type (c) led to exclusive formation of the alcohol products (figure 4.4).

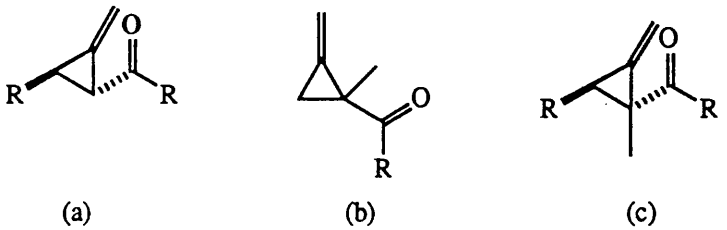
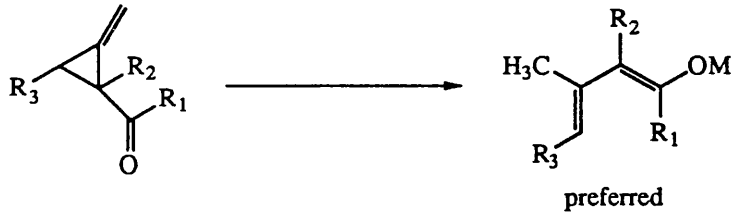


figure 4.4

We have advanced a theory on the formation of the alcohol products in which we argue that they arise as a result of further reduction on the addition of the ammonium

chloride. Thus, it appears that the nature of the products do not reflect the disposition of the starting alkylidene substrate. Nevertheless, the pattern of alcohol verses ketone formation on protic work up is not clear at the present time, and further work is certainly required in order to devise and control the inherent possibilities which exist for both regio and stereocontrolled generation of complex conjugated tetrasubstituted enolate systems. Moreover, protonation of the allylic anion at the dianion stage also appears to be regiospecific, and as a result of equilibration of the allyl anion geometry displays in addition, a preference for controlled alkene formation (scheme 4.36)



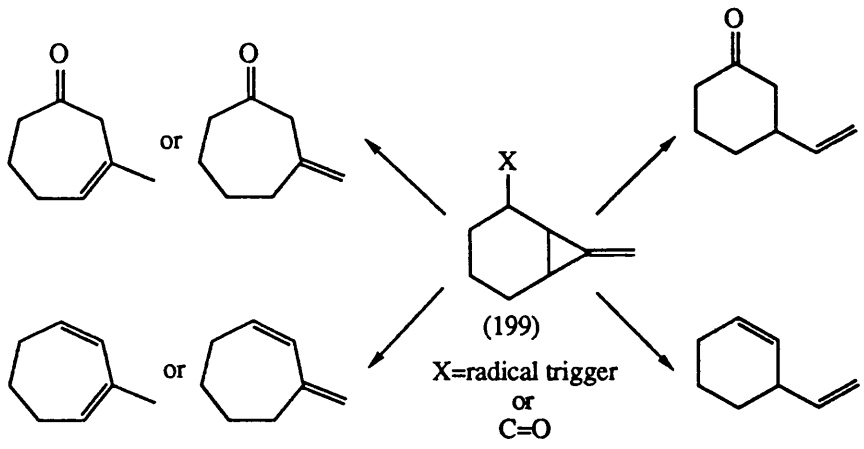
scheme 4.36

Thus, in contrast to our samarium enolate studies, the corresponding investigation of lithium enolates proved far more fruitful, in bringing us yet closer to the direct formation of tetrasubstituted enolates under stereochemical control. Unfortunately, due to the constraints of time upon us, a more systematic study was out of the question. Nevertheless, it is clear from the initial results, that there is great potential for further elaboration in this area, since we are limited not only to O-trapping, but alkylation at the carbon can also lead to a variety of α-substituted carbonyl derivatives. Of more synthetic importance, however, and also conceivable with such systems, is the stereoselective assembly of quaternary centres *via* the aldol reaction.

Chapter Five

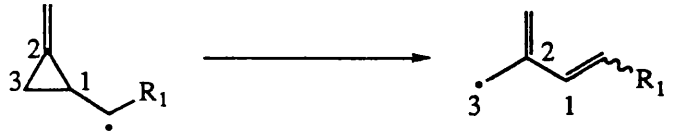
5.1 RING CLEAVAGE REACTIONS OF THE 7-METHYLENEBICYCLO[4.1.0] SYSTEM.

It is clear from the introductory discussion that the chemical literature contains a great many examples of ring cleavage reactions of the bicyclo[n.1.0]alk-2-yl radicals and similarly substituted systems. In contrast, however, the analogous 7-methylenebicyclo[4.1.0] system (199), to the best of our knowledge, has not been explored. Therefore, we thought it would be interesting to study the ring opening reactions of such systems *via* generation of both the carbon centred radical and the ketyl radical anions using the methods which we have previously discussed (scheme 5.1).



scheme 5.1

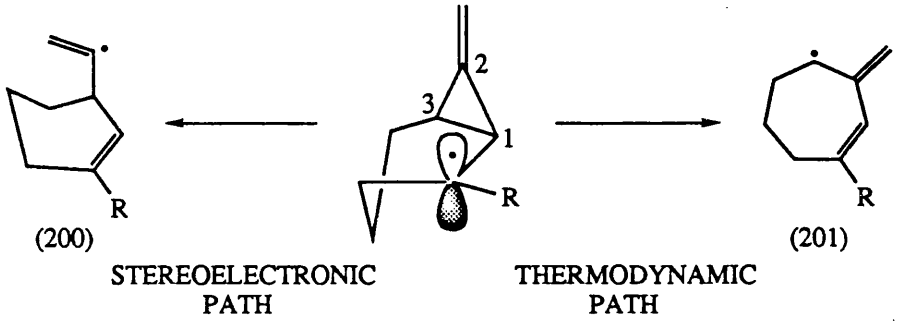
As we have seen in our studies of the monocyclic series, where free rotation is possible, there is an overwhelming preference for formation of products derived *via* the anticipated cleavage of the C_1-C_3 bond (scheme 5.2).



scheme 5.2

In bicyclic systems, however, the rigidity is such that orbital overlap of the SOMO

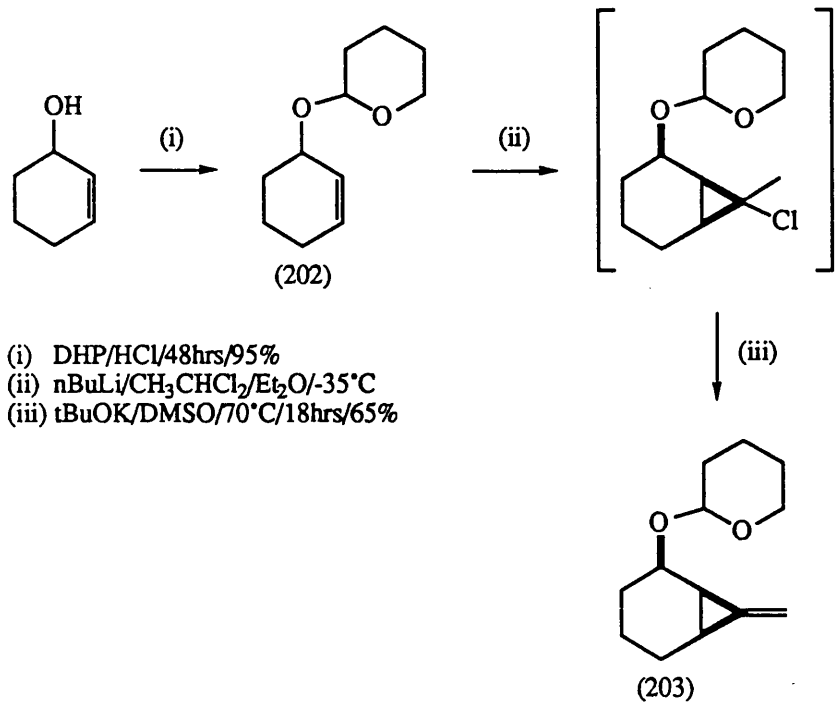
with the stronger exocyclic bond is stereoelectronically favoured and hence, this particular system might well be expected to afford the vinylic radical (200) despite the fact that the internal C_1-C_3 bond is inherently weaker and the resultant low energy allylic radical (201) is also favoured on thermodynamic grounds (scheme 5.3). The outcome of this battle between stereoelectronic control and thermodynamics was not readily predictable and therefore of interest to explore.



scheme 5.3

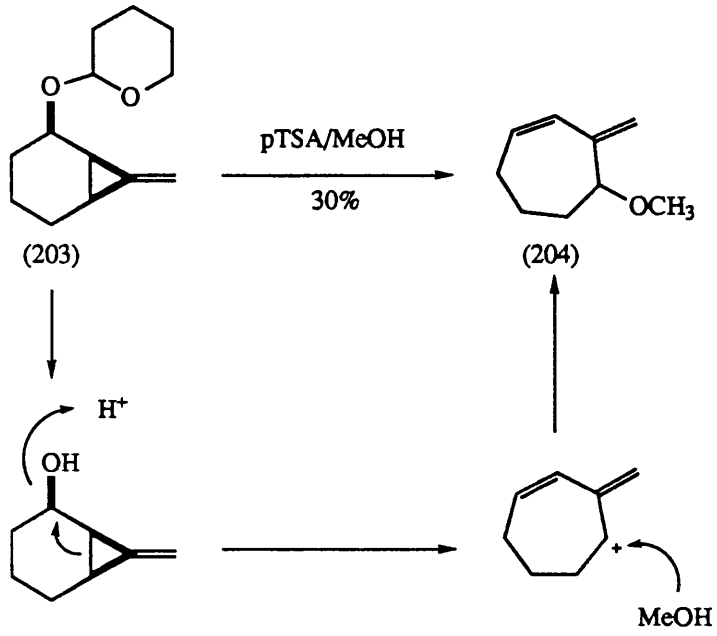
5.1.1 Generation of Carbon Centred Radicals.

Construction of the requisite precursors for this investigation initially employed methodology identical to that used for the assembly of the monocyclic counterparts. Protection of 2-cyclohexen-1-ol as its THP ether proceeded in 95% yield and introduction of the methylenecyclopropyl moiety was successfully accomplished affording (203) in 65% yield (scheme 5.4).



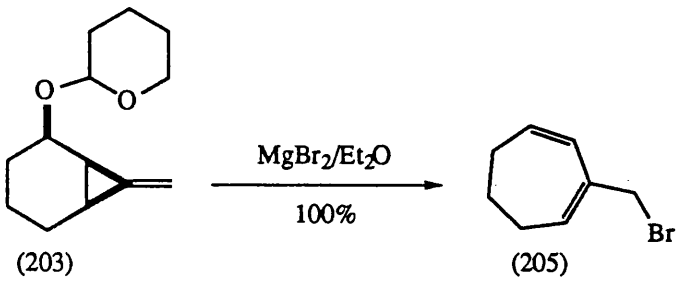
scheme 5.4

In contrast to the monocyclic systems, removal of the protecting group proved somewhat problematic. Deprotection in the normal manner with *p*-toluenesulfonic acid in methanol yielded only the ring opened cycloheptene derivative (204). We postulate that deprotection proceeds to give the desired alcohol, but this acid labile product spontaneously ring opens, not unexpectedly due to the extra strain associated with the *exo*-methylene double bond, to give an intermediate diene which is then attacked by methanol affording 4-methoxy-3-methylenecyclohept-1-ene (204) in 30% yield (scheme 5.5).



scheme 5.5

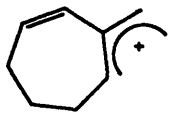
Thus, we turned our attention to a milder method of deprotection hoping to eliminate or at least limit this ring opening. A group of Korean workers[158] have reported such deprotections to occur in excellent yields in the presence of magnesium bromide in ether. Application of this method to our system, however, this time yielded only the ring opened bromide (205) in quantitative yield (scheme 5.6). Interestingly, and in contrast to the attack of methanol, the endocyclic diene was formed.



scheme 5.6

Presumably, a similar mechanism operates here. Initial co-ordination of the Lewis acid results in loss of the protecting group to give intermediate (206) as before. This is then attacked by the bromide anion from the most accessible position to give (205) (figure 5.1). However, the inherent instability of the product prevented complete

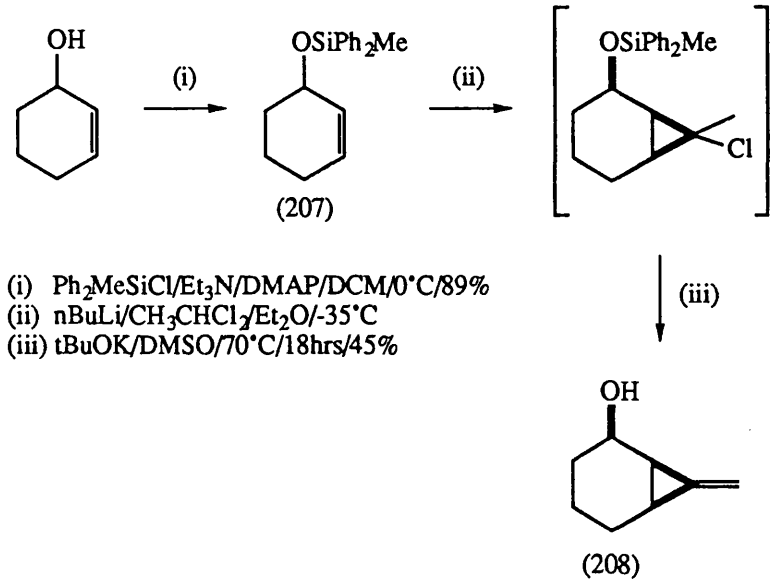
characterisation of the cycloheptyl bromide derivative.



(206)

figure 5.1

Re-evaluation of the situation led us to consider an alternative alcohol protecting group, namely one which could be removed under near neutral conditions. Protection of 2-cyclohexen-1-ol with diphenylmethylchlorosilane yielded the silyl ether (207) in 89% yield; carbene addition, followed by elimination of hydrogen chloride to generate the methylenecyclopropyl derivative (208) proceeded in modest yield. Fortunately, deprotection of the alcohol was not found to be necessary, since under the forcing conditions of the previous step, loss of the silyl protecting group was found to occur, possibly by some form of chloride assistance to give the desired alcohol (208) (scheme 5.7).



scheme 5.7

It is interesting to note that the approach of the carbene species is directed by the ether oxygen. Hence, in stereochemical terms this anchoring effect results in a *cis*-

relationship between the alcohol and the alkylidene cyclopropyl moiety (figure 5.1).

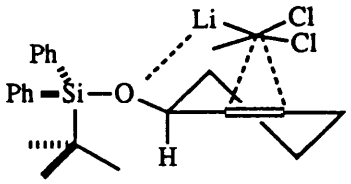


figure 5.1

In a effort to verify the stereochemical assignment of alcohol (208) a series of nOe experiments were conducted. Unfortunately, no conclusion could be drawn about the orientation of the alcohol with respect to the cyclopropane ring in this particular system (figure 5.2). Alternatively, the magnitude of the coupling constant between H_1 and H_2 would confirm the stereochemical relationship in question. Due to the broading affect of the alcohol, however, it was not possible to determine this by such an approach.

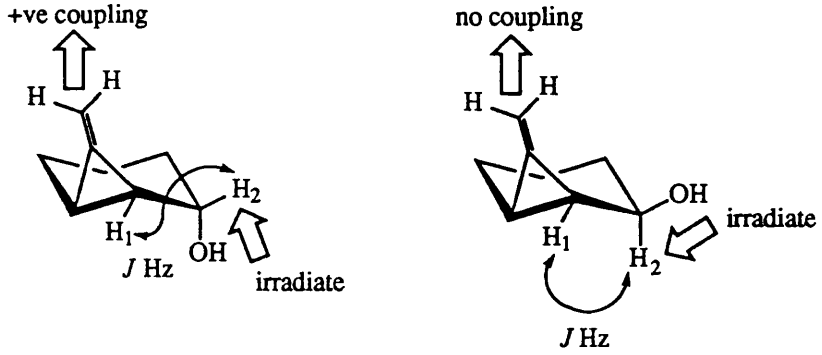
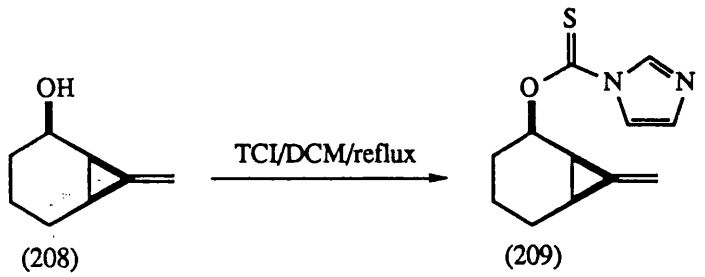


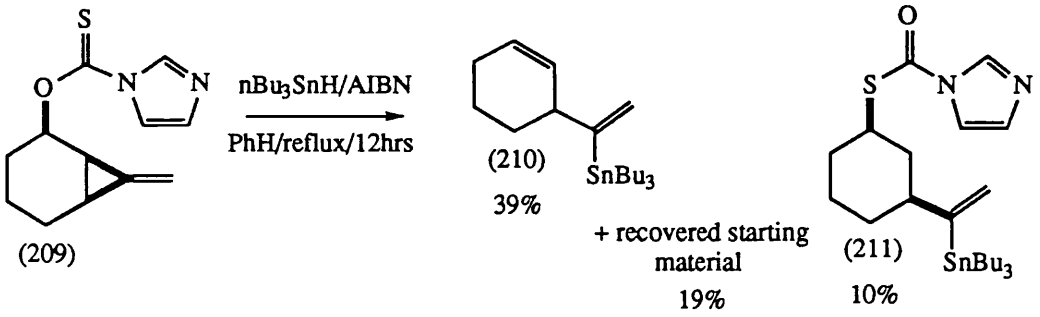
figure 5.2

We were now in a position to replace the hydroxyl group of (208) with a radical trigger, this was achieved as described previously with 1,1'-thiocarbonyldiimidazole (scheme 5.7). Examination of both the ^1H and ^{13}C spectra of the resultant product, however, showed the presence of two very similar thiocarbonylimidazolide derivatives; all the resonances were doubled up and of similar δ value, except for the methine protons sited at C_1, which resonated at the expected value of 4.15ppm and not so expected 4.85ppm; traces of ring opened products were also evident.



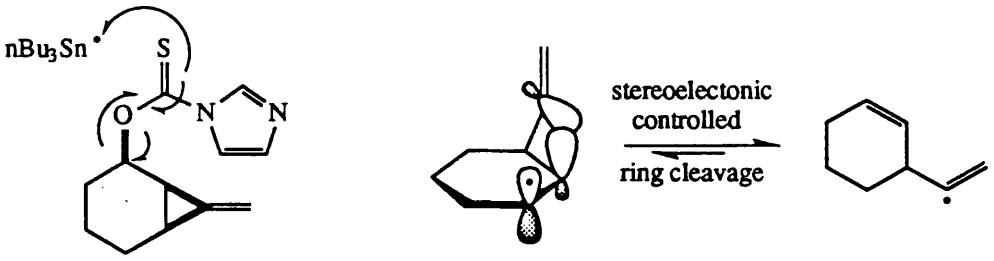
scheme 5.7

Nevertheless we decided to treat the mixture (209) with tri-*n*-butylstannane to initiate the radical reaction. The latter with AIBN as a solution in benzene, which had previously been thoroughly degassed, was introduced into a solution of the thiocarbonylimidazole derivative (209) in benzene over a period of 2 hours, and stirring continued at reflux for a further 12 hours. Tlc visualisation of the resultant reaction mixture showed the presence of two less polar products, which we identified as (210) in 39% yield and (211) in 10% yield, accompanied by 19% of the unreacted starting material (scheme 5.8).



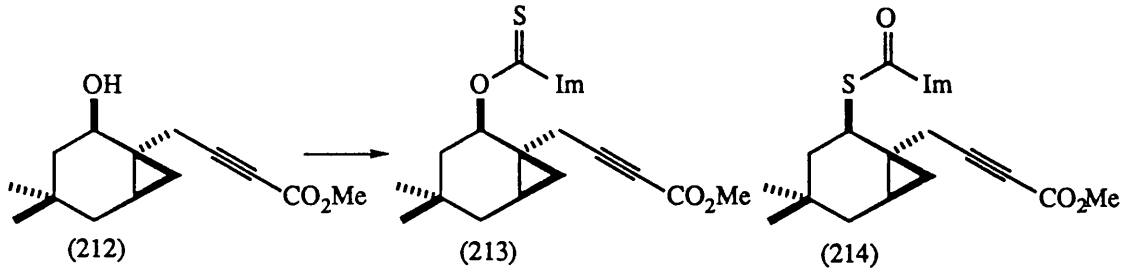
scheme 5.8

We initially anticipated that the reaction would be controlled by stereoelectronic factors, i.e. the cyclopropane bond which is cleaved is that which aligns most efficiently with the radical *p*-orbital and so provides the best overlap for the developing π-orbitals leading to the formation of 3-ethenylcyclohexene (scheme 5.9).



scheme 5.9

From the isolation of (210) and (211) it is clear, however, that some other effect must be operating. In terms of the formation of the thioester a similar phenomenon[19] has been observed within our group in the preparation of the corresponding thiocarbonylimidazolide derivative . from the alcohol (212). The former was in fact a mixture of the thiocarbonyl (213) and the rearranged carbonyl compound (214) (scheme 5.10).



scheme 5.10

This thermodynamically favoured thiocarbonyl interconversion originates from π-stacking between the acetylene and the imidazole moieties (figure 5.3)

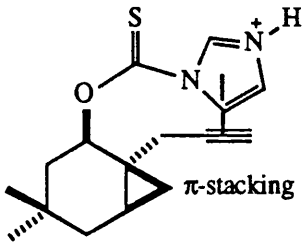
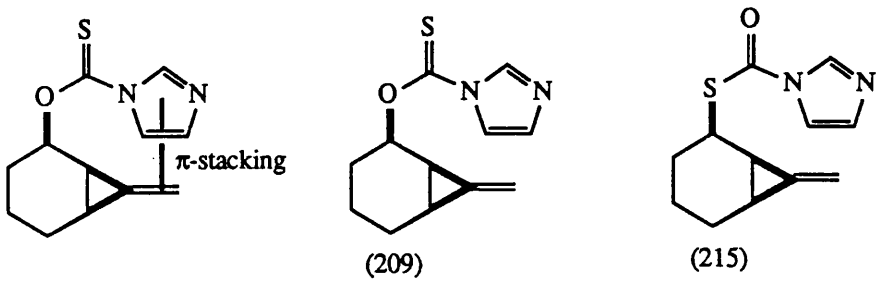


figure 5.3

We feel that a similar effect is operating within our bicyclic system, namely π-

stacking between the olefin and the imidazole group, which induces this rearrangement, leading to a mixture of the thiocarbonyl (209) and the rearranged carbonyl compound (215) (figure 5.4).

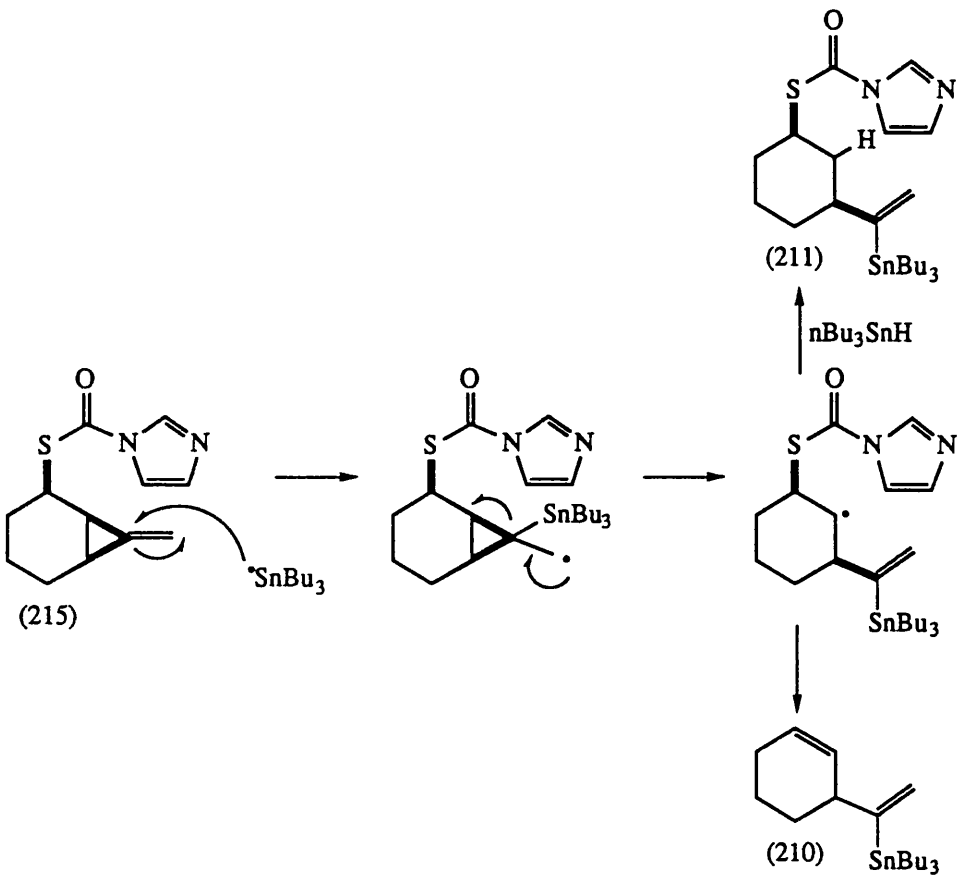


(209) (215)

figure 5.4

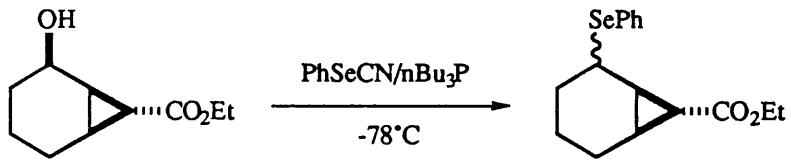
This rearrangement was strongly suggested by analysis of the ir spectrum, it showed a very strong peak at 1687 cm^{-1} which was ascribed to be the carbonyl stretch of the rearranged product (215). Nevertheless, the thiocarbonyl stretch was also evident at 1215 cm^{-1}.

Thus, when this mixture was treated with tri-*n*-butylstannane and AIBN initial attack by the tin radical occurred on the *exo*-double bond, which was followed by rapid ring opening of the cyclopropyl methyl radical to give the diene (210) in 39% yield. Together with the ring opened product we also isolated what appeared to be the reduced product (211) in 9% yield which was somewhat surprising (scheme 5.11). This phenomenon of radical addition on to alkylidene cyclopropanes has previously been observed but only in monocyclic systems, and curiously, the addition of tin radicals has never been seen to occur (see section 2.3).



scheme 5.11

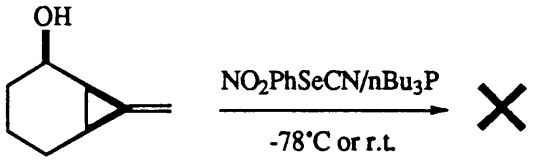
As the use of the thiocarbonylimidazolide group as a radical trigger was proving to be somewhat unsatisfactory for this particular system, thus, we decided to examine an alternative. Clive[82] (see section 2.3) has shown that alcohols may be transformed into their corresponding phenylselenides with phenylseleno cyanate in connection with his work on cyclopropylcarbinyl radicals (scheme 5.12).



scheme 5.12

Adoption of Clive's modified version of Grieco's[159] method, namely the slow addition of the selenocyanate to a mixture of the alcohol and tributylphosphine at -78°C gave only diphenyldiselenide together with recovered starting material in 57%

yield. Reverting to Grieco's original procedure, which involved treatment of a solution of the alcohol and phenylseleno cyanate with the phosphine at room temperature, led unfortunately, to a complex mixture of products (scheme 5.13).



(208)

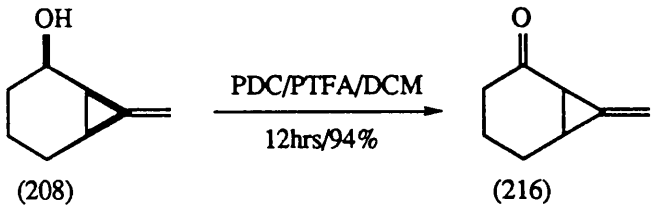
scheme 5.13

Analysis of the ^1H nmr spectrum of the crude reaction mixture suggested that ring opened products were also present. Control experiments using both procedures were conducted on the simple alcohol derivative 2-cyclohexen-1-ol to establish whether formation of the selenide derivative was reproducible in our hands. Unfortunately, in both cases a complex mixture of products was isolated, the major component in both cases being not unexpectedly diphenyldiselenide.

Thus, attempts to generate carbon centred radicals in such bicyclic systems appears to mirror that of the monocyclic counterparts. Due to circumstances beyond our control both systems failed to operate as initially anticipated. More success was seen when ketyl radical anion generation was attempted with the monocyclic systems and hence, we turned our attention to this alternative method for generating the radical α to the alkylidene cyclopropane.

5.1.2 Radical Anion Generation.

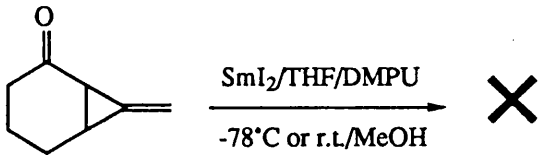
The requisite precursor for our forthcoming studies was obtained by a simple PDC oxidation of the alcohol (208). As usual, this proceeded cleanly to give the ketone (216) in near quantitative yield (scheme 5.14).



(208) (216)

scheme 5.14

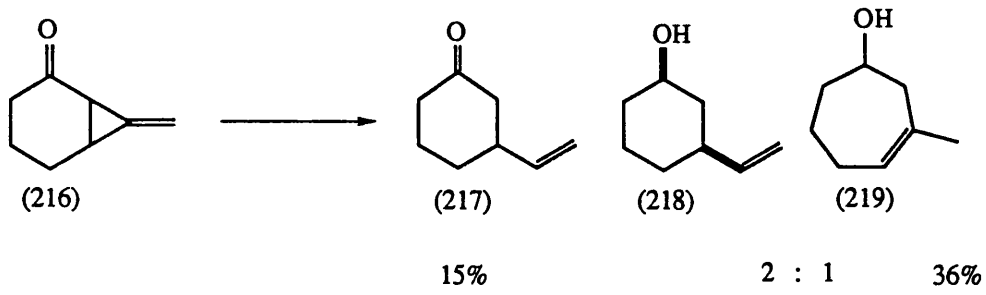
We were now in a position to investigate the nature of the ring opening of (216). Although samarium(II) iodide reductive ring cleavage of our monocyclic alkylidene derivatives (see section 4.1.2) was met with disappointment, we were more confident that samarium(II) iodide reduction of the bicyclic congener would be more successful. But alas, under various samarium(II) iodide mediated conditions only a complex mixture of products was obtained (scheme 5.15).



(216)

scheme 5.15

More pleasing results were seen in the presence of a lithium in liquid ammonia reductive environment. Subjection of (216) to the usual experimental conditions led to the isolation of two products. In total contrast to the monocyclic series, the product arising from cleavage of the stereoelectronically favoured exocyclic cyclopropane bond was obtained, albeit in a mere 15% yield. We speculated that the more polar product would therefore be the corresponding alcohol arising from further reduction of (217). However, on closer scrutiny, both the ^{1}H and ^{13}C nmr spectra showed this more polar component to be a mixture of two products. The major constituent of which was indeed the alcohol (218), accompanied by a second alcohol derivative (219) arising from cleavage of the alternative internal bond (scheme 5.16).



scheme 5.16

Evidently, the intrinsic resonance stabilisation available to the conjugated intermediates (220) and (221) arising from cleavage of the thermodynamically favoured weaker endocyclic bond also play an important role towards the formation of (219) (figure 5.5).

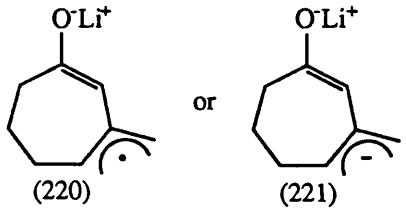
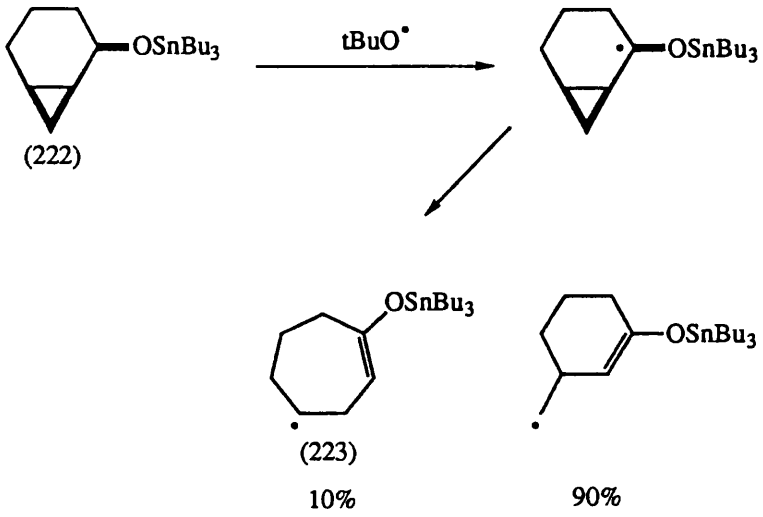


figure 5.5

Cleavage of the internal bond is not totally alien to the chemical world. Davies[137] has reported that the ring opening of the bicycloheptyl derivative (222) yields products arising from cleavage of both the *exo*cyclic and *endo*cyclic bonds (scheme 5.17). However, no reason was forwarded for the formation of (223)



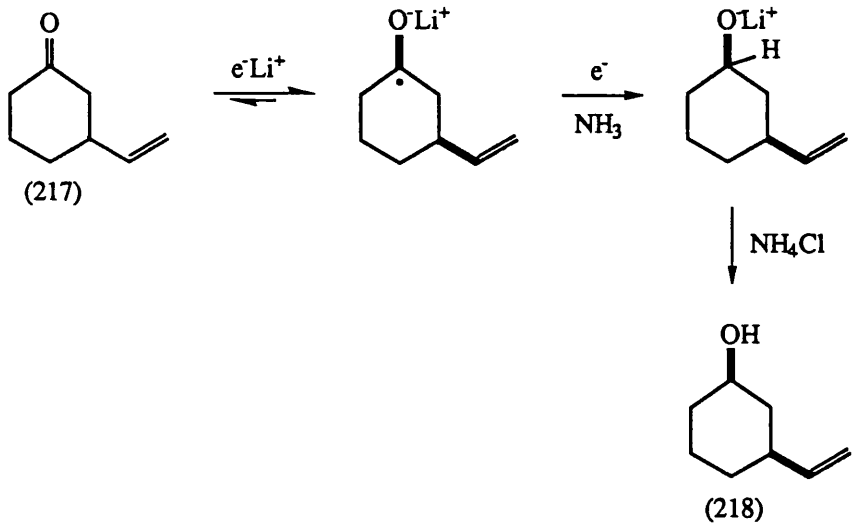
scheme 5,17

The direction of ring-opening in bicyclic systems is ascribed to the preferential overlap of the σ* orbitals of the exocyclic bond with the adjacent *p*-orbitals of the radical SOMO when the cyclohexane ring is in the more stable chair conformation (224). However, adoption of the boat geometry (225) can lead to cleavage of the desired bond, but obviously reaction *via* such a conformation is not energetically favoured. Thus , it appears that the reaction proceeds through such a conformation, and that thermodynamics out weigh the stereoelectronic factor in this example (figure 5.6).

figure 5.6

The presence of the alcohol (218) arises as previously explained as a result of further reduction of the ketone by the excess lithium in solution on addition of solid ammonium chloride (scheme 5.18). Presumably (219) is formed as a result of a

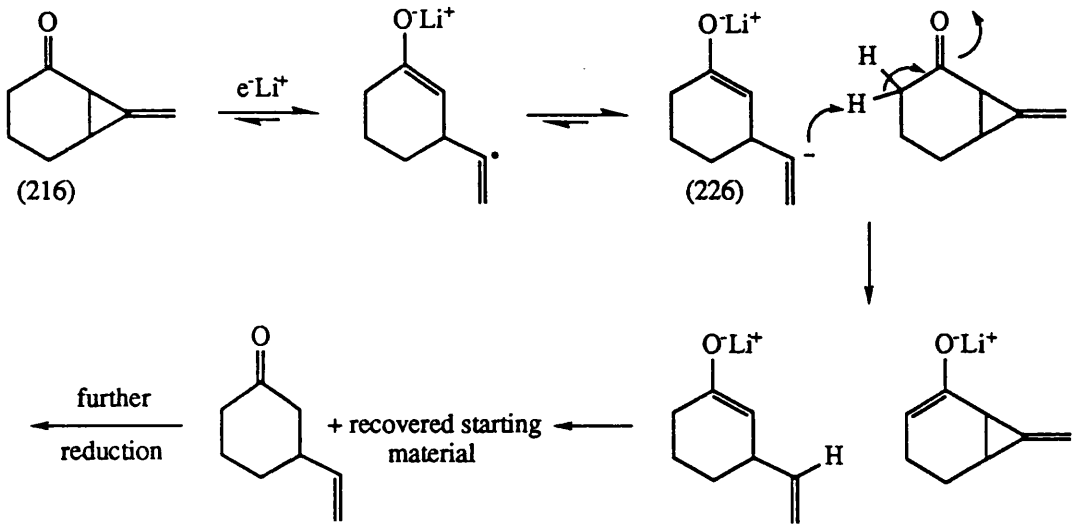
similar process.



(217) (218)

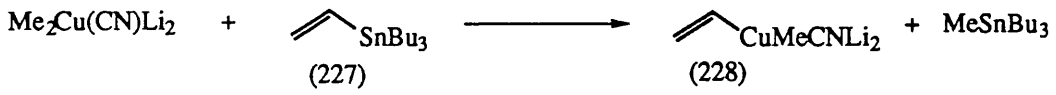
scheme 5.18

Returning to the ketone (217) its formation can be explained as follows. Initial electron transfer gives the ketyl radical anion which as a result of stereoelectornic control results in cleavage of the exocyclic bond to give, after second electron delivery species (226). The intermediate dianion (226) may then abstract a proton either from the solvent, or alternatively an aspect not previously emphasised, from the starting material as a result of the inherent acidity of the protons α to the ketone functionality. This latter possibility suggests that the enolate of the starting material would be formed. However, upon purification of the crude material the presence of the starting material was not observed, thus decreasing the credibility of this reaction pathway (scheme 5.19).



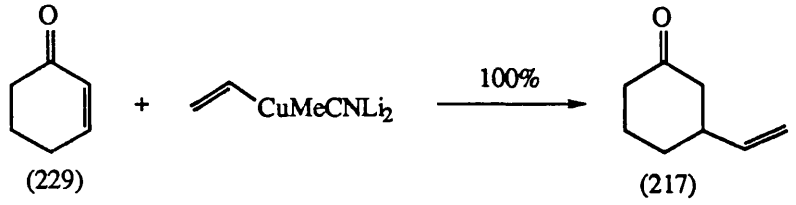
scheme 5.19

In order to further verify the presence of the alcohol product (218) as well as its parent ketone (217), we turned to the literature in order to synthesise authentic samples. Exposure of commercially available vinylstannane (227) to one equivalent of the cuprate $Me_2Cu(CN)Li_2$ (generated by the addition of a solution of methyllithium to copper(I) cyanide at 0°C) led to the quantitative *insitu* generation of the higher order reagent (228) and a tetraalkyltin derivative[160] (scheme 5.20).



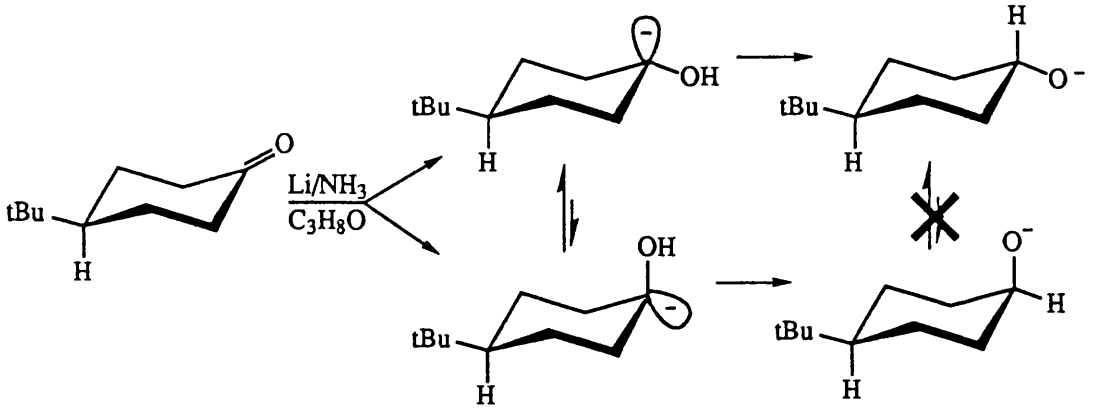
scheme 5.20

This ligand exchange reaction appears to be quantitative, presumably driven by the preferential release of the vinyl group from the tin as well as the presumed dπ* backbonding gained by attachment to the copper. Subsequent addition of enone (229) at low temperature, smoothly executed the 1,4-addition of the vinyl residue with complete selectivity of vinyl transfer over that of the methyl group, to afford the desired β-substituted ketone (217) in excellent yield. This was identical in all respects to the ketone isolated from our ring-opening of the bicyclic system (216) (scheme 5.21).



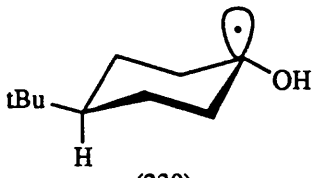
scheme 5.21

We can perceive that a simple reduction of (217) would then furnish the corresponding alcohol. It is widely accepted that dissolving metal reductions of saturated ketones give rise to either exclusively the thermodynamically stable alcohol or to mixtures where this isomer predominates. For example, 4-*tert*-Butylcyclohexanone[161] gives the more stable diequatorial *trans* alcohol almost exclusively on reduction with lithium and propanol in liquid ammonia. The formation of the more stable product has been explained by assuming that the carbanion intermediate has a definite though easily inverted tetrahedral configuration (scheme 5.22). Barton[162] suggested that the initially formed tetrahedral anion adopts the most stable configuration, that is the one with the oxygen equatorial, which on protonation affords the most stable alcohol.



scheme 5.22

House[94] put forward a similar argument suggesting that the free radical intermediate (230) adopts the more stable configuration with an equatorial hydroxyl group (figure 5.7). Further reduction and protonation takes place with retention of configuration at the carbon atom to give the equatorial alcohol.



(230)

figure 5.7

Thus, it is clear that reduction of our bicyclic system also leads to the thermodynamically more stable alcohol (218). Therefore, we need another means of generating this alcohol from the parent ketone. Generally,[162] reduction of cyclohexanones with sodium borohydride or lithium aluminium hydride predominantly affords the equatorial epimer if the ketone group is not hindered, and the axial epimer if it is hindered, by approach of the reagent from the least hindered side. Thus, axial approach towards (231) may be hampered by steric factors, hence, favouring equatorial approach and formation of the axial isomer (figure 5.8).

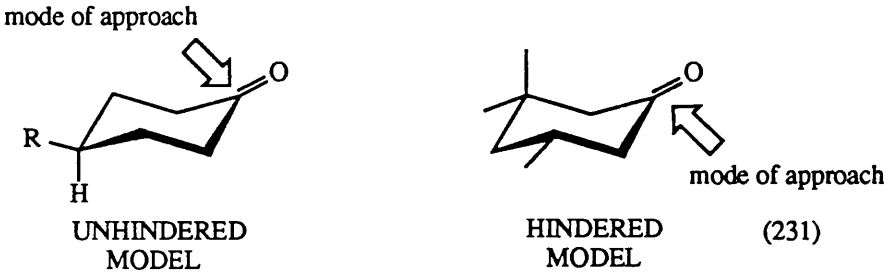
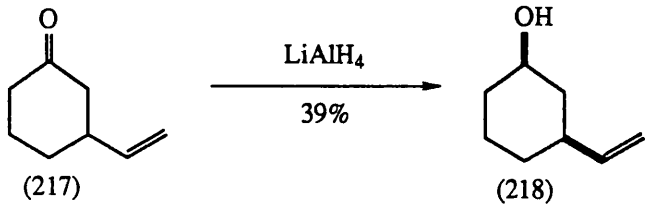


figure 5.8

Lithium aluminium hydride reduction of our relatively unhindered ketone (217) afforded the alcohol (218) as the sole isomer in a modest 39% yield (scheme 5.23).



(217) (218)

scheme 5.23

This was identical in all respects to the alcohol obtained from our lithium in liquid ammonia studies of the bicyclic cyclopropane (216). Further justification that we had infact made this isomer came from the inspection of the ^1H nmr spectrum. If the*trans* isomer had been formed, we should have observed an equatorial-equatorial coupling and an equatorial-axial coupling both in the region of 0-5Hz, but this clearly was not the case. Couplings of 11 and 4Hz, corresponding to axial-axial and axial equatorial couplings respectively were seen (figure 5.9).

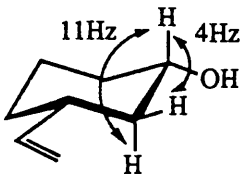
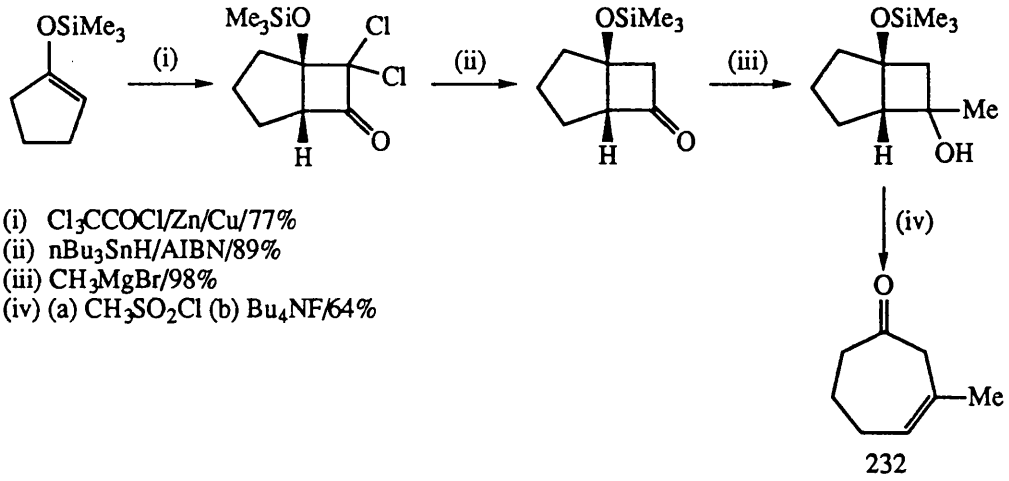


figure 5.9

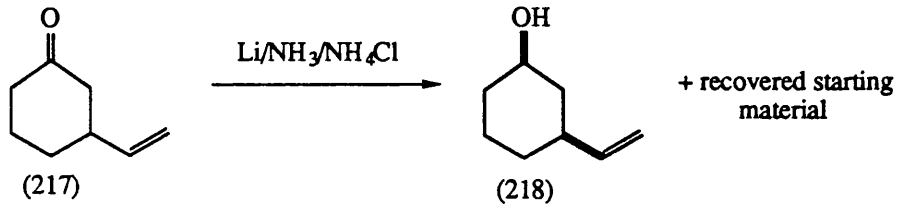
Evidence for the formation of (219) was also warranted, and thus, we set out to synthesis an authentic sample. A search of the literature, however, revealed only one lengthy procedure for the synthesis of 3-methyl-3-cyclohepten-1-one[163] (232), which would on reduction generate the desired alcohol (219) (scheme 5.24). But with the constraints of time upon us we felt it inappropriate to pursue this avenue further.



scheme 5.24

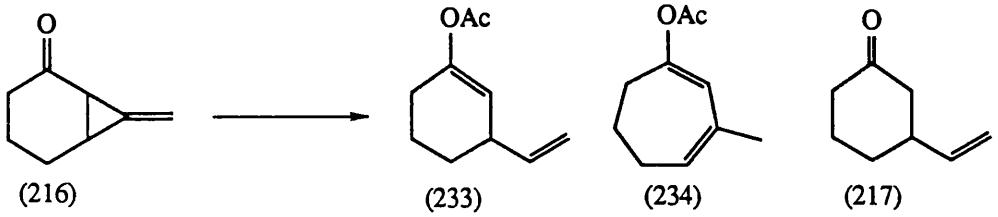
Before bring this section to a close, one further lithium in liquid ammonia reduction

was conducted. Addition of the ketone (217) to a solution of lithium in liquid ammonia followed by the usual ammonium chloride quench gave the expected alcohol (218) in 58% yield, together with recovered starting material in 27% yield (scheme 5.25). Thus, this proves that reduction of ketone (217) under such conditions dose infact yield the alcohol (218).



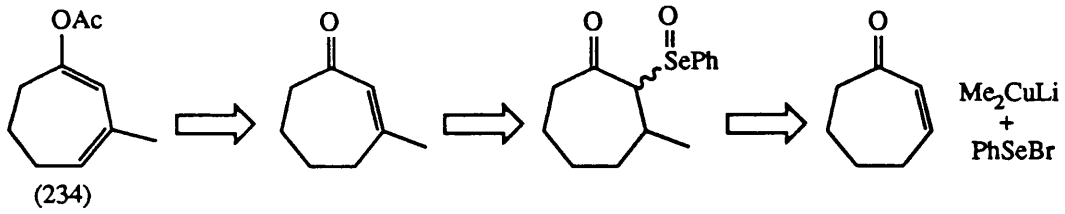
scheme 5.25

We though it would also be of interest to trap the lithium enolate formed previously with acetic anhydride. Thus, reduction of our model substrate (216) followed by an acetic anhydride quench gave, to our delight, the ring opened enol acetates (233) and (234) as an inseparable mixture in a combined yield of 31%. Formation of the ring opened ketone, was also observed, not unexpectedly, in 16% yield (scheme 5.26).



scheme 5.26

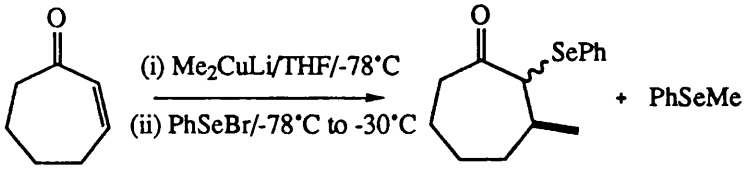
In order to confirm the presence of (234), we conceived an alternate synthetic route as illustrated by the retrosynthetic analysis in scheme 5.27.



(234)

scheme 5.27

Conjugate addition of lithium dimethylcuprate to 2-cycloheptenone in THF at -78°C was followed by the addition of phenylseleno bromide and the solution warmed to -30°C and quenched with methanol. The desired product (235) was isolated in 31% yield, unfortunately predominant formation of methylphenyl selenide was observed to occur in 66%, even though the literature protocol for cyclohexenone[164] had been closely followed (scheme 5.28).



(235)

31% 66%

scheme 5.28

In comparison to the six membered ring counterparts, it appears that at this temperature the reaction of the cuprate with the selenium electrophile was competing with the addition to the cycloheptanone. This may in part be due to the nature of the cycloheptane ring, which in turn hinders the approach of the methyl group from the cuprate (scheme 5.29).

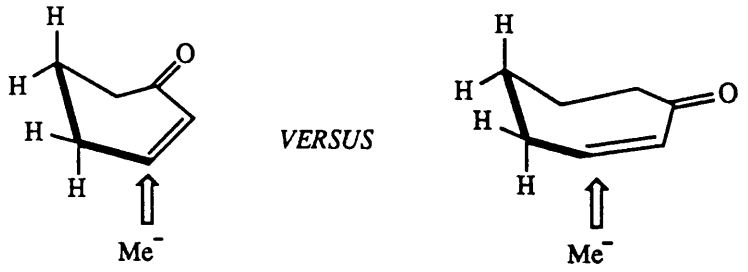
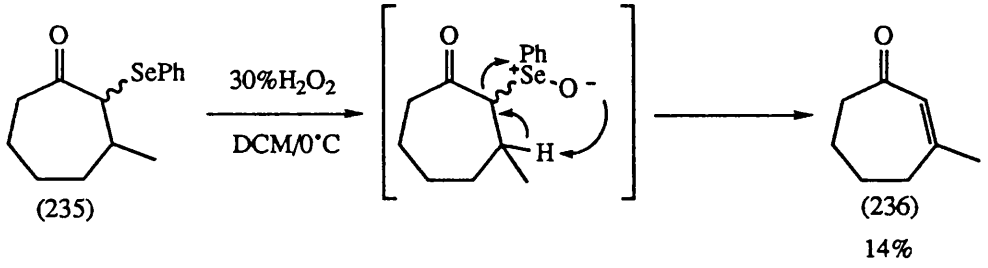


figure 5.29

We therefore felt that addition of the electrophile at -40°C might limit the formation of this undesired side product. Under these conditions the major product was again found to be methylphenyl selenide in 50% and the required selenide (235) being isolated in only 23% yield. Nevertheless, to a solution of the selenide (235) in dichloromethane at 0°C was added a 30% solution of hydrogen peroxide, which as a result of a *syn* elimination of the selenoxide afforded the desired methylated cycloheptanone derivative (236) in 14% yield (scheme 5.30).

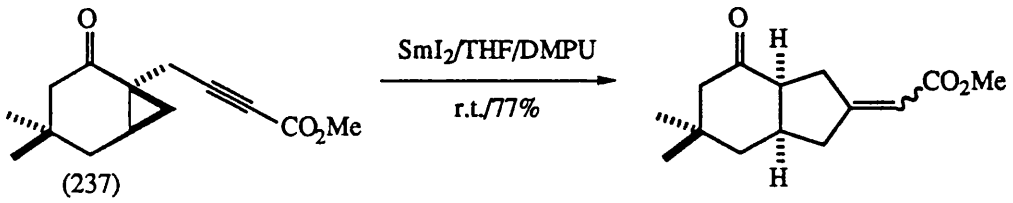


scheme 5.30

Attempts to bring through more of the latter *via* (235) proved unsuccessful since optimisation of the procedure could not be achieved and in view of the time constraint we were unable to proceed further. However, the final step would have been achieved by refluxing the α,β-unsaturated ketone (236) with isopropenylacetate in the presence of a catalytic amount of tosic acid. It can be envisaged that this would, therefore, give predominately the thermodynamically more stable product (234) (scheme 5.27).

Concomitant with our studies in this area of radical generation from our simple

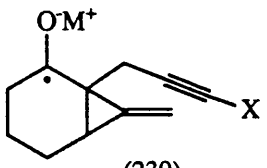
bicyclic methylenecyclopropyl derivative (216), we wished also to exploit a more complex system, concentrating in particular on the generation of ketyl radical anions. As already mentioned (see section 3.1.1) samarium(II) iodide induced ring cleavage of systems such as (237) proceeded to give the bicyclic skeleton in excellent yield (scheme 5.31). We therefore wondered whether equal success could be attained with the alkylidene equivalent.



(237)

scheme 5.31

Thus, since there has been no reported example of a methylene cyclopropylcarbinyl radical rearrangement in tandem with a 5-*exo* cyclisation onto an alkyne (or an alkene for that matter) be it activated or not, the model system (238) was selected for study (scheme 5.32). The reaction can be envisaged to occur by cleavage of either the endocyclic or exocyclic bonds. From a kinetic standpoint, cleavage of the external bond seems quite favourable. Thus rapid ring opening of the initially formed radical species (239) (figure 5.10) should be followed by a 5-*exo* ring closure process.

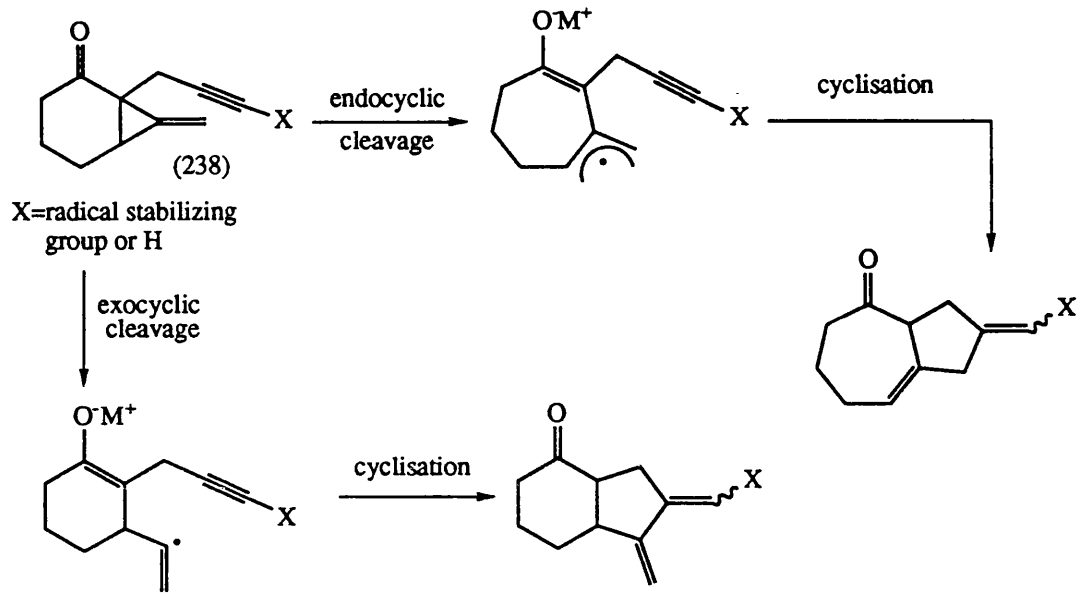


(239)

figure 5.10

Alternatively, cleavage of the internal bond could also be followed by a 5-*exo* dig cyclisation. As already stated, *exo*cyclic bond cleavage should dominate, as this bond overlaps with the π-system of the carbonyl (or a p-orbital containing the radical on the carbon atom of the carbonyl group) to a greater degree. Therefore, it was of

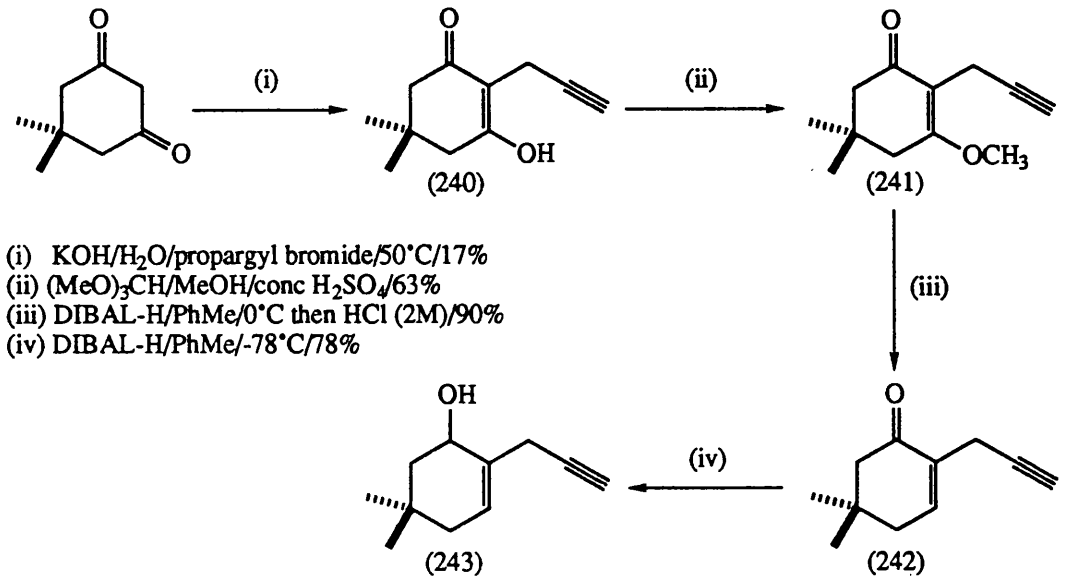
interest, in terms of gaining some understanding of the relative rates of external and internal ring opening and reclosure to determine which product would be formed.



scheme 5.32

Attempted formation of the desired cyclopropyl ketone derivative (238) was achieved using a near identical strategy to that described by Harling.[19] C-alkylation of dimedone at the C_2 position led to the alkylated product (240) in 17% yield. This reaction poses all the classical problems of C vs O and mono- vs dialkylation. The procedure,[94] namely the use of aqueous potassium hydroxide as the base with propargyl bromide, essentially failed to discriminate between mono- and dialkylation though O-alkylation was largely suppressed. The failure to obtain cleanly the mono C-alkylated product cleanly was due largely to the fact that it did not crystallise out as it was formed in the reaction mixture. Even so, the reaction can be carried out on a large scale and isolation of (240) is facilitated by its ability to be extracted into aqueous potassium hydroxide and then crystallised out upon acidification of the solution. Reaction of (240) with trimethylorthoformate in acidified methanol gave the corresponding mono-methyl enol ether[165] (241) in 63% yield. Diisobutylaluminium hydride reduction followed by protic workup then gave the enone (242) in 90% yield, and a further DIBAL-H reduction furnished the allylic

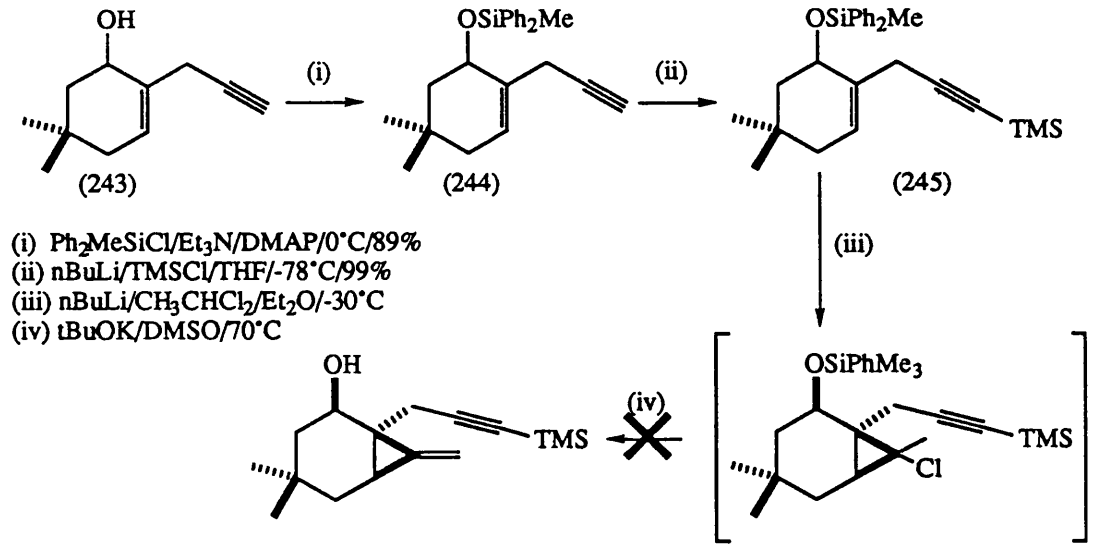
alcohol (243) in 78% yield, which had been previously been prepared in our group (scheme 5.33).



scheme 5.33

With the allylic alcohol in hand, we were now ready to construct the methylene cyclopropyl portion. Protection of (243) as its silyl ether proceeded in 89% yield. Prior to carbene addition to the double bond, the acetylene which would eventually act as the radical trap, was protected as its TMS ether; this was deemed necessary since the acidic nature of the acetylenic hydrogen would have otherwise proved problematic, and furthermore, there is evidence that the trimethylsilyl group can activate an acetylene towards the capture of nucleophilic alkyl radicals, presumably by back donation of electron density from the acetylene π-bonds into its vacant *d* -orbitals.

Introduction of the alkylidenecyclopropyl moiety was executed in the normal fashion by slow addition of a solution of *n*-butyllithium to a solution of the alkene and 1,1'-dichloroethane at -35°C followed by potassium *tert*-butoxide induced elimination (scheme 5.34). Unfortunately, we were unable to detect or isolate any new product from this reaction even though all the starting material had been consumed.

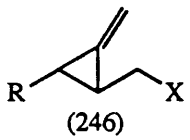


scheme 5.34

The presence of the alkyne group is therefore clearly detrimental, and future strategies in this area will of necessity require elaboration of the alkyne or other radical side chain acceptor after the introduction of the alkylidene cyclopropane.

5.2 SUMMARY AND CONCLUSIONS.

Thus, on reflection, generation of carbon centred radicals from alkylidene cyclopropyl systems of the type (246) (figure 5.11) did not operate as initially anticipated due to the lability of the conjugated dienes thus generated.



(246)

figure 5.11

Surprisingly, whereas samarium(II) iodide induced ring opening of the corresponding ketone derivatives (figure 5.12) proved thoroughly disappointing, in comparison the analogous lithium in liquid ammonia reactions fulfilled their initial expectations, with predictable regiospecific cleavage being observed.

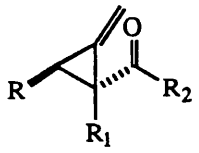


figure 5.12

A brief summary of the results shows that the formation of both ketonic and the "unexpected" alcohol products were observed, and that their relative ratios in no way reflects the nature of the starting ketone derivatives (table 5.1). Thus, it is clear that further work is necessary in this area before any hard and fast rules can be formulated.

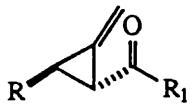
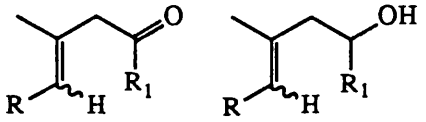
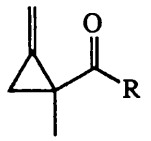
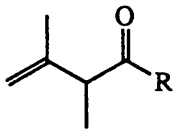
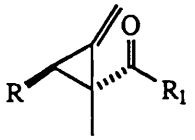
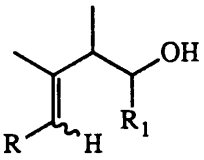
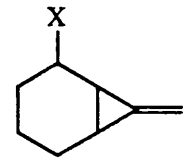
KETONE	PRODUCT
	
	
	

table 5.1

From the discussion in section 4.2, it is apparent that few methods exist for the direct stereocontrolled formation of tetrasubstituted enolates. However, we feel we have made a valid contribution to this otherwise perplexing domain by our stereoselective enol acetate formation. It is evident that we have only touched the tip of the iceberg, and there is great potential for further elaboration of highly stereoselective dienolate derivatives within this area.

Ultimately, our work terminated with the study of the radical induced ring opening of the analogous bicyclic congener (199) (figure 5.13). Even though attempts to generate carbon centred radicals did not proceed in the manner that we initially anticipated, it was interesting to observe addition to the exomethylene moiety, and the novel fragmentation which ensued to give a vinyl stannane dreivative.

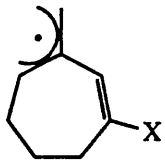


X=radical trigger

(199)

figure 5.13

In such systems, the rigidity is such that orbital overlap of the radical SOMO with the exocyclic bond is stereoelectronically favoured. However, under radical anion induced ring cleavage conditions, we were intrigued to observe that endocyclic cleavage to give the ring enlarged cycloheptyl derivatives also occurs. Thus it appears that formation of the lower energy allylic radical (247) (figure 5.14) *via* cleavage of the weaker internal bond competes effectively with the formation of the product arising from stereoelectronic control.



(247)

figure 5.14

Experimental

Chapter Six

6.1 General Experimental

^{1}H and ^{13}C nmr spectra were recorded at 200MHz on a Varian XL-200 instrument; at 250MHz on a Bruker WM-250 instrument; at 270MHz and 67.9MHz respectively on a Joel GSX 270 instrument; at 400MHz and 100MHz respectively on a Joel GSX 400 instrument; at 500MHz and 125.8MHz on a Bruker AM-500 instrument, with a residual protic solvent as the internal standard, i.e. $CHCl_3$ (δ_H=7.26ppm, δ_C=77.0ppm). Spectra were recorded in d-chloroform. Infrared spectra were recorded on a Perkin Elmer 983G and FT-IR 1600 spectrometers as thin films on sodium chloride plates. Mass spectra and accurate mass measurements were recorded by EI (electron impact) on a VG 7070B instrument at Imperial College, on a VG 12 253 and VG ZAB-e instruments by the SERC mass spectrometry service and by EI and CI (chemical ionisation) with NH_3 as the carrier gas, and FAB (fast atom bombardment) on a VG 7070 instrument at University College London. Elemental analyses were performed by the Imperial College and University College Chemistry Department microanalytical service. Melting points were determined on a Reichert hot-stage and are uncorrected.

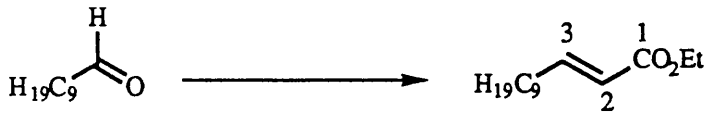
Petrol refers to petroleum ether b.pt. 40-60°C and 30-40 petrol to petroleum ether b.pt. 30-40°C, both of which were distilled prior to use. Diethyl ether, (referred to as "ether"), tetrahydrofuran and benzene, used as reagents, were distilled from sodium-benzophenone ketyl under argon, immediately prior to use. Toluene was distilled from sodium under an atmosphere of argon immediately prior to use. Dichloromethane was distilled from phosphorus pentoxide under an atmosphere of argon immediately prior to use. Acetonitrile was distilled from CaH_2 under a atmosphere of argon immediately prior to use. Dimethyl sulfoxide and DMPU were distilled from calcium hydride at reduced pressure, and stored over 4Å molecular sieves under argon. Triethylamine was distilled from potassium hydroxide and stored over 4Å molecular sieves under argon. Chlorotrimethylsilane was distilled from CaH_2 immediate prior to use and any HCl removed by storing over sodium.

All other solvents and reagents were purified by standard means.

All reactions were performed using oven dried glass ware under an atmosphere of dry argon or nitrogen unless otherwise stated.

Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400) mesh. Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F_{254}) and visualised using ultra violet light (254nm), iodine, potassium permanganate [add 62.5g of Na_2CO_3 in water (1.25l) to 12.5g of $KMnO_4$ in water (1.25 l)], acidic ammonium molybdate(IV) [conc. H_2SO_4 (250ml), ammonium molybdate.$4H_2O$, water (2.25 l)] and vanillin [4-hydroxy-3-methoxy benzaldehyde (2.5g), conc. H_2SO_4 (2.5ml), ethanol (100ml), stored in the dark) as appropriate.

Preparation of *(E)*-ethyl dodec-2-enoate (80).[20]



(80)

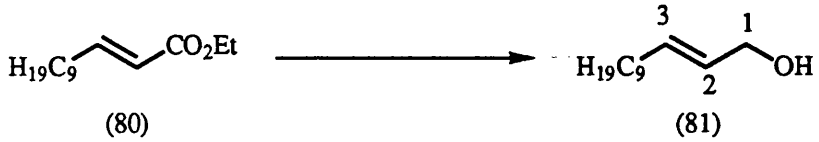
A solution of decanal (7.8g, 49.9mmol) and (carboethoxymethylene)triphenylphosphorane (24.5g, 70.4mmol) in dry dichloromethane (100ml) was stirred at room temperature for 24 hours. The resulting solution was concentrated, petrol added and the triphenylphosphine oxide removed by filtration. Removal of the solvent *in vacuo*, followed by distillation afforded ***(E)-ethyl dodec-2-enoate*** **(80)** (10.1g, 89%) as a clear oil (b.pt. 164°C at 1mm Hg, 95:5, E/Z, NMR);

IR (film) ν_{max} 2927, 2855, 1722, 1654, 1464, 1309, 1266, 1182, 1045 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 6.98 (1H, dt, *J* 15.6, 7.0Hz, H_3), 5.80 (1H, dt, *J* 15.6, 1.7Hz, H_2), 4.18 (2H, q, *J* 7.0Hz, OCH_2CH_3), 2.18 (2H, m, 2*H_4), 1.45 (2H, m, 2*H_5), 1.39-1.19 (12H, m, CH_2 envelope), 1.28 (3H, t, *J* 7.2Hz, OCH_2CH_3), 0.87 (3H, t, *J* 6.0Hz, terminal CH_3).

m/z (EI) 226 (M^+), 197 (M^+- C_2H_5), 181 (M^+-OC_2H_5), 138, 127, 101.

Preparation of *(E)*-2-dodecen-1-ol (81).[20]



(80) (81)

To a solution of *(E)*-ethyl dodec-2-enoate (8.5 g, 37mmol) in toluene (100ml) at -78°C under argon was added diisobutylaluminium hydride (59.5ml of a 1.5M solution in toluene) dropwise. The solution was stirred for 1 hour and quenched with water (5ml). Ethyl acetate (250ml) was added and the solution allowed to warm to

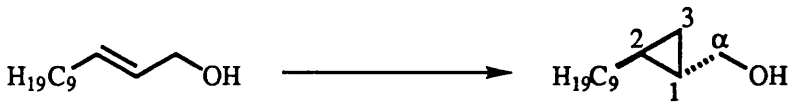
room temperature. Excess Na_2SO_4 was added and the solution stirred for a further hour. Removal of the solvent *in vacuo* and column chromatography (10% ether/petrol, silica) afforded ***(E)-2-dodecen-1-ol*** **(81)** (6.7g, 98%) as a colourless oil;

IR (film) ν_{max} 3322, 2925, 2854, 1672, 1464, 1378 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 5.67 (2H, m, H_2, H_3), 4.08 (2H, brd, *J* 4.9Hz, 2*H_1), 2.05 (2H, brq, *J* 6.1Hz, 2*H_4), 1.60 (1H, brs, OH), 1.40-1.22 (14H, m, CH_2 envelope), 0.90 (3H, t, *J* 6.3Hz, terminal CH_3).

m/z (EI) 166 (M^+-H_2O), 138, 123, 82, 57.

Preparation of (1R*, 2R*)-1-methanol-2-nonylcyclopropane (82).[20]



(81) (82)

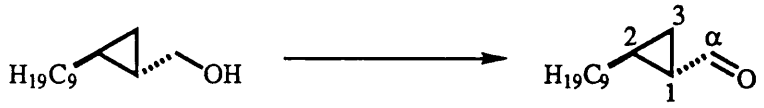
Zinc powder (7.83g, 120mmol) was added to a solution of silver acetate (151mg, 0.90mmol) in acetic acid (60ml) at 80°C, and the solution stirred for 2 minutes. The solvent was decanted and the zinc-silver couple thus formed was washed with acetic acid (30ml), and repeatedly with ether (50ml) until no futher smell of acetic acid remained. Freshly distilled ether (70ml) was added to the couple, followed by the slow addition of diiodomethane (5.42ml, 67.3mmol), and the solution heated to reflux. A solution of the alcohol (81) (4.00g, 21.7mmol) in ether (20ml) was added, and the mixture stirred vigorously at reflux for 2.5 hours. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl solution added dropwise. The solution was then decanted from the zinc and extracted with ether (50ml). The combined organic extracts were washed with brine (100ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (20-30% ether/petrol, silica) afforded ***(1R*, 2R*)-1-methanol-2-nonylcyclopropane*** **(82)** (3.24g, 75%) as a colourless oil;

IR (film) ν_{max} 3343, 2924, 2854, 1466, 1031 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.43 (2H, m, 2*Hα), 1.65 (1H, brs, OH), 1.44-1.15 (16H, m, CH_2 envelope), 0.86 (3H, t, *J* 6.6Hz, terminal C*H*$_3$), 0.80 (1H, m), 0.59 (1H, m), 0.32 (2H, m) [total 4H, cyclopropyl H's].

m/z (EI) 180 (M^+-H_2O), 157, 97, 83, 69.

Preparation of (1R*, 2R*)-1-methanal-2-nonylcyclopropane (83).[20]



(82) (83)

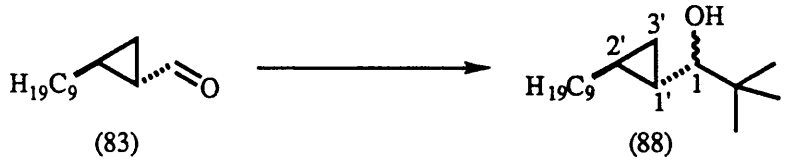
To a solution of the alcohol (82) (426mg, 2.15mmol) in dichloromethane (10ml) at room temperature under argon, was added pyridinium dichromate (425mg, 2.15mmol), and the solution stirred for 20 hours. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (20% ether/petrol, silica) gave ***(1R*, 2R*)-1-methanal-2-nonylcyclopropane*** **(83)** (405mg, 96%) as a colourless oil (which was carried through to the next step as soon as possible because of possible trimerisation).

IR (film) ν_{max} 2925, 2854, 1707, 1460, 1169, 1027 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 8.90 (1H, d, *J* 5.6Hz, Hα), 1.60 (1H dddd, *J* 8.0, 5.6, 4.2, 3.9Hz, H_1), 1.50-1.21 (18H, m, CH_2 envelope, 2*cyclopropyl H's), 0.95-0.85 (4H, m, terminal C*H*$_3$, cyclopropyl H).

m/z (EI) 196 (M^+), 178 (M^+-H_2O), 152, 140, 111, 83, 70, 55, 41.

Preparation (1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-ol (88).



(83) (88)

To a solutiion of the aldehyde (83) (755mg, 3.85mmol) in ether (12ml) at -78°C under argon, was added dropwise a solution of *t*-butyllithium (3.40ml of a 1.7M solution in Et_2O). After stirring for 2 hours, the solution was allowed to warm to room temperature, poured into water (15ml), and extracted with ether (3x30ml). The combined organic extracts were washed with brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (10% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-ol*** **(88)** as two separable diastereomers:

less polar diastereomer (440mg, 45%) as a colourless oil;

IR (film) ν_{max} 3445, 2923, 2854, 1465, 1363, 1051 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.51 (1H, d, *J* 8.6Hz, H_1), 1.56 (1H, brs, OH), 1.39-1.00 (16H, m, CH_2 envelope), 0.95 (9H, s, 3*CH_3), 0.87 (3H, t, *J* 6.4Hz, terminal CH_3), 0.66-0.58 (2H, m), 0.47-0.33 (2H, m) [total 4H, cyclopropyl H's].

m/z (CI) 254 (M^++NH_4^+-H_2O), 237 (M^+-OH), 179, 109, 95, 81, 58.

Observed: (M^++NH_4^+-H_2O), 254.2843. $C_{17}H_{36}N$ requires 254.2848.

more polar diastereomer (480mg, 49%) as a colourless oil;

IR (film) ν_{max} 3417, 2925, 2853, 1466, 1363 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.52 (1H, m, H_1), 1.59 (1H, brs, OH), 1.46-1.20 (16H, m, CH_2 envelope), 0.97 (9H, s, 3*CH_3), 0.89 (3H, t, *J* 6.6Hz, terminal CH_3), 0.71-0.63 (2H, m, $H_{1'}$, $H_{2'}$), 0.41-0.35 (1H, m, 1*$H_{3'}$), 0.27-0.20 (1H, m, 1*$H_{3'}$).

m/z (CI) 254 (M^++NH_4^+-H_2O), 237 (M^+-OH), 179, 109, 95, 81, 58;

Observed: (M^++NH_4^+-H_2O), 254.2848. $C_{17}H_{36}N$ requires 254.2848.

Preparation of 1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]- 2,2-dimethylpropan-1-one (89).

(88) (89)

To a solution of the alcohol (89) (920g, 3.62mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (2.04g, 5.42mmol), followed by pyridinium trifluoroacetate (280mg, 1.45mmol) and the solution stirred for 5 days. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one*** **(89)** (707mg, 77%) as a colourless oil;

IR (film) ν_{max} 2925, 2855, 1692, 1466, 1366, 1095 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 1.87 (1H, m, $H_{1'}$), 1.37-1.20 (18H, CH_2 envelope, 2*$H_{3'}$), 1.19 (9H, s, 3*CH_3), 0.87 (3H, t, *J* 6.6Hz, terminal CH_3), 0.69 (1H, m, $H_{2'}$).

δ_C (67.9MHz, $CDCl_3$) 215.01 (C=O), 43.99 (C_2), 33.42, 31.87, 29.56, 29.33, 29.28, 29.16 (CH_2's), 26.39 (2*CH_3's), 26.25, 23.81 ($C_{1'}$, $C_{2'}$), 22.65, 18.17 (CH_2's), 14.07 (terminal CH_3).

m/z (EI) 252 (M^+), 195 (M^+-C_4H_9), 177, 111, 97, 83, 57, 43.

Observed: M^+, 252.2453. $C_{17}H_{32}O$ requires 225.2453.

Preparation of 2, 2-dimethylpentadecane-2-one (101).

(89) (101)

To a solution of the cyclopropyl ketone (89) (90mg, 0.36mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (3.92ml of a 0.1M solution in tetrahydrofuran) at room temperature under argon, until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml), and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded ***2,2-dimethylpentadecane-2-one*** **(101)** (81mg, 90%) as a colourless oil;.

IR (film) ν_{max} 2927, 2855, 1709, 1466, 1366, 1066 cm^{-1}.

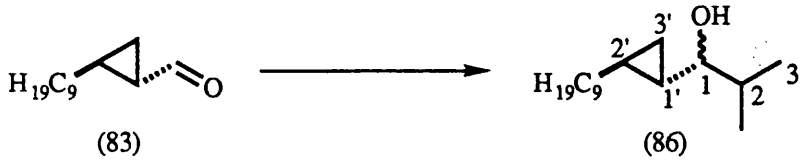
δ_H (270MHz, $CDCl_3$) 2.45 (2H, t, *J* 7.1Hz, 2*H_4), 1.53 (2H, m, 2*H_5), 1.29-1.12 (18H, m, CH_2 envelope, 2*H_6), 1.11 (9H, s, 3*C*H*$_3$), 0.88 (3H, t, *J* 6.3Hz, terminal C*H*$_3$).

δ_C (125MHz, $CDCl_3$) 216.06 (C=O), 44.06 (C_2), 36.42, 33.41, 31.89, 29.63, 29.60, 29.50, 29.33, 29.25 (CH_2's), 26.39 (3*CH_3's), 23.95, 22.66 (CH_2's), 14.07 (terminal CH_3).

m/z (CI) 272 (M^++NH_4^+), 255 (MH^+), 254 (M^+), 197 (M^+-C_4H_9), 58.

Observed: (M^++NH_4^+), 272.2953. $C_{17}H_{38}NO$ requires 272.2953.

Preparation of (1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-ol (86).



(83) (86)

To a solution of isopropylmagnesium chloride (3.03ml of a 2.0M solution in Et_2O) at -30°C under argon, was added a solution of the aldehyde (83) (916mg, 4.67mmol) in ether (40ml) dropwise, and stirring continued for 1 hour. A further portion of isopropylmagnesium chloride (0.3ml, 0.6mmol) was added and stirring continued for a futher 30 minutes, before warming the reaction mixture to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (10-20% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-ol*** **(86)** as two separable diastereomers:

less polar diastereomer (349mg, 31%) as a colourless oil;

IR (film) ν_{max} 3440, 2923, 2855, 1465,1378, 1019 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.63 (1H, m, H_1), 1.78 (1H, dsept., *J* 1.2, 5.6Hz, H_2), 1.57 (1H, bs, OH), 1.43-1.18 (16H, m, CH_2 envelope), 0.97 (6H, d, *J* 6.8Hz, 2*CH_3), 0.88 (3H, t, *J* 6.4Hz, terminal CH_3), 0.66-0.59 (2H, m), 0.43-0.32 (2H, m) [total 4H, cyclopropyl H].

m/z (EI) 240 (M^+), 223 (M^+-H_2O), 197 (M^+-C_3H_7), 179, 123, 95, 81, 57, 45.

Observed: (M^++NH_4^+), 258.2797. $C_{16}H_{36}NO$ requires 258.2797.

more polar diastereomer (655mg, 58%) as a colourless oil;

IR (film) ν_{max} 3389, 2956, 2854, 1466, 1379, 1029 cm^{-1}.

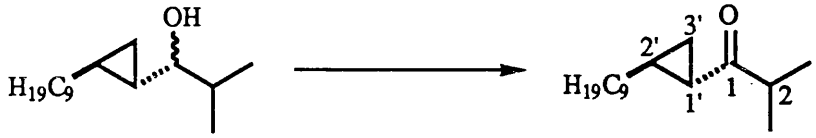
δ_H (270 MHz, $CDCl_3$) 2.62 (1H, dd, *J* 5.6, 2.9Hz, H_1), 1.80 (1H, dsept., *J* 1.2, 5.6Hz, H_2), 1.58 (1H, brs, OH), 1.45-1.26 (16H, m, CH_2 envelope), 0.99 (3H, d, *J*

6.8Hz, C*H*3), 0.98 (3H, d, *J* 6.8Hz, C*H*3), 0.88 (3H, t, *J* 6.4Hz, terminal C*H*3), 0.71-0.60 (2H, m, cyclopropyl H's), 0.43-0.36 (1H, dt, *J* 8.6, 4.4Hz, cyclopropyl H), 0.20 (1H, dt, *J* 8.6, 4.4Hz, cyclopropyl H).

m/z (EI) 240 (M^+), 223 (M^+-H_2O), 197 (M^+-C_3H_7), 179, 123, 95, 81, 57, 45.

Observed: M^+, 240.2693. $C_{16}H_{32}O$ requires 240.2691.

Preparation of 1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-one (87).



(86) (87)

To a solution of the alcohol (86) (1.00g, 4.14mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (2.35g, 6.26mmol), followed by pyridinium trifluoroacetate (322mg, 1.67mmol) and the solution stirred for 5 days. The reaction mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-one*** **(87)** (785mg, 79%) as a colourless oil;

IR (film) ν_{max} 2926, 2855, 1696, 1467, 1069 cm^{-1}.

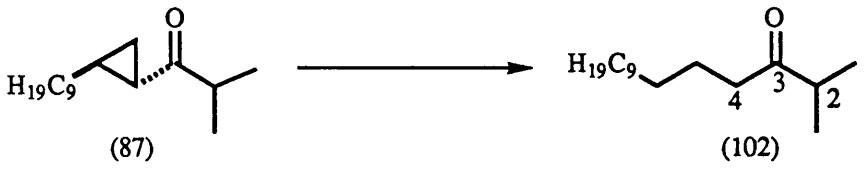
δ_H (270MHz, $CDCl_3$) 2.72 (1H, sept., *J* 7.0Hz, H_2), 1.72 (1H, m, $H_{1'}$) 1.41-1.16 (18H, CH_2 envelope, 2*$H_{3'}$), 1.15 (3H, d, *J* 7.1Hz, C*H*3), 1.12 (3H, d, *J* 7.1Hz, C*H*3), 0.87 (3H, t, *J* 6.6Hz, terminal C*H*3), 0.70 (1H, m, $H_{2'}$).

δ_C (67.9MHz, $CDCl_3$) 214.03 (C=O), 41.57 (C_2), 33.53, 31.87, 29.56, 29.29, 29.16 (CH_2's), 26.70, 26.01 ($C_{1'}$, $C_{2'}$), 22.65 (CH_2), 18.32, 18.17 (2*CH_3), 17.98 (CH_2), 14.07 (terminal CH_3).

m/z (EI) 238 (M^+), 195 (M^+-C_3H_7), 177, 167, 152, 113, 97, 71.

Observed: M^+, 238.2297. $C_{16}H_{30}O$ requires 238.2297.

Preparation of 2-methylpentadecan-3-one (102).



To a solution of the cyclopropyl ketone (87) (119mg, 0.50mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (6.0ml of a 0.1M solution in tetrahydrofuran) at room temperature under argon, until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml), and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$, and the solvent removed *in vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded ***2-methylpentadecan-3-one*** **(102)** (95mg, 79%) as a colourless oil;

IR (film) ν_{max} 2923, 2851, 1708, 1461, 1379, 1097 cm^{-1}.

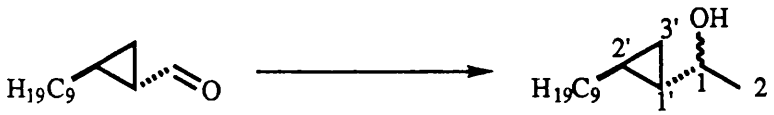
δ_H (270MHz, $CDCl_3$) 2.57 (1H, sept., *J* 6.8Hz, H_2), 2.42 (2H, t, *J* 7.3Hz, 2*H_4), 1.54 (2H, m, 2*H_5), 1.24-1.09 (18H, m, CH_2 envelope, 2*H_6), 1.07 (6H, d, *J* 6.8Hz, 2*C*H*$_3$), 0.86 (3H, m, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$), 215.04 (C=O), 40.78 (C_2), 40.37, 31.91, 29.64, 29.62, 29.49, 29.45, 29.33, 23.81, 22.68 (CH_2's), 18.26 (2*CH_3's), 14.10 (CH_3).

m/z (EI) 240 (M^+), 197, 149, 109, 89, 71, 57, 43.

Observed: M^+, 240.2456. $C_{16}H_{32}O$ requires 240.2453.

Preparation of (1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-ethan-1-ol (84).[20]



(83) (84)

To a solution of the cyclopropyl aldehyde (83) (400mg, 2.04mmol) in ether (15ml) at -78°C under argon, was added methylmagnesium bromide (0.88ml of a 3.0M solution in Et_2O). After stirring for 30 minutes a further portion of methylmagnesium bromide (0.60ml of a 3.0M solution in Et_2O) was added and the solution stirred for 30 minutes before warming to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (10-20% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-ethan-1-ol*** **(84)** as two separable diastereomers:

less polar diastereomer (163mg, 55%) as a colourless oil;

IR (film) ν_{max} 3409, 2926, 2854, 1464, 1378, 1103, 1024 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.13 (1H, m, H_1), 1.56 (1H, brs, OH), 1.42-1.16 (19H, m, CH_2 envelope, 3*H_2), 0.88 (3H, t, *J* 6.8Hz, terminal CH_3), 0.68-0.61 (2H, m), 0.36-0.25 (2H, m), [total 4H, cyclopropyl H's].

m/z (EI) 212 (M^+), 197 (M^+-CH_3), 194 (M^+-H_2O), 157, 109, 97, 83, 71, 58.

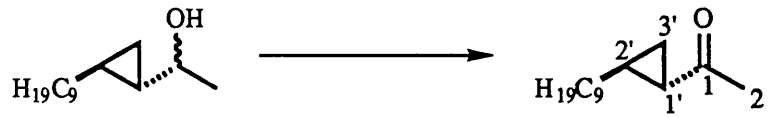
more polar diastereomer (149mg, 38%) as a colourless oil;

IR (film) ν_{max} 3373, 2923, 2853, 1461, 1368, 1293, 1105, 1079 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.09 (1H, m, H_1), 1.61 (1H, brs, OH), 1.33-1.23 (19H, m, CH_2 envelope, 3*H_2), 0.88 (3H, t, *J* 6.8Hz, terminal CH_3), 0.63-0.58 (2H, m, $H_{1'}$, $H_{2'}$), 0.44 (1H, dt, *J* 8.5, 4.4Hz, $H_{3'}$), 0.29 (1H, dt, *J* 7.8, 4.4Hz, $H_{3'}$).

m/z (EI) 212 (M^+), 197 (M^+-CH_3), 194 (M^+-H_2O), 157, 109, 97, 83, 71, 58.

Preparation of 1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-ethan-1-one (85).[20]



(84) (85)

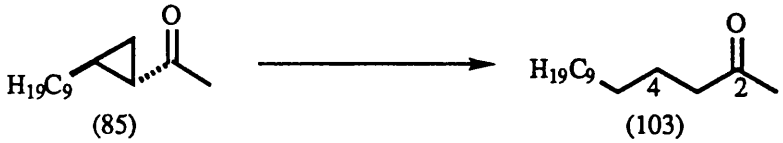
To a solution of the alcohol (84) (547mg, 2.58mmol) in dichloromethane (10ml), at room temperature under argon, was added pyridinium dichromate (1.45g, 3.86mmol), followed by pyridinium trifluoroacetate (199mg, 1.03mmol), and the solution stirred for 2 days. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-ethan-1-one*** **(85)** (481mg, 87%) as a colourless oil;

IR (film) ν_{max} 2925, 2854, 1698, 1403, 1357, 1172 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.21 (3H, s, 3*H_2), 1.69 (1H, m, $H_{1'}$), 1.43-1.16 (18H, m, CH_2 envelope, $H_{2'}$, 1*$H_{3'}$), 0.87 (3H, *J* 6.4Hz, terminal CH_3), 0.74 (1H, m, 1*$H_{3'}$).

m/z (EI) 210 (M^+), 195 (M^+-CH_3), 192 (M^+-H_2O), 181 (M^+-C_2H_5), 152, 111, 97, 71, 55.

Preparation of tetradecan-2-one (103).



(85) (103)

To a solution of the cyclopropyl ketone (85) (90mg, 0.49mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (4.2ml of a 0.1M solution in tetrahydrofuran) at room temperature under argon, until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous

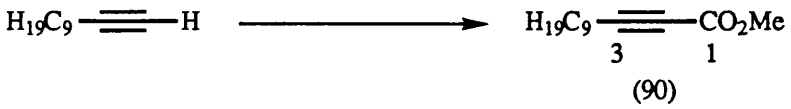
$NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml), and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded ***tetradecan-2-one*** **(103)** (56mg, 54%) as a white solid (m.pt. 28-29°C; lit.[166], 32-33°C);

IR (film) ν_{max} 2923, 2851, 1715, 1459, 1356, 1161 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.41 (2H, t, *J* 7.3Hz, 2*H_3), 2.12 (3H, s, 3*H_1), 1.54 (2H, m, 2*H_4), 1.35-1.20 (18H, m, CH_2 envelope), 0.88 (3H, m, terminal C*H*$_3$).

m/z (EI) 212 (M^+), 197 (M^+-CH_3), 154, 124, 111, 96.

Preparation of methyl dodec-2-ynoate (90).



(90)

To a solution of undecyne (16.0g, 105mmol) in tetrahydrofuran (200ml) at -78°C under argon, was added dropwise, a solution of *n*-butyllithium (44.5ml of a 2.5M solution in hexanes), and stirring continued for 30 minutes. Methylchloroformate (29.8ml, 388mmol) was added, and after a further hour, the solution was allowed to warm to room temperature. Saturated aqueous NH_4Cl solution was added, the mixture diluted with water, and extracted with ether (2x200ml). The combined organic extracts were dried over $MgSO_4$, and the solvent removed *in vacuo*. Distillation of the red oil afforded ***methyl dodec-2-ynoate*** **(90)** (23.4g, 100%) as a colourless oil (b.pt. 134°C at 7mmHg);

IR (film) ν_{max} 2929, 2238, 1713, 1435, 1265, 1078 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.75 (3H, s, OC*H*$_3$), 2.32 (2H, t, *J* 7.0Hz, 2*H_4), 1.57 (2H, m, 2*H_5), 1.40 (12H, m, CH_2 envelope), 0.87 (3H, t, *J* 6.0Hz, terminal C*H*$_3$).

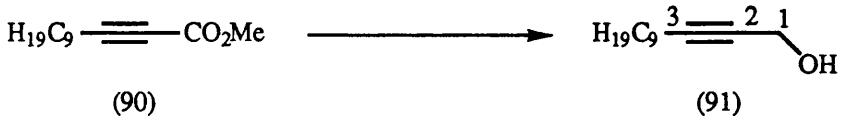
δ_C (100MHz, $CDCl_3$) 154.25 (C=O), 89.94 (C_2), 72.78 (C_3), 52.50 (OCH_3), 31.81, 29.34, 29.21, 28.98, 28.79, 27.48, 25.41, 22.63, 18.62 (CH_2's), 14.07 (terminal

CH_3).

m/z (CI) 228 (M^++NH_4^+), 211(MH^+), 179, 154, 121, 107, 94, 81, 69.

Observed: M^+ 210.1259. $C_{13}H_{22}O_2$ requires 210.1255.

Preparation of 2-dodecyn-1-ol (91).



(90) (91)

To a solution of the alkynoate ester (90) (5.00g, 23.8mmol) in toluene (60ml) at room temperature under argon was added dropwise a solution of diisobutylaluminium hydride (38.0ml of a 1.5M solution in toluene). The solution was stirred for an hour and then quenched with water (20ml). Ethyl acetate (150ml) was added followed by excess solid Na_2SO_4 and stirring continued for a further hour. Removal of the solvent *in vacuo*, followed by column chromatography (20-30% ether/petrol, silica), afforded ***2-dodecyn-1-ol*** **(91)** (3.0g, 69%) as a colourless oil;

IR (film) ν_{max} 3346, 2927, 2857, 2226, 1464, 1379, 1228, 1138, 1019 cm^{-1}.

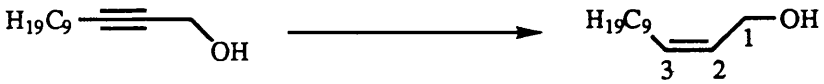
δ_H (270MHz, $CDCl_3$) 4.24 (2H, m, 2*H_1), 2.19 (2H, m, 2*H_4), 1.48 (2H, m, 2*H_5), 1.24 (13H, m, CH_2 envelope, OH), 0.87 (3H, t, *J* 6.4Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 86.68, 78.22 (C_2, C_3), 51.43 (C_1), 31.86, 29.46, 29.27, 29.13, 28.86, 28.59, 22.66, 18.72 (CH_2's), 14.10 (terminal CH_3).

m/z (CI) 200 (M^++NH_4^+), 182 (M^+), 165 (M^+-OH), 151 (M^+-CH_2OH), 121, 109, 95.

Observed: (M^++NH_4^+), 200.2010. $C_{12}H_{26}NO$ requires 200.2014.

Preparation of *(Z)*-2-dodecen-1-ol (92).



(91) (92)

A suspension of palladium on calcium carbonate poisoned with lead (450mg) in petrol (100ml) was treated with quinoline (15 drops) and stirred under a hydrogen atmosphere at room temperature for 30 minutes The suspension was cooled to -10°C and a solution of the alkyne (91) (5.0g, 27.5mmol) added dropwise. After 2 hours the reaction mixture was warmed to room temperature, filtered through a celite pad and the solvent removed *in vacuo* to afford ***(Z)-2-doecen-1-ol*** **(92)** (5.0g, 99%) as a colourless oil;

IR (film) ν_{max} 3331, 2924, 2854, 1645, 1466, 1014 cm^{-1}.

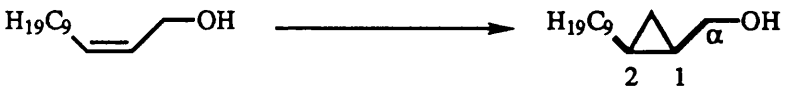
δ_H (270MHz, $CDCl_3$) 5.56 (2H, m, H_2, H_3), 4.20 (2H, m, 2*H_1), 2.07 (2H, brq, *J* 6.4Hz, 2*H_4), 1.42-1.12 (15H, m, CH_2 envelope, OH), 0.88 (3H, t, *J* 6.8Hz, terminal CH_3).

δ_C (67.9MHz, $CDCl_3$) 133.14, 128.34 (C_2, C_3), 58.53 (C_1), 31.86, 29.59, 29.53, 29.45, 29.28, 29.19, 27.40, 22.26 (CH_2's), 14.06 (CH_3).

m/z (EI) 184 (M^+), 166 (M^+-H_2O), 138, 124, 110, 96, 82, 68, 57.

Found: C 78.02, H 13.28. $C_{12}H_{24}O$ requires: C 78.20, H 13.12%.

Preparation of (1R*, 2S*)-1-methanol-2-nonylcyclopropane (93).



(92) (93)

Zinc powder (17.6g, 270mmol) was added to a solution of silver acetate (339mg, 2.34mmol) in acetic acid (135ml) at 80°C, and the solution stirred for 2 minutes.

The solvent was decanted and the zinc-silver couple thus formed was washed with acetic acid (50ml) and repeatedly washed with several portions of ether (100ml) until no further smell of acetic acid remained. Freshly distilled ether (160ml) was added to the couple followed by the slow addition of diiodomethane (12.2ml, 151mmol), and the solution heated to reflux. A solution of the alcohol (92) (9.0g, 48.8mmol) in ether (40ml) was then added and the mixture stirred vigorously at reflux for 2.5 hours. The reaction mixture was cooled to room temperature and saturated aqueous NH_4Cl solution added dropwise. It was then decanted from the zinc, and extracted with ether (50ml). The combined organic extracts were washed with brine (100ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (20-30% ether/petrol, silica) afforded ***(1R*, 2S*)-1-methanol-2-nonylcyclopropane*** **(93)** (3.24g, 42%) as a yellow oil;

IR (film) ν_{max} 3353, 2923, 2853, 1466, 1033 cm^{-1}.

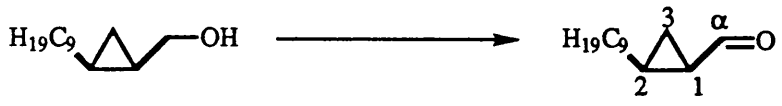
δ_H (270MHz, $CDCl_3$) 3.61 (2H, m, 2*H_α), 1.48-1.26 (17H, m, CH_2 envelope, OH), 1.05 (2H, m, cyclopropyl H), 0.88 (3H, t, *J* 6.8Hz, terminal CH_3), 0.71 (1H, m), -0.01 (2H, m) [total 2H, cyclopropyl H's].

δ_C (125MHz, $CDCl_3$) 63.31 (C_α), 31.90, 30.15, 29.63, 29.60, 29.53, 29.32, 28.55, 22.66 (CH_2's), 18.15, 16.15 (C_1, C_2), 14.07 (CH_3), 9.45 (CH_2).

m/z (EI) 180 (M^+-H_2O), 157, 123, 109, 83, 71, 58, 43.

Found: C 78.67, H 13.17. $C_{13}H_{26}O$ requires: C 78.72, H 13.21%.

Preparation of (1R*, 2S*)-1-methanal-2-nonylcyclopropane (94).



(93) (94)

To a solution of the alcohol (93) (1.0g, 5.04mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (2.82g,

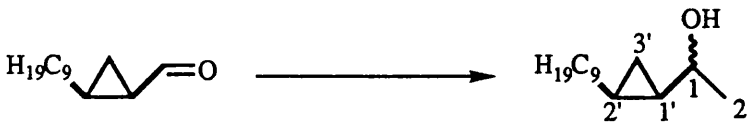
7.49mmol), and the solution stirred for 20 hours. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***(1R*, 2S*)-1-methanal-2-nonylcyclopropane*** **(94)** (950mg, 96%) as a colourless oil (which was carried through to the next step as soon as possible because of possible trimerisation);

IR (film) ν_{max} 2925, 2855, 1707, 1467, 1178, 1057 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 9.34 (1H, d, *J* 5.9Hz, H_α), 1.85 (1H, m, H_1), 1.48-1.15 (19H, m, CH_2 envelope, 3*cyclopropyl H's), 0.86 (3H, t, *J* 6.4Hz, terminal C*H*$_3$).

m/z (EI) 196 (M^+), 178 (M^+-H_2O), 152, 140, 124, 121, 83, 70, 55, 41.

Preparation of (1RS)-1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]ethan-1-ol (95).



(94) (95)

To a solution of the cyclopropyl aldehyde (94) (500mg, 2.55mmol) in ether (17ml) at -78°C under argon, was added methylmagnesium bromide (1.3ml of a 3.0M solution in Et_2O). After stirring for 30 minutes the solution was warmed to room temperature, quenched with saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (10-20% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]ethan-1-ol*** **(95)** as two separable diastereomers:

less polar diastereomer (250mg, 46%) as a colourless oil;

IR (film) ν_{max} 3329, 2925, 2854, 1467, 1078 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.39 (1H, m, H_1), 1.58 (1H., brs, O*H*), 1.46-1.16 (19H, m, CH_2 envelope, 3*H_2), 0.89 (5H, m, terminal C*H*$_3$, 2*cyclopropyl H's), 0.68 (1H, m), -0.13 (1H, m) [total 2H, cyclopropyl H's].

m/z (CI) 212 (M^++NH_4^+-H_2O), 195, 156, 139, 125, 111, 95, 81, 70, 58.

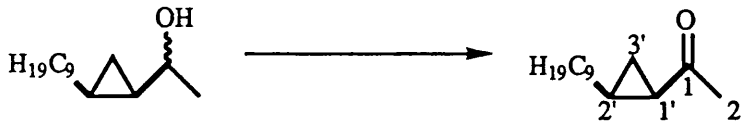
more polar diastereomer (224mg, 41%) as a colourless oil;

IR (film) ν_{max} 3400, 2926, 2853, 1466, 1372, 1289, 1103, 1024 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 3.36 (1H, m, H_1), 1.54-1.12 (20H, m, CH_2 envelope, 3*H_2,O*H*), 1.05 (1H, m, 1*cyclopropyl H), 0.86 (4H, m, terminal C*H*$_3$, 1*cyclopropyl H), 0.71 (1H, m), 0.04 (2H, m) [total 3H, cyclopropyl H's].

m/z (CI) 212 (M^++NH_4^+-H_2O), 195, 161, 149, 136, 124, 110, 96, 84, 72, 58, 45.

Preparation of 1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]ethan-1-one (96).



(95) (96)

To a solution of the alcohol (95) (474mg, 2.24mmol) in dichloromethane (10ml), at room temperature under argon, was added pyridinium dichromate (1.26g, 3.35mmol), followed by pyridinium trifluoroacetate (173mg, 0.90mmol) and the solution stirred for 5 days. The reaction mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) gave ***1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]ethan-1-one*** **(96)** (470mg, 99%) as a colourless oil;

IR (film) ν_{max} 2925, 2855, 1699, 1466, 1383, 1166 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.27 (3H, s, 3*H_2), 2.03 (1H, m, $H_{1'}$), 1.49-1.14 (16H, m, CH_2 envelope), 1.06 (2H, m, 2*cyclopropyl H's), 0.95 (1H, m, cyclopropyl H), 0.87 (3H, *J* 6.3Hz, terminal C*H*$_3$).

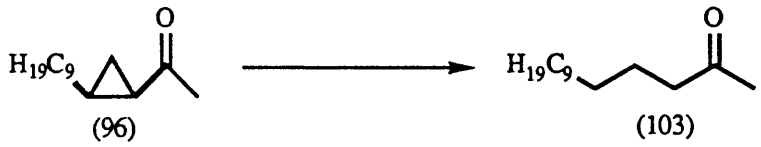
δ_C (67.9MHz; $CDCl_3$) 207.03 (C=O), 31.95 (C_2), 31.88, 29.89, 29.59, 29.56, 29.32, 29.29 (CH_2's), 26.40 ($C_{1'}$), 26.23 (CH_2), 25.62 ($C_{2'}$), 22.65, 14.44 (CH_2), 14.07 (terminal CH_3).

m/z (EI) 210 (M^+), 195 (M^+-CH_3), 192 (M^+-H_2O), 181 (M^+-C_2H_5), 152, 111, 96,

82, 72, 43;

Observed: M^+, 210.1984. $C_{14}H_{26}O$ requires 210.1984.

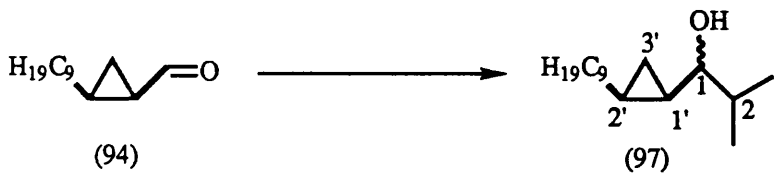
Preparation of tetradecan-2-one (103).



(96) (103)

To a solution of the cyclopropyl ketone (96) (90mg, 0.49mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (7.2ml of a 0.1M solution in tetrahydrofuran) at room temperature under argon, until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml) and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$, filtered and the solvent removed in *vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded ***tetradecan-2-one*** **(103)** (56mg, 65%) (data identical to that described previously).

Preparation of (1RS)-1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-ol (97).



(94) (97)

To a solution of isopropylmagnesium chloride (3.08ml of a 2.0M solution in Et_2O) at -30°C under argon, was added a solution of the aldehyde (94) (932mg, 4.75mmol) in ether (46ml) dropwise and stirring continued for an hour. A further portion of

isopropylmagnesium chloride (0.50ml of a 2.0M solution in Et_2O) was added and stirring continued for a further 30 minutes before warming to room temperature. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (15% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-ol*** **(97)** as two separable diastereomers:

less polar diastereomer (263mg, 23%) as a colourless oil;

IR (film) ν_{max} 3363, 2957, 2854, 1466, 1020 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.96 (1H, m, H_1), 1.80 (1H, dsept., *J* 1.0, 5.9Hz, H_2), 1.57 (1H, brs, OH), 1.49-1.23 (17H, m, CH_2 envelope, 1*cyclopropyl H), 0.99 (3H, d, *J* 6.8Hz, C*H*$_3$), 0.98 (3H, d, *J* 6.8Hz, C*H*$_3$), 0.88 (3H, t, *J* 6.4Hz, terminal C*H*$_3$), 0.82-0.70 (2H, m), -0.007 (1H, m) [total 3H, cyclopropyl H's].

m/z (CI) 240 (M^++NH_4^+-H_2O), 223, 197 (M^+-C_3H_7), 167, 153, 139, 111, 97, 81, 57.

Observed (M^++NH_4^+-H_2O), 240.2691. $C_{16}H_{34}N$ requires 240.2691.

more polar diastereomer (798mg, 70%) as a colourless oil;

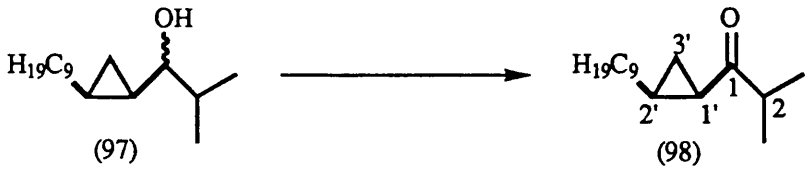
IR (film) ν_{max} 3384, 2925, 2854, 1466, 1026 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.99 (1H, m, H_1), 1.76 (1H, dsept., *J* 1.5, 5.4Hz, H_2), 1.56 (1H, brs, OH), 1.43-1.27 (18H, m, CH_2 envelope, 2*cyclopropyl H's), 0.99 (3H, d, *J* 7.0Hz, C*H*$_3$), 0.98 (3H, d, *J* 7.0Hz, C*H*$_3$), 0.88 (3H, t, *J* 6.4Hz, terminal C*H*$_3$), 0.71 (1H, m, cyclopropyl H), 0.012 (1H, m, cyclopropyl H).

m/z (CI) 240 (M^++NH_4^+-H_2O), 223, 197 (M^+-C_3H_7), 167, 153 139, 111, 97, 83, 57.

Observed: (M^++NH_4^+-H_2O), 240.2797. $C_{16}H_{34}N$ requires 240.2797.

Preparation of 1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-one (98).



To a solution of the alcohol (97) (1.06g, 4.39mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (2.48g, 6.61mmol), followed by pyridinium trifluoroacetate (340mg, 1.76mmol) and the solution stirred for 8 days. The reaction mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-one*** **(98)** (912mg, 87%) as a colourless oil;

IR (film) ν_{max} 2924, 2855, 1696, 1467, 1393, 1065 cm^{-1}.

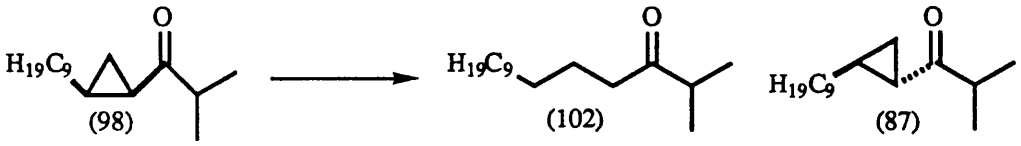
δ_H (270MHz, $CDCl_3$) 2.74 (1H, sept., *J* 6.7Hz, H_2), 2.06 (1H, m, $H_{1'}$) 1.35-1.18 (16H, CH_2 envelope), 1.13 (3H, d, *J* 6.8Hz, CH_3), 1.12 (3H, d, *J* 6.8Hz, CH_3), 1.05 (1H, m, 1*cyclopropyl H), 0.95 (2H, m, 2*cyclopropyl H's) 0.87 (3H, t, *J* 6.6Hz, terminal CH_3).

δ_C (67.9MHz, $CDCl_3$) 212.77 (C=O), 42.27 (C_2), 31.89, 29.83, 29.62, 29.56, 29.33, 29.29, 26.29 (CH_2's), 25.54, 24.25 ($C_{1'}$, $C_{2'}$), 22.66 (CH_2), 18.34, 18.17 (2*CH_3), 14.33 (CH_2), 14.07 (terminal CH_3).

m/z (EI) 239 (MH^+), 195 (M^+-C_3H_7), 177, 124, 111, 97, 83, 71, 55.

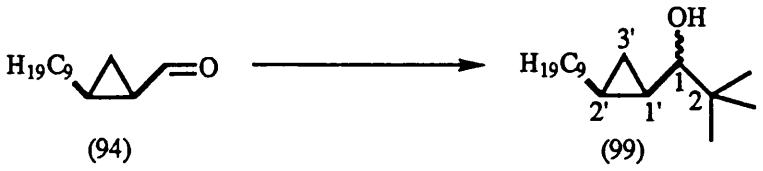
Observed: (MH^+), 239.2375. $C_{16}H_{31}O$ requires 239.2375.

Preparation of 2-methylpentadecan-3-one (102) and 1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2-methylpropan-1-one (87).



To a solution of the cyclopropyl ketone (98) (119mg, 0.50mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (11.0ml of a 0.1M solution in tetrahydrofuran) at room temperature under argon, until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml), and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded in order of elution ***2-methylpentadecan-3-one*** **(102)** (71mg, 59%) as a clear oil and ***1-[(1R*, 2R*)-2-nonylcyloprop-1-yl]-2-methylpropan-1-one*** **(87)** (17mg, 14%) (data identical to that described previously).

Preparation of (1RS)-1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-ol (99).



To a solution of the aldehyde (94) (878mg, 4.47mmol) in ether (13ml) at -78°C under argon, was added dropwise a solution of *t*-butyllithium (3.95ml of a 1.7M solution in Et_2O). After stirring for 45 minutes the solution was allowed to warm to room temperature poured into water (20ml) and extracted with ether (3x30ml). The

combined organic extracts were washed with brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (5% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 2S*)-2-nonylcyclopropyl-1-yl]-2,2-dimethylpropan1-ol*** (**99**) as two separable diastereomers:

less polar diastereomer (667mg, 59%);

IR (film) ν_{max} 3481, 2926, 2854, 1463, 1363 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.86 (1H, dd, *J* 10.0, 3.9Hz, H_1), 1.68 (1H, m, $H_{1'}$), 1.56 (1H, brs, OH), 1.41 (2H, m, 2*$H_{4'}$), 1.35-1.27 (14H, m, CH_2 envelope), 0.95 (9H, s, 3*C*H*$_3$), 0.87 (3H, t, *J* 6.4Hz, terminal C*H*$_3$), 0.78 (2H, m), 0.06-0.04 (1H, m) [total 3H, cyclopropyl H's].

m/z (CI) 254 (M^++NH_4^+-H_2O), 237 (M^+-OH), 197 (M^+-C_4H_9), 167, 153, 139, 125, 95, 81, 57.

Observed: (M^++NH_4^+-H_2O), 254.2854. $C_{17}H_{36}N$ requires 254.2848.

more polar diastereomer (455mg, 40%) as a colourless oil;

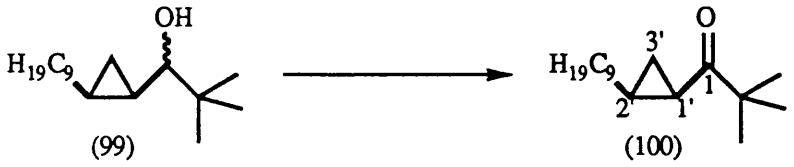
IR (film) ν_{max} 3399, 2925, 2855, 1465, 1363, 1002 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 2.90 (1H, dd, *J* 10.3, 3.5Hz, H_1), 1.60 (1H, m, $H_{1'}$), 1.32-1.21 (17H, m, CH_2 envelope, OH), 0.97 (9H, s, 3*C*H*$_3$), 0.87 (3H, t, *J* 6.9Hz, terminal C*H*$_3$), 0.68 (2H, m), -0.011 (1H, m) [total 3H, cyclopropyl H's].

m/z (CI) 254 (M^++NH_4^+-H_2O), 237 (M^+-OH), 197 (M^+-C_4H_9), 179, 123, 109, 95, 81, 57.

Observed: (M^++NH_4^+-H_2O), 254.2855. $C_{17}H_{36}N$ requires 254.2848.

Preparation of 1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one (100).



To a solution of the alcohol (99) (1.06g, 4.17mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (2.35g, 6.24mmol), followed by pyridinium trifluoroacetate (323mg, 1.67mmol) and the solution stirred for 5 days. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) gave ***1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one*** **(100)** (919mg, 87%) as a colourless oil;

IR (film) ν_{max} 2956, 2855, 1692, 1478, 1394, 1005 cm^{-1}.

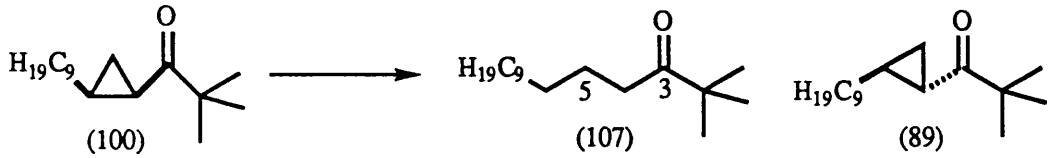
δ_H (270MHz, $CDCl_3$) 2.22 (1H, m, $H_{1'}$), 1.41-1.12 (18H, CH_2 envelope, 1*$H_{3'}$, $H_{2'}$), 1.18 (9H, s, 3*C*H*3), 1.08 (1H, m, 1*$H_{3'}$), 0.87 (3H, t, *J* 6.7Hz, terminal C*H*3).

δ_C (67.9MHz, $CDCl_3$) 213.70 (C=O), 44.33 (C_2), 31.89, 29.74, 29.61, 29.56, 29.35, 29.29 (CH_2's), 26.54 (3*CH_3), 26.05 (CH_2), 25.40 ($C_{1'}$ or $C_{2'}$), 22.66 (CH_2), 21.34 ($C_{1'}$ or $C_{2'}$), 14.29 (CH_2), 14.08 (terminal CH_3).

m/z (EI) 253 (MH^+), 195 (M^+-C_4H_9), 177, 167, 111, 97, 83, 69, 57.

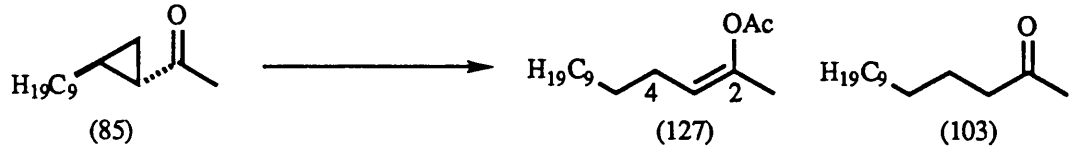
Observed: M^+, 252.2453. $C_{17}H_{32}O$ requires 252.2453.

Preparation of 2,2-dimethylpentadecan-3-one (107) and 1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one (89).



To a solution of the cyclopropyl ketone (100) (90mg, 0.36mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml), was added dropwise a solution of samarium(II) iodide (0.1M solution in tetrahydrofuran, 3.92ml) at room temperature under argon until a mauve/purple colouration persisted. After 5 minutes the reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (15ml). The solution was extracted with ether (3x25ml) and the combined organic extracts washed with water (20ml), brine (20ml), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography (5-10% ether/petrol, silica) afforded, in order of elution, ***2,2-dimethylpentadecane-3-one*** **(107)** (64mg, 70%) and ***1-[(1R* , 2R*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one*** **(89)** (15mg, 17%) (data identical to that described previously).

Preparation of (Z)-2-acetoxy-2-tetradecene (127) and tetradecan-2-one (103).



To a solution of the cyclopropyl ketone (85) (90mg, 0.429mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml) at room temperature under argon, was added dropwise a solution of samarium(II) iodide (9.44ml of a 0.1M solution in tetrahydrofuran), until a mauve/purple colouration persisted. The heterogeneous solution was immediately cooled to -78°C and acetyl

chloride (400μl, 4.29mmol) added. After stirring for 90 minutes the mixture was allowed to warm to room temperature. The solution was stirred for a further 45 minutes and poured into saturated aqueous $NaHCO_3$ solution (25ml) and extracted with ether (3x25ml). The combined organic extracts were washed with water (30ml), brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (2-4% ether/petrol, silica) afforded in order of elution ***(Z)-2-acetoxy-2-tetradecene*** **(127)** as a colourless oil;

IR (film) ν_{max} 2925, 2854, 1759, 1680, 1370, 1214 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 4.99 (1H, t, *J* 6.6Hz, H_3), 2.19 (3H, s, CH_3-Ac), 2.15-2.11 (2H, m, 2*H_4), 2.14 (3H, s, 3*H_1), 1.41-1.13 (18H, m, CH_2 envelope), 0.88 (3H, t, *J* 7.0Hz, terminal CH_3).

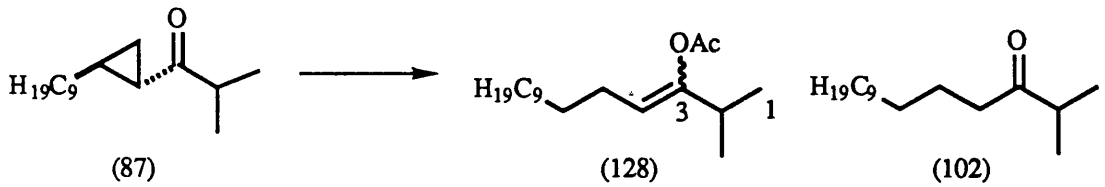
δ_C (67.9MHz, $CDCl_3$) 168.92 (C=O), 144.63 (C_2), 117.18 (C_3), 32.50, 31.91, 29.67, 29.64, 29.59, 29.43, 29.34, 29.25, 29.04, 25.38, 22.69 (CH_2's), 20.78 (C_1), 14.11 (terminal CH_3),

m/z (EI) 242 (M^+), 183 (M^+-OAc), 169, 127, 85, 71, 43.

Observed: M^+, 242.1091. $C_{16}H_{30}O_2$ requires 242.1097,

and ***tetradecan-2-one*** **(103)** (50mg, 53%) (data identical to that described previously).

Preparation of 3-acetoxy-2-methyl-3-pentadecene (128) and 2-methylpentadecan-3-one (102).



(87) (128) (102)

To a solution of the cyclopropyl ketone (87) (119mg, 0.50mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml) at room temperature under argon, was added dropwise a solution of samarium(II) iodide

(8.5ml of a 0.1M solution in tetrahydrofuran) until a mauve/purple colour persisted. The heterogeneous solution was immediately cooled to -78°C and acetyl chloride (500µl, 5.36mmol) added. After stirring for 90 minutes at -78°C the mixture was allowed to warm to room temperature. The solution was stirred for a futher 45 minutes and then poured into saturated aqueous $NaHCO_3$ solution (25ml) and extracted with ether (3x25ml). The combined organic extracts were washed with water (30ml), brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (2% ether/petrol, silica) afforded an inseparable mixture of ***3-acetoxy-2-methyl-3-tetradecene*** **(128)** (see below for data) and ***2-methylpentadecan-3-one*** **(102)** (data identical to that described previously) (2:1, 77mg) as a colourless oil;

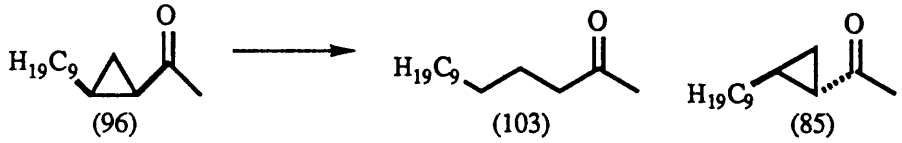
IR (film) ν_{max} 2925, 2851, 1766, 1715, 1673, 1466, 1370, 1207, 1045 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 5.00 (1H, t, 7.0Hz, H_4), 2.59 (1H, sept., *J* 7.1Hz, H_2), 2.16 (3H, s, CH_3-Ac), 1.86 (2H, m, 2*H_5), 1.58-1.19 (18H, m, CH_2 envelope), 1.03 (6H, d, *J* 6.8Hz, 2*CH_3), 0.88 (3H, t, *J* 6.4Hz, terminal CH_3).

m/z (CI) 300 (M^++NH_4^+), 283 (MH^+), 152, 123, 109, 86, 71, 43.

Observed: (M^++NH_4^+), 300.2903. $C_{18}H_{38}NO_2$ requires 300.2903.

Attempted Samarium Enolate Trapping of 1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]ethan-1-one (96).

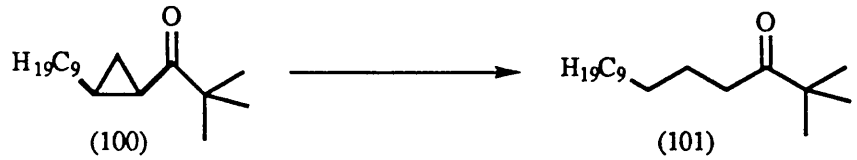


(96) (103) (85)

To a solution of the cyclopropyl ketone (96) (90mg, 0.50mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml) at room temperature under argon, was added dropwise a solution of samarium(II) iodide (9.44ml of a 0.1M solution in tetrahydrofuran), until a mauve/purple colour

persisted. The heterogeneous solution was immediately cooled to -78°C and acetyl chloride (400µl, 4.29mmol) added. After stirring for 90 minutes the mixture was allowed to warm to room temperature. The solution was futher stirred for 45 minutes and then poured into saturated aqueous $NaHCO_3$ solution (25ml) and extracted with ether (3x25ml). The combined organic extracts were washed with water (30ml), brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (2-4% ether/petrol, silica) afforded in order of elution recovered starting material (29mg, 32%), ***tetradecan-2-one*** **(103)** (30mg, 33%), and ***1-[(1R*, 2R*)-2-nonylcycloprop-1-yl]ethan-1-one*** **(85)** (10mg, 11%) (data identical to that described previously).

Attempted Samarium enolate trapping of 1-[(1R*, 2S*)-2-nonylcycloprop-1-yl]-2,2-dimethylpropan-1-one (100).

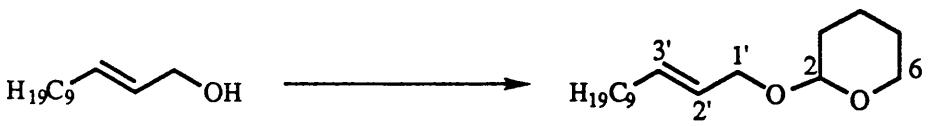


(100) (101)

To a solution of the cyclopropyl ketone (100) (90mg, 0.36mmol) in tetrahydrofuran / 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) (9:1, 7.0ml) at room temperature under argon, was added dropwise a solution of samarium(II) iodide (7.14ml of a 0.1M solution in tetrahydrofuran), until a mauve/purple colouration persisted. The heterogeneous solution was immediately cooled to -78°C and acetyl chloride (337µl, 3.57mmol) added. After stirring for 90 minutes the mixture was allowed to warm to room temperature. The solution was further stirred for 45 minutes and then poured into saturated aqueous $NaHCO_3$ solution (25ml) and extracted with ether (3x25ml). The combined organic extracts were washed with water (30ml), brine (30ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (2-4% ether/petrol, silica) afforded **2,2-**

dimethylpentadecan-3-one (101) (64mg, 72%) (data identical to that described previously).

Preparation of 2-[*(E)*-2-dodecenyloxy]tetrahydropyran (129).



(81) (129)

To a solution of *(E)*-2-dodecen-1-ol (81) (11g, 58mmol) in 3,4-dihydro-2*H*-pyran (6.54ml, 72mmol) at 0°C under argon, was added concentrated HCl (2 drops), and stirring continued for 48 hours. Solid $NaHCO_3$ was added and after a futher 10 minutes, the solution was poured into water and extracted with ether (3x50ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent distillation afforded ***2-[(E)-2-dodecenyloxy]tetrahydropyran*** **(129)** (15.3g, 95%) as a colourless oil (b.pt. 170°C at 1mm Hg);

IR (film) ν_{max} 2929, 2853, 1648, 1466, 1379, 1261, 1184, 1078 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 5.68 (1H, m, $H_{2'}$ or $H_{3'}$), 5.55 (1H, m, $H_{2'}$ or $H_{3'}$), 4.61 (1H, t, *J* 3.9Hz, H_2), 4.16 (1H, ddd, *J* 11.9, 5.6, 0.98Hz, 1*$H_{1'}$), 3.90 (1H, ddd, *J* 11.9, 5.6, 0.98Hz, 1*$H_{1'}$), 3.84 (1H, m, 1*H_6), 3.48 (1H, m, 1*H_6), 2.02 (2H, brq, *J* 6.6Hz, 2*$H_{4'}$), 1.84-1.47 (6H, m, 2*H_3, 2*H_4, 2*H_5), 1.38-1.16 (14H, m, CH_2 envelope), 0.86 (3H, t, *J* 6.4Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 134.70, 125.95 ($C_{2'}$, $C_{3'}$), 97.61 (C_2), 67.82, 62.12 ($C_{1'}$, C_6), 32.27, 31.85, 30.61, 29.52, 29.44, 29.63, 29.16, 29.01, 25.43, 22.62, 19.50 (CH_2's) 14.03 (terminal CH_3).

m/z (EI) 268 (M^+), 222, 195, 182, 166, 111, 97, 85.

Observed: M^+, 268.2369. $C_{17}H_{32}O_2$ requires 268.2375.

Preparation of 2-[(1R*, 3R*)-1-(2-methylene-3-nonyl-1-cyclopropyl)methyloxy]tetrahydropyran (131).

(129) (131)

n-Butyllithium (22.4ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period by means of a syringe pump, to a stirred solution of the protected alcohol (129) (15g, 56mmol), and 1,1-dichloroethane (1.31ml, 15.6mmol) in ether (50ml) under argon at -35°C. Futher portions of 1,1-dichloroethane (1.0ml, 10.8mmol) were added 0.5, 1.5, 2.5 and 3.5 hours after the initial addition. The mixture was allowed to warm to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (100ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloromethylcyclopropane was dissolved in DMSO (7ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (9.18g, 82.4mmol) in DMSO (19ml) at 70°C under argon. After stirring for 20 hours the resulting dark brown solution was cooled to 0°C, poured into ice-cold water (200ml) and extracted with ether (3x100ml). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (4-7% ether/petrol, silica), afforded ***2-[(1R*, 3R*)-1-(2-methylene-3-nonyl-1-cyclopropyl)-methyloxy]tetrahydropyran*** **(131)** (as a mixture of diastereomers) (11.5g, 70%) as an orange oil ;

IR (film) ν_{max} 2933, 2851, 1754, 1462, 1354, 1200, 1113, 1030 cm^{-1}.

δ_H (270Hz, $CDCl_3$) 5.34 (2H, m, 2*$H_{2''}$), 4.67 (1H, m, H_2), 3.84 (1H, m, 1*H_6), 3.65 (1H, dd, *J* 10.6, 6.4Hz, 1*H_α), 3.51 (1H, m, 1*H_6), 3.41 (1H, dd, *J* 10.8,

7.8Hz, 1*Hα), 1.86-0.93 (24H, m, CH_2 envelope, $H_{1'}$, 2*H_3, $H_{3'}$, 2*H_4, 2*H_5), 0.86 (3H, t, *J* 6.4Hz, terminal C*H*3).

δ_C (100MHz, $CDCl_3$) 139.74, [139.27] ($C_{2'}$), 103.31, [103.16] ($C_{2''}$), 97.91 (C_2), 69.49, [69.33], 62.12, [62.00] (C_α, C_6), 32.24, 32.20, 31.90, 30.73, 30.68, 29.63, 29.34, 29.23, 29.18, 25.15 (CH_2's), 24.13, [23.65], 22.68, [22.24] ($C_{1'}$, $C_{3'}$), 19.51 (CH_2), 14.10 (terminal CH_3).

m/z (EI) 295 (MH^+), 193 (M^+-OTHP), 179, 165, 151, 137, 123, 85, 57.

Observed: M^+, 294.2561. $C_{19}H_{34}O_2$ requires 294.2559.

Preparation of (1R*, 3R*)-1-methanol-2-methylene-3-nonylcyclopropane (132).

(131) (132)

To a solution of the methylenecyclopropane (131) (2.0g, 6.79mmol), in methanol (15ml) was added *p*-toluenesulphonic acid (346mg, 1.84mmol), and the reaction mixture stirred for 18 hours. Anhydrous potassium carbonate was added and after a further 20 minutes the solvent was removed *in vacuo*. The residue was diluted with water (100ml), extracted with ether (2x100ml), the combined organic extracts dried over $MgSO_4$ and the solvent was removed *in vacuo*. Subsequent column chromatography (20% ether/petrol, silica) gave ***(1R*, 3R*)-1-methanol-2-methylene-3-nonylcyclopropane*** **(132)** (1.22g, 85%) as a colourless oil;

IR (film) ν_{max} 3332, 2923, 2853, 1724, 1466, 1038 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.41 (2H, m, 2*$H_{2'}$), 3.54 (1H, m, 1*Hα), 3.49 (1H, m, 1*Hα), 1.47-1.20 (19H, m, CH_2 envelope, H_1, H_3, OH), 0.87 (3H, t, *J* 6.4Hz, terminal C*H*3).

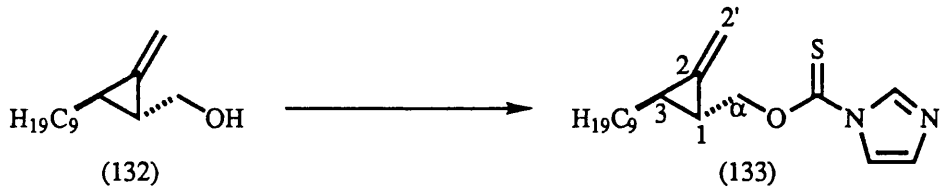
δ_C (125MHz, $CDCl_3$) 139.03 (C_2), 103.27 ($C_{2'}$), 64.92 (C_α), 32.11, 31.83, 29.52,

29.36, 29.25, 29.23 (CH_2's), 24.87 (C_1), 22.60 (CH_2), 21.63 (C_3), 14.00 (terminal CH_3).

m/z (EI) 211 (MH^+), 194 (M^+-OH), 179 (M^+-CH_2OH), 123, 107, 95, 81, 71, 55.

Observed: (MH^+), 211.2069. $C_{14}H_{27}O$ requires 211.2062.

Preparation of [((1R*, 3R*)-2-methylene-3-nonyl-cyclopropyl)methyloxythiocarbonyl]-1-imidazole (133).



(132) (133)

To a solution of the alcohol (132) (924mg, 4.39mmol) in dichloromethane (70ml) under argon, was added 1,1'-thiocarbonyldiimidazole (5.13g, 28.8mmol) and the solution stirred at reflux for 18 hours. On cooling the orange liquid was diluted with dichloromethane (70ml), washed sequentially with 2M HCl saturated aqueous $NaHCO_3$ solution, water, brine, dried over $MgSO_4$ and the solvent removed*in vacuo*. Subsequent column chromatography (50% ether/petrol, silica) afforded ***[((1R*, 3R*)-2-methylene-3-nonyl-cyclopropyl)methyloxythiocarbonyl]-1-imidazole (133)*** (588mg, 42%) as a yellow oil;

IR (film) ν_{max} 2924, 2853, 1725, 1530, 1464, 1388, 1230, 1094 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 8.33 (1H, s, Ar-*H*), 7.62 (1H, d, *J* 1.5Hz, Ar-*H*), 7.01 (1H, d, *J* 1.5Hz, Ar-*H*), 5.44 (2H, m, 2*$H_{2'}$), 4.64 (1H, dd, *J* 11.4, 6.8Hz, 1*H_α), 4.48 (1H, dd, *J* 11.4, 6.8Hz, 1*H_α), 1.63 (1H, m, H_1), 1.45-1.23 (17H, m, CH_2 envelope, H_3), 0.83 (3H, t, *J* 6.3Hz, terminal CH_3).

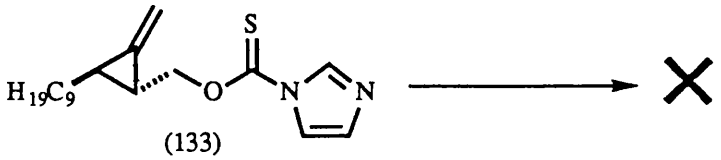
δ_C (125MHz, $CDCl_3$) 184.23 (C=S), 136.88, 136.72 (C_2, $C_{2''}$), 130.75, 117.77 ($C_{4''}$, $C_{5''}$), 105.05 ($C_{2'}$), 76.03 (C_α), 31.83, 29.50, 29.25, 29.20, 29.12 (CH_2's), 22.84 (C_1), 22.61 (CH_2), 20.03 (C_3), 14.04 (CH_3).

m/z (EI) 320 (M^+), 287, 259, 253 (M^+-Im), 225, 193 (M^+-OC(S)Im), 109, 95, 81,

69, 55.

Found: C, 67.17. H, 8.53. N, 8.80. $C_{18}H_{28}N_2OS$ requires C, 67.46. H 8.81. N, 8.74%.

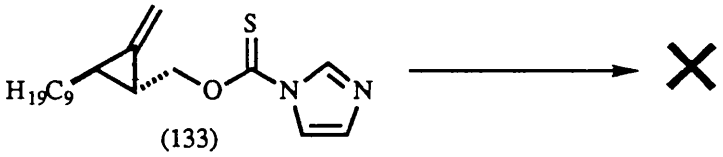
Attempted rearrangement of [((1R*, 3R*)-2-methylene-3-nonyl-cyclopropyl)methyloxythiocarbonyl]-1-imidazole (133).



(133)

A solution of AIBN (21mg, 0.13mmol) and tri-*n* -butylstannane (419µl, 1.55mmol) in benzene (2ml) was introduced over a 30 minute period by means of a syringe pump to a rapidly stirred degassed solution of the thiocarbonylimidazole derivative (133) (250mg, 0.78mmol) in benzene (13ml) at 80°C under argon. After a further 12 hours, the reaction mixture was allowed to cool to room temperature where upon carbon tetrachloride (20ml) and iodine were added. Stirring was continued until a persistent colouration was observed (1hour), adding further iodine if necessary, and stirring continued for a further hour. The solvent was removed *in vacuo*, the residue taken up in ethyl acetate (20 ml), saturated aqueous KF solution (10 ml) added and the solution stirred vigorously for 30 minutes. The suspension was filtered, extracted with ethyl acetate (2x20ml), the combined organic extracts washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (15% DCM/petrol, silica) afforded a complex mixture of products.

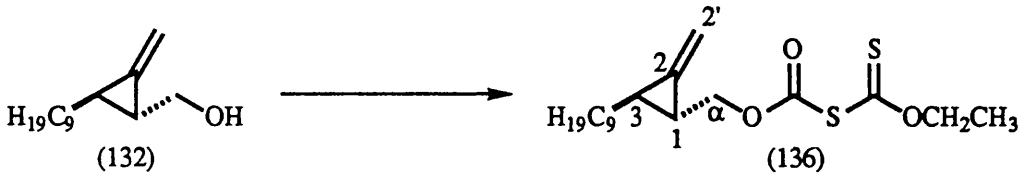
Attempted rearrangement and trapping of [((1R*, 3R*)-2-methylene-3-nonyl-cyclopropyl)methyloxythiocarbonyl]-1-imidazole (133).



(133)

A solution of AIBN (21mg, 0.13mmol) and tri-*n*-butylstannane (419µl, 1.55mmol) in benzene (2ml) was introduced over a 30 minute period by means of a syringe pump, to a rapidly stirred degassed solution of the thiocarbonylimidazole derivative (133) (250mg, 0.78mmol) and ethyl acrylate (845µl, 7.80mmol) in benzene (13ml) at 80°C under argon. After a further 12 hours, the reaction mixture was allowed to cool to room temperature where upon carbon tetrachloride (20ml) and iodine were added. Stirring was continued until a persistent colouration was observed (1hour), adding futher iodine if necessary. The solution was diluted with ether (50ml), washed with saturated aqueous KF solution (3x40ml) and dried over $MgSO_4$. Removal of the solvent *in vacuo* followed by nmr analysis of the crude material showed none of the expected products.

Preparation of *S*-ethyl xanthate (136).



(132) (136)

To a solution of the alcohol (132) (700mg, 3.33mmol) in tetrahydrofuran (15ml) at room temperature under argon was added a solution of phosgene (5.17ml of a 1.93M solution in toluene) dropwise and stirring continued for an hour. The mixture was concentrated *in vacuo* and the residue taken up in acetone/tetrahydrofuran (5:1,

24ml) and cooled to 0°C. A solution of potassium-*S*-ethyl xanthate (528mg, 3.33mmol) in acetone (10ml) was added, the solution warmed to room temperature and the solvent removed *in vacuo* . The residue was taken up in water, extracted with dichloromethane (3x20ml), the combined organic extracts dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (10% DCM/petrol, silica) afforded ***S-ethyl xanthate* (136)** (640mg, 54%) as a yellow oil;

IR (film) ν_{max} 2923, 2851, 1749, 1456, 1369, 1261, 1102, 1027 cm^{-1}.

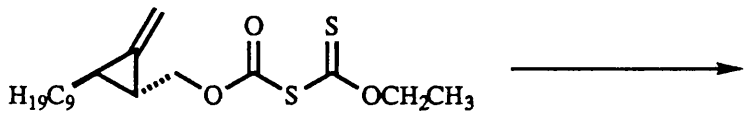
δ_H (270MHz, $CDCl_3$) 5.42 (2H, m, 2*$H_{2'}$), 4.69 (2H, q, *J* 7.1Hz, OCH_2CH_3), 4.25 (1H, dd, *J* 11.2, 6.6Hz, 1*H_α), 4.07 (1H, dd, *J* 11.2, 6.6Hz, 1*H_α), 1.50 (3H, t, *J* 7.1Hz, OCH_2CH_3), 1.42-1.25 (18H, m, CH_2 envelope, H_1, H_3), 0.86 (3H, t, *J* 6.9Hz, terminal CH_3).

δ_C (125MHz, $CDCl_3$) 204.00 (C=S), 163.33 (C=O), 137.30 (C_2), 104.71 ($C_{2'}$), 77.00 (C_α), 70.87 (OCH_2CH_3), 31.90, 29.75, 29.60, 29.35, 29.12, 27.44 (CH_2's), 22.78 (C_1), 22.69 (CH_2), 20.80 (C_3), 14.13 (terminal CH_3), 13.52 (OCH_2CH_3).

m/z (CI) 376 (M^++NH_4^+), 315, 256, 193, 151, 137, 123, 109, 95.

Observed: (M^++NH_4^+), 376.1980. $C_{18}H_{34}NO_3S_2$ requires 376.1980.

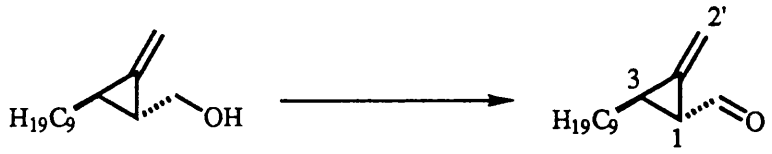
Attempted rearrangement of *S*-ethyl xanthate (136).



(136)

A degassed solution of the anhydride (136) (250mg, 0.96mmol) in heptane (30ml) was irradiated with a 500W tungsten filament for 21 hours. The solution was allowed to cool to room temperature and the solvent removed *in vacuo*. Subsequent column chromatography (50% ether/petrol, silica) of the orange oil gave only the starting xanthate (70mg, 23%).

Preparation of (1R*, 3R*)-1-methanal-2-methylene-3-nonylcyclopropane (144).



(132) (144)

To a solution of the alcohol (132) (900mg, 4.28mmol) in dichloromethane (10ml) at room temperature under argon, was added pyridinium dichromate (2.42g, 6.4mmol), and the solution stirred for 20 hours. The mixture was then diluted with ether, filtered through a short pad of silica and the solvent removed *in vacuo* to afford ***(1R*, 3R*)-1-methanal-2-methylene-3-nonylcyclopropane*** **(144)** (724mg, 81%) as a coluorless oil;

IR (film) ν_{max} 2925, 2855, 1709, 1462, 1090 cm^{-1}.

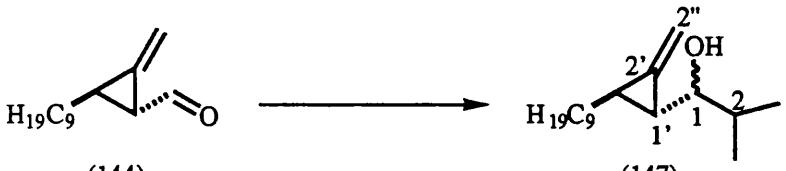
δ_H (400MHz, $CDCl_3$) 8.71 (1H, d, *J* 6.1Hz, C*H*O), 5.60 (1H, t, *J* 2.2Hz, 1*$H_{2'}$), 5.54 (1H, t, *J* 2.2Hz, 1*$H_{2'}$), 2.14 (2H, m, H_1, H_3), 1.75-1.20 (16H, m, CH_2 envelope), 0.88 (3H, t, *J* 6.6Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 197.69 (C=O), 140.75 (C_2), 106.50 ($C_{2'}$), 35.83 (C_1), 31.94, 31.21, 29.57, 29.36, 29.16, 28.91, 28.82, 24.67, 22.74 (C_3, CH_2's), 14.15 (terminal CH_3).

m/z (EI) 208 (M^+), 167, 149, 109, 95, 82, 67, 55.

Observed: M^+ 208.1818. $C_{14}H_{24}O$ requires 208.1827.

Preparation of (1RS)-1-[(1R*, 3R*)-2-methylene-3-nonylcycloprop-1-yl]-2-methylpropan-1-ol (147).



(144) (147)

To a solution of isopropylmagnesium chloride (3.15ml of a 2.0M solution in Et_2O) at -30°C under argon was added a solution of the aldehyde (144) (1.0g, 4.50mmol) in ether (40ml) dropwise and stirring continued for 1 hour. A further portion of isopropylmagnesium chloride (1.0ml) was added and stirring continued for a further 30 minutes before warming to room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (15% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 3R*)-2-methylene-3-nonylcycloprop-1-yl]-2-methylpropan-1-ol*** **(147)** (as a mixture of diastereomers) (901mg, 79%) as colourless crystals (m.p. 23-25°C);

IR (film) ν_{max} 3450, 2958, 2873, 1468, 1378, 1029 cm^{-1}.

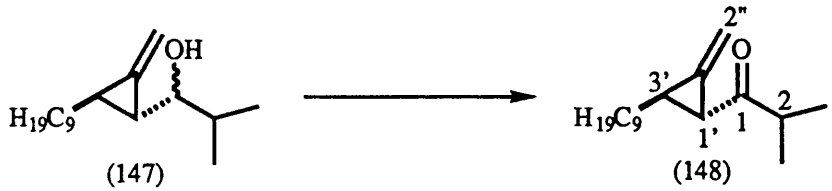
δ_H (400MHz, $CDCl_3$) 5.38 (2H, m, 2*$H_{2''}$), 3.00 (1H, m, H_1), 1.81 (1H, dsept., *J* 6.8, 1.1Hz, H_2), 1.42 (1H, m, $H_{1'}$), 1.36-1.20 (17H, m, CH_2 envelope, $H_{3'}$), 0.99 (3H, d, *J* 6.8Hz, C_2-CH_3), 0.98 (3H, d, *J* 6.8Hz, C_2-CH_3), 0.87 (3H, t, *J* 6.7Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 139.37 ($C_{2'}$), 103.54 ($C_{2''}$), 78.85 ($C_{1'}$), 34.47 (C_2), 32.15, 31.89, 29.58, 29.56, 29.35, 29.32, 29.25 (CH_2's), 26.62 ($C_{1'}$), 22.67, 21.36 (CH_2's), 18.51, 18.05, 14.11 (CH_3's).

m/z (CI) 252 (M^++NH_4^+-H_2O), 235 (M^+-H_2O), 209, 179, 123, 95.

Observed: (M^++NH_4^+-H_2O), 252.2691. $C_{17}H_{34}N$ requires 252.2691.

Preparation of 1-[(1R*, 3R*)-2-methylene-3-nonylcycloprop-1-yl]-2-methylpropan-1-one (148).



(147) (148)

To a solution of the alcohol (147) (900mg, 3.56mmol) in dichloromethane (17ml) at room temperature under argon was added pyridinium dichromate (2.01g, 5.35mmol), followed by pyridinium trifluoroacetate (276mg, 1.43mmol) and the solution stirred for 14 days. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (10% ether/petrol, silica) gave ***1-[(1R*, 3R*)-2-methylene-3-nonylcycloprop-1-yl]-2-methylpropan-1-one*** **(148)** (748mg, 84%) as a yellow oil;

IR (film) ν_{max} 2995, 2854, 1700, 1466, 1382, 1099, 1054 cm^{-1}.

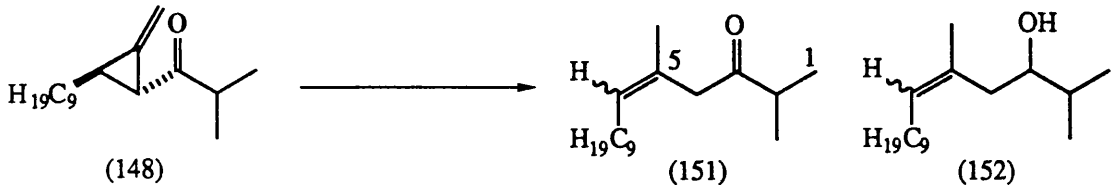
δ_H (400MHz, $CDCl_3$) 5.40 (1H, t, *J* 2.2Hz, 1*$H_{2''}$), 5.29 (1H, t, *J* 2.2Hz, 1*$H_{2''}$), 2.64 (1H, sept., *J* 6.9Hz, H_2), 2.25 (1H, m, $H_{1'}$), 2.13 (1H, m, $H_{3'}$), 1.41-1.23 (16H, m, CH_2 envelope, 2*$H_{4'}$, 2*$H_{5'}$), 1.11 (3H, d, *J* 6.8Hz, C_2-CH_3), 1.10 (3H, d, *J* 6.8Hz, C_2-CH_3), 0.85 (3H, t, *J* 6.7Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 210.30 (C=O), 138.38 ($C_{2'}$), 102.28 ($C_{2''}$), 40.43, 32.01 ($C_{1'}$, C_2), 31.86, 31.72, 29.52, 29.49, 29.21, 29.11, 28.91 (CH_2's), 26.72 (C_3), 22.65 (CH_2), 18.32, 18.18, 14.09 (CH_3's).

m/z (EI) 251 (MH^+), 235 (M^+-CH_3), 207 (M^+-C_3H_7), 165, 137, 124, 109, 95, 81, 67, 55, 43.

Observed: M^+, 250.2290. $C_{17}H_{30}O$ requires 250.2297.

Preparation of *(E)* and *(Z)*-2,5-dimethyl-5-pentadecen-3-one (151) and *(E,Z)*-2,5-dimethyl-5-pentadecen-3-ol (152).



(148) (151) (152)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (30ml) was allowed to condense into the reaction vessel. Lithium shot (55mg) which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (148) (100mg, 0.40mmol) in ether (8ml) was added dropwise over 10 minutes, the cold bath was removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml) and the mixture saturated with solid NaCl. The ethereal layer was separated and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) afforded ***(E) and (Z)-2,5-dimethyl-5-pentadecen-3-one*** **(151)** (as a mixture of isomers) (47mg, 48%) as a colourless oil;

IR (film) ν_{max} 2294, 2854, 1714, 1467, 1382, 1052 cm^{-1}.

major isomer;

δ_H (400MHz, $CDCl_3$) 5.33 (1H, m, H_6), 3.14 (2H, s, 2*H_4), 2.67 (1H, m, H_2), 1.93 (2H, m, 2*H_7), 1.66 (3H, s, C_5-CH_3), 1.40-1.15 (14H, m, CH_2 envelope), 1.07 (3H, d, *J* 7.9Hz, C_2-CH_3), 1.05 (3H, d, *J* 7.9Hz, C_2-CH_3), 0.85 (3H, t, *J* 7.0Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 212.59 (C=O), 129.10 (C_6), 128.31 (C_5), 44.09 (C_4), 39.97 (C_2), 31.88, 29.66, 29.60, 29.55, 29.35, 29.31, 29.29, 28.34, 28.08 (CH_2's), 24.15

(C_5-CH_3), 22.66 (CH_2), 18.41, 18.35, 14.10 (CH_3's).

minor isomer;

δ_H (400MHz, $CDCl_3$) 5.22 (1H, m, H_6), 3.07 (2H, s, 2*H_4), 2.67 (1H, m, H_2), 1.97 (2H, m, 2*H_7), 1.57 (3H, s, C_5-C*H*$_3$), 1.40-1.15 (14H, m, CH_2 envelope), 1.07 (3H, d, *J* 7.9Hz, C_2-C*H*$_3$), 1.05 (3H, d, *J* 7.9Hz, C_2-C*H*$_3$), 0.85 (3H, t, *J* 7.0Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 213.44 (C=O), 129.93 (C_6), 128.76 (C_5), 51.75 (C_4), 39.97 (C_2), 39.58, 31.88, 29.66, 29.60, 29.55, 29.31, 28.34, 28.08 (CH_2's), 24.15 (C_5-CH_3), 22.66 (CH_2), 18.41, 18.35, 14.10 (CH_3's).

m/z (EI) 252 (M^+), 209 (M^+-C_3H_7), 181 (M^+-COC_3H_7), 166, 125, 97, 83, 71.

Observed: M^+ 252.2458. $C_{17}H_{32}O$ requires 252.2453.

and ***(E) and (Z)-2,5-dimethyl-5-pentadecen-3-ol*** **(152)** (as a mixture of isomers) (22mg, 22%) as a colourless oil;

IR (film) ν_{max} 3465, 2958, 2853, 1456, 1379, 1260, 1173, 1126 cm^{-1}.

major isomer;

δ_H (400MHz, $CDCl_3$) 5.35 (1H, m, H_6), 3.46 (1H, m, H_3), 2.25 (1H, m, 1*H_4), 1.92 (1H, m, 1*H_4), 1.70 (3H, s, C_5-C*H*$_3$), 1.65 (2H, m, 2*H_7), 1.41-1.20 (15H, m, CH_2 envelope, O*H*), 0.93 (6H, m, C_2-C*H*$_3$'s), 0.85 (3H, t, *J* 6.7Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 131.73 (C_5), 129.51 (C_6), 73.81 (C_3), 36.56 (C_4), 33.48 (C_2), 31.89, 30.05, 29.75, 29.55, 29.33, 27.97 (CH_2's), 23.58 (C_5-CH_3), 22.67 (CH_2), 18.62, 17.77, 14.10 (C*H*$_3$'s).

minor isomer;

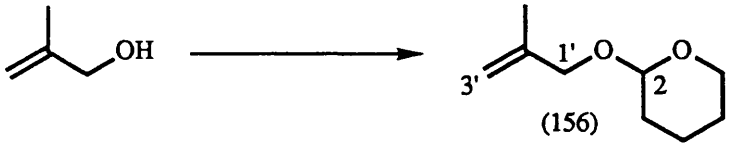
δ_H (400MHz, $CDCl_3$) 5.24 (1H, m, H_6), 3.45 (1H, m, H_3), 2.19 (1H, m, 1*H_4), 1.99 (2H, m, 1*H_4, OH), 1.61 (3H, s, C_5-C*H*$_3$), 1.65 (2H, m, 2*H_7), 1.41-1.20 (14H, m, CH_2 envelope), 0.93 (6H, m, C_2-C*H*$_3$'s), 0.85 (3H, t, *J* 6.7Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 132.07 (C_5), 129.09 (C_6), 72.68 (C_3), 44.71 (C_4), 33.26 (C_2), 31.89, 30.05, 29.75, 29.55, 29.33, 27.97 (CH_2's), 23.58 (C_5-CH_3), 22.67 (CH_2), 18.62, 17.77, 14.10 (CH_3's).

m/z (CI) 272 (M^++NH_4^+), 253 (MH^+), 237 (M^+-OH), 182, 154, 123, 95, 81, 69.

Observed: (MH^+) 253.2688. $C_{17}H_{35}O$ requires 253.2688.

Preparation of 2-(2-methyl-2-propenyloxy)tetrahydropyran (156).[167]



(156)

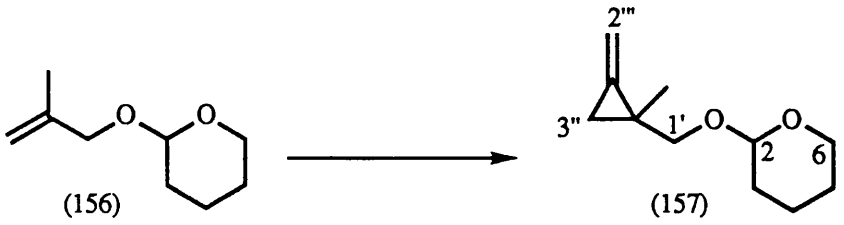
To a solution of 2-methyl-2-propen-1-ol (50g, 0.70mol) in 3,4-dihydro-2*H* -pyran (95ml, 1.03mol) at 0°C under argon, was added concentrated HCl (5 drops) and stirring continued for 48 hours. Solid $NaHCO_3$ was added and after a further 10 minutes the solution was poured into water (200ml) and extracted with ether (3x100ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent distillation afforded ***2-(2-methyl-2-propenyloxy)tetrahydropyran*** **(156)** (92g, 70%) as a colourless oil (bp 84°C at 20mmHg);

IR (film) ν_{max} 2944, 2871, 1655, 1453, 1383, 1184, 1079 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 4.98 (1H, bs, 1*$H_{3'}$), 4.86 (1H, bs, 1*$H_{3'}$), 4.62 (1H, t, *J* 3.7Hz, H_2), 4.09 (1H, d, *J* 12.2Hz, 1*$H_{1'}$), 3.91-3.82 (2H, m, 1*H_6, 1*$H_{1'}$), 3.88 (1H, d, *J* 12.0Hz, 1*$H_{1'}$), 3.49 (1H, m, 1*H_6), 1.86-1.49 (3H, m, 2*H_3, 2*H_4, 2*H_5), 1.74 (3H, s, C*H*$_3$).

m/z (EI) 156 (M^+), 155 (M^+-H), 141 (M^+-CH_3), 127, 109, 85, 55, 41.

Preparation of 2-[1-(1-methyl-2-methylenecyclopropyl)methyloxy]tetrahydropyran (157).[167]



(156) (157)

n-Butyllithium (78ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period by means of a syringe pump, to a stirred solution of the protected alcohol (156) (30g, 192mmol), and 1,1-dichloroethane (4.7ml, 55mmol) in ether (100ml) under argon at -35°C. Further portions of 1,1-dichloroethane (3.0ml, 35mmol) were added 0.5, 1.5, 2.5 and 3.5 hours after the initial addition. The mixture was allowed to warm to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (150ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloro-methylcyclopropane was dissolved in DMSO (20ml) and added dropwise to a stirred solution of potassium *tert* - butoxide (26.1g, 230mmol) in DMSO (35ml) at 70°C under argon. After stirring for 20 hours, the resulting dark brown solution was cooled to 0°C, poured into ice-cold water (200ml) and extracted with ether (3x200ml). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (10% ether/petrol, silica) afforded ***2-[1-(1-methyl-2-methylenecyclopropyl)methyloxy]tetrahydropyran*** **(157)** (15g, 43%) as an orange oil (as a mixture of diastereomers 1:1);

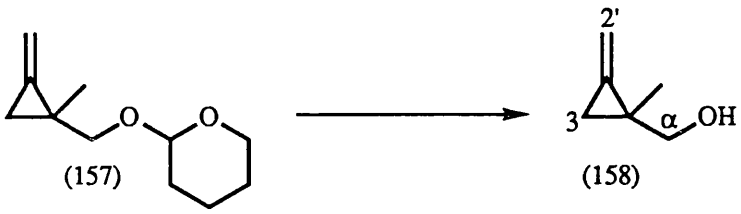
IR (film) ν_{max} 2944, 2882, 1748, 1446, 1256, 1112, 1036 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.40 (1H, t, *J* 2.5Hz, 1*$H_{2'''}$), [5.37 (1H, t, *J* 2.5Hz, 1*$H_{2'''}$)], 5.30 (1H, brs, 1*$H_{2'''}$), 4.63 (1H, t, *J* 3.4Hz, H_2), [4.59 (1H, t, *J* 3.1Hz, H_2)], 3.84

(1H, m, 1*H6), [3.62 (1H, d, *J* 10.2Hz, 1*H1')], 3.56 (1H, d, *J* 10.3Hz, 1*H1'), 3.45 (1H, m, 1*H6), 3.28 (1H, d *J* 10.3Hz, 1*H1')], 3.18 (1H, d, *J* 10.2Hz, 1*H1'), 1.89-1.47 (6H, m, 2*H3, 2*H4, 2*H5), 1.22 (3H, s, C*H*3), [1.21 (3H, s, C*H*3), 1.13-0.95 (2H, m, 2*H3'').

m/z (EI) 183 (MH^+), 182 (M^+), 169, 143, 127, 117, 109, 101, 85.

Preparation of 1-methyl-2-methylenecyclopropyl-methanol (158).[167]



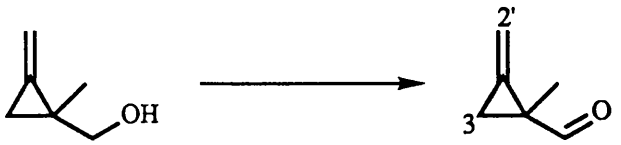
To a solution of the protected alcohol (157) (2.20g, 12.1mmol) in methanol (20ml) was added *p*-toluenesulfonic acid (501mg, 2.7mmol), and the reaction mixture stirred for 18 hours. Anhydrous potassium carbonate was added and after a further 20 minutes the solvent was removed by distillation at atmospheric pressure, the residue was dissolved in ether (50ml), washed with water (2x15ml) and the combined organic extracts dried over $MgSO_4$. The solvent was again removed by distillation at atmospheric pressure, and subsequent column chromatography (30% ether/petrol, silica) afforded ***1-methyl-2-methylenecyclopropyl-methanol*** **(158)** (833mg, 70%) as a colourless oil;

IR (film) ν_{max} 3333, 2923, 2872, 1743, 1485, 1056 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.41 (1H, td, *J* 2.5, 0.8Hz, H2'), 5.39 (1H, brs, H2'), 3.45 (2H, brs 2*Hα), 1.56 (1H, t, *J* 5.6Hz, OH), 1.22 (3H, s, C*H*3), 1.10 (1H, dt, *J* 8.7, 2.5Hz, 1*H3), 0.95 (1H, dt, *J* 8.7, 2.2Hz, 1*H3).

m/z (EI) 97 (M^+-H), 83, 69 (M^+-CH_2OH), 57, 41, 28.

Perparation of 1-methyl-2-methylenecyclopropyl-methanal (159).



(158) (159)

To a solution of the alcohol (158) (924mg, 9.4mmol) in dichloromethane (20ml) at room temperature under argon, was added pyridinium dichromate (5.32g, 14.1mmol) and the solution stirred for 20 hours. The mixture was then diluted with ether, filtered through a short pad of silica and the solvent removed at atmospheric pressure to yield ***1-methyl-2-methylenecyclopropyl-methanal*** **(159)** (910mg, 100%) as a colourless oil;

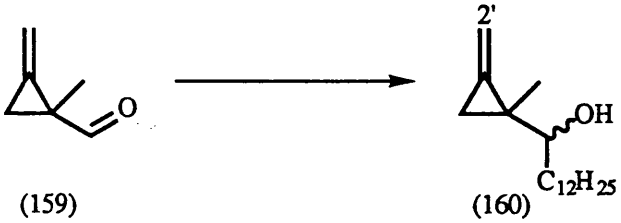
IR (film) ν_{max} 2974, 2862, 1702, 1456, 1379, 1287, 1103 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 8.60 (1H, s, C*H*O), 5.62 (1H, brt, *J* 1.9Hz, 1*$H_{2'}$), 5.56 (1H, t, *J* 2.7Hz, 1*$H_{2'}$), 1.91 (1H, dt, *J* 9.5, 2.5Hz, 1*H_3), 1.58 (1H, dt, *J* 9.5, 2.5Hz, 1*H_3), 1.32 (3H, s, C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 198.20 (C=O), 133.97 (C_2), 106.65 ($C_{2'}$), 33.14 (C_1), 16.79 (C_3), 14.52 (CH_3).

m/z 96 (M^+), 95 (M^+-H), 81, 67, (M^+-CHO), 52, 41, 38.

Preparation of 1-(1-hydroxytridecanyl)-1-methyl-2-methylenecyclopropane (160).



(159) (160)

To a solution of dodecylmagnesium bromide (8.0ml of a 1.0M solution in Et_2O) at

0°C under argon, was added a solution of the aldehyde (159) (550mg, 5.73mmol) in ether (40ml) dropwise and stirring continued for 30 minutes. The solution was warmed to room temperature and poured into saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (20% ether/petrol, silica) afforded ***1-methyl-1-(1-hydroxytridecanyl)-2-methylenecycloprpane*** **(160)** (as a mixture of diastereomers 1:1) (756mg, 50%) as a yellow oil ;

IR (film) ν_{max} 3392, 2920, 2859, 1747, 1460, 1370, 1072 cm^{-1}.

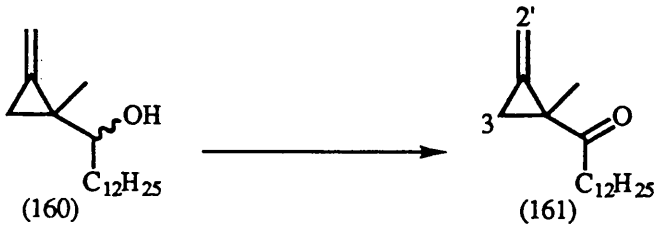
δ_H (400MHz, $CDCl_3$) 5.44 (1H, t, *J* 2.5, 1*$H_{2'}$), [5.34-5.33 (2H, m, 1*$H_{2'}$)], 5.32 (1H, brs, 1*$H_{2'}$), 3.13 (1H, m, C*H*OH), [3.09 (1H, m, C*H*OH)], 1.61-1.19 (23H, m, CH_2 envelope, O*H*), 1.13 (3H, s, C*H*$_3$), [1.12 (3H, s, C*H*$_3$)], 1.08 (1H, dt, *J* 10.5, 2.0Hz, 1*H_3), 0.93 (1H, dq, *J* 8.7, 2.1Hz, 1*H_3), 0.86 (3H, t, *J* 6.6Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 140.67, [139.74] (C_2), 103.11, [102.28] ($C_{2'}$), 76.72, [76.34] (CHOH), 34.08, 33.78, 31.92, 29.72, 29.67, 29.65, 29.62, 29.36, 26.21, 26.14 (CH_2's), 25.25, [24.62] (C_1), 22.69 (CH_2), 16.76, [16.35] (CH_3), 15.67 (CH_2), 14.81, [14.13] (terminal CH_3).

m/z (EI) 265 (M^+-H), 249 (M^+-OH), 197, 179, 161, 147, 123, 109, 95, 81, 69, 55.

Observed (CI): (M^++NH_4^+), 284.2953. $C_{18}H_{38}NO$ requires 284.2953.

Preparation of 1-(1-tridecyloxo)-1-methyl-2-methylenecylopropane (161).



To a solution of the alcohol (160) (550mg, 2.07mmol) in dichloromethane (15ml) at

room temperature under argon, was added pyridinium dichromate (1.17g, 3.11mmol), followed by pyridinium trifluoroacetate (160mg, 0.83mmol) and the solution stirred for 8 days. The mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (15% ether/petrol, silica) afforded ***1-methyl-1-(1-tridecyloxo)-2-methylenecyclopropane*** **(161)** (506mg, 93%) as a yellow oil;

IR (film) ν_{max} 2923, 2834, 1629, 1453, 1215, 1061 cm^{-1}.

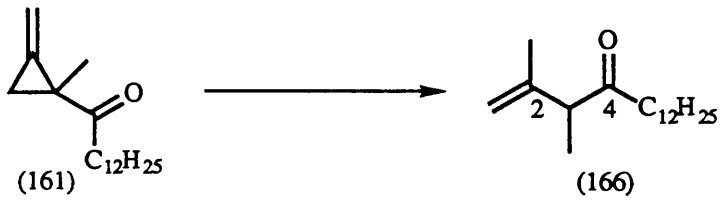
δ_H (400MHz, $CDCl_3$) 5.46 (2H, m, 2*$H_{2'}$), 2.14 (2H, m, $COCH_2$), 1.94 (1H, dt, *J* 9.1, 2.4Hz, 1*H_3), 1.47 (2H, m, $COCH_2CH_2$), 1.39 (1H, dt, *J* 9.2, 2.4Hz, 1*H_3), 1.34 (3H, s, CH_3), 1.31-1.19 (18H, m, CH_2 envelope), 0.87 (3H, t, *J* 6.7Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 208.84 (C=O), 138.00 (C_2), 103.53 ($C_{2'}$), 35.88 (CH_2), 32.08 (C_1), 31.90, 29.64, 29.60, 29.48, 29.42, 29.34, 29.22, 24.60, 22.68, 18.80 (CH_2's), 18.39 ($C_{1'}$), 14.12 (terminal CH_3).

m/z (EI) 265 (MH^+), 264 (M^+), 263 (M^+-H), 197, 123, 109, 98, 85, 71, 57, 43.

Observed (CI): (M^++NH_4^+), 282.2792. $C_{18}H_{36}NO$ requires 282.2797.

Preparation of 2,3-dimethyl-1-hexadecen-4-one (166).



A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (30ml) was allowed to condense into the reaction vessel. Lithium shot (55mg), which had been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (161) (100mg,

0.38mmol) in ether (8ml) was added dropwise over 2 hours, the cold bath removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml) and the mixture saturated with solid NaCl. The ethereal layer was separated and the the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded ***2,3-dimethyl-1-hexadecen-4-one*** **(166)** (79mg, 78%) as a yellow oil;

IR (film) ν_{max} 2928, 2853, 1712, 1671, 1458, 1373, 1129, 1077 cm^{-1}.

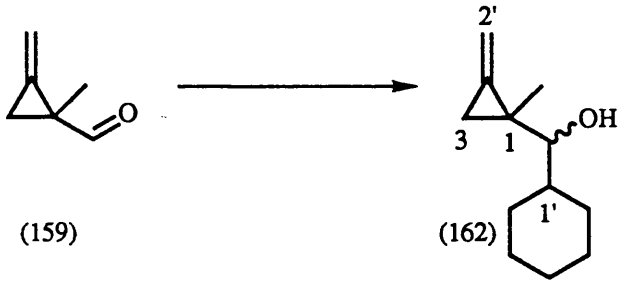
δ_H (400MHz, $CDCl_3$) 4.87 (2H, m, 2*H_1), 3.20 (1H, q, *J* 7.0Hz, H_3), 2.45 (1H, dt, *J* 17.1, 7.3Hz, 1*H_5), 2.36 (1H, dt, *J* 16.8, 7.1Hz, 1*H_5), 1.64 (3H, d, *J* 1.0Hz, C_2-CH_3), 1.50 (2H, m, 2*H_6), 1.41-1.15 (18H, m, CH_2 envelope), 1.13 (3H, d, *J* 6.9Hz, C_3-CH_3), 0.87 (3H, t, *J* 6.8Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 211.63 (C=O), 144.54 (C_2), 113.42 (C_1), 54.49 (C_3), 40.27 (C_5), 31.91, 29.62, 29.60, 29.48, 29.42, 29.34, 29.21, 23.87, 22.68, 20.16 (CH_2's), 14.57, 14.11 (CH_3's).

m/z (EI) 266 (M^+), 251 (M^+-CH_3), 205, 197, 179, 163, 137, 123, 109, 97, 85, 71, 57, 43.

Observed (CI): (M^++NH_4^+), 284.2953. $C_{18}H_{38}NO$ requires 284.2953.

Preparation of (RS)-1-(1-methyl-2-methylenecycloprop-1-yl)-1-cyclohexylmethanol (162).



(159) (162)

To a solution of cyclohexylmagnesium chloride (7.3ml of a 2.0M solution in Et_2O) at 0°C under argon, was added a solution of the aldehyde (159) (1.0g, 10.4mmol) in ether (60ml) dropwise and stirring continued for 30 minutes. The solution was warmed up to room temperature and poured into saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (30% ether/petrol, silica) afforded ***(RS)-1-(1-methyl-2-methylenecycloprop-1-yl)-1-cyclohexylmethanol*** **(162)** (as a mixture of diastereomers 1:1.3) (375mg, 20%) as a colourless oil ;

IR (film) ν_{max} 3415, 2923, 2851, 1748, 1451, 1379, 1268, 1015 cm^{-1}.

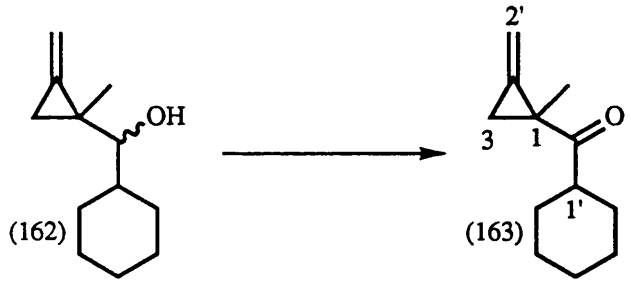
δ_H (400MHz, $CDCl_3$) [5.47 (1H, t, *J* 2.4Hz, 1*$H_{2'}$)], 5.33 (1H, brs, 1*$H_{2'}$), 5.31 (1H, t, *J* 1.7Hz, 1*$H_{2'}$), [2.78 (1H, d, *J* 8.9Hz, C*H*OH)], 2.62 (1H, d, *J* 9.3Hz, C*H*OH), 2.07-0.88 (14H, m, $H_{1'}$, 2*$H_{2'}$, 2*H_3, 2*$H_{3'}$, 2*$H_{4'}$, 2*$H_{5'}$, 2*$H_{6'}$, OH), [1.12 (3H, s, C_1-C*H*$_3$)], 1.10 (3H, s, C_1-C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 140.20, [140.08] (C_2), 103.86, [102.62] ($C_{2'}$), 81.10 (CHOH), 41.31, [41.27] (C_1), 30.20, [29.65], 29.33, [29.07], 26.59, [26.47], 26.43, [26.39], 26.19, [26.01] (C_3, CH_2's), 16.31, [16.22] (CH_3's).

m/z (EI) 180 (M^+), 165 (M^+-CH_3), 149, 139, 123, 97, 83, 69.

Observed M^+, 180.1522. $C_{12}H_{20}O$ requires 180.1514.

Preparation of 1-(1-methyl-2-methylenecycloprop-1-yl)-1-cyclohexylmethanone (163).



To a solution of the alcohol (162) (280mg, 1.55mmol) in dichloromethane (15ml) at room temperature under argon, was added pyridinium dichromate (875mg, 2.33mmol) followed by pyridinium trifluoroacetate (120mg, 0.62mmol) and the solution stirred for 3 days. The mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (20% ether/petrol, silica) afforded ***1-(1-methyl-2-methylenecycloprop-1-yl)-1-cyclohexylmethanone*** **(163)** (as a mixture of diastereomers) (254mg, 92%) as a yellow oil ;

IR (film) ν_{max} 2933, 2841, 1749, 1687, 1446, 1374, 1271, 1061 cm^{-1}.

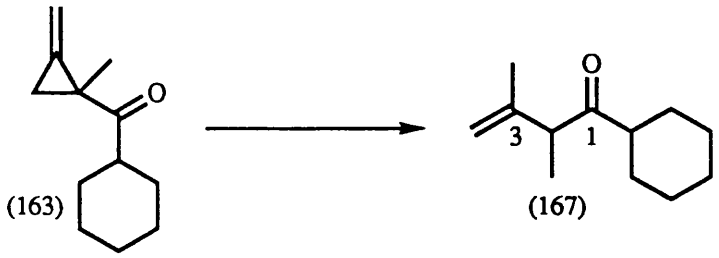
δ_H (400MHz, $CDCl_3$) 5.45 (2H, m, 2*$H_{2'}$), 2.19 (1H, tt, *J* 11.4, 3.3Hz, $H_{1'}$), 1.91 (1H, dt, *J* 9.0, 2.4Hz, 1*H_3), 1.77-1.11 (10H, m, 2*$H_{2'}$, 2*$H_{3'}$, 2*$H_{4'}$, 2*$H_{5'}$, 2*$H_{6'}$), 1.36 (1H, dt, *J* 9.0, 2.4Hz, 1*H_3), 1.31 (3H, s, C_1-CH_3).

δ_C (100MHz, $CDCl_3$) 211.49 (C=O), 137.68 (C_2), 103.08 ($C_{2'}$), 43.93 ($C_{1'}$), 31.25 (C_1), 30.12, 29.18 (CH_2's), 25.58 (2*CH_2's), 18.41 (CH_3), 18.35 (CH_2).

m/z (EI) 178 (M^+), 163 (M^+-CH_3), 149, 135, 122, 109, 95.

Observed: M^+, 178.1358. $C_{12}H_{18}O$ requires 178.1358.

Preparation of 1-cyclohexyl-3,4-dimethylbuten-1-one (167).



A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (45ml) was allowed to condense into the reaction vessel. Lithium shot (82mg), which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (163) (100mg, 0.56mmol) in ether (12ml) was added dropwise over 2 hours, the cold bath removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml), and the mixture saturated with solid NaCl. The ethereal layer was separated and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded ***4-cyclohexyl-2,3-dimethylbuten-4-one*** **(167)** (63mg, 63%) as a colourless oil;

IR (film) ν_{max} 2931, 2855, 1708, 1643, 1449, 1368, 1284, 1137 cm^{-1}.

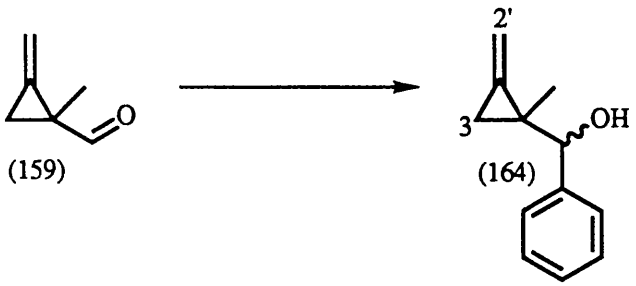
δ_H (400MHz, $CDCl_3$) 4.87 (1H, t, *J* 1.5Hz, 1*H_4), 4.82 (1H, brs, 1*H_4), 2.52 (1H, m, H_2), 1.75-1.11 (11H, m, $H_{1'}$, 2*$H_{2'}$, 2*$H_{3'}$, 2*$H_{4'}$, 2*$H_{5'}$, 2*$H_{6'}$), 1.64 (3H, s, C_3-C*H*$_3$), 1.10 (3H, d, *J* 6.9Hz, C_2-C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 214.28 (C=O), 144.40 (C_3), 113.37 (C_4), 52.63 (C_2), 48.87 ($C_{1'}$), 29.48, 28.34, 25.94, 25.80, 25.38 (CH_2's), 20.35, 14.98 (CH_3's).

m/z (EI) 180 (M^+), 149, 140, 131, 119, 111, 97, 83, 79.

Observed: M^+, 180.1510. $C_{12}H_{20}O$ requires 180.1514.

Preparation of (RS)-1-methyl-1-hydroxybenzyl-2-methylenecyclopropane (164).



(159) (164)

To a solution of the aldehyde (159) (270mg, 2.81mmol) in ether (25ml) at 0°C under nitrogen was added phenylmagnesium bromide (1.31ml of a 3.0M solution in Et_2O) dropwise and stirring continued for 45 minutes. The solution was warmed to room temperature poured into saturated aqueous NH_4Cl solution (40ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (40% ether/petrol, silica) afforded ***(RS)-1-methyl-1-hydroxybenzyl-2-methylenecyclopropane*** **(164)** (as a mixture of diastereomers in the ratio of 1.7:1) (200mg, 41%) as a colourless oil;

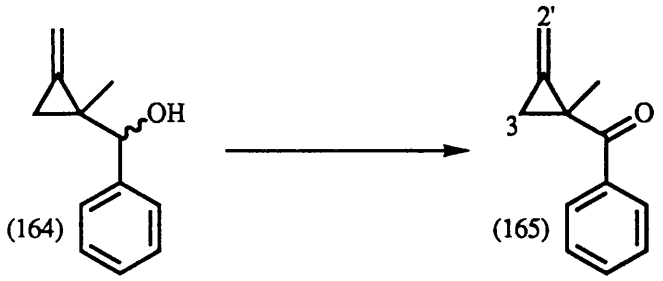
IR (film) ν_{max} 3395, 3056, 2964, 2872, 1749, 1600, 1492, 1451, 1369, 1230, 1194 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 7.40-7.22 (5H, m, Ar-*H*), 5.57 (1H, t, *J* 2.5Hz, 1*$H_{2'}$), 5.44 (1H, m, 1*$H_{2'}$), 4.42 (1H, d, *J* 4.2Hz, C*H*OH), [4.39 (1H, d, *J* 2.2Hz, C*H*OH)], [1.95 (1H, d, *J* 2.5Hz, O*H*)], 1.86 (1H, d, *J* 4.3Hz, O*H*), 1.43 (1H, dt, *J* 8.8, 2.2Hz, 1*H_3), [1.32 (1H, dt, *J* 8.8, 2.2Hz, 1*H_3)], [1.03 (3H, s, C*H*$_3$)], 1.02 (3H, s, C*H*$_3$), 1.06-1.00 (1H, m, 1*H_3).

m/z (EI) 173 (M^+-H), 157 (M^+-OH), 145, 129, 115, 105, 91, 77.

Observed (CI): (M^++NH_4^+-H_2O), 174.1283. $C_{12}H_{16}N$ requires 174.1283.

Preparation of 1-methyl-2-methylene-1-phenyloxocyclopropane (165).



To a solution of the alcohol (164) (170mg, 0.98mmol) in dichloromethane (8ml) at room temperature under argon, was added pyridinium dichromate (370mg, 1.46mmol) followed by pyridinium trifluoroacetate (75mg, 0.39mmol) and the solution stirred for 24 hours. The mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded ***1-methyl-2-methylene-1-phenyloxocyclopropane*** **(165)** (134mg, 80%) as an yellow oil;

IR (film) ν_{max} 3072, 2978, 2919, 1672, 1596, 1443, 1279, 1172 cm^{-1}.

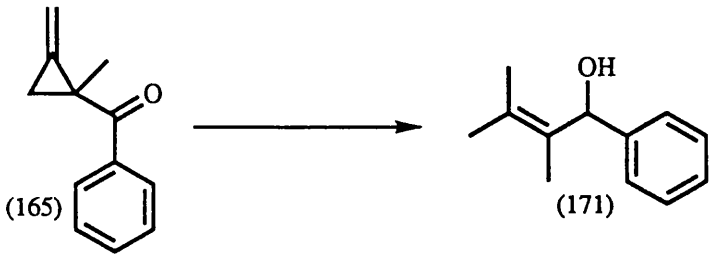
δ_H (400MHz, $CDCl_3$) 7.85 (2H, m, Ar-*H*), 7.48 (3H, m, Ar-*H*), 5.63 (1H, t, *J* 2.7Hz, 1*$H_{2'}$), 5.53 (1H, t, *J* 2.0Hz, 1*$H_{2'}$), 2.03 (1H, dt, *J* 9.2, 2.4Hz, 1*H_3), 1.54 (3H, s, C*H*$_3$), 1.37 (1H, dt, *J* 9.6, 2.6Hz, 1*H_3).

δ_C (100MHz, $CDCl_3$) 199.70 (C=O), 136.97 (C_2), 136.48, 132.07 (2*Ar-C), 128.62 (2*Ar-C), 128.26 (2*Ar-C), 104.01 ($C_{2'}$), 31.97 (C_1), 21.46 (CH_3), 17.16 (C_3).

m/z (EI) 173 (MH^+), 172 (M^+), 154, 149, 137, 123, 115, 105, 95, 81, 77, 69, 55.

Observed (CI): (M^++NH_4^+), 190.1232. $C_{12}H_{16}NO$ requires 190.1232.

Preparation of 2,3-dimethyl-1-hydroxy-1-phenylbut-2-en (171).



(165) (171)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen was flushed with ammonia, and then ammonia (45ml) was allowed to condense into the reaction vessel. Lithium shot (76mg), which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (165) (90mg, 0.52mmol) in ether (11ml) was added dropwise over 90 minutes, the cold bath removed and refluxing continued for 1 hour. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml), and the mixture saturated with solid NaCl. The ethereal layer was separated and the the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded ***2,3-dimethyl-1-hydroxy-1-phenylbut-2-en*** **(171)** (44mg, 48%) as a yellow oil;

IR (film) ν_{max} 3361, 3015, 2921, 2869, 1601, 1491, 1449, 1376, 1255, 1105 cm^{-1}.

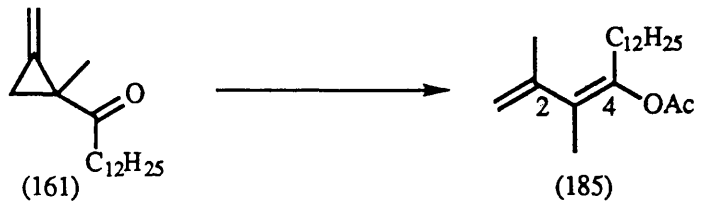
δ_H (400MHz, $CDCl_3$) 7.36 (4H, m, Ar-*H*), 7.24 (1H, m, Ar-*H*), 5.84 (1H, m, C*H*OH), 1.89 (4H, brs, C*H*$_3$, O*H*), 1.72 (3H, bs, C*H*$_3$), 1.46 (3H, m, C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 143.14 (Ar-C), 129.39, 128.53 (C_2, C_3), 128.07 (2*Ar-C), 126.65 (2*Ar-C), 125.46 (Ar-C), 72.11 (CHOH), 21.12, 20.24, 12.18 (CH_3's).

m/z (EI) 176 (M^+), 175 (M^+-H), 159 (M^+-OH), 143 (M^+-H_2O-CH_3), 128, 117, 105, 99 (M^+-C_6H_5), 91, 77, 69, 51, 41.

Observed (CI): (M^++NH_4^+), 194.1545. $C_{12}H_{20}NO$ requires 194.1545.

Preparation of *(E)*-4-acetoxy-2,3-dimethylhexadeca-1,3-diene (185).



(161) (185)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (30ml) was allowed to condense into the reaction vessel. Lithium shot (55mg) which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (161) (100mg, 0.38mmol) in ether (8ml) was added dropwise over 40 minutes, the cold bath removed and refluxing continued for 40 minutes. The ammonia was allowed to evaporate and the residue taken up in ether (10ml). The milky white suspension was stirred vigorously under a nitrogen atmosphere and then pipetted into a flask containing acetic anhydride (292µl, 2.81mmol) at 0°C and stirring continued for 18 hours. The reaction mixture was poured into a cold solution of saturated aqueous $NaHCO_3$ and pentane and sitrred for a futher 30 minutes, during which time portions of solid $NaHCO_3$ were added. The organic phase was separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (15% ether/petrol, silica) afforded ***(E)-4-acetoxy-2,3-dimethylhexadeca-1,3-diene*** **(185)** (30mg, 26%) as a colourless oil;

IR (film) ν_{max} 2922, 2856, 1756, 1639, 1461, 1367, 1228, 1172, 1116 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 4.94 (1H, m, 1*H_1), 4.77 (1H, m, 1*H_1), 2.33 (2H, m, 2*H_5), 2.13 (3H, s, CH_3-Ac), 1.80 (3H, s, C_3-C*H*$_3$), 1.58 (3H, s, C_2-C*H*$_3$), 1.39-1.02 (20H, m, CH_2 envelope), 0.85 (3H, t, *J* 6.7Hz, terminal C*H*$_3$).

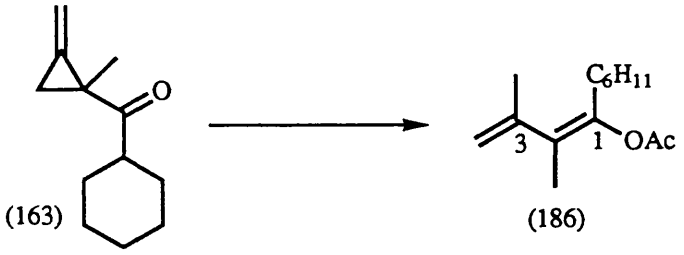
δ_C (100MHz; $CDCl_3$) 168.82 (C=O), 144.30, 144.04, 126.24 (C_2, C_3, C_4), 113.62 (C_1), 31.91, 30.31, 29.64, 29.57, 29.50, 29.43, 29.35, 29.32, 27.40, 22.69, 22.02

(CH_2's), 20.79, 15.31, 14.12 (CH_3's).

m/z (EI) 309 (MH^+), 293 (M^+-CH_3), 266 (M^+-OAc), 251, 237, 197, 167, 154, 139, 125, 112, 97, 83, 69, 55, 41.

Observed: (MH^+), 309.2799. $C_{20}H_{36}O_2$ requires 309.2794.

Preparation of 1-acetoxy-1-cyclohexyl-2,3-dimethylbuta-1,3-diene 186.



(163) (186)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (45ml) was allowed to condense into the reaction vessel. Lithium shot (82mg) which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (163) (100mg, 0.56mmol) in ether (12ml) was added dropwise over 40 minutes, the cold bath removed and refluxing continued for 40 minutes. The ammonia was allowed to evaporate and the residue taken up in ether (20ml). The milky white suspension was stirred vigorously under a nitrogen atmosphere and then pipetted into a flask containing acetic anhydride (433µl, 4.17mmol) at 0°C and stirring continued for 18 hours. The reaction mixture was poured into a cold solution of saturated aqueous $NaHCO_3$ and pentane and stirred for a further 30 minutes, during which time portions of solid $NaHCO_3$ were added. The organic phase was separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) afforded ***1-acetoxy-1-cyclohexyl-2,3-dimethylbuta-1,3-diene*** **(186)** (44mg, 35%) as a yellow oil;

IR (film) ν_{max} 2919, 2860, 1755, 1678, 1637, 1449, 1367, 1219, 1184, 1049 cm^{-1}.

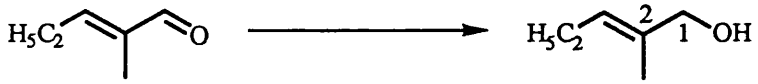
δ_H (400MHz, $CDCl_3$) 4.91 (1H, brq, *J* 1.5Hz, 1*H4), 4.79 (1H, m, 1*H4), 2.57 (1H, m, 1*H1'), 2.16 (3H, s, CH_3-Ac), 1.84 (3H, brs, C_3-C*H*3), 1.80-1.59 (4H, m, 4*cyclohexyl H's), 1.53 (3H, s, C_2-C*H*3), 1.24-1.16 (6H, m, 6*cyclohexyl H's).

δ_C (100MHz, $CDCl_3$) 168.56 (C=O), 146.96, 144.63, 125.37 (C_1, C_2, C_3), 113.23 (C_4), 40.13 ($C_{1'}$), 30.65 (2C), 26.12 (2C), 25.93 (CH_2's), 22.28, 20.64, 15.91 (CH_3's).

m/z (EI) 222 (M^+), 205, 180, 165, 149, 139, 111, 97, 83.

Observed: M^+, 222.1626. $C_{14}H_{22}O_2$ requires 222.1620.

Preparation of *(E)*-2-methyl-2-penten-1-ol (187).



(187)

To a solution of 2-methyl-2-pentenal (15g, 153mmol) in toluene (400ml) at -78°C under argon was added diisobutylaluminium hydride (113ml of a 1.5M solution in toluene) dropwise. The solution was stirred for 2 hours, and quenched with water (50ml). Ethyl acetate (400ml) was added and the solution allowed to warm to room temperature. Excess Na_2SO_4 was added and the solution stirred for a futher 1 hour. Filtration was followed by removal of the solvent *in vacuo* and subsequent column chromatography (30% ether/petrol, silica) afforded ***(E)-2-methyl-2-penten-1-ol*** **(187)** (15g, 98%) as a colourless oil;

IR (film) ν_{max} 3322, 2933, 2867, 1667, 1456, 1389, 1211, 1072 cm^{-1}.

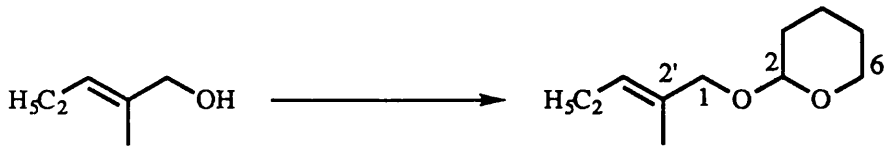
δ_H (400MHz, $CDCl_3$) 5.34 (1H, t, m, H3), 3.92 (2H, brs, 2*H1), 2.13 (1H, brs, O*H*), 1.99 (2H, m, 2*H4), 1.60 (3H, s, C_2-C*H*3), 0.91 (3H, t, *J* 7.5Hz, 3*H5).

δ_C (100MHz, $CDCl_3$) 133.95 (C_2), 127.91 (C_3), 68.88 (C_1), 20.77 (C_4), 13.93, 13.36 (CH_3's).

m/z (EI) 100 (M^+), 82 (M^+-H_2O), 71 (M^+-C_2H_5), 67, 57, 41.

Observed: M^+, 100.0882. $C_6H_{12}O$ requires 100.0888.

Preparation of 2-[*(E)*-2-methyl-2-pentenyloxy]tetrahydropyran (188).



(187) (188)

To a solution of the alcohol (187) (15g, 150mmol), in 3,4-dihydro-2*H*-pyran (18.1ml, 184mmol) at 0°C under argon, was added concentrated HCl (5 drops), and stirring continued for 24 hours. Solid $NaHCO_3$ was added and after a futher 10 minutes the solution was poured into water (200ml) and extracted with ether (3x100ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent distillation yielded ***2-[(E)-2-methyl-2-pentenyloxy]tetrahydropyran*** **(188)** (25g, 89%) as a colourless oil (b.pt. 120°C at 10mmHg);

IR (film) ν_{max} 2944, 2877, 1456, 1356, 1261, 1077, 978, 817 cm^{-1}.

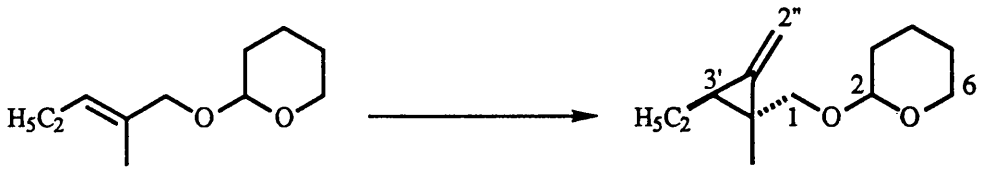
δ_H (270MHz, $CDCl_3$) 5.40 (1H, t, *J* 7.1Hz, H3'), 4.58 (1H, t, *J* 3.4Hz, H_2), 4.07 (1H, d, *J* 11.5Hz, 1*$H_{1'}$), 3.86 (1H, m, 1*H_6), 3.81 (1H, d, *J* 11.6Hz, 1*$H_{1'}$), 3.47 (1H, m, 1*H_6), 2.12 (2H, m, C*H*$_2$CH$_3$), 1.85-1.48 (6H, m; 2*H_3, 2*H_4, 2*H_5), 1.63 (3H, s, $C_{2'}$-C*H*$_3$), 0.94 (3H, t, *J* 7.6Hz, CH_2C*H*$_3$).

δ_C (100MHz; $CDCl_3$) 131.15 ($C_{2'}$), 129.99 ($C_{3'}$), 97.40 (C_2), 72.99 ($C_{1'}$), 62.12 (C_6), 30.65, 25.49, 20.94, 19.52 (CH_2's), 13.98, 13.86 (CH_3's).

m/z (EI) 184 (M^+), 183 (M^+-H), 169 (M^+-CH_3), 149, 137, 109, 101, 85, 67, 55, 41.

Observed: (MH^+), 185.1547. $C_{11}H_{21}O_2$ requires 185.1542.

Preparation of 2-[(1R*, 3R)-1-(3-ethyl-1-methyl-2-methylenecyclopropyl)methyloxy]tetrahydropyran (189).



(188) (189)

n-Butyllithium (54.6ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period, by means of a syringe pump, to a stirred solution of the protected alcohol (188) (25g, 136mmol) and 1,1-dichloroethane (3.2ml, 37mmol) in ether (100ml) under argon, at -35°C. Further portions of 1,1-dichloroethane (2.2ml, 27mmol) were added 0.5, 1.5, 2.5 and 3.5 hours after the initial addition. The mixture was allowed to warm to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (150ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloromethylcyclopropane was dissolved in DMSO (18ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (22.7g, 200mmol) in DMSO (45ml) at 70°C under argon. After stirring for 20 hours, the resulting dark brown solution was cooled to 0°C, poured into ice-cold water (200ml) and extracted with ether (3x200ml). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (10% ether/petrol, silica) afforded ***2-[(1R*, 3R)-1-(3-ethyl-1-methyl-2-methylenecyclopropyl)methyloxy]tetrahydropyran*** **(189)** (as a mixture of diasteriomers 1:1) (20g, 70%) as an orange oil ;

IR (film) ν_{max} 2944, 2868, 1744, 1456, 1344, 1200, 1116 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.28 (2H, m, 2*$H_{2''}$), 4.64 (1H, t, *J* 3.2Hz, H_2), [4.61 (1H, t, *J* 3.4Hz, H_2)], 3.82 (1H, m, 1*H_6), 3.57 (1H, d, *J* 5.1Hz, 1*H_1), [3.54 (1H, d, *J*

5.1Hz, 1*H_1)], 3.45 (1H, m, 1*H_6), 3.22 (1H, t, *J* 10.7Hz, 1*H_1), 1.84-1.48 (9H, m, 2*H_3, H_3' 2*H_4, CH_2CH_3 2*H_5), 1.14 (3H, s, C_1' -CH_3), 0.98 (3H, t, *J* 7.2Hz, CH_2CH_3).

δ_C (100MHz, $CDCl_3$) 145.54, [144.79] (C_2'), 101.26, [101.06] (C_2''), 98.09, [97.56] (C_2), 74.63, [73.95], 62.14, [61.93] (C_1, C_6), 30.72, 30.64, 27.21, 26.73, 25.54, 23.71, 23.37, 21.31, 21.18, 19.58, 19.41 (CH_2's), 14.39, 14.33, 14.20 (CH_3's).

m/z (FAB) 233 (M^++Na), 219, 193, 176, 154, 136, 123, 109.

Observed: (M^++Na), 233.1515. $C_{13}H_{22}NaO_2$ requires 233.1518.

Preparation of (1R*, 3R*)-3-ethyl-1-methanol-1-methyl-2-methylenecyclopropane (190).

To a solution of the protected alcohol (189) (3.0g, 14.3mmol), in methanol (32ml) was added *p* -toluenesulphonic acid (727mg, 3.89mmol) and the reaction mixture stirred for 18 hours at room temperature. Anhydrous potassium carbonate was added and after a further 20 minutes the solvent was removed *in vacuo,* the residue taken up in water (20ml) and extracted with ether (2x50ml). The combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo.* Subsequent column chromatography (10-30% ether/petrol, silica) afforded ***(1R*, 3R*)-3-ethyl-1-methanol-1-methyl-2-methylenecyclopropane*** **(190)** (1.48g, 82%) as a yellow oil;

IR (film) ν_{max} 3333, 2968, 2867, 1744, 1456, 1372, 1156 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.32 (2H, m, 2*H_2'), 3.46 (2H, m, 2*H_α), 1.41 (2H, m, CH_2CH_3), 1.25 (1H, m, H_3), 1.18 (3H, s, C_1-CH_3), 1.00 (3H, t, *J* 7.3Hz, CH_2CH_3).

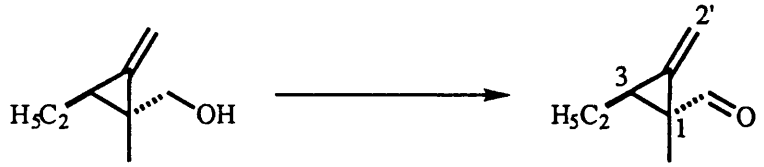
δ_C (100MHz; $CDCl_3$) 144.62 (C_2), 101.51 (C_2'), 70.45 (C_α), 26.61 (C_3), 25.97

(C_1), 21.17 (CH_2), 14.27, 13.88 (CH_3's).

m/z (EI) 127 (MH^+), 109 (M^+-H_2O), 94, 86, 72, 58.

Observed: (MH^+), 127.1129. $C_8H_{15}O$ requires 127.1123.

Perparation of (1R*, 3R*)-3-ethyl-1-methanal-1-methyl-2-methylenecyclopropane (191).



(190) (191)

To a solution of the alcohol (190) (1.4g, 11.1mmol) in dichloromethane (25ml) at room temperature under argon, was added pyridinium dichromate (6.27g, 16.6mmol), and the solution stirred for 20 hours. The mixture was then diluted with ether, filtered through a short pad of silica and the solvent removed at atmospheric pressure to yield ***(1R*, 3R*)-3-ethyl-1-methanal-1-methyl-2-methylenecyclopropane*** **(191)** (1.07g, 77%) as a colourless oil;

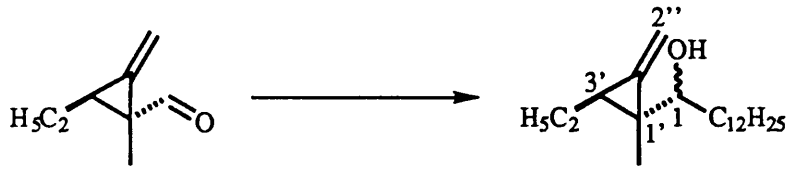
IR (film) ν_{max} 2966, 2860, 1696, 1455, 1384, 1273, 1149 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 8.56 (1H, s, C*H*O), 5.52 (1H, d, *J* 2.0Hz, 1*$H_{2'}$), 5.43 (1H, d, *J* 2.0Hz, 1*$H_{2'}$), 2.05 (1H, tt, *J* 7.1, 2.0Hz, 1*H_3), 1.56 (2H, m, 2*H_4), 1.25 (3H, s, C_1-C*H*$_3$), 1.04 (3H, t, *J* 7.4Hz, CH_2C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 198.82 (C=O), 138.79 (C_2), 104.74 ($C_{2'}$), 31.32 (C_1), 28.81 (C_3), 20.66 (C_4), 13.68, 9.59 (CH_3's).

m/z (EI) 125 (MH^+), 124 (M^+), 123, 109 (M^+-CH_3), 96, 84, 67, 49.

Preparation of (1RS)-1-[(1R*, 3R*)-3-ethyl-1-methyl-2-methylenecycloprop-1-yl]-1-hydroxytridecane (192).



(191) (192)

To a solution of dodecylmagnesium bromide (11.3ml of a 1.0M solution in Et_2O) at 0°C under argon, was added a solution of the aldehyde (191) (1.0g, 8.05mmol) in ether (55ml) dropwise and stirring continued for 30 minutes. The solution was warmed to room temperature and poured into saturated aqueous NH_4Cl solution (50ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (20% ether/petrol, silica) afforded ***(1RS)-1-[(1R*, 3R*)-3-ethyl-1-methyl-2-methylenecycloprop-1-yl]-1-hydroxytridecane*** **(192)** (as a mixture of diastereomers) (2.35g, 99%) as a pale yellow oil;

IR (film) ν_{max} 3389, 2922, 2856, 1750, 1461, 1300, 1156 cm^{-1}.

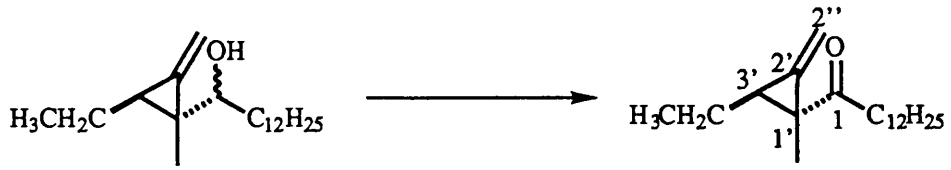
δ_H (400MHz, $CDCl_3$) 5.32 (1H, m, 1*$H_{2'}$), 5.25 (1H, m, 1*$H_{2'}$), 3.06 (C*H*OH), [3.01 (1H, C*H*OH), 1.64-1.12 (26H, m, CH_2 envelope, $H_{3'}$, OH), [1.06 (3H, d, *J* 1.3Hz, C_1-C*H*$_3$)], 1.04 (3H, d, *J* 1.3Hz, C_1-C*H*$_3$), 0.98 (3H, m, CH_2C*H*$_3$), 0.86 (3H, t, *J* 6.2Hz, terminal C*H*$_3$).

δ_C (100MHz, $CDCl_3$) 146.01, [144.90] (C_2), 101.73, [100.75] ($C_{2'}$), 78.61, [77.69] (CHOH), 33.81, 33.56, 31.93, 29.67, 29.64, 29.37 (CH_2's, C_1), 27.26, [26.45] (C_3), 26.33, 26.23, 22.70, 21.06, 20.96 (CH_2's), 14.36, 14.24, 14.11 (CH_3's).

m/z (EI) 294 (M^+), 277 (M^+-OH), 265, 247, 197, 179, 151, 137, 121, 109, 97, 81, 69, 55, 41.

Observed: M^+, 294.2928. $C_{20}H_{38}O$ requires 294.2923.

Preparation of 1-[(1R*, 3R*)-3-ethyl-2-methylene-1-methylcycloprop-1-yl]tridecan-1-one (193).



(192) (193)

To a solution of the alcohol (192) (1.3g, 4.41mmol) in dichloromethane (35ml) at room temperature under argon was added pyridinium dichromate (2.49g, 6.62mmol), followed by pyridinium trifluoroacetate (341mg, 1.77mmol) and the solution stirred for 3 days. The mixture was then diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (2% ether/petrol, silica) afforded ***1-[(1R*, 3R*)-3-ethyl-2-methylene-1-methylcycloprop-1-yl]tridecan-1-one*** **(193)** (700mg, 54%) as a yellow oil;

IR (film) ν_{max} 2922, 2867, 1689, 1456, 1379, 1205, 1056 cm^{-1}.

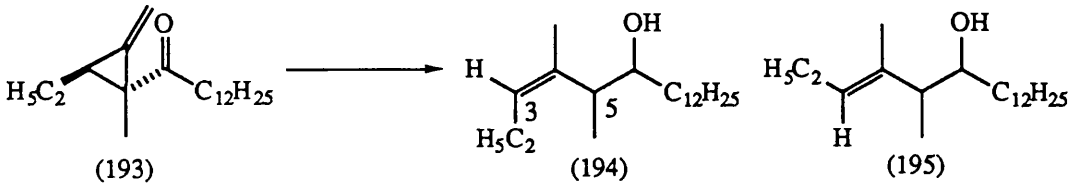
δ_H (400MHz, $CDCl_3$) 5.36 (1H, d, *J* 2.0Hz, 1*$H_{2'}$), 5.30 (1H, d, *J* 2.7Hz, 1*$H_{2'}$), 2.15 (2H, m, $COCH_2$), 2.05 (1H, m, $H_{3'}$), 1.52 (4H, m, CH_2CH_3, $COCH_2CH_2$), 1.27 (3H, s, $C_{1'}$-CH_3), 1.22-1.12 (18H, m, CH_2 envelope), 1.01 (3H, t, *J* 7.3Hz, CH_2CH_3), 0.85 (3H, t, *J* 6.9Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 209.33 (C=O), 143.03 ($C_{2'}$), 101.80 ($C_{2''}$), 36.30 (CH_2), 36.04 ($C_{1'}$), 31.91 (CH_2), 30.18 ($C_{3'}$), 29.65, 29.62, 29.49, 29.43, 29.34, 29.27, 24.75, 22.69, 21.42 (CH_2's), 14.12, 13.81, 12.68 (CH_3's).

m/z (EI) 293 (MH^+), 292 (M^+), 291 (M^+-H), 277 (M^+-CH_3), 263 (M^+-C_2H_5), 249, 221, 193, 151, 137, 123, 109, 95, 81, 69, 55, 41.

Observed (CI): M^+, 292.2763 $C_{20}H_{36}O$ requires 292.2766.

Preparation of *(E)* and *(Z)*-4,5-dimethyl-3-octadecen-6-ol (194) and (195).



(193) (194) (195)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (33ml) was allowed to condense into the reaction vessel. Lithium shot (60mg) which had been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (193) (120mg, 0.41mmol) in ether (10ml) was added dropwise over 2 hours, the cold bath removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml), and the mixture saturated with solid NaCl. The ethereal layer was separated and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded in order of elution ***(Z)-4,5-dimethyl-3-octadecen-6-ol*** **(194)** (19mg, 16%) as a colourless oil;

IR (film) ν_{max} 3509, 2921, 2856, 1719, 1458, 1376, 1289 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.28 (1H, t, *J* 7.1Hz, H_3), 3.36 (1H, m, H_6), 2.02 (3H, m, H_5, 2*H_2), 1.56 (3H, s, C_4-CH_3), 1.51-1.43 (2H, m, 2*H_7), 1.35-1.22 (20H, m, CH_2 envelope), 0.94 (6H, m, C_5-CH_3, 3*H_1), 0.86 (3H, t, *J* 6.7Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 135.98 (C_4), 130.16 (C_3), 72.15 (C_6), 49.58 (C_5), 33.99, 31.93 (CH_2's), 30.31 (C_4-CH_3), 29.90, 29.63, 29.56, 29.37, 25.54, 22.70, 20.90 (CH_2's), 15.45, 14.32, 14.13 (CH_3's).

m/z (EI) 297 (MH^+), 279 (M^+-OH), 209, 199, 180, 167, 153, 125.

Observed: (MH^+), 297.3167. $C_{20}H_{41}O$ requires 297.3157;

and ***(E)-4,5-dimethyl-3-octadecen-6-ol*** **(195)** (56mg, 46%) as a colourless oil;

IR (film) ν_{max} 3358, 2918, 2855, 1710, 1460, 1371, 1072 cm^{-1}.

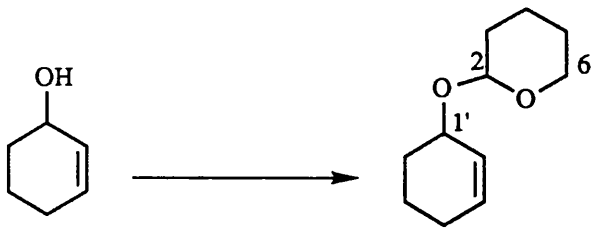
δ_H (400MHz, $CDCl_3$) 5.20 (1H, brt, *J* 7.0Hz, H_3), 3.51 (1H, m, H_6), 2.07 (1H, m, H_5), 1.99 (2H, m, 2*H_2), 1.58 (3H, s, C_4-CH_3), 1.45-1.38 (2H, m, 2*H_7), 1.24 (20H, m, CH_2 envelope), 1.00 (3H, d, *J* 7.0Hz, C_5-CH_3), 0.93 (3H, t, *J* 7.6Hz, 3*H_1), 0.86 (3H, t, *J* 6.7Hz, terminal CH_3).

δ_C (100MHz, $CDCl_3$) 136.67 (C_4), 127.79 (C_3), 76.61 (C_6), 47.57 (C_5), 37.74, 31.93, 30.33, 29.83 (C_4-CH_3), 29.72, 29.65, 29.36, 26.14, 22.69, 21.04 (CH_2's), 14.29, 14.11, 13.28 (CH_3's).

m/z (EI) 297 (MH^+), 279 (M^+-OH), 209, 199, 180, 167, 153, 125.

Observed: (MH^+), 297.3167. $C_{20}H_{41}O$ requires 297.3157.

Preparation of 2-(2-cyclohexenyloxy)tetrahydropyran (202).



(202)

To a solution of 2-cyclohexene-1-ol (15g, 153mmol), in 3,4-dihydro-2*H*-pyran (15g, 183mmol) at 0°C under argon, was added concentrated HCl (2 drops), and stirring continued for 48 hours. Solid $NaHCO_3$ was added and after a further 10 minutes, the solution was poured into water and extracted with ether (3x50ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography (7% ether/petrol, silica) afforded ***2-(2-cyclohexenyloxy)tetrahydropyran*** **(202)** (as a mixture of diastereomers) (26g, 95%) as a colourless oil ;

IR (film) ν_{max} 2939, 2852, 1629, 1453, 1201, 1156, 1078, 993 cm^{-1}.

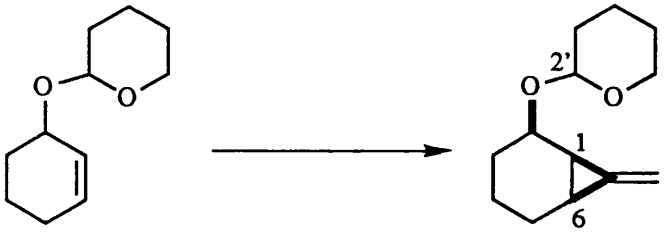
δ_H (400MHz, $CDCl_3$) 5.84 (1H, m, $H_{2'}$), 5.75 (1H, m, $H_{3'}$), 4.74 (1H, m, 1*H_2), 4.19 (1H, m, $H_{1'}$), 3.91 (1H, m, 1*H_6), 3.49 (1H, m, 1*H_6), 2.07-1.46 (12H, m, 2*H_3, 2*H_4, 2*$H_{4'}$, 2*H_5, 2*$H_{5'}$, 2*$H_{6'}$).

δ_C (100MHz, $CDCl_3$) 130.76, [130.53] ($C_{2'}$), 128.76, [127.56] ($C_{3'}$), 97.89, [96.52] (C_2), 70.65, [69.23] ($C_{1'}$), 62.69, [62.55] ($C_{4'}$), 31.23, [31.12], 30.12, 28.01, 25.48, [25.09], 19.84, [19.77], 19.58, [19.10] (CH_2's).

m/z (EI) 182 (M^+), 136, 121, 96, 82, 77, 61, 47, 33.

Found: C, 72.71. H, 10.08. $C_{11}H_{18}O_2$ requires C, 72.49. H, 9.95%.

Preparation of 2-(7-methylenebicyclo[4.1.0]-2-heptyloxy)tetrahydropyran (203).



(202) (203)

n-Butyllithium (55ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period by means of a syringe pump, to a stirred solution of the protected alcohol (202) (25g, 138mmol) and 1,1-dichloroethane (3.2ml, 38mmol) in ether (100ml) under argon at -35°C. Futher portions of 1,1-dichloroethane (2.0ml, 24mmol) were added after 0.5, 1.5, 2.5 and 3.5 hours of the initial addition. The mixture was allowed to warm to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (200ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloro-methylcyclopropane was dissolved in DMSO (17ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (22g, 200mmol) in DMSO (46ml) at 70°C under argon. After stirring for 20 hours the resulting dark brown solution was cooled to

0°C, poured into ice-cold water (200ml) and extracted with ether (3x200ml). The combined organic extracts were washed with water, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (10% ether/petrol, silica), afforded ***2-(7-methylenebicyclo[4.1.0]-2-heptyloxy)tetrahydropyran*** **(203)** (as a mixture of disteriomers 1:1) as an orange oil ;

IR (film) ν_{max} 2933, 2861, 1744, 1441, 1349, 1200, 1113, 1020 cm^{-1}.

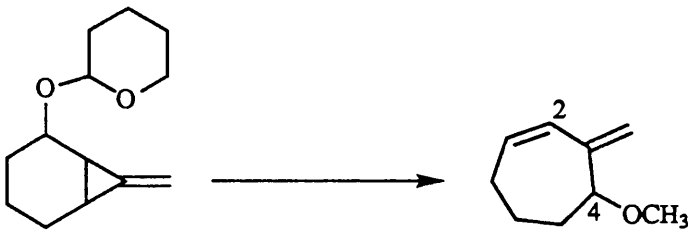
δ_H (400MHz, $CDCl_3$) 5.34 (2H, m, $H_{7'}$) , 4.78 (1H, dd, *J* 3.0, 1*$H_{2'}$), [4.65 (1H, dd, *J* 1*$H_{2'}$)], 3.93 (2H, m, 1*$H_{6'}$, H_2), 3.48 (1H, m, 1*$H_{6'}$), 1.85-1.08 (14H, m, H_1, 2*H_3, 2*$H_{3'}$, 2*H_4, 2*$H_{4'}$, 2*H_5, 2*$H_{5'}$, H_6).

δ_C (100MHz; $CDCl_3$) 139.24, [138.86] (C_7), 102.79, [102.56] ($C_{7''}$), 97.606, [96.98] ($C_{2'}$), 71.05, [69.58] (C_2), 63.02, [62.79] ($C_{6'}$), 31.32, [31.30], 28.97, [26.05], 25.54, [25.52], 22.30, [22.17], 20.10, [19.92] (CH_2's), 19.61, [18.80] (C_1), 16.43, [15.82] (CH_2), 14.04, [13.55] (C_6).

m/z (EI) 209 (MH^+), 208 (M^+), 191, 165, 107, 85, 41.

Observed: MH^+, 209.1542. $C_{13}H_{21}O_2$ requires 209.1542.

Preparation of 4-methoxy-3-methylenecycloheptene (204).



(203) (204)

To a solution of the methylenecyclopropane (203) (1.25g, 5.99mmol) in methanol (20ml) was added *p*-toluenesulphonic acid (300mg, 1.62mmol). The reaction mixture was stirred for 18 hours, anhydrous potassium carbonate was added and after a further 20 minutes the methanol was removed by distillation at atmospheric pressure. The residue was diluted with water (100ml), extracted with ether

(2x100ml), the combined organic extracts were dried over $MgSO_4$ and the solvent carefully removed *in vacuo* (0°C). Subsequent column chromatography (5% ether/petrol, silica) gave ***4-methoxy-3-methylenecycloheptene*** **(204)** (245mg, 30%) as a yellow oil;

IR (film) ν_{max} 2933, 2851, 1641, 1446, 1374, 1194, 1107 cm^{-1}.

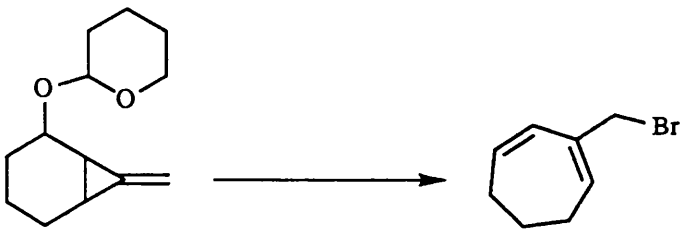
δ_H (400MHz, $CDCl_3$) 6.08 (1H, m, H_2), 5.77 (1H, dt, *J* 11.2, 5.4Hz, H_1), 5.13 (1H, brs, 1*$H_{3'}$), 5.02 (1H, brs, 1*$H_{3'}$), 3.89 (1H, t, *J* 5.3Hz, H_4), 3.28 (3H, s, OCH_3), 2.30-1.66 (6H, m, 2*H_5, 2*H_6, 2*H_7).

δ_C (400MHz, $CDCl_3$) 145.83 (C_3), 133.09, 129.24 (C_1, C_2), 114.58 ($C_{3'}$), 83.31 (C_4), 56.49 (OCH_3), 34.11, 28.81, 23.08 (C_5, C_6, C_7).

m/z (CI) 156 (MH^++NH_4^+), 139 (MH^+), 124, 107 (M^+-OCH_3), 52.

Observed (EI): (MH^+), 139.1123. $C_9H_{15}O$ requires 139.1123.

Preparation of 2-bromomethyl-1,3-cycloheptadiene (205).



(203) (205)

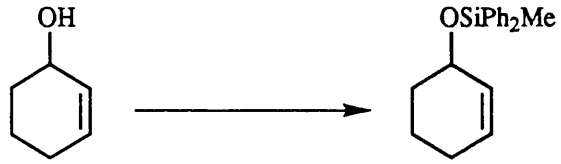
To a solution of the protected alcohol (203) (1.00g, 4.8mmol), in ether (20ml) at room temperature under argon, was added magnesium bromide (2.65mmol, 14.4mmol), and stirring continued for 12 hours. The solution was poured into an aqueous saturated solution of $NaHCO_3$ (20ml), and extracted with ether (2x20ml). The combined organic extracts were washed with brine (30ml), dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (4% ether/petrol, silica) afforded ***2-bromomethyl-1,3-cycloheptadiene*** **(205)** (581mg, 100%) as a colourless oil;

IR (film) ν_{max} 3005, 2933, 2830, 1651, 1487, 1210, 1085, 1003 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.93 (2H, m, 1*H_1, 1*H_4), 5.45 (1H, d, *J* 11.8Hz, H_3), 3.93 (2H, s, 2*$H_{2'}$), 2.26 (4H, m, 2*H_5, 2*H_7), 1.79 (2H, m, 2*H_6).

m/z (EI) 107 (M^+-H), 91, 79, 65, 51.

Preparation of 1-diphenylmethylsilyloxy-2-cyclohexene (207).



(207)

To a solution of diphenylmethylchlorosilane (35ml, 153mmol), triethylamine (23ml, 168mmol) and DMAP (200mg, 1.53mmol) in dichloromethane (120ml) at 0°C under argon, was added 2-cyclohexen-1-ol (15g, 153mmol) and the solution stirred for 2 hours. The reaction mixture was allowed to warm to room temperature poured into water (150ml) and extracted with dichloromethane (3x100ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7%, ether/petrol, silica) afforded ***1-diphenylmethylsilyloxy-2-cyclohexene*** **(207)** (40g, 89%) as a clear oil;

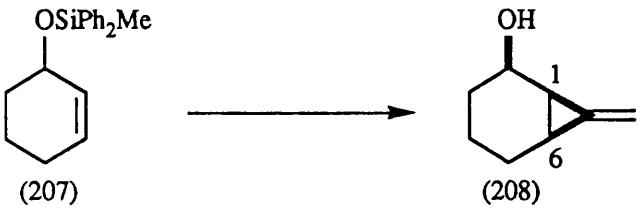
IR (film) ν_{max} 3067, 3025, 2933, 2862, 1646, 1548, 1426, 1323, 1251, 1128, 1072 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 7.70 (4H, m, Ar-*H*), 7.43 (6H, m, Ar-*H*), 5.82 (1H, dt, *J* 10.1, 3.5Hz, H_2), 5.73 (1H, dq, *J* 10.1, 2.4Hz, H_3), 4.42 (1H, m, H_1), 2.08-1.56 (6H, m, 2*H_4, 2*H_5, 2*H_6), 0.75 (3H, s, C*H*$_3$).

δ_C (400MHz, $CDCl_3$) 136.61, 134.35 (Ar-C), 133.94, 130.48 (C_2, C_3), 129.65, 127.74 (Ar-C), 67.07 (C_1), 32.20, 24.92, 19.46 (C_4, C_5, C_6), -2.16 (CH_3).

m/z (EI) 294 (M^+), 279 (M^+-CH_3), 216, 197, 156, 137, 77.

Preparation of 7-methylenebicyclo[4.1.0]heptan-2-ol (208).



(207) (208)

n-Butyllithium (62ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period by means of a syringe pump, to a stirred solution of the protected alcohol (207) (40g, 136mmol) and 1,1-dichloroethane (3.7ml, 44mmol) in ether (80ml), under argon at -35°C. Futher portions of 1,1-dichloroethane (2.4ml, 28mmol) were added after 0.5, 1.5, 2.5 and 3.5 hours of the initial addition. The mixture was allowed to warm to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (200ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloro-methylcyclopropane was dissolved in DMSO (20ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (25g, 230mmol) in DMSO (20ml) at 70°C under argon. After stirring for 20 hours the resulting dark brown solution was cooled to 0°C, poured into ice-cold water (200ml) and extracted with ether (3x200ml). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (10% ether/petrol, silica), afforded ***7-methylene-bicyclo[4.1.0]heptan-2-ol*** **(208)** (7.5g, 44%) as an orange oil;

IR (film) ν_{max} 3338, 2985, 2852, 1742, 1446, 1348, 1088, 1043, 975 cm^{-1}.

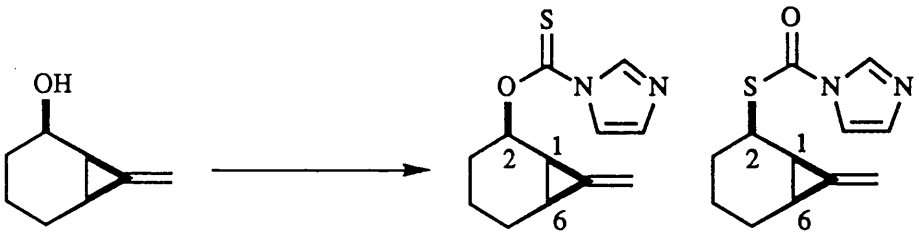
δ_H (400MHz, $CDCl_3$) 5.36 (2H, m, 2*$H_{7'}$) , 4.03 (1H, brt, *J* 6Hz, H_2), 2.72 (1H, brs, O*H*), 1.87-0.8 (8H, m, H_1, 2*H_3, 2*H_4, 2*H_5, H_6).

δ_C (100 MHz, $CDCl_3$) 138.69 (C_7), 102.68 ($C_{7'}$), 65.71 (C_2), 30.12 , 22.13 (C_3, C_5), 21.07 (C_1), 15.54, 13.57 (C_4, C_6).

m/z (EI) 123 (M^+), 107, 91, 79, 67, 55, 39.

Observed: (MH^+), 125.0966. $C_8H_{13}O$ requires 125.0966.

Preparation of imidazole thiocarbonyl derivative (209) and imidazole carbonyl derivaive (215) of 7-methylenebicyclo[4.1.0]heptan-2-ol.



(208) (209) (215)

To a solution of the alcohol (208) (600mg, 4.84mmol) in dichloromethane (60ml) under argon, was added 1,1'-thiocarbonyldiimidazole (5.64g, 31.65mmol) and the solution stirred at refluxed for 18 hours. On cooling, the orange liquid was diluted with dichloromethane (60ml), and washed sucessively with 2M HCl, saturated aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$ and the solvent remonved *in vacuo*. Subsequent column chromatography (50% ether/petrol, silica) afforded an inseparable mixture of **(209) and (215)** as a yellow oil;

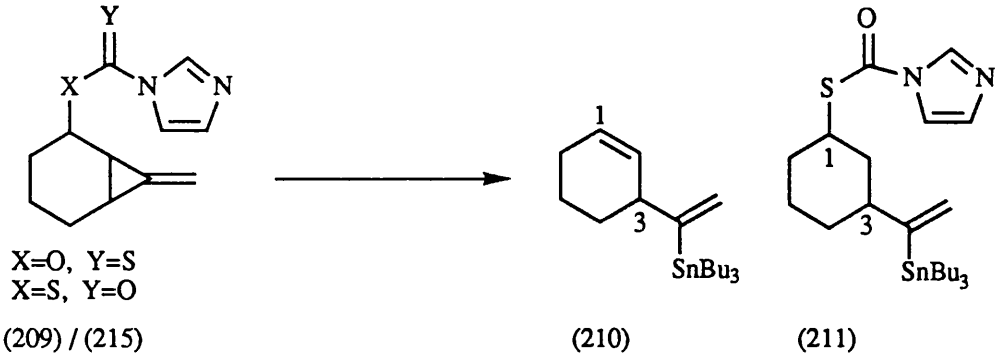
IR (film) ν_{max} 2933, 2851, 1687, 1466, 1292, 1215 cm^{-1}.

δ_H (400MHz. $CDCl_3$) (8.20, 3/4H, t, *J* 0.9Hz, Ar-*H*), 8.18 (1/4H, m, Ar-*H*), 7.47 (3/4H, t, *J* 1.7Hz, Ar-*H*), 7.45 (1/4H, t, *J* 1.6Hz, Ar-*H*), 7.09 (1/4H, dd, *J* 1.7, 0.8, Ar-*H*), 7.07 (1/4H, m, Ar-*H*), 5.5 (1H, t, *J* 1.5Hz, 1*H7'), 5.50 (1/4H, t, *J* 1.8Hz, 1*H7'), 5.49 (4/3H, t, *J* 1.8Hz, 1*H7'), 4.30 (1/4H, m, C*H*O), 4.11 (3/4H, H, brt, *J* 5.5Hz, C*H*S), 1.94-1.33 (8H, m, H_1, 2*H_3, 2*H_4, 2*H_5, H_6).

m/z (EI) 235 (MH^+), 173, 139, 107, 91, 79, 53.

Observed: (MH^+), 235.0905. $C_{12}H_{15}N_2OS$ requires 235.0905.

Preparation of 3-(1-tributylstannylethenyl)cyclohexene (210) and 3-(1-tributylstannylethenyl) cyclohexane-thiolcarbonyl imidazole (211).



A solution of AIBN (21mg, 0.11mmol) and tri-*n*-butylstannane (320µl, 1.28mmol) in benzene (7ml) was introduced over 2 hours *via* uniform motor-driven syringe addition, to a rapidly stirred solution of the thiocarbonylimidazole derivative (209/215) (250mg, 1.07mmol) in benzene (20ml) at 80°C under argon. After a further 12 hours, the reaction mixture was allowed to cool to room temperature whereupon carbon tetrachloride (10ml) and iodine were added. Stirring was continued until a persistent colouration was observed (1hour), adding further iodine if necessary. The solvent was removed *in vacuo*, the residue washed with saturated aqueous KF solution (10ml) and extracted with ether (3x50ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (40% ether/petrol, silica) afforded in order of elution ***3-(1-tributylstannylethenyl)cyclohexene*** **(210)** (164mg, 39%) as a yellow oil;

IR (film) ν_{max} 3018, 2926, 2854, 1646, 1463, 1376, 1292, 1072 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.73 (1H, m, H_2), 5.67 (1H, dd, *J* 1.0, 2.6Hz, 1*$H_{4''}$), 5.49 (1H, m, H_1), 5.13 (1H, m, 1*$H_{4''}$), 2.95 (1H, m, H_3), 1.95 (2H, m, 2*H_6), 1.70 (2H, m, 2*H_4), 1.47 (6H, m, 3*CH_2 (Bu)), 1.30 (8H, m, 3*CH_2 (Bu), 2*H_5), 0.86 (15H, m, 3*CH_2 , 3*CH_3 (Bu)).

δ_C (100 MHz, $CDCl_3$) 159.51 ($C_{4'}$), 130.64, 127.76 (C_1, C_2), 124.63 ($C_{4''}$), 46.30

(C_3), 30.07, 29.11, 27.43, 25.15, 21.00 (CH_2's), 13.70 (CH_3 (Bu)), 10.10 (CH_2);

m/z (EI) 341 (M^+-Bu), 308, 285, 235, 177, 121, 107, 91, 79, 67, 57, 41.

Observed: (M^+-Bu), 341.1291. $C_{16}H_{29}{}^{120}Sn$ requires 341.1291.

and ***3-(1-tributylstannylethenyl)- cyclohexane-thiolcarbonyl imidazole*** **(211)** (53mg, 10%) as a yellow oil;

IR (film) ν_{max} 3011, 2923, 2859, 1687, 1642, 1589, 1454, 1336, 1260, 1125, 1072, 1007 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 8.12 (1H, s, Ar-*H*), 7.39 (1H, d, *J* 1.5Hz, Ar-*H*), 7.03 (1H, d, *J* 1.3Hz, Ar-*H*), 5.70 (1H, d, *J* 2.2Hz, 1*H4''), 5.12 (1H, d, *J* 2.2Hz, 1*H4''), 3.49 (1H, m, H_1), 2.30 (1H, m, H_3), 1.81 (4H, m, 2*H_2, 2*H_6), 1.48 (8H, m, 3*C*H*$_2$ (Bu), 2*H_4), 1.23 (8H, m, 3*C*H*$_2$ (Bu), 2*H_5), 0.88 (15H, m, 3*C*H*$_2$, 3*C*H*$_3$);

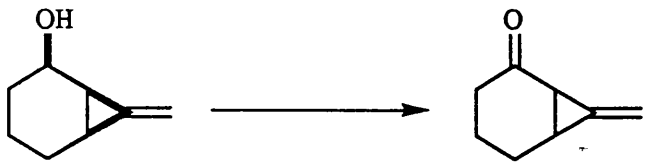
δ_C (100MHz, $CDCl_3$) 165.73 (C=O), 157.55 (C_4'), 135.29, 130.59 (Ar-C), 126.60 (C_4''), 115.81 (Ar-C), 54.12 (C_3), 50.01 (C_1), 35.04, 34.49. 29.03, 27.37, 26.41, 25.37 (CH_2's), 13.06 (CH_3), 10.46 (CH_2).

m/z (EI) 527 (MH^+), 469 (M^+-C_4H_9), 359, 308, 291, 247, 187, 121, 107, 91, 79, 68, 57, 41.

Observed: (MH^+), 527.2119. $C_{24}H_{42}N_2OS^{120}Sn$ requires 527.2120.

and recovered starting material (48mg, 19%).

Preparation of 7-methylenebicyclo[4.1.0]heptan-2-one (216).



(208) (216)

To a solution of the alcohol (208) (250mg, 2.01mmol) in dichloromethane (17ml) at room temperature under argon was added pyridinium dichromate (1.14g, 3.02mmol), followed by pyridinium trifluoroacetate (156mg, 0.80mmol) and the

solution stirred for 12 hours. The mixture was diluted with ether, filtered, and the solvent removed *in vacuo*. Subsequent column chromatography (50% ether/petrol, silica) afforded ***7-methylenebicyclo[4.1.0]heptan-2-one*** **(216)** (232mg, 94%) as a yellow oil;

IR (film) ν_{max} 2993, 2861, 1759, 1695, 1339, 1231, 1116, 1069 cm^{-1}.

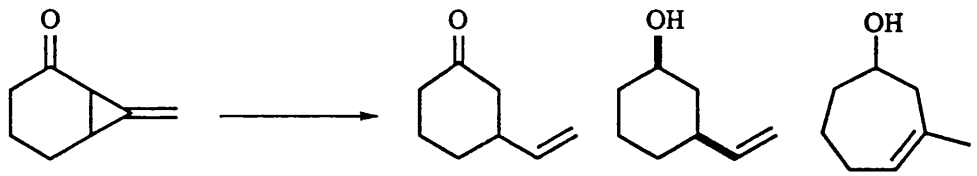
δ_H (400MHz, $CDCl_3$) 5.60 (1H, bt, *J* 2.2Hz, 1*H7'), 5.53 (1H, bt, *J* 2.0Hz, 1*H7'), 2.29 (3H, m, 2*H_3, H_1), 2.01-1.60 (5H, m, 2*H_4, 2*H_5, H_6).

δ_C (100MHz, $CDCl_3$) 206.00 (C=O), 132.00 (C_7), 107.11 ($C_{7'}$), 37.38 (C_3), 30.66 (C_1), 21.29 (C_4 or C_5), 21.25 (C_6), 17.54 (C_4 or C_5).

m/z (EI) 123 (MH^+), 122 (M^+), 107, 94, 91, 79, 66, 55, 39.

Observed: (MH^+), 123.0810. $C_8H_{11}O$ requires 123.0810.

Preparation of 3-ethenylcyclohexanone (217), 3-ethenylcyclohexanol (218) and 3-methyl-3-cyclohepten-1-ol (219).



(216) (217) (218) (219)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (60ml) was allowed to condense into the reaction vessel. Lithium shot (113mg) which had been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (216) (100mg, 0.82mmol) in ether (10ml) was added dropwise over 2 hours, the cold bath removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia allowed to evaporate. To the residue was added ether (75ml) and water (75ml), and the mixture saturated with solid NaCl. The ethereal layer was separated

and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7% ether/petrol, silica) afforded in order of elution ***3-ethenylcyclohexanone*** **(217)** (15mg, 15%) as a colourless oil;

IR (film) ν_{max} 3067, 2954, 2882, 1708, 1641, 1446, 1318, 1220 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.78 (1H, ddd, *J* 21.5, 10.6, 6.2Hz, $H_{4'}$), 5.00 (2H, m, $2*H_{5'}$), 2.52-1.45 (9H, m, $2*H_2$, H_3, $2*H_4$, $2*H_5$, $2*H_6$).

δ_C (100MHz, $CDCl_3$) 211.16 (C=O), 141.23 ($C_{4'}$), 113.73 ($C_{5'}$), 46.84 (CH_2), 42.23 (C_3), 41.21, 30.90, 24.89 (CH_2's).

m/z (EI) 124 (M^+), 96, 81, 67, 53, 36, 24 .

Observed: MH^+, 125.0966. $C_8H_{13}O$ requires 125.0966.

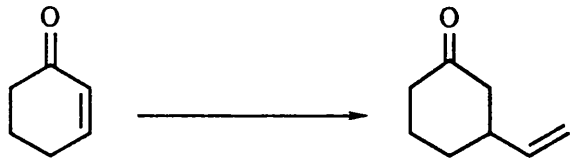
and an inseparable mixture of ***3-ethenylcyclohexanol*** **(218)** (for data see below) and ***3-methyl-3-cyclohepten-1-ol*** **(219)** (37mg, 36%, in the ratio of 1:2) as a yellow oil.

IR (film) ν_{max} 3343, 2923, 2851, 1666, 1641, 1441, 1364, 1261, 1041, 913 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.63 (1H, brt, *J* 6.7Hz, H_4), 3.65 (1H, m, H_1), 2.45-0.99 (12H, $2*H_2$, $2*H_5$, $2*H_6$, $2*H_7$, OH, CH_3), 1.71 (3H, s, CH_3).

m/z (EI) 126 (M^+), 108 (M^+-H_2O), 93, 82, 67, 55.

Preparation of 3-ethenylcylohexanone (217)[160].

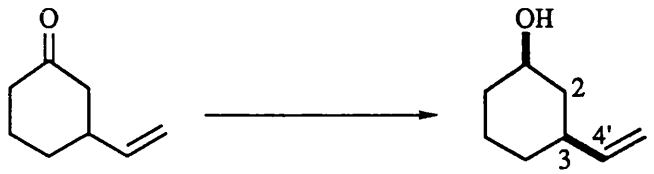


(229) (217)

Methyllithium (18.4ml of 1.4M solution in Et_2O) was added dropwise to a solution of copper(I) cyanide (1.05g, 11.7mmol) in THF (12ml) at 0°C under nitrogen. The cooling bath was removed and a solution of the vinylstannane (3.82ml, 13.13mmol) in THF (12ml) added and stirring continued for 90 minutes at room temperature. The

mixture was cooled to -64°C and a solution of the enone (229) (800mg, 8.32mmol) in THF (12ml) added rapidly. The temperature was allowed to rise to -35°C and the mixture poured into a solution of saturated aqueous NH_4Cl / NH_3OH (9:1, 50ml). The aqueous phase was extracted with ether (2x50ml), washed with brine (75ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (40% ether/petrol, silica) afforded ***3-ethenylyclohexanone*** **(217)** (1.34g, 100%) as a colourless oil (data identical to that described previously).

Preparation of 3-ethenylcyclohexanol (218).



(217) (218)

To a solution of lithium aluminium hydride (31mg, 0.81mmol) in THF (5ml) at 0°C under nitrogen was added dropwise a solution of the ketone (217) (200mg, 1.61mmol) and stirring continued at this temperature for 30 minutes. The suspension was allowed to warm to room temperature and quenched cautiously with a 2M solution of NaOH. The organic phase was separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (60% ether/petrol, silica) afforded ***3-ethenylyclohexanol*** **(218)** (79mg, 39%) as a yellow oil;

IR (film) ν_{max} 3339, 2915, 2848, 1639, 1453, 1354, 1038 cm^{-1}.

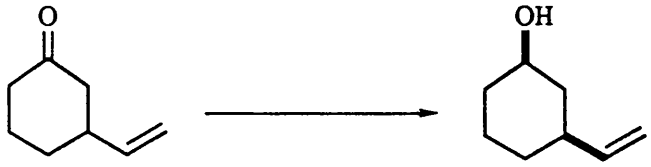
δ_H (400MHz, $CDCl_3$) 5.76 (1H, ddd, *J* 17.0, 10.0, 6.0Hz, $H_{4'}$), 4.96 (1H, dt, *J* 17.0, 1.7Hz, $H_{5'}$), 4.89 (1H, dt, *J* 10.4, 1.2Hz, $H_{5'}$), 3.60 (1H, tt, *J* 10.9, 4.1Hz, H_1), 2.06-0.88 (10H, m, 2*H_2, H_3, 2*H_4, 2*H_5, 2*H_6, O*H*).

δ_C (100MHz, $CDCl_3$) 143.16 ($C_{4'}$), 112.19 ($C_{5'}$), 70.46 (C_1), 41.42 (C_2), 40.20 (C_3), 35.26, 31.33, 23.88 (CH_2's).

m/z (CI) 144 (M^++NH_4), 108 (M^+-H_2O), 93, 78, 67, 54, 39, 27.

Observed: (MH^+), 127.1123. $C_8H_{11}5O$ requires 127.1123.

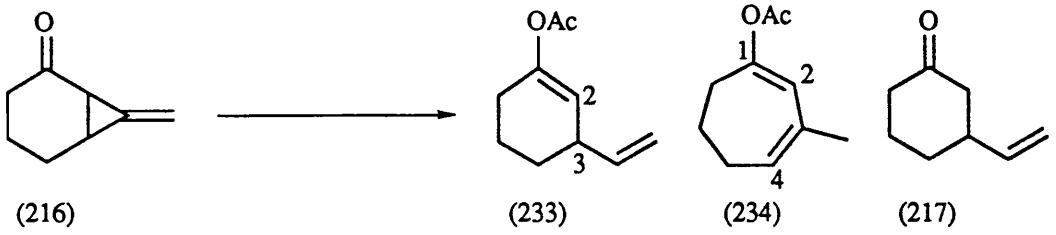
Preparation of 3-ethenylcyclohexanol (218).



(217) (218)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (65ml) was allowed to condense into the reaction vessel. Lithium shot (105mg) which had been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (217) (90mg, 0.72mmol) in ether (15ml) was added dropwise over 2 hours, the cold bath removed and refluxing continued for 40 minutes. Solid NH_4Cl (100% excess) was added and the ammonia was allowed to evaporate. To the residue was added ether (75ml) and water (75ml), and the mixture saturated with solid NaCl. The ethereal layer was separated and the aqueous phase extracted with ether (2x50ml). The combined organic extracts were washed with brine (50ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (20% ether/petrol) afforded ***3-ethenylcyclohexanol*** **(218)** (53mg, 58%) and recovered starting material (24mg, 27%) (data identical to that described previously).

Preparation of 1-acetoxy-3-ethenyl-2-cyclohexene (233), 1-acetoxy-3-methyl-1,4-cycloheptadiene (234) and 3-ethenylcyclohexanone (217).



(216) (233) (234) (217)

A 2 necked flask equipped with a dry-ice condenser and cold bath under nitrogen, was flushed with ammonia, and then ammonia (60ml) was allowed to condense into the reaction vessel. Lithium shot (113mg) which had previously been washed with anhydrous hexane was added to the vigorously stirred solution. The blue ammoniacal solution was allowed to reflux for 30 minutes. A solution of the ketone (216) (100mg, 0.82mmol) in ether (10ml) was added dropwise over 40 minutes, the cold bath removed and refluxing continued for 40 minutes. The ammonia was allowed to evaporate and the residue taken up in ether (20ml). The milky white suspension was stirred vigorously under a nitrogen atmosphere and then pipetted into a flask containing acetic anhydride (633µl, 6.10mmol) at 0°C and stirring continued for 18 hours. The reaction mixture was poured into a cold solution of saturated aqueous $NaHCO_3$ and pentane and stirred for a further 30 minutes, during which time portions of solid $NaHCO_3$ were added. The organic phase was separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (15% ether/petrol, silica) afforded in order of elution an inseparable mixture of ***1-acetoxy-3-ethenyl-2-cyclohexene*** **(233) and** ***1-acetoxy-3-methyl-1,4-cycloheptadiene*** **(234)** (42mg, 31%) as a colourless oil;

IR (film) ν_{max} 2933, 2866, 1756, 1683, 1633, 1427, 1366, 1216, 1127, 1033 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.76 (1H, ddd, *J* 17.2, 10.0, 6.9Hz, $H_{4'}$), 5.26 (1H, m, H_2), 5.00 (2H, m, 2*$H_{5'}$), 2.93 (1H, m, H_3), 2.45-1.82 (6H, m, 2*H_4, 2*H_5, 2*H_6), 2.09 (3H, s, CH_3-Ac).

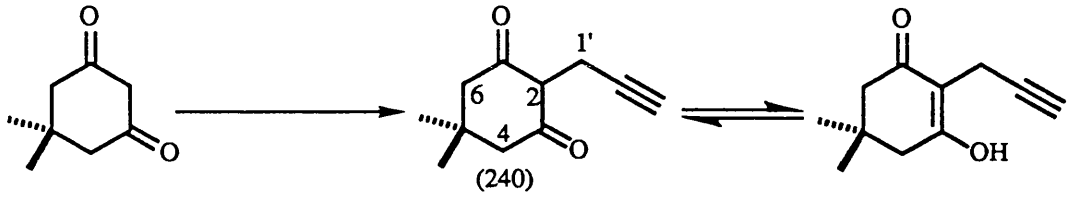
δ_H (400MHz; $CDCl_3$) 5.63 (1H, brt, *J* 6.5Hz, H_4), 5.43 (1H, s, H_2), 2.45-1.82 (9H, m, 2*H_5, 2*H_6, 2*H_7, CH_3-Ac), 1.43 (3H, s, C*H*$_3$).

m/z (EI) 166 (M^+), 124, 109, 96, 81, 67, 55, 41.

Observed: M^+, 166.0994. $C_{10}H_{14}O_2$ requires 166.0994.

and ***3-ethenylcyclohexanone*** **(217)** (15.8mg, 16%) (data identical to that described previously).

Preparation of 5,5-dimethyl-2-(prop-2-ynyl)cyclohexan-1,3-dione (240).[19]



To a solution of potassium hydroxide (20g, 360mmol) in water (240ml) was added dimedone (50g, 360mmol), and the solution heated to 50°C. Propargyl bromide (28ml, 400mmol) was added and vigorous stirring continued for 2 hours. The solution was allowed to cool to room temperature, a futher portion of potassium hydroxide added (20g, 360mmol) and the aqueous and organic phases separated. The former was acidified with 1M HCl to pH5 and the white solid filtered off. Subsequent column chromatography (70% ether/petrol, silica) afforded ***5,5-dimethyl-2-(prop-2-ynyl)cyclohexan-1,3-dione*** **(240)** (10g, 16%) as a white crystalline solid (m.pt. 112-113°C);

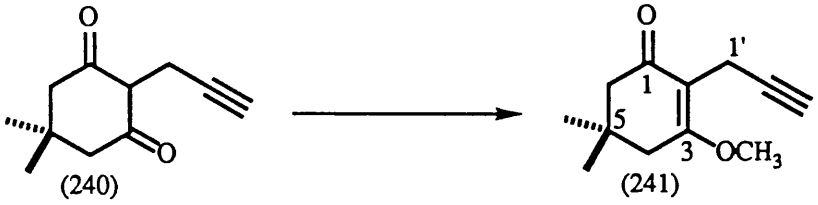
IR (film) ν_{max} 3302, 3056, 2964, 2308, 1735, 1703, 1379, 1041 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 3.55 (0.4H, t, *J* 5.0Hz, H_2 of diketone tautomer), 3.27 (1.2H, d, *J* 2.8Hz, propargyl CH_2 of enol tautomer), 2.71-2.30 (5.4H, m, O*H* of enol tautomer, propargyl CH_2 of diketone tautomer, 2*H_4, 2*H_6 of both tautomers), 2.18 (0.6H, t, *J* 2.5Hz, acetylene CH of enol tautomer), 1.89 (0.4H, t, *J* 2.5Hz, acetylene CH of diketone tautomer), 1.18 (1.2H, s, gem C*H*$_3$ of enol tautomer), 1.04 (3.6H, s,

gem C*H*3 of enol tautomer), 0.80 (1.2H, s, gem C*H*3 of diketone tautomer).

m/z (EI) 178 (M^+), 169, 163, 145, 135, 122, 94, 83, 79.

Preparation of 3-methoxy-5,5-dimethyl-2-(prop-2-ynyl)-2-cyclohexenone (241).[19]



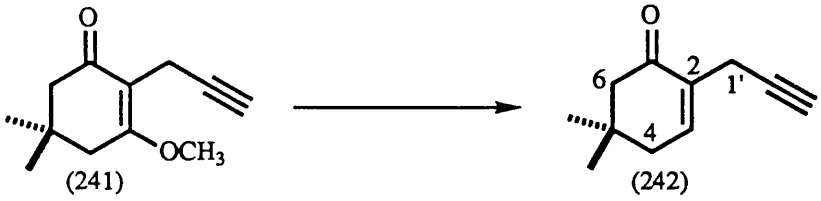
To a solution of the dione (240) (10.5g, 60mmol) in methanol (400ml) was added trimethylorthoformate (57ml) and conc. H_2SO_4 (4ml) and stirring continued for 12 hours. The resulting solution was concentrated and the residue neutralised to pH7 with aqueous $NaHCO_3$. The mixture was extracted with chloroform (3x200ml), the combined organic extracts dried over Na_2SO_4 and the solvent removed *in vacuo*. Subsequent column chromatography (40% EtOAc/petrol, silica) afforded ***3-methoxy-5,5-dimethyl-2-(prop-2-ynyl)2-cyclohexenone*** **(241)** (7.0g, 61%) as colourless needles (m.pt. 87-88°C);

IR (film) ν_{max} 3303, 3046, 2953, 2117, 1621, 1369, 1267, 1078 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 3.81 (3H, s, OC*H*3), 3.13 (2H, d, *J* 2.7Hz, 2*$H_{1'}$), 2.40 (2H, s, 2*H_4), 2.21 (2H, s, 2*H_6), 1.78 (1H, t, *J* 2.7Hz, $H_{3'}$), 1.05 (6H, s, C_5-C*H*3's).

m/z (EI) 192 (M^+), 177 (M^+-CH_3), 135, 121, 105, 91, 78, 65, 51, 39.

Preparation of 5,5-dimethyl-2-(prop-2-ynyl)-2-cyclohexenone (242).[19]



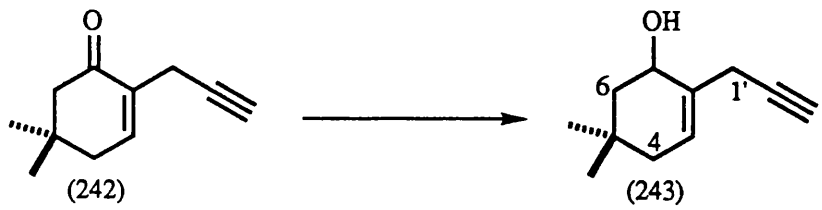
To a solution of the ketone (241) (7.1g, 37mmol) in toluene (100ml) at 0°C under argon was added dropwise a solution of diisobutylaluminium hydride (37ml of a 1.5M solution in toluene). The solution was stirred for 90 minutes, water was added (30ml) followed by 2M HCl (20ml) and stirring continued for a further 30 minutes. The aqueous phase was separated and extracted with ether (2x30ml) and combined organic extracts washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford ***5,5-dimethyl-2-(prop-2-ynyl)-2-cyclohexenone*** **(242)** (6.0g, 99%) as a colourless oil;

IR (film) ν_{max} 3290, 2957, 2121, 1673, 1378 cm^{-1}.

δ_H (270MHz, $CDCl_3$) 7.05 (1H, m, H_3), 3.18 (2H, m, 2*$H_{1'}$), 2.32 (4H, bsr, 2*H_4, 2*H_6), 2.19 (1H, t, *J* 2.7Hz, $H_{3'}$), 1.05 (6H, s, C_5-CH_3's).

m/z (EI) 163 (MH^+), 147, 133, 119, 105, 91, 78, 65, 51, 39.

Preparation of 5,5-dimethyl-2-(prop-2-ynyl)-2-cyclohexen-1-ol (243).[19]



To a solution of the enone (242) (6.0g, 37mmol) in toluene (100ml) at -78°C under argon was added dropwise a solution of diisobutylaluminium hydride (25ml of a 1.5M solution in toluene) over a period of 20 minutes. The solution was stirred for 2

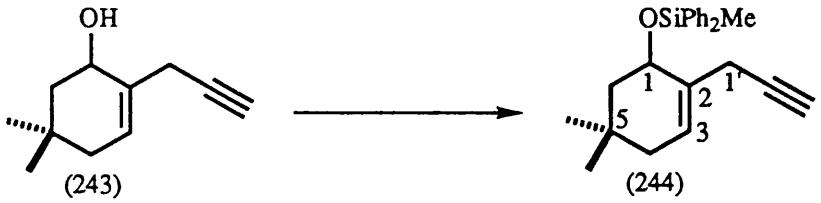
hours, water (15ml) added and the mixture allowed to warm to room temperature. Ethyl acetate (250ml) was added followed by a large excess of Na_2SO_4 and stirring continued overnight. The solid alum was filtered off and the solvent removed *in vacuo*. Subsequent column chromatography (20% ether/petrol, silica) afforded ***5,5-dimethyl-2-(prop-2-ynyl)-2-cyclohexen-1-ol*** **(243)** (4.7g, 78%) as a colourless oil;

IR (film) ν_{max} 3426, 2953, 2862, 2117, 1374, 1043 cm^{-1}.

δ_H (400MHz, $CDCl_3$) 5.75 (1H, m, H_3), 4.24 (1H, brm, H_1), 3.08 (2H, m, 2*$H_{1'}$), 2.12 (1H, t, *J* 2.7Hz, $H_{3'}$), 1.96-1.76 (3H, m, 2*H_4, 1*H_6), 1.58 (1H, brd, *J* 6.9Hz, O*H*), 1.40 (1H, dd, *J* 12.9, 8.7Hz, 1*H_6), 0.99 (3H, s, C_5-CH_3), 0.90 (3H, s, C_5-CH_3).

m/z (CI) 182 (M^++NH_4^+), 164 (M^+), 147, 125, 108.

Preparation of 5,5-dimethyl-1-diphenylmethylsilyloxy-2-(prop-2-ynyl)-2-cyclohexen-1-ol (244).



(243) (244)

To a solution of diphenylmethylchlorosilane (6.58ml, 31.6mmol), triethylamine (4.3ml, 31.6mmol) and DMAP (40mg, 0.29mmol) in dichlormethane (30ml), at 0°C under argon, was added the alcohol (243) (4.72g, 28.7mmol) and the solution stirred for a hour. The reaction mixture was allowed to warm to room temperature poured into water (30ml) and extracted with dichloromethane (3x20ml). The combined organic extracts were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Subsequent column chromatography (7%, ether/petrol, silica) afforded ***5,5-dimethyl-1-diphenylmethylsilyloxy-2-(prop-2-ynyl)-2-cyclohexen-1-ol*** **(244)** (9.70g, 87%) as a colourless oil;

IR (film) ν_{max} 3308, 3070, 1295, 2868, 2120, 1590, 1469, 1428, 1365, 1254 cm^{-1}.

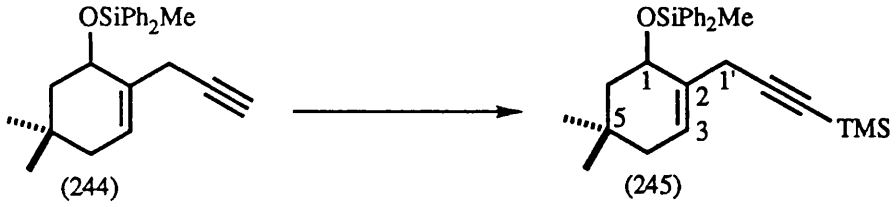
δ_H (400MHz, $CDCl_3$) 7.60 (4H, m, Ar-*H*), 7.38 (6H, m, Ar-*H*), 5.77 (1H, m, H_3), 4.32 (1H, m, H_1), 3.11 (1H, m, 1*$H_{1'}$), 2.85 (1H, m, 1*$H_{1'}$), 2.07 (1H, t, *J* 2.7Hz, $H_{3'}$), 1.95-1.47 (4H, m, $2H_4$, $2H_6$), 0.93 (3H, s, C_5-C*H*$_3$), 0.77 (3H, s, C_5-C*H*$_3$), 0.70 (3H, s, $OSiPh_2CH_3$).

δ_C (400MHz, $CDCl_3$) 136.42, 136.33 (C_2, Ar-C), 134.44, 127.75, 127.73 (Ar-C), 124.27 (C_3), 82.08 ($C_{3'}$), 70.73 ($C_{2'}$), 68.78 (H_1), 45.55, 39.17 (C_4, C_6), 30.78, 26.38 (C_5-CH_3's), 22.74 ($C_{1'}$), -2.27 ($OSiPh_2CH_3$).

m/z (EI) 360 (M^+), 333, 322, 243, 197, 165, 137, 105, 91, 77, 41.

Observed (CI): (M^++NH_4^+), 378.2253. $C_{24}H_{32}NOSi$ requires 378.2253.

Preparation of 5,5-dimethyl-1-diphenylmethylsilyloxy-2-(3-trimethylsilylprop-2-ynyl)-2-cyclohexen-1-ol (245).



(244) (245)

To a solution of the acetylene (244) (10g, 28mmol) in tetrahydrofuran (45ml) at -78°C under argon, was added dropwise a solution of *n*-butyllithium (12.2ml of a 2.5M solution in hexanes), and stirring continued for 30 minutes. Freshly distilled TMSCl (4.07ml, 30.6mmol) was added, and after a futher 30 minutes the solution was warmed to 0°C and stirred for a further 30 minutes. After warming to room temperature the reaction mixture was poured into water (200ml) and extarcted with ether (3x100ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, and the solvent removed *in vacuo*. Subsequent column chromatography (5% ether/petrol, silica) afforded ***5,5-dimethyl-1-diphenylmethylsilyloxy-2-(3-trimethylsilylprop-2-ynyl)-2-cyclohexen-1-ol*** **(245)** (12g, 99%) as a yellow oil;

IR (film) ν_{max} 3055, 2944, 2878, 2175, 1581, 1464, 1365, 1250, cm^{-1}.

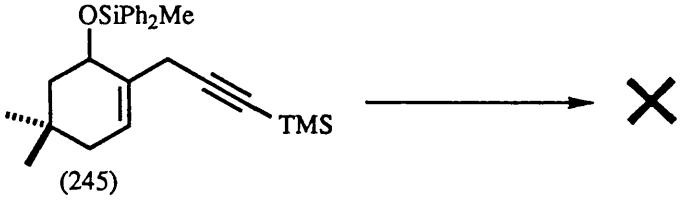
δ_H (400MHz, $CDCl_3$) 7.57 (4H, m, Ar-*H*), 7.35 (6H, m, Ar-*H*), 5.77 (1H, m, H_3), 4.33 (1H, m, H_1), 3.20 (1H, m, 1*$H_{1'}$), 2.90 (1H, m, 1*$H_{1'}$), 1.97-1.12 (4H, m, 2*H_4, 2*H_6), 0.18 (9H, s, $Si(CH_3)_3$).

δ_C (400MHz, $CDCl_3$) 136.54, 13640 (C_2, Ar-C), 134.41, 129.73, 127.73 (Ar-C), 124.14 (C_3), 104.74 ($C_{3'}$), 87.24 ($C_{2'}$), 68.82 (C_1), 45.56, 51.17 (C_4, C_6), 30.79, 26.34 (C_5-CH_3's), -0.58, -2.32 (CH_3's).

m/z (EI) 432 (M^+), 417 (M^+-CH_3), 359 (M^+-TMS), 225, 209, 171, 156, 142, 128.

Observed (EI): M^+, 432.5808. $C_{27}H_{36}OSi_2$ requires 432.5819.

Attempted cyclopropanation of 5,5-dimethyl-1-methyldiphenylsilyloxy-2-(3-trimethylsilylprop-2-ynyl)-2-cyclohexen-1-ol (245).



(245)

n-Butyllithium (12.2ml of a 2.5M solution in hexanes) was added dropwise over a 4 hour period, by means of a syringe pump, to a stirred solution of the protected alcohol (245) (12g, 28mmol), and 1,1-dichloroethane (726µl, 8.63mmol) in ether (20ml), under argon at -35°C. Futher portions of 1,1-dichloroethane (471µl, 5.60mmol) were added 0.5, 1.5, 2.5 and 3.5 hours after the initial addition. The mixture was allowed to warm up to room temperature, stirred overnight, recooled to -35°C and the above procedure repeated. The reaction mixture was again warmed to room temperature, poured into water (200ml), the organic phase separated, dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude chloro-methylcyclopropane was dissolved in DMSO (8ml) and added dropwise to a stirred solution of potassium *tert*-butoxide (4.9g, 42mmol) in DMSO (10ml) at 70°C under

argon. After stirring for 20 hours, the resulting dark brown solution was cooled to 0°C, poured into ice-cold water (100ml) and extracted with ether (3x100ml). The combined organic extracts were washed with water, dried over $MgSO_4$, and the solvent removed *in vacuo*. Nmr analysis of the crude material showed none of the desired product.

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Corrigenda

Page	Correction
2	ammmonia ➪ ammonia
23	electronetivities ➪ elecronegativies
42	O_2)C=X ➪ O)$_2$C=X (scheme 2.12 (47))
49	alkyl-2-yl ➪ alk-2-yl
61	electrophilies ➪ electrophiles
69	Kagans's ➪ Kagan's
97	consuned ➪ consumed
104	sincethe ➪ since the
105	the*cis* ➪ the *cis*
107	traping ➪ trapping
115	*insitu* ➪ *in situ*
120	promoted us pursue ➪ promoted us to pursue
122	prehaps ➪ perhaps
122	preformed ➪ performed
122	repaeted ➪ repeated
135	*insitu* ➪ *in situ*
142	difavoured ➪ disfavoured (scheme 4.35)
163	synthesis ➪ synthesise
164	alternate ➪ alternative
164	dose ➪ does
177	futher ➪ further
179	solutiion ➪ solution
259	C.A.Coluson ➪ C.A. Coulson
265	A.D. Meljere ➪ A.D. Meijere