Rearrangement and Trapping of

Organozinc Carbenoids

A Thesis Presented by

Donogh John Roger O'Mahony

In Partial Fulfilment of the Requirements

for the Award of the Degree

DOCTOR OF PHILOSOPHY

of the

UNIVERSITY OF LONDON

Christopher Ingold Laboratories,

Department of Chemistry,

University College London,

London WC1H 0AJ.

August 1995

ProQuest Number: 10016794

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.
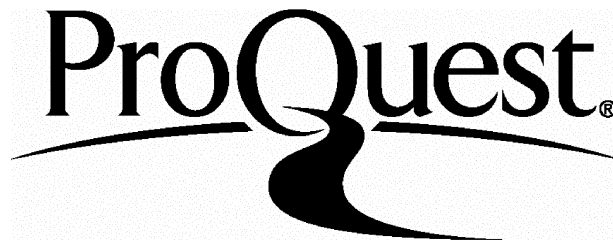
ProQuest 10016794

Abstract

This thesis is divided into six chapters. Chapter one presents a review on metallocarbenoid chemistry and is divided into three parts. The first part gives a general survey of the influence of substituents on the reactivity and stability of free carbenes. The second part describes the reactions of transition metal carbenoids, particularly in relation to the oxidation state of the metal and the stoichiometry of carbenoid generation. The final part discusses the reactions of zinc carbenoids and the means of their formation.

Chapter two is prefaced by a review on the generation and reactivity of organozinc carbenoids within the group, coupled with a mechanistic study of their formation. Studies on the hydrogen migration in open chain and more rigid cyclic ketone derived zinc carbenoids are presented. The organozinc carbenoids were shown to exhibit greater overall selectivity for the more thermodynamically favoured alkene isomer. Finally, the one-step conversion of aldehydes to terminal alkenes is presented. This conversion is shown to be accelerated by the addition of Lewis acids, particularly zinc chloride.

Chapter three describes the direct one-pot conversion of acetals and ketals to organozinc carbenoids. It was found that carbenoids could be prepared efficiently from ketals containing the 1,3-dioxane, 1,3-dioxolane or dimethoxy moiety. However, for the acetal derivatives, only the dimethoxy and 1,3-dioxolane acetals could be readily reduced to the carbenoid.

In chapter four, the carbenoids derived from aromatic aldehydes were shown to cyclopropanate olefins, and a brief study some of the steric and electronic effects of the alkene component is presented. The derived dimethoxy and 1,3-dioxolane acetals were also shown to cyclopropanate some simple olefins, with the *syn:anti* ratio dependant on the amount of added zinc chloride. Chapter five concludes the results and discussion, and gives a perspective to further work.

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

Contents

3. The use of the Acetal Function as a Carbenoid Synthon

4. Cyclopropanation Reactions using Organozinc Carbenoids

5. Conclusions and Perspectives

6. Experimental

Acknowledgements

Zinc, Zinck, zinco: they make tubs out of it for laundry, it is not an element which says much to the imagination, it is gray and its salts are colourless, it is not toxic, nor does it produce stinking chromatic reactions; in short, it is a boring metal.

from The Periodic Table by Primo Levi.

Abbreviations

Ac	Acetyl
Ar	Unspecified aromatic group
atm.	Atmospheres
ax	Axial
B	Base
Bn	Benzyl
b.p.	Boiling point
br	Broad
^{n}Bu	n-Butyl
^{t}Bu	*tertiary*-Butyl
Bz	Benzoyl
cap	Caproate
cat.	Catalytic/catalyst as appropriate
CI	Chemical ionisation
Cp	η^5-Cyclopentadienyl
Cp*	Pentamethyl η^5-cyclopentadienyl
Δ	Heat
d	Doublet
DCM	Dichloromethane
de	Diastereomeric excess
DEC	Diethylene glycol diethyl ether
DMAD	Dimethyl acetylene dicarboxylate
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
E	Unspecified electrophile
ee	Enantiomeric excess

EI	Electron impact
eq.	Equivalents or equatorial as appropriate
Et	Ethyl
Et$_2$O	Diethyl ether
FAB	Fast atom bombardment
Fp	Cyclopentadienyldicarbonyliron
FTIR	Fourier transform infra red
GC	Gas chromatography
GCMS	Gas chromatography coupled mass spectrometry
HMPA	Hexamethylphosphoric(V)triamide
hv	Light
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
hr	Hours
L	Unspecified ligand
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
M	Unspecified metal
m	Multiplet
Me	Methyl
min.	Minutes
MNOBA	*meta*-Nitrobenzyl alcohol
m.p.	Melting point
NMR	Nuclear magnetic resonance
Np	*neo*-Pentyl
Nu	Unspecified nucleophile
p	Pentet
pet.	Petroleum

pfb	Perfluorobutyrate
Ph	Phenyl
Piv	Pivaloyl
^{i}Pr	*iso*-Propyl
ppm	Parts per million
PVP	poly-4-Vinylpyridine
py	Pyridine
q	Quartet
quant.	Quantitative
R	Unspecified carbon substituent
r.t.	Room temperature
s	Singlet
t	Triplet
TBDMS	*tertiary*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
tfa	Trifluoroacetate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N,N-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
w/u	Work-up
X	Unspecified heteroatom
Y, Z	Unspecified substituent
)))	Ultrasound

Stereochemical Notation

Throughout this thesis, the graphical representation of stereochemistry us 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.
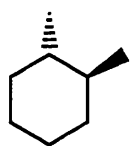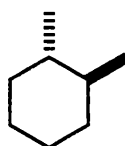
single enantiomer   racemic

---

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

1

The Influence of a Metal on

Carbenoid Reactivity

1.1 Introduction

This thesis is concerned with the generation and reactivity of organozinc carbenoids from carbonyl compounds, and related congeners. The presence of a carbon-hydrogen bond α- to the resultant carbenoid generates an alkene. In the absence of such functionality, and particularly when conjugated to an aromatic ring, the resultant carbenoid is stable enough to cyclopropanate alkenes.

The following introduction opens with a general survey of the influence of substituents in the reaction of "free" carbenes. The second section deals with the influences on reactivity of the binding of a metal centre to these free carbenes. Since the most significant advances of the past 30 years have been made using transition metals as the moderating influence, attention will be focused on the reactivity of transition metal carbenoids, both stoichiometric and catalytic, and detail some general methods for their preparation.

The final section of the introduction will discuss the preparation and behaviour of organozinc carbenoids.

1.2 Generation and Reactivity of Free Carbenes

A divalent carbon species or carbene may have two electronic states: either the triplet state where each unpaired electron occupies a different energetically equivalent sp^3 orbital, or the more bent singlet state with one filled sp^2 orbital and one empty p orbital.[1] Although the simplest carbene, methylene, is known to have a non-linear triplet ground state structure, with an energy difference of ca. 38 kJ/mol separating it from the more strongly bent singlet state (Figure 1.1),[2] thermal carbene generation will normally generate the singlet carbene through conservation of orbital symmetry.
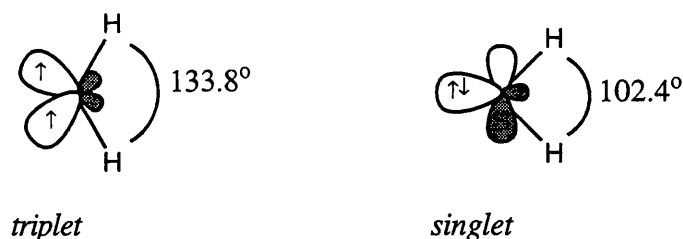
triplet   singlet

Figure 1.1

Triplet carbenes are usually generated by photolysis of diazo compounds, although the presence of a π system on an atom α- to the carbene carbon can promote intersystem crossing from the singlet state. The reactions of triplet carbenes proceed *via* stepwise biradical mechanisms, and are frequently unselective. This review will concentrate primarily on singlet carbenes which undergo concerted reaction and bear some similarity to the reactions of metallocarbenoids.

A variety of routes to singlet free carbenes exist: thermal routes include pyrolysis of diazirines (**1**), diazoalkanes (**2**) or tosylhydrazone salts (**3**) in aprotic media (Scheme 1.1.a). A number of routes also exist for generation of singlet carbenes through deprotonation of haloalkanes[3] (**4**), metal-halogen exchange of di- or trihaloalkanes[4] (**5**), and pyrolysis of tin and mercury compounds of the form $L_nM\text{-}CRR'X^5$ (**6**) (Scheme 1.1.b). These latter carbenes are not true "free" carbenes, however, and the term "carbenoid" has been adopted for the reactive intermediates.[6] The influence of the metal can be paramount and frequently introduces greater chemo- and stereoselectivity in C-H insertion reactions and olefin cyclopropanations.
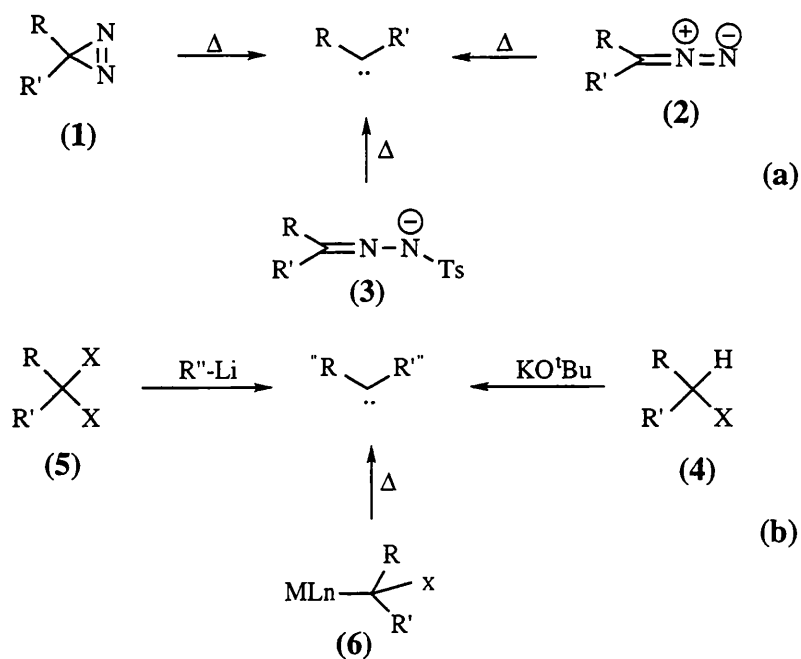
Scheme 1.1

Binding of groups to methylene other than hydrogen significantly influences the behaviour of the resultant carbene. The simplest case is replacement of one, or both, of the hydrogens of methylene with an alkyl group. These alkyl substituted carbenes are unstable and normally undergo intramolecular C-H insertion. An α–C-H insertion reaction generates an alkene, and is the favoured route for these carbenes where possible. β–C-H insertion generates a cyclopropane, and transannular insertion – a diagnostic reaction of carbene intermediates – generates bicyclic ring systems (Scheme 1.2).[7]

50 : 43.5 : 6.5
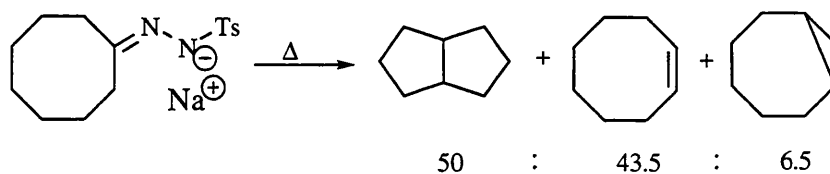
Scheme 1.2

The insertion reactions are selective, but the selectivity is governed more by steric factors than by activation of the C-H bond. However when steric factors are similar, α–C-H insertion to generate the alkene will occur where the migrating hydrogen has the greatest hydride character. (Scheme 1.3).[8]
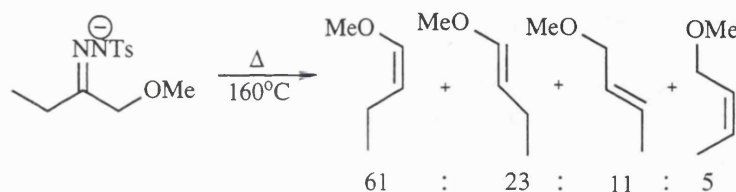
Scheme 1.3

Replacement of one, or both, of the hydrogens of methylene with phenyl groups, or other groups capable of overlap with the empty p orbital on the carbene, significantly reduces the carbene's electrophilicity, and induces a degree of selectivity when compared to the normally indiscriminate reaction of methylene. A simple molecular orbital diagram in Figure 1.2 shows the effect of a π symmetry orbital overlap with the singlet carbene. The carbene LUMO is shifted to higher energy owing to a π destabilising interaction with the filled donor orbital of X. The carbene HOMO is lowered in energy due to the inductive effect of the more electronegative X substituent, and the HOMO/LUMO energy gap is widened. This increased σ–π energy gap also results in the greater likelihood of a ground state singlet carbene.

Figure 1.2

16
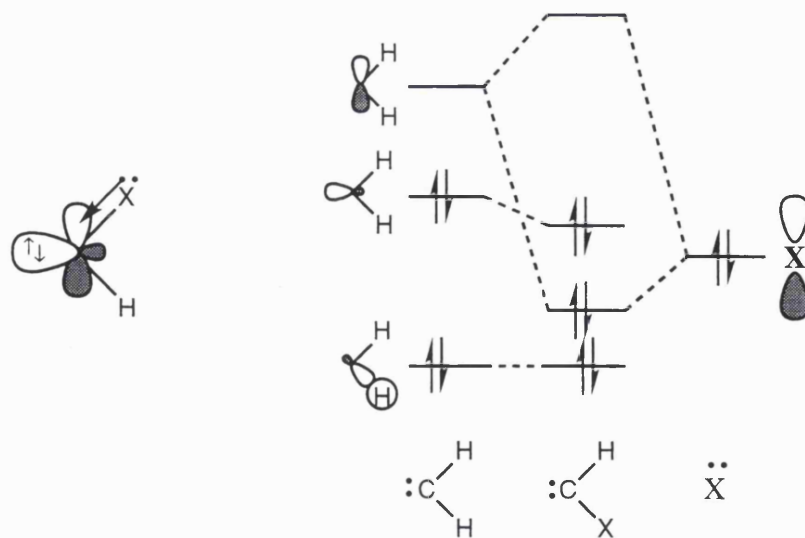
The standard route to these stabilised free carbenes is again thermolysis of their respective diazoalkanes or tosylhydrazone salts. Replacement of a hydrogen in methylene with a phenyl group gives a singlet carbene more selective for cyclopropanation over C-H insertion. The resulting stability conferred on the carbene by the phenyl group and the presence of a conjugated π system allows more rapid intersystem crossing to the triplet ground state, and some isomerisation of alkene geometry takes place during cyclopropanation (Scheme 1.4.a).[9a,b] However, the bulk of the phenyl group does not introduce any great stereoselectivity. The presence of a second aryl group on the carbene renders intersystem crossing even easier and ortho biaryl coupling to generate fluorenes as significant byproducts (Scheme 1.4.b)[9b,c] can then occur.
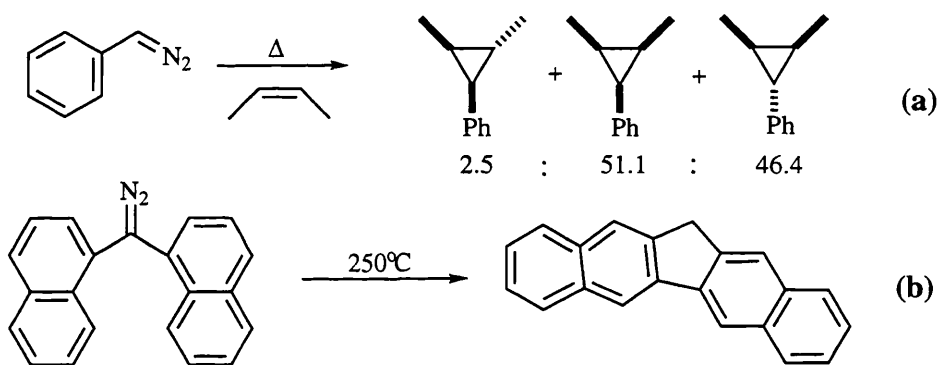
Scheme 1.4

However the presence of non-aromatic C=C bonds conjugated to the carbene leads exclusively to intramolecular reaction to generate cyclopropenes (Scheme 1.5).[10] Yields are typically in the range 30-75%.

Scheme 1.5

17
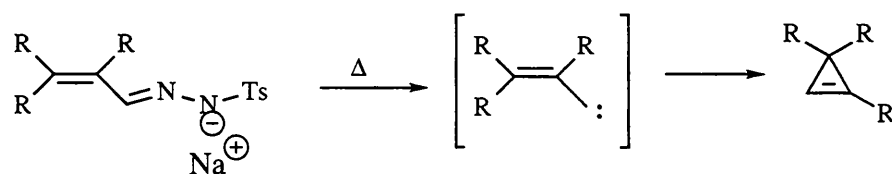
The presence of an amino group on the carbene decreases its electrophilicity greatly and gives carbenes that are rather unreactive. The presence of two amino groups on a carbene, as in (7), renders them sufficiently stable to be isolated.[11]

$$
\begin{array}{c}
\text{Ph} \\
\vert \\
\text{N} \\
\diagdown \\
\text{C :} \\
\diagup \\
\text{N} \\
\vert \\
\text{Ph}
\end{array}
$$
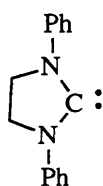
(7)

Simple alkoxycarbenes have received little attention, but dialkoxycarbenes are unstable and readily decompose, giving a variety of products. The simplest of the dialkoxycarbenes, dimethoxycarbene, will dimerise, however, when generated from neat precursor (Scheme 1.6).[12]
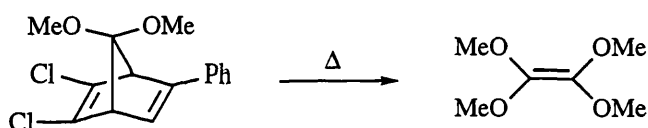
Scheme 1.6

Phenyl alkoxy carbenes though can be used to cyclopropanate alkenes, although yields are very low. In contrast to phenyl carbene, a small degree of stereoselection takes place in the cyclopropanation (Scheme 1.7).[13]

1.8 : 1.0
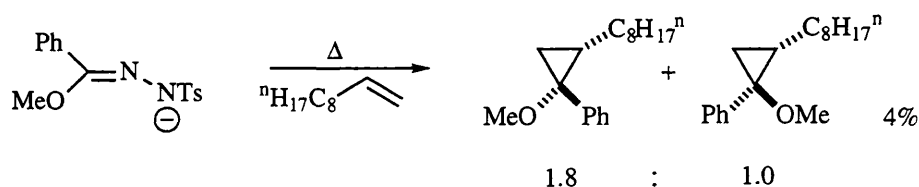
Scheme 1.7

In contrast to their oxygen counterparts, sulfur substituted carbenes, although weakly electrophilic, require very electron rich olefins (Scheme 1.8).[14]
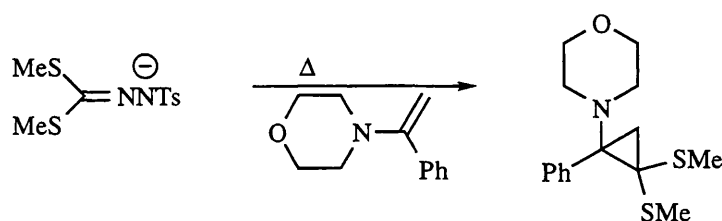
Scheme 1.8

Halocarbenes also benefit from the stabilisation introduced by the lone pairs on the halogen. This is reflected in the ready generation of bromo- and chlorocarbene from the parent diazoalkane at -30°C. Both carbenes show a distinct preference for cyclopropanation over C-H insertion.[15] The bromocarbene also shows a higher preference for secondary over primary insertion compared to its chloro counterpart, even though it is more sterically demanding (Scheme 1.9.a).[15] However, in common with the cyclopropanation reactions of many other free carbenes, these carbenes show virtually no stereoselectivity in cyclopropanation (Scheme 1.9.b).[15]

A/(B+C+D) = ca. 1/1 X = Cl, Br

B/(C+D) = 20/1, X=Cl
        = 25/1, X=Br
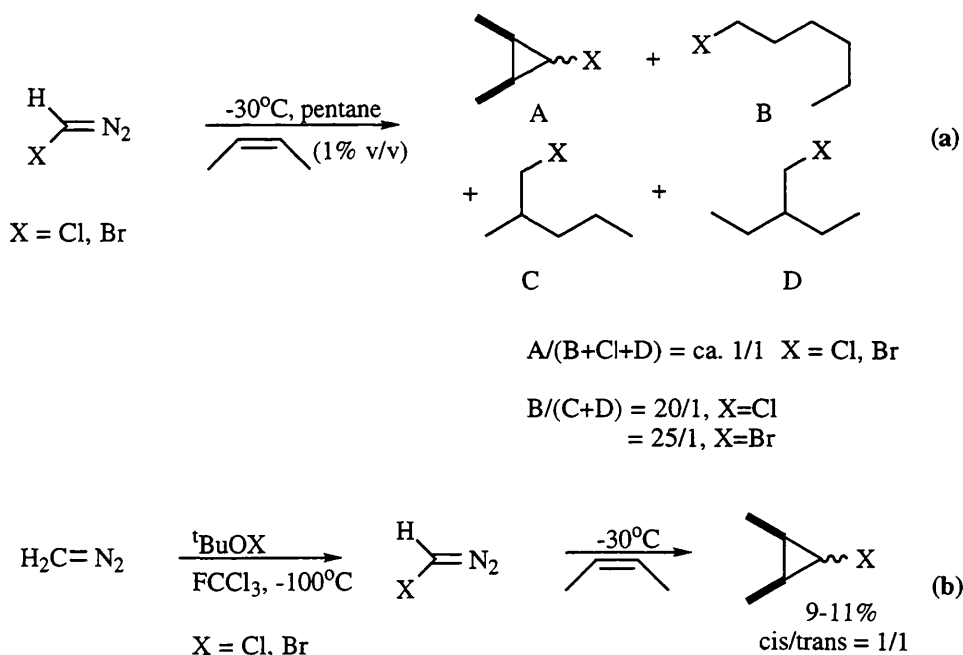
Scheme 1.9

19

Dihalocarbenes, and other halocarbenes such as FHC: and IHC: are not easily accessible as their free carbenes, and have been studied as the carbenoids. Comparative studies of these carbenoids generated by metal-halogen exchange, deprotonation, and thermal extrusion (*vide supra*) show electrophilicities in the order: F_2C: < Cl_2C: < Br_2C: < I_2C:, and F_2C: < FHC: < H_2C:, in both cyclopropanation and C-H insertion.[16]

Carbenes with conjugative electron withdrawing functionality are not as electrophilic as might be expected. Those bearing ester groups have been found to be less reactive than their halocarbene analogues, but show a wider range of selectivity in the cyclopropanation of alkenes (Scheme 1.10.a).[15b] Ketocarbenes, on the other hand, frequently undergo Wolff rearrangement to give ketenes (Scheme 1.10.b).[9b, 11b]

			Relative reactivity
1.0	1.0	1.0	
1.4	1.15	1.34	(a)
0.50	0.48	1.47	
2.61		1.35	
	2.08	1.59	
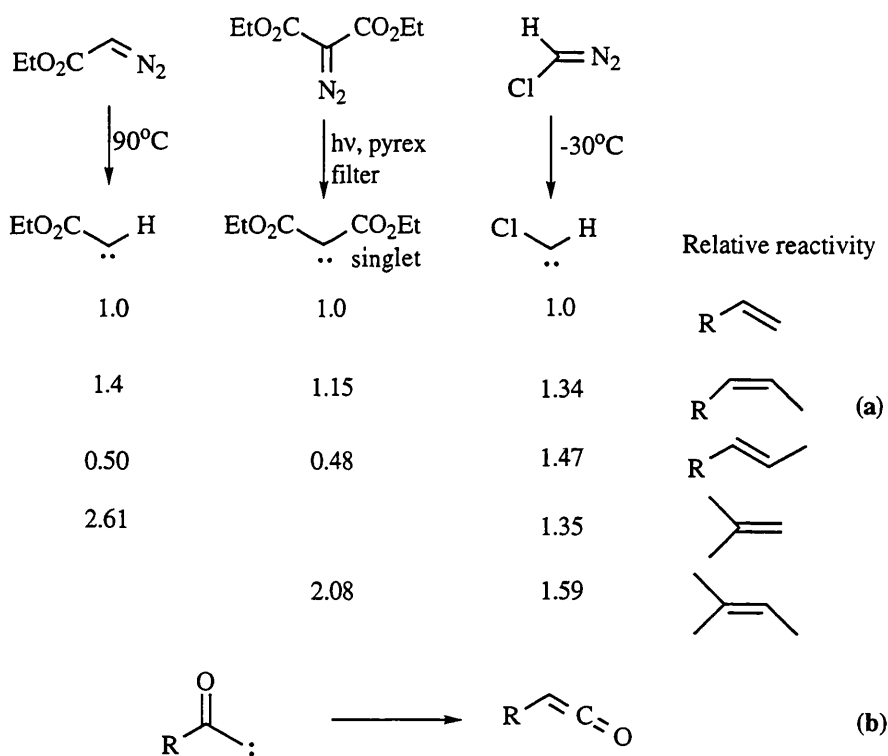
Scheme 1.10

Cyano stabilised carbenes have received little attention and display a contrasting reactivity to their carbonyl stabilised analogues. Dicyanocarbene readily reverts to the triplet ground state even when generated thermally (Scheme 1.11).[17]
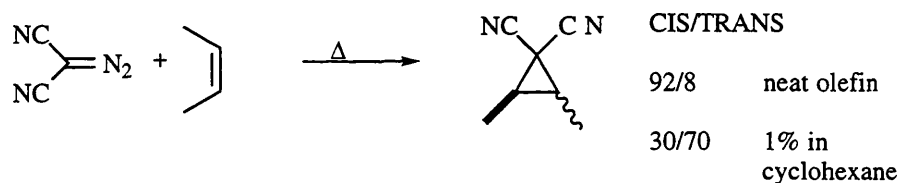
Scheme 1.11

Thus, within free carbene chemistry, the influence the functional groups bound to the carbene carbon plays the dominant role in determining stability and reactivity. The binding of a metal centre to the carbene, however, can alter this range of reactivity as we will see in the following section.

1.3 Transition Metal Carbenoids

1.3.1 General Influences on Metal Carbenoid Reactivity

While the reactions of free carbenes have been well documented, the binding of a metal atom to a carbene will lead to a significant modification of its reactivity, and as we shall see, in certain cases, will give products from pathways that do not occur with the corresponding free carbenes themselves.

The carbene carbon may have two distinct hybridisation modes in a metal carbenoid. In the sp^2 configuration the metal and carbene carbon form a double bond, either covalently or in a donor-acceptor relationship, i.e. $L_nM=CRR'$. In the sp^3 configuration the carbene carbon is bound to both a metal and a leaving group, X, i.e. $L_nM-CRR'X$ and this is often the configuration preferred by most main group metal carbenoids (e.g. M=Li, Al, Si, Sn).[4] This mode of binding is also preferred for the carbenoids of the end d-block metals: zinc and mercury. However, while this configuration is the resting mode, carbenoid reaction may take place *via* the sp^2 form following loss of the leaving group. Such a pattern of reactivity has been observed for iron carbenoids,[18]

and reaction *via* the M=C configuration is the dominant pathway for the transition metal carbenoids described below.

Although many metals have been used to effect methylene transfer reactions such as cyclopropanation, the presence of atoms other than hydrogen on the carbene carbon will significantly modify the reactivity of the resultant carbenoids, much as for the analogous free carbenes. Apart from the nature of the groups bound to the parent carbene carbon, the metal centre of the carbenoid introduces four new influences on the overall carbenoid behaviour. These are (i) the nature of the metal, (ii) the oxidation state of the metal, (iii) the coordinative unsaturation of the metal, (iv) the ligands on the metal. Only the transition metals have the breadth of bonding capability to allow selective variance of all four properties.

Amongst all these influences, oxidation state is dominant. This is particularly well illustrated by the elements of Group 6 (Cr, Mo, W) which form carbenes in both high and low oxidation states. Those where the metal is in a low oxidation state, e.g.$(CO)_5M=CR(OR')$, first described by Fischer in 1964,[19] are sufficiently stable to be chromatographed, and will cyclopropanate electron rich olefins. Their binding is dominated by a donor-acceptor relationship. The high oxidation state analogues, Schrock carbenes, e.g. $(RO)_2X_2W=CH^tBu$, often termed alkylidenes, need to be handled anaerobically, and often undergo ready reaction with electrophiles such as protons and carbonyl groups. They bind in a more covalent linkage, the metal and carbene carbon sharing one electron each in each σ and π bond, and cleave olefins,[20] exchanging the carbene carbon for one of the alkene carbons, a process termed metathesis (Scheme 1.12).

$$L_nM= \quad + \quad R\diagup\!\!=\!\!\diagdown R \quad \longrightarrow \quad L_nM\!=\!\diagdown_R \quad + \quad R\diagdown\!\!\diagup\!\!\diagdown$$
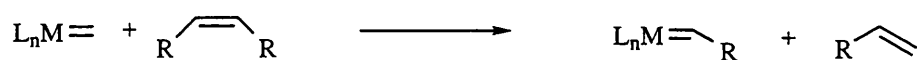
Scheme 1.12

Coupled with these stoichiometric metal carbenoids, a third class of catalytically generated carbenoids exists, which have a very wide range of behaviour, but whose reactivity patterns are close to the reactions of typical free carbenes.

Although the binding of a metal centre to a carbene often introduces a range of extra electrophilic and/or nucleophilic components, the metal-carbene segment of the molecule frequently bears the frontier molecular orbitals. Thus, although the most positively charged carbon of the complex $(CO)_5Cr=CR(OR')$ is one of the carbonyl ligands – (*ab initio* calculations suggest the carbene carbon bears a net negative charge)[21] – the LUMO is localised to a great extent on the carbene carbon,[21, 22] and it reacts as an electrophile. Since the majority of metal carbenoids prepared are those of transition metals, it may be assumed that the relative energy levels of these frontier metal d orbitals and ligand (carbene) p-type (π) orbitals should hold great sway on the resultant character of the metallocarbenoid. A simplified molecular orbital picture is shown in Figure 1.3 below.
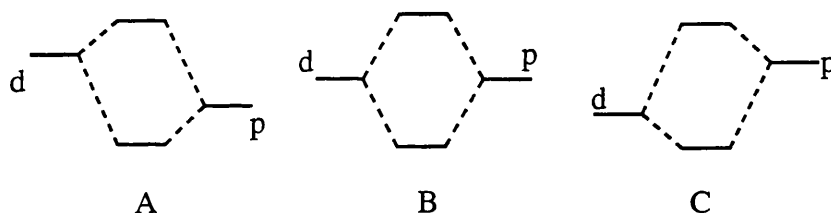
Figure 1.3

In case A the ligand π orbitals are lower in energy and the HOMO has mostly ligand character. The ligand will essentially behave as a closed shell anion and π donor to the metal. The π^* orbitals are principally metal d orbitals and the ligand will act as a nucleophile. This type is uncommon for carbene reactivity.

In case B the p orbital is involved in a covalent bond to the metal d orbital. Here the nucleophilicity of the $\alpha-$ atom on the ligand (the carbene carbon itself) is somewhat reduced as is the electrophilicity of the metal. The LUMO (π^*) has a node between the metal and the ligand, nucleophilic attack on either atom should be possible and electrophiles should attack the bond side-on. This is the common scenario for many Schrock-type alkylidenes.

In case C the metal d orbitals act as π donors to the ligand and the LUMO is located principally on the ligand. The ligand should therefore be susceptible to nucleophilic attack in much the same manner as for a simple carbene. Thus, again, the ligands on the carbene

can have a substantial effect on the overall carbenoid character and the HOMO/LUMO energy balance.

1.3.2 Fischer Carbenes

The stoichiometric low oxidation state metal carbenes, or Fischer-type, carbenes are generally prepared *via* three distinct routes.[23] The first, addition of an organolithium reagent to transition metal carbonyls, followed by alkylation of the resulting alkoxide, was the original route used by Fischer (Scheme 1.13.a).[19] The alkoxy group may be subsequently displaced by heteroatom nucleophiles. Reaction with hydride or further organolithium reagents gives a metal alkyl. Direct loss of the leaving group, with or without prior activation, gives a metal stabilised carbocation (Scheme 1.13.b), a resonance form of the carbene with backbonding from the metal. The third route is the reaction of an alkenyl metal or metal acyl complex with an electrophile, usually a proton source or hard alkylating agent (Scheme 1.13.c). Routes (a) and (b) are the standard routes to carbenes from group 6, while routes (b) and (c) are used to generate the cationic iron carbene complexes.
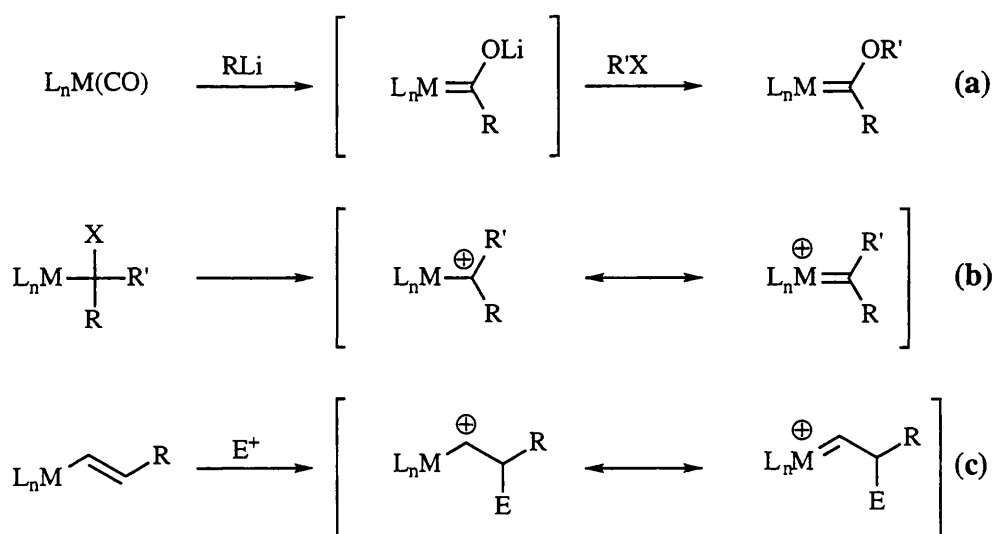
Scheme 1.13

Ligands on the carbene

The behaviour of simple alkyl transition metal carbene complexes is very similar to their free carbene analogues. Such species frequently undergo intramolecular C-H insertion, almost exclusively α-C-H insertion. However, some notable exceptions exist, primarily for the cationic iron carbene complexes $[Cp(CO)LFe=CRR']^+$ (L= CO, PPh$_3$).[24] These highly electrophilic carbenoids display distinct chemoselectivity in alkene cyclopropanation,[25] yet an ethylidene moiety can be transferred at room temperature.[26] Higher homologues decompose much more readily: the propylidene complex (**8**) has a half life of one hour at -40°C (Scheme 1.14.a).[27] However good yields in cyclopropanation can be obtained in the intramolecular reaction of higher homologues (Scheme 1.14.b).[28]

The dimethyl carbenoid, however, is more stable than the monosubstituted carbenes, but the increased bulk and decreased electrophilicity inhibit reaction to such an extent that hydride migration is still a competitive side reaction.[29]
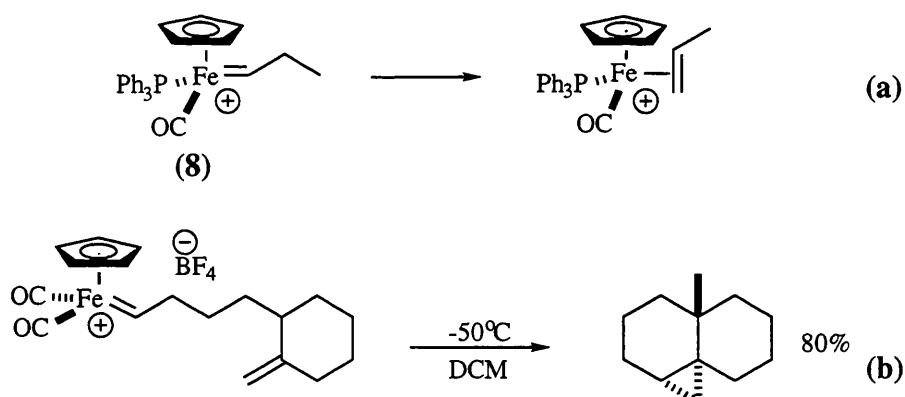
Scheme 1.14

Conjugation of metallocarbenoids with heteroatom lone pairs or other π systems has also been used to modify the reaction of metallocarbenoids. The reactions and stabilities of a series of substituted tungsten carbenes $(CO)_5W=CRR'$ is indicative of the relative stabilities that each of these groups imparts. The first stable metal-carbene complexes to be prepared were $(CO)_5M=CR(OMe)$, $(R=Me, Ph; M=Cr, Mo, W)$ by Fischer in 1964, and they are stable to chromatography.[19] These will only undergo reaction with electron rich or poor alkenes above ambient temperature, and are stable to decomposition up to 130°C (Scheme 1.15.a).[30] $(CO)_5W=C(Ph)_2$ will not react with alkenes below 40°C but will cyclopropanate simple 'neutral' alkenes (Scheme 1.15.b).[31] The complex bearing only one phenyl carbene ligand is highly reactive and cyclopropanates a wide range of neutral and electron rich alkenes, even at -78°C, but undergoes thermal decomposition above -55°C (Scheme 1.15.c).[32] The analogous iron carbenoid $[Cp(CO)_2Fe=CHPh]^+PF_6^-$ can be isolated as a stable crystalline solid, although it is more reactive towards alkenes, and gives greater stereoselection in cyclopropanation reactions. [33]

$$(OC)_5W = \underset{OMe}{\overset{Ph}{<}} \quad + \quad EtO \diagdown\!\!\!\diagdown \quad \xrightarrow[50°C]{100 \text{ atm. CO,}} \quad \underset{OEt}{\overset{Ph \quad OMe}{\times}} \quad \textbf{(a)}$$

$$(OC)_5W = \underset{Ph}{\overset{Ph}{<}} \quad + \quad EtO \diagdown\!\!\!\diagdown \quad \xrightarrow{37°C, 3 \text{ hr}} \quad \underset{OEt}{\overset{Ph \quad Ph}{\times}} \quad \textbf{(b)}$$

$$(OC)_5W = \underset{H}{\overset{Ph}{<}} \quad + \quad \diagup\!\!\!\diagup \quad \xrightarrow{-78°C} \quad \overset{Ph}{\underset{Me}{\triangle}} \quad \textbf{(c)}$$
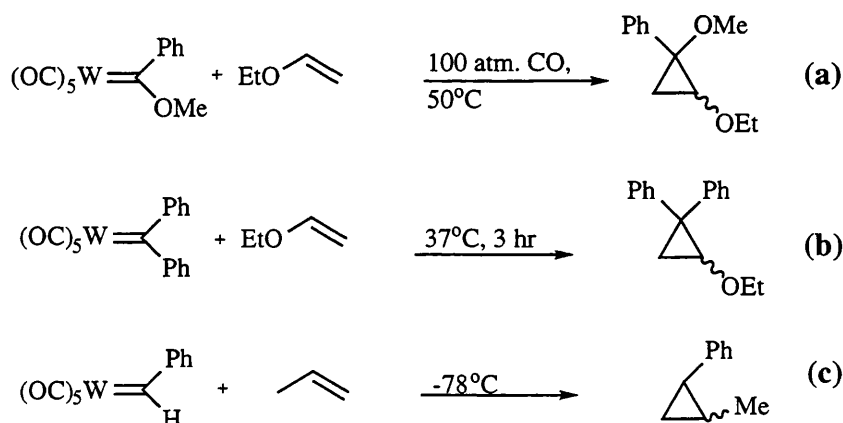
Scheme 1.15

Coordinative Unsaturation

The presence of vacant coordination sites on a metal carbenoid can have significant effects on the reactivity, allowing selective substrate binding or opening up pathways to decomposition. A spectacular case occurs in the reaction of the Fischer carbenes $(CO)_5M=CPh(OMe)$, (M=Cr, Mo, W) with olefins. The reaction of these carbenes with electron rich olefins to give cyclopropanes only takes place under high carbon monoxide pressure, while at atmospheric pressure metathesis occurs (Scheme 1.16.a).[30] It seems even more surprising then that electron deficient alkenes should give cyclopropanes at slightly higher temperatures but at atmospheric pressure.[30b] The electron deficient olefins, good π acids, bind to the vacant coordination site left by a departing carbon monoxide ligand. The olefin orbitals are ideally aligned to form a metallacyclobutane and reductive elimination of the metal gives a cyclopropane. A reverse [2+2] cycloaddition (olefin scission) would yield either the starting olefin-carbene complex, or a new olefin-carbene complex with a higher energy electron deficient carbene (Scheme 1.16.b).[30b] Simple neutral alkenes, inert under normal conditions, will form cyclopropanes when the olefin is tethered to the carbene (Scheme 1.16.c).[34]

(CO)₅Cr with Ph, OMe + EtO—

neat, 33°C,
3 hr, 46%

neat, 50°C, 65 hr,
100 atm. CO, 61%

0	:	0	:	100
76	:	24	:	0

(a)

(CO)₅Cr with Ph, OMe + _/_CO₂Me neat, 90°C, 3 hr, 60%

29 : 71

(b)

(CO)₅W = ⟶ 70°C, -CO ⟶ (CO)₄W = ⟶

85-95%

(c)
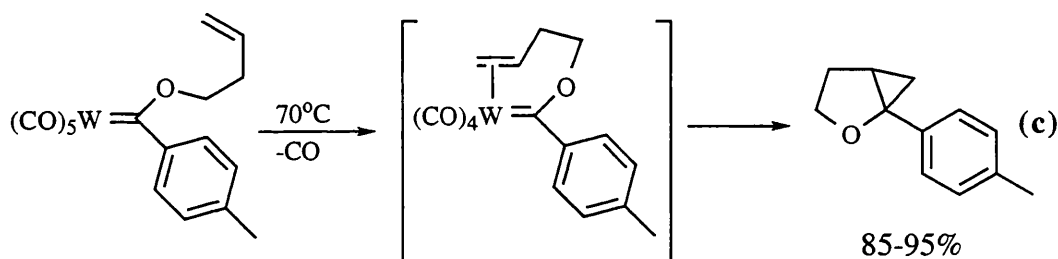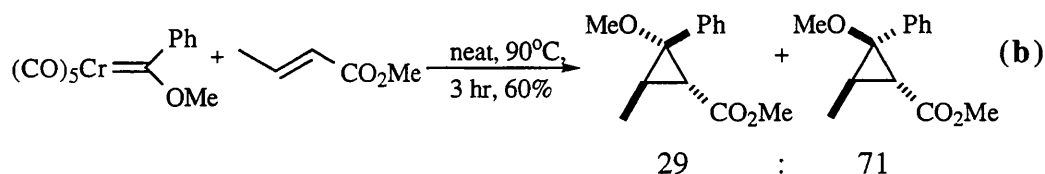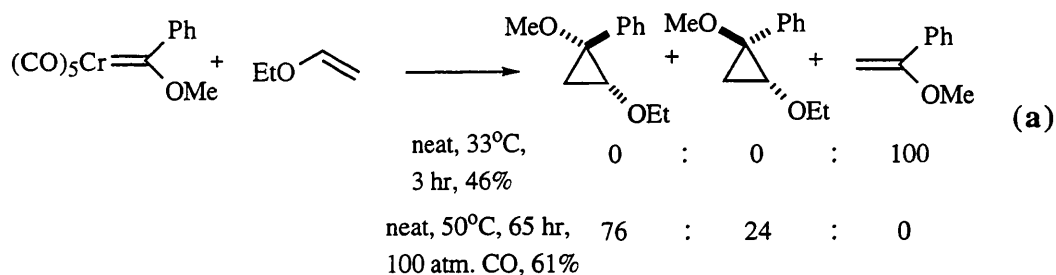
Scheme 1.16

1.3.3 Schrock carbenes

A wide variety of synthetic routes are available for the formation of high oxidation state transition metal alkylidenes, but the most important fall into five categories.[23a, 35] The first is the elimination of an alkyl ligand due to excessive steric crowding around the metal (Scheme 1.17.a). This pathway is often spontaneous for poly-alkyl metals, and is the route by which the first of these high oxidation state alkylidenes was discovered by Schrock. The addition of strongly coordinating trialkyl phosphines has also been used to promote this pathway. The second is base induced α-elimination, by removal of HX from the complex (Scheme 1.17.b). The third method is protonation of an alkylidyne complex with possible rearrangement, or loss of a heteroatomic ligand (Scheme 1.17.c). The counterion may also bind to the metal. The fourth route is the donation of the carbene ligand from

another complex, frequently a phosphorane (Scheme 1.17.d). A fifth, and rather versatile

route, is metathesis with a previously prepared stable alkylidene ligand (Scheme 1.17.e).
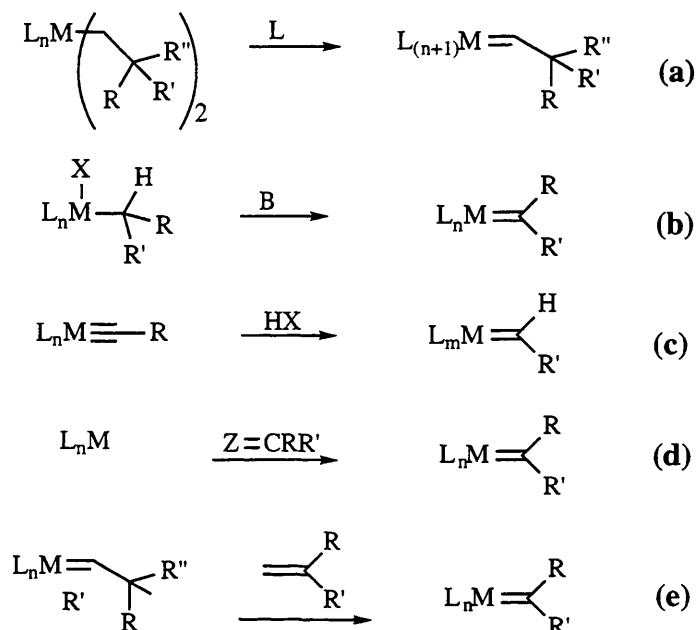
Scheme 1.17

Nature of the metal

Differences in descending a group can have drastic influences on essentially similar

complexes. Higher homologues of the "Tebbe-Grubbs" methylidenation reagent are

unstable,[36] and decompose readily by β-hydride elimination. However, the zirconium

analogue functions as an efficient alkylidene transfer reagent,[36b, 37] although higher

temperatures are required to effect reaction (Scheme 1.18).[36a, 37a]
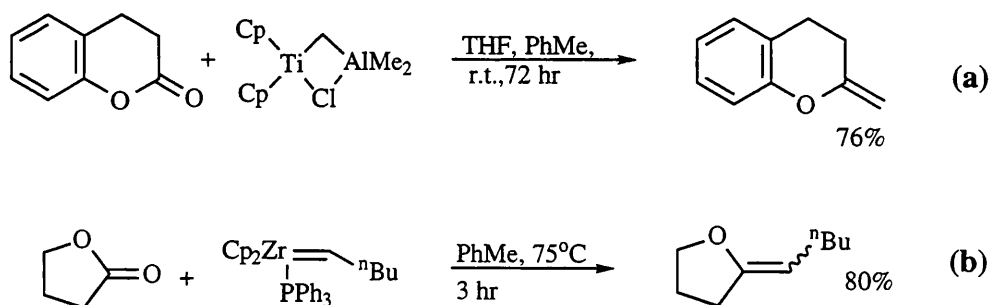
Scheme 1.18

A similar difference in reactivity occurs on changing the metal centre from molybdenum to tungsten in $((F_3C)_2MeCO)_2.(NAr).M=C(H)tBu$, when comparing their reaction with alkenes. While both are effective catalysts for olefin metathesis, the molybdenum analogue may be used in the presence of diverse organic functionality including ethers, acetals, and carbonyl compounds,[38] while the more Lewis acidic tungsten analogue is rendered inactive by reaction with a variety of commonly encountered functional groups.[39] Of significant interest to the organic chemist is that these catalysts will metathesise α,ω diolefins to give good yields of medium ring cycloalkenes. A recent example by Martin was the construction of an eight membered ring in his route towards Manzamine A (Scheme 1.19).[40]
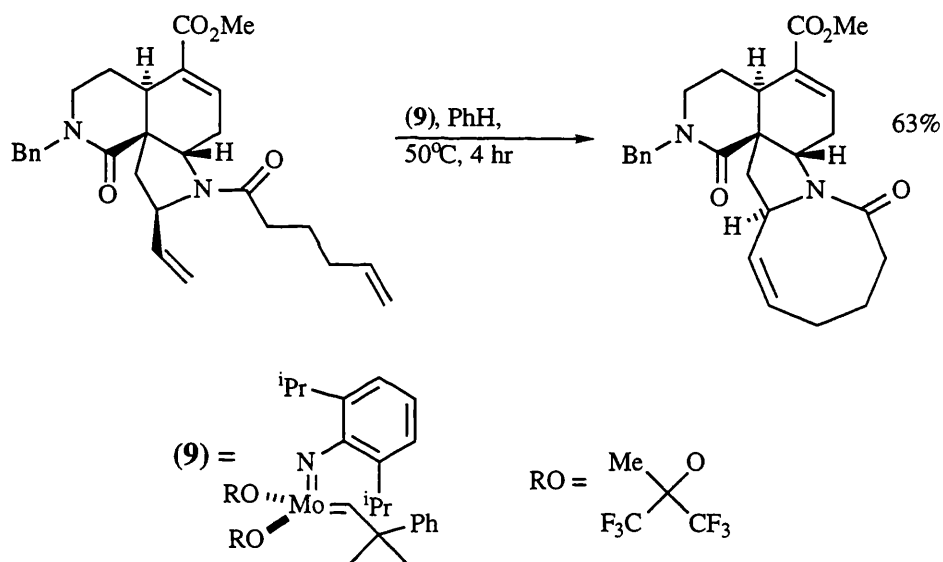
Scheme 1.19

Coordinative unsaturation

The reactivity of Schrock carbenes in metathesis reactions relies on the presence of a vacant coordination site. Blocking this coordination site will not only render the alkylidene inactive, but can also block pathways of decomposition. Alkyl substituted alkylidenes are frequently susceptible to β-hydride elimination, but blocking of the vacant coordination site of the tungsten complex (10) allowed isolation and characterisation of (11) as shown in Scheme 1.20.[41]

(10)   (11)
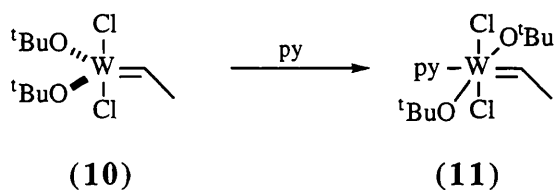
Scheme 1.20

Ligands on the metal

Subtle changes in ligands on many Schrock alkylidenes can have drastic effects on their reactivity. For the pentavalent tungsten alkylidenes (12), the reactivity of the complex decreases with decreasing π electron donating ability of the axial ligands X (Scheme 1.21).[42] NMR studies of similar complexes, $(NpO)_2X_2W=CH^tBu$, also indicate that the positive character of the alkylidene carbon increases in the same order.[43]

(12)

X =	time/ hr	yield %
NpO	0.17	82
Cl	1	90
Br	2.5	95
I	30	95
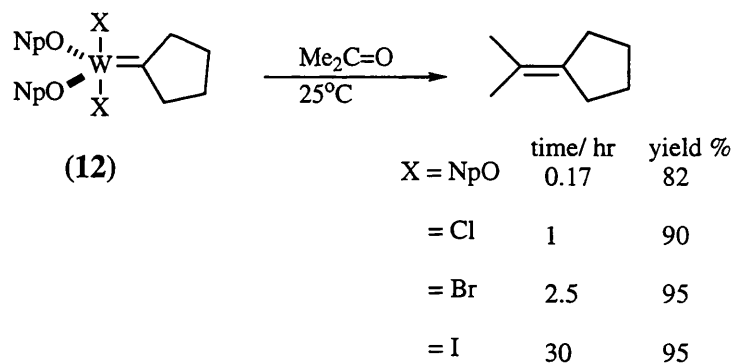
Scheme 1.21

Similarly, subtle, and not so subtle, changes to the original Schrock catalysts (13),[44] and (14),[45] have increased the scope and reactivity of subsequent metathesis

catalysts. Although the very early Schrock metathesis catalysts were effective for ring opening metathesis of strained cyclic alkenes, they showed poor catalytic profiles with simple acyclic and unstrained alkenes. The replacement of the alkyl and cyclopentadienyl ligands with π donating halogens gave catalysts (15) that would react with simple alkenes, but gave only tail to tail dimerisation (Scheme 1.22).[46] Replacement of the Cp* ligand with an imido ligand favours the formation of the metallacyclobutane from the alkylidene-olefin complex as the imido function becomes triply bound, overlapping with the vacant d orbital. Use of harder alkoxide, and the even harder perfluoroalkoxide ligands, gives a more electrophilic metal centre increasing the binding favourability of alkenes.[47] Collecting all these factors together, and satisfying metal valence criteria gives the very efficient Grubbs metathesis catalysts (16) in Scheme 1.22 below,[48] which will react with a wide range of olefins rapidly at room temperature, and are Lewis acid free.
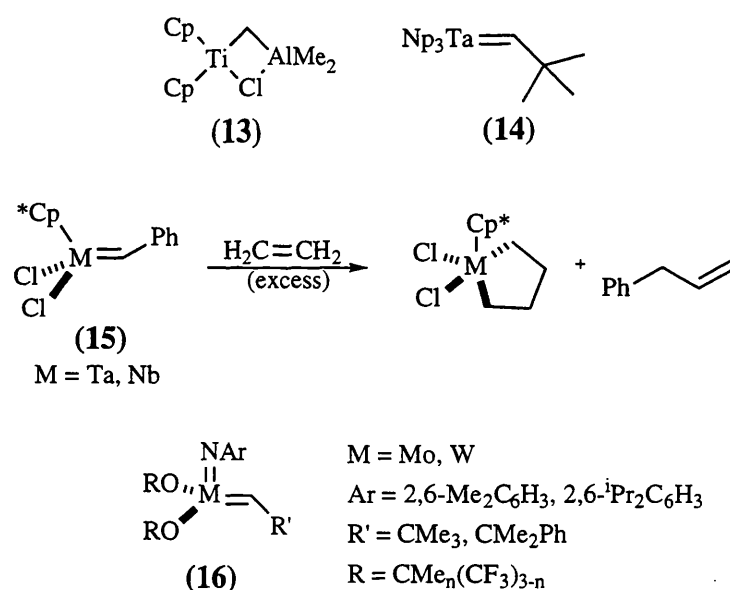
Scheme 1.22

1.3.4 Carbenoids as Catalytically Generated Intermediates

The primary route to catalytically generated transition metal carbenoids is *via* transfer from diazo compounds. The catalytic cycle is believed to take place *via*

nucleophilic attack on the electrophilic metal centre, and generates the carbenoid (**17**) with extrusion of nitrogen. A wide variety of metal complexes have been used as the catalytic Lewis acid in this process.[49] Transfer of the carbenoid moiety to an electron rich substrate regenerates the Lewis acid, and completes the catalytic cycle (Scheme 1.23). Due to their easier preparation and stability, conjugated diazo compounds, especially α-diazocarbonyl compounds, are the most amenable to synthetic use. Simple alkyl diazo compounds are significantly less stable, and undergo preferential polymerisation or dimerisation in the presence of metal catalysts. The unsuitability of diazo compounds in some cases has lead to the investigation of the use of other ylides, e.g. iodonium ylides $RI=CR^1R^2$, as carbene precursors.[50]

R   R

L_nM $L_nM=CR_2$
                    (**17**)

$R_2C=N_2$ N_2

$L_n\overset{\ominus}{M}-CR_2$
$\underset{N_2\oplus}{|}$
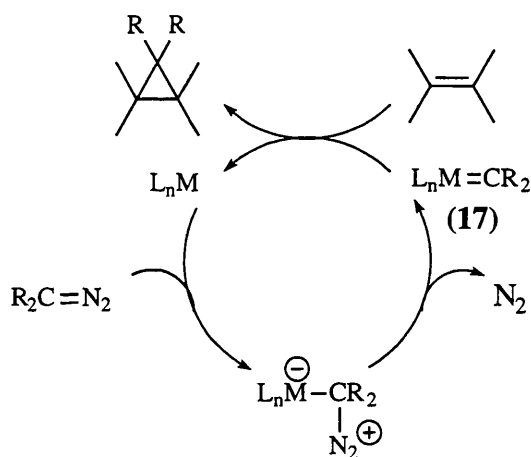
Scheme 1.23

The 'catalytic carbenes' show a range of reactivity similar to their free carbene counterparts in reactions such as cyclopropanation, ylide formation, and insertion into C-H bonds (with a preference for forming five membered rings), and other X-H bonds,[51] but more importantly show much higher chemo-, regio-, and stereoselectivities. The most important metal catalysts are based on soluble copper salts and dirhodium carboxylates.

Ligands on the carbene

The presence of electron withdrawing groups on metallocarbenoids is usually only observed for the carbenoids formed by transfer from diazo species. Alkyl ligands may

suffer the same fate as free carbenes, i.e. α–C-H insertion. For rhodium and copper carbenoids substituted with both an alkyl, and an electron withdrawing keto or ester group, insertion into an α–C-H bond has been observed to take place at rates comparable to other intramolecular reactions. Notably in the case of the rhodium carbenoids insertion gives only the *cis* alkene,[52] with selectivity dependent on the electrophilicity of the metal (Scheme 1.24).[52b] The *cis* selectivity is postulated to arise from preferential migration of the α-hydrogen, H_A, (18) in the same manner as for free carbene rearrangements (Scheme 1.24).[53]

L= OPiv	85	:	15	97%
= OBz	78	:	22	88%
= tfa	66	:	34	93%
= OAc	52	:	48	92%

(18)
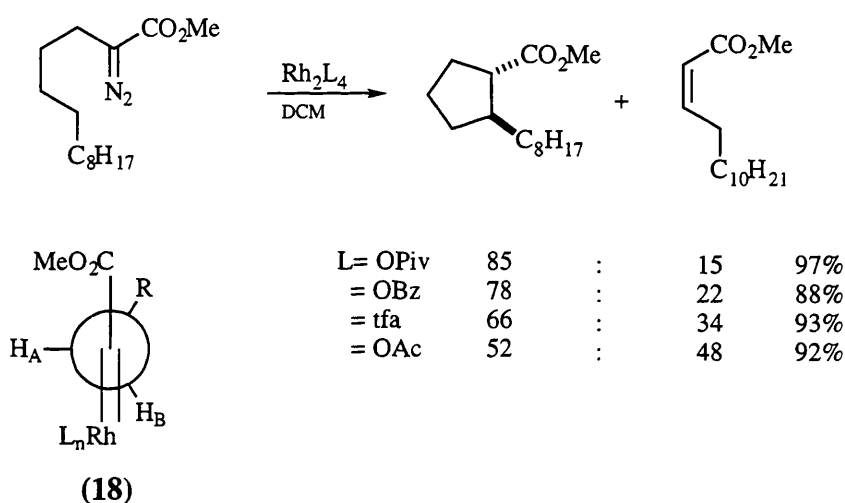
Scheme 1.24 ---

The presence of even two electron withdrawing groups on the carbenoid is common for the species generated using rhodium acetate (Scheme 1.25).[54] The more electron deficient carbenoid (Y = CO_2Et) shows a distinct preference for capture of the lone pairs on the bromine to give the alkene *via* an ylide rearrangement.

Y = H	76%	28 : 72
Y = CO$_2$Et	92%	93 : 7
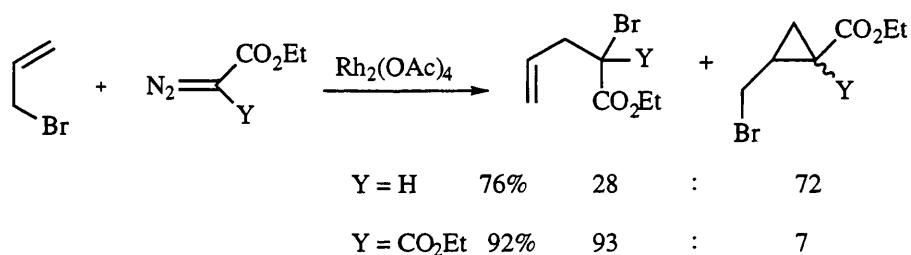
Scheme 1.25

In some cases ligands on a metal carbenoid are stabilised relative to their free carbene counterparts. Free vinyl carbenes do not normally undergo intermolecular reaction, but cyclise to cyclopropenes (*vide supra*). However a propylidene moiety can be transferred to alkenes from vinyl diazomethane using copper catalysis (Scheme 1.26).[55]
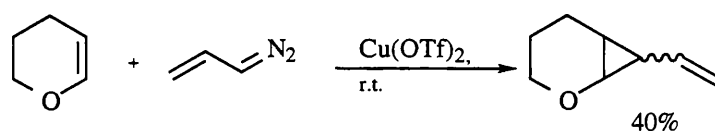
Scheme 1.26

Nature of the metal

Tight correlation of reaction with identical substrates is rare between elements on opposite sides of the transition series. However a mechanistic study by Doyle *et al.* showed that for both an electron donating and an electron withdrawing carbene ligand, the correlation of *cis/trans* cyclopropane isomer ratios was constant for a wide range of electron rich and neutral alkenes.[56] He suggested that for both metal centres in (CO)$_5$W and Rh$_2$(OAc)$_4$, the carbene was bound to the metal embedded in a wall of ligands (Figure 1.4), and that the isomer ratios were dependent on the relative electrophilicities of the metal centres.

M

CR$_2$
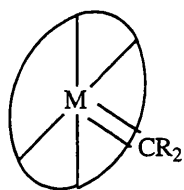
Figure 1.4

A startling difference in reactivity can be seen in the products of the reaction of the carbene derived from ethyl diazoacetate when treated with the low-valent catalysts Rh$_2$(OAc)$_4$, Pd(OAc)$_2$, and CuOTf,[49] compared to the harder Lewis acids BF$_3$, SnCl$_2$ and SnCl$_4$,[57] and ZrCl$_4$.[58] The former group prefer to transfer the carbene to electron rich groupings such as C=C double bonds to give cyclopropanes, heteroatoms to give ylides, and C-H insertion in electron rich C-H bonds. The latter group, on the other hand, transfer the carboethoxy carbene moiety with good selectivity to the very electron deficient C-H bond of aldehydes. This sequence was used to good effect in the endgame of the first reported synthesis of Tetronasin, in the presence of a multitude of other carbenophilic functionality (Scheme 1.27).[58a]
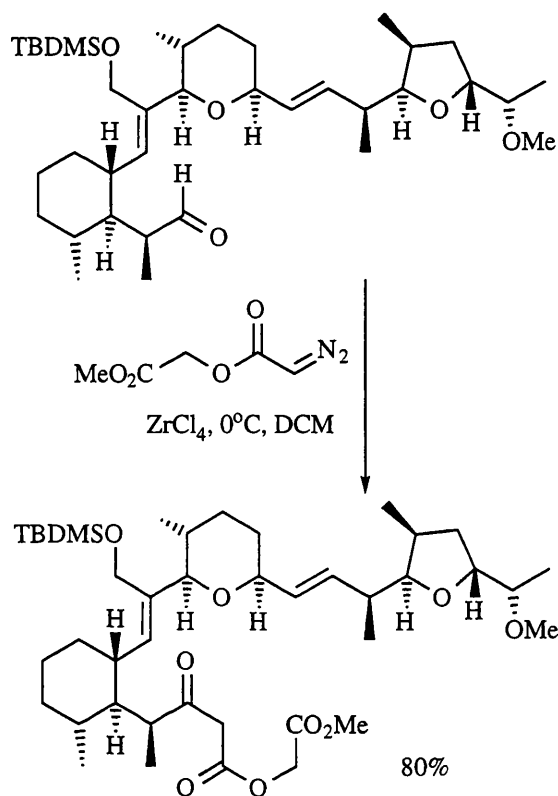
Scheme 1.27

Coordinative unsaturation

A comparative study of the reactivity of a series of olefins in cyclopropanation reactions of ethyl diazoacetate with $Cu(OTf)_2$ showed that the olefin selectivities were dependent on the relative molar ratios of the starting olefin (Scheme 1.28).[56] Selective binding of particular olefins to the metal was occurring prior to cyclopropanation. Hoewver, the *cis/trans* ratios remained constant, and bore a linear relationship to a number of other metal catalysts which have only one binding site per metal atom: $Rh_2(OAc)_4$, $(CO)_5W$, $CuCl.P(O^iPr)_3$.[56] Some palladium reagents, e.g. $Pd(OAc)_2$ but not $PdCl_2.PhCN_2$ will also show this olefin selectivity.[49b]

37
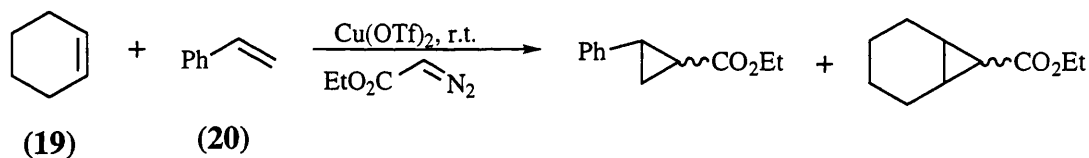
	(19)/(20)		
	0.25	1.6	:	1
	2.0	3.3	:	1

Scheme 1.28

Ligands on the metal

Since the discovery of rhodium and copper catalysed alkylidene transfer from diazoalkanes, much effort has been directed towards discovery of the factors governing selectivity induced by the ligands round the metal. Although rhodium catalysts have been known for over 20 years, it is only in the last two years that a fully comprehensive study of ligand effects has been published.[51c] The selectivities of various reaction types were shown to be governed both by charge localisation, and the frontier molecular orbitals. Calculations on $RhL_4Rh=CH_2$ showed that the charge localisations for acetate and acetimidate are very similar, while extended Hückel calculations show the frontier molecular orbital energies are almost identical for acetate and trifluoroacetate. Thus in terms of functional group selectivity acetate frequently rests between perfluorobutyrate and caproate (Scheme 1.29).[51c]

L = pfb	0	:	100	56%
= OAc	44	:	56	97%
= cap	100	:	0	76%
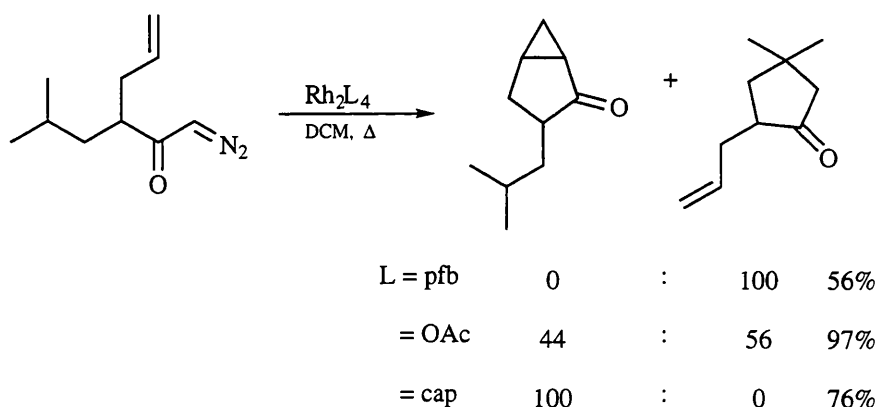
Scheme 1.29

1.4 Formation and Reactions of Organozinc Carbenoids

Before proceeding to summarise the work already carried out within our own group in this area (*vide infra*), it is appropriate to mention other studies relating to the generation, structure and uses of zinc carbenoids.

Although zinc is located at the end of the d-block metals, its carbenoids bear many similarities in behaviour to those of other transition metal carbenoids. The behaviour of organozinc carbenoids has been noted since the introduction of the Clemmensen reduction,[59] but their identity went largely unnoticed until the discovery of the Simmons-Smith reaction.[60] These transient organozinc carbenoids are most frequently prepared from *gem*-dihalo compounds, although diazo compounds have also been used (*vide infra*).

1.4.1 Zinc Carbenoids from *Gem*-Dihalo and Diazo Compounds

The formation of cyclopropanes by methylene transfer to alkenes is among the most well-known uses of zinc compounds in organic synthesis. The method of formation of such Simmons-Smith reagents may be divided into three general classes:

(i)   Oxidative addition of an α,α-dihaloalkyl to zinc metal (the original Simmons-Smith procedure).[60, 61]

(ii) The addition of a diazoalkane to a Zn(II) salt, first reported by Wittig.[62]

(iii) A metal-halogen exchange between an alkylzinc and an α,α-dihaloalkane, a procedure commonly referred to as the Furukawa modification.[63]

Type (i) addition is the most commonly used procedure, originally employing a zinc-copper couple, generating the carbenoid in the presence of an alkene in an ethereal solvent (Scheme 1.30).[60a]

CH₂I₂, Zn/Cu,
Et₂O, reflux

86-92%
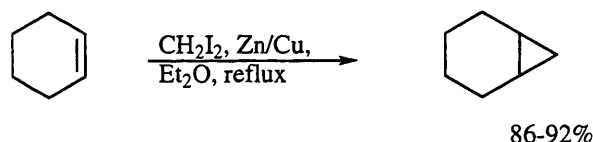
Scheme 1.30

In the first instance, the reaction suffered from poor reproducibility in the hands of other workers, and modifications in the preparation of activated zinc couples such as those of copper[64] and silver[65] soon followed. More recently, further methods have been introduced for the activation of the zinc *in situ*, including the use of $Zn/TiCl_4/CH_2I_2$,[66] $Zn/AcCl/CuCl/CH_2I_2$,[67] and $Zn/TMSCl/CH_2I_2$.[68]

Sonication of the reaction,[69] and electrochemical processes[70] have allowed the replacement of CH_2I_2 with the cheaper and more stable CH_2Br_2 (Scheme 1.31).[69, 70]

i) or
ii)

i) Zn/Cu, Et₂O,))) , 72%
ii) Zn anode, 40°C, I = 200mA, 9:1 DCM:DMF, 64%
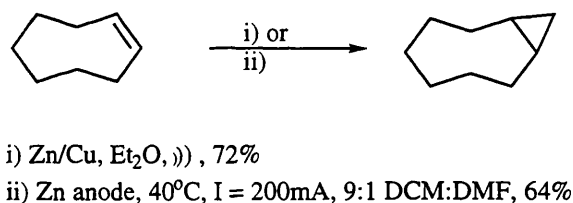
Scheme 1.31

Type (ii) generation from diazoalkanes has received little attention, especially since the introduction of soluble rhodium and copper salts for the catalytic formation of these carbenoids. The diazoalkane is added to an ethereal solution of the Zn(II) salt: [$ZnCl_2$, $ZnBr_2$, ZnI_2 or $Zn(OBz)_2$] and the alkene at room temperature or below.[62, 71] Studies on this process have given much information on the factors influencing the electrophilicity and behaviour of organozinc carbenoids. Thus phenyldiazomethane gives a homogeneous carbenoid when added to zinc chloride in ether, which rapidly cyclopropanates simple olefins with preferential formation of the more hindered *syn* or *endo* isomer (Scheme 1.32).[71a]
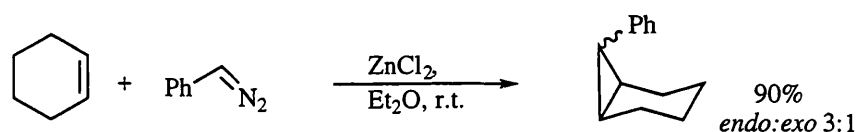
Scheme 1.32

Type (iii) generation involved the addition of diethylzinc to a diiodo-[63, 72] or haloiodoalkane,[73] and was first reported by Furukawa. This method has offered the greatest practical advance in the Simmons-Smith reaction, allowing generation of the carbenoid in a variety of solvents,[74] and without any of the reproducibility problems associated with the heterogeneous reaction. Recent work on this reaction system by Denmark *et al.* has shown that the reaction occurs cleanly and most rapidly when carried out in polar non-coordinating solvents,[74] such as 1,2 dichloroethane (DCE), and that ethereal solvents lead to a significant decrease in the rate of cyclopropanation due, they argued, to saturation of the vacant d orbitals on zinc.[75] Another interesting feature of this study is the far greater reactivity of the chloro-substituted zinc carbenoid over its iodo congener.

Although an ethylidene zinc carbenoid has been used to cyclopropanate olefins with modest stereoselectivity (Scheme 1.33.a),[72a,b] higher homologues are unstable and give products typical of the decomposition of the analogous free carbenes (Scheme 1.33.b),[76] but with a much higher selectivity for the products of α-C-H insertion.
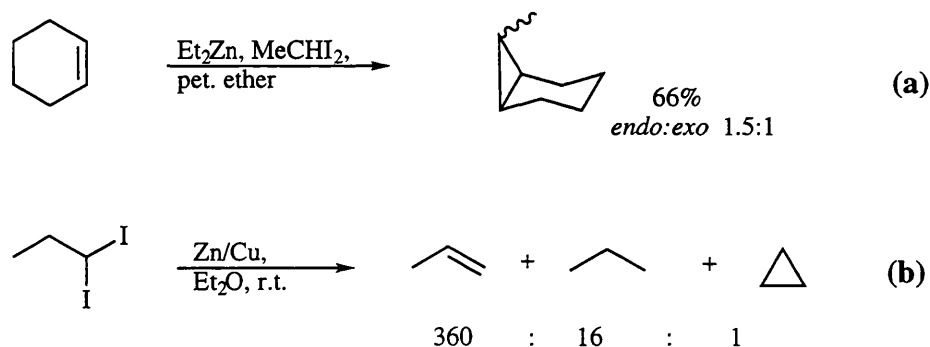
Scheme 1.33

Conjugation to an adjacent π system, such as a carbonyl group[77] or an aromatic

41

ring,[71, 72c, d] gives carbenoids which are still sufficiently reactive to cyclopropanate

alkenes in much the same manner as the catalytic rhodium and copper carbenoids (Scheme

1.34).[71a, 77a]

X = Y = Br, I
X = Br, Y = I

Zn, Δ
DME

20-45%

ZnI₂,
Et₂O, r.t.

60%
syn:anti 21:1
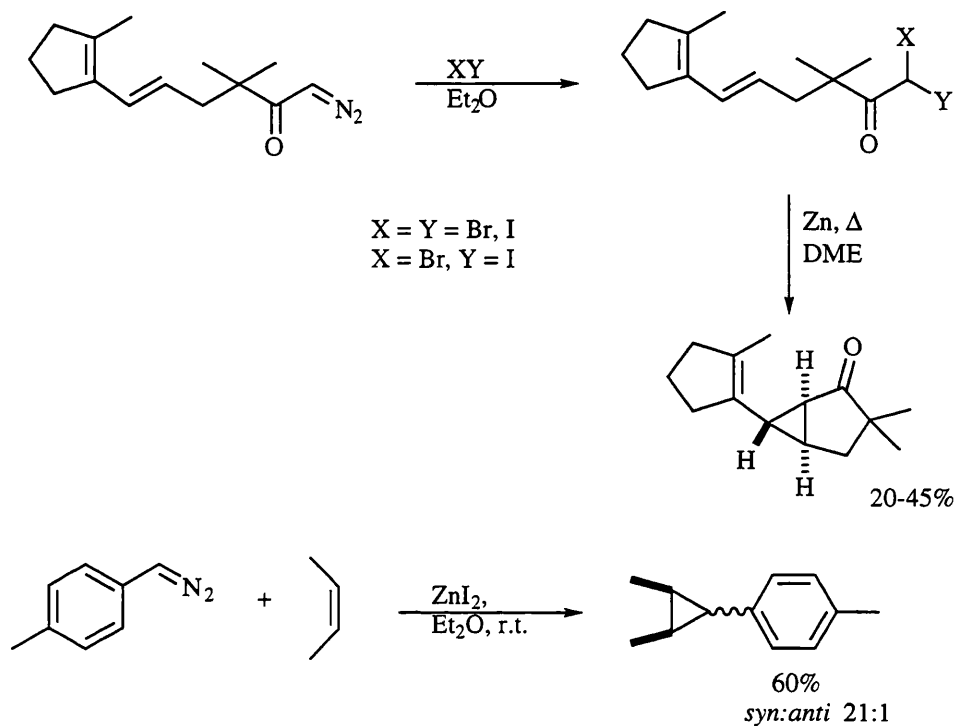
Scheme 1.34

While zinc carbenoids are primarily known as cyclopropanation agents, they will

react with other heteroatomic functionalities in certain cases.[78] A study by Cohen *et al.*

showed that cyclopropanation by the Simmons-Smith reagent was inhibited in the presence

of thioethers.[78a] Reaction with allyl thioethers instead takes place on sulfur generating an

ylide which subsequently rearranges to the homologated thioether (Scheme 1.35).[78a]
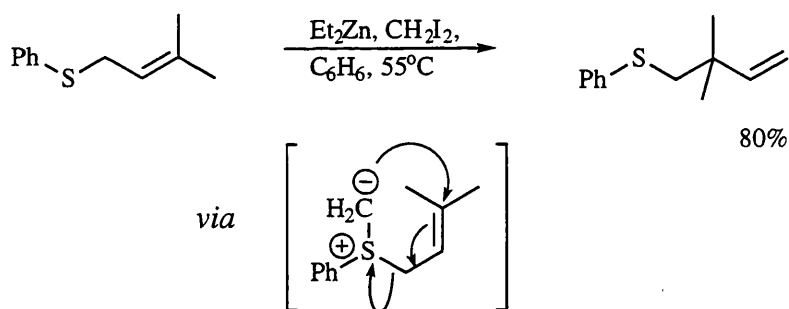
Scheme 1.35

Such ylide chemistry has not been observed for oxonium ylides with zinc carbenoids, presumably due to the tighter lone pairs on oxygen. Instead complexation of the zinc has allowed the use of ethers and alcohols as directing groups. Indeed, the directing effect of ethers and alcohols has long been recognised, primarily for allylic,[79] and to a lesser extent, homoallylic[80] oxygen functionality. The effect is strongest for allylic alcohols, and diastereoselective delivery of the alkylidene group takes place on the same face as the hydroxy group. For substrates with more than one alkene unit, regioselective delivery of the alkylidene occurs on the alkene with an allylic hydroxy group in preference to isolated double bonds (Scheme 1.36).[81]
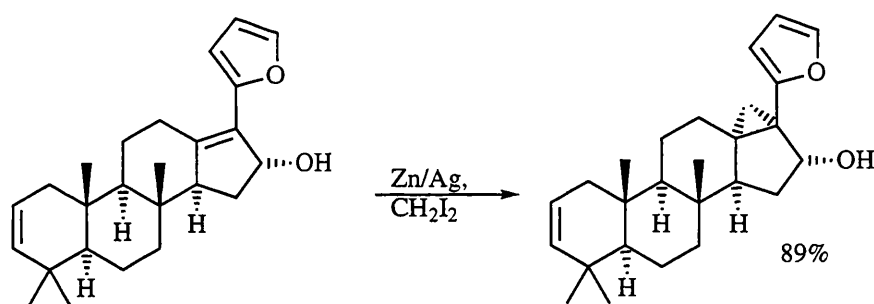
Scheme 1.36

This effect has been used to prepare chiral cyclopropanes through the use of oxygenated chiral auxiliaries as anchors for the carbenoid (Scheme 1.37).[82]
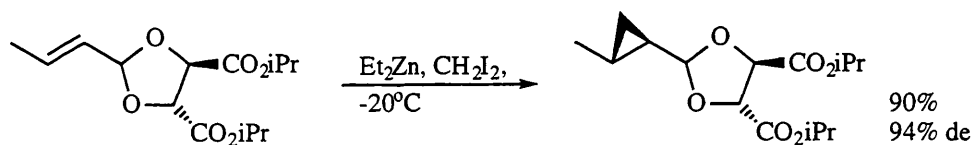
Scheme 1.37

In a recent report, prochiral allylic alcohols have been cyclopropanated directly in the presence of a catalytic amount of a disulfonamide ligand (Scheme 1.38).[83] Asymmetric induction is believed to occur *via* a trimolecular complex, wherein the zinc chelated by the sulfonamide ligand binds to both the allylic oxygen, and the iodine atom of the iodomethylzinc moiety.
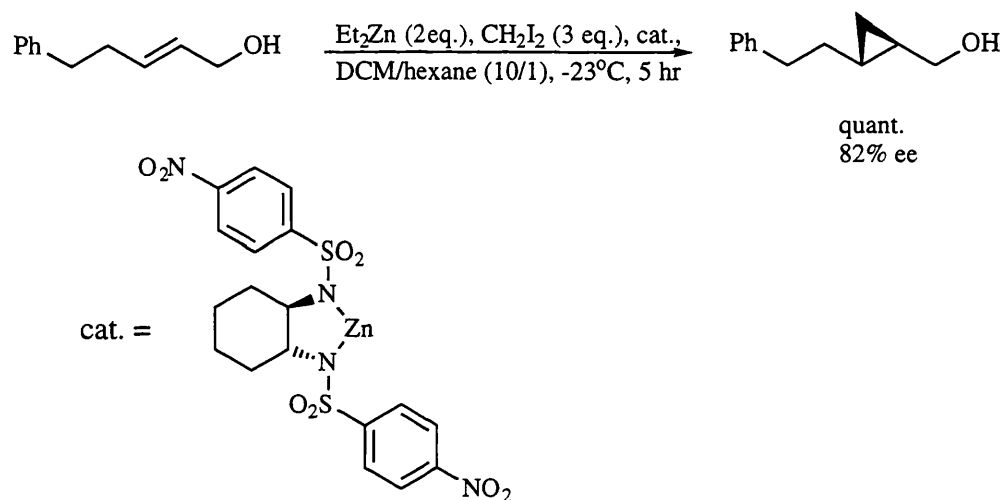
Scheme 1.38

1.4.2 Zinc Carbenoids from Carbonyl Compounds

Although diazo compounds and α,α-dihaloalkanes have been used to prepare organozinc carbenoids, the intermediacy of the species first occurred under Clemmensen reduction conditions at low proton concentration.[59] The resultant conversion of a ketone to an alkene, however, went largely unnoticed for some forty years.

Carbonyl compounds would, of course, be ideal starting materials for

metallocarbenoids. The delivery of two electrons from a metal, or metal complex M, and the addition of two equivalents of an electrophilic reagent (E^+Y^-) would give a metallocarbenoid intermediate (21). Further transformation of the metallocarbenoid may take place *via* the loss of the leaving group E_2O and/or capture of the anion Y^- (Scheme 1.39).
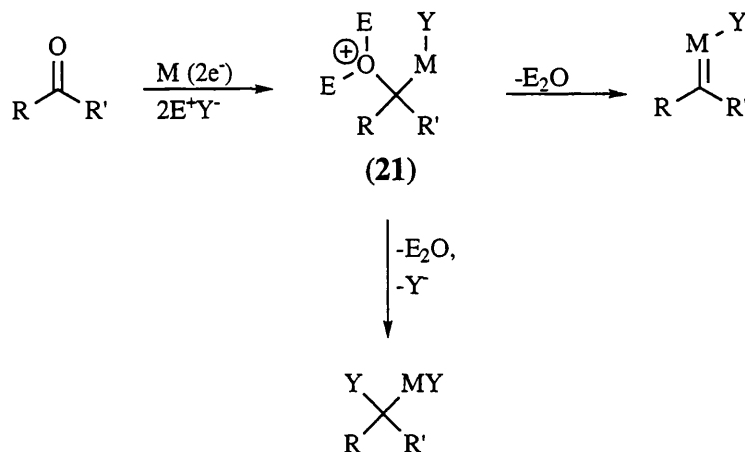
Scheme 1.39

In early work Clemmensen had noted that reduction of acetophenone in dilute acid gave styrene rather than ethyl benzene. However, the possible intermediacy of a carbenoid was not inferred and the alkene was thought to have arisen *via* elimination of the alcohol PhCH(OH)Me in the acidic media.[84] In contrast to other dissolving metal reductions in protic media, alcohols are not important intermediates.[85] One of the first detailed early studies by Brewster *et al.* proposed that the reduction of the carbonyl group took place after 'chemisorption' of the aldehyde or ketone on the zinc surface by delivery of two electrons and capture of chloride ion by zinc.[86] The resultant alkoxide was then rapidly protonated to give the intermediate (22). Experimental and kinetic data of later work by Nakabayashi[85] supported this proposal, the rate determining step requiring zinc, chloride ion and the carbonyl group. Further protonation of the alcohol and elimination of water gives a zinc-stabilised carbonium ion (23), an intermediate which may also be represented as a zinc carbenoid. Further protonation of the C-Zn bond and reduction of the carbonium ion will give the methylene compound (24) (Scheme 1.40).[85]

45
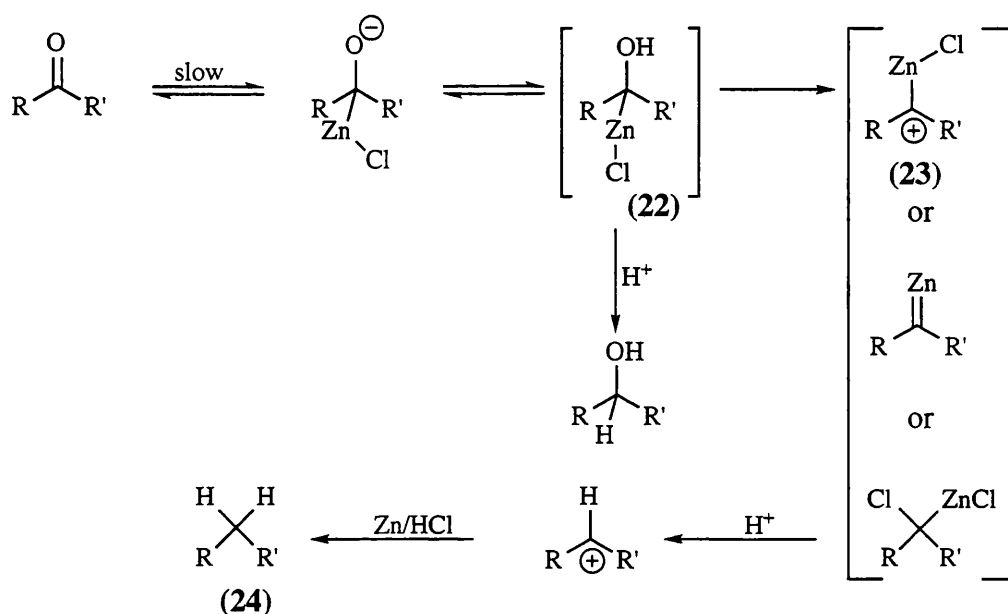
Scheme 1.40

Nakabayashi also noted that the production of pinacols, the product of one electron reduction, increased with decreasing zinc concentration in the zinc amalgam used. At very low zinc concentration this process predominated and he argued that the one electron reduction was an entirely different 'electrochemical' pathway.[85] It should be noted that the Clemmensen reduction occurs only with zinc, and not with other metals of similar redox potential.[85] In these other cases pinacol production occurs, and the process has also been achieved electrochemically.

Additional evidence for the intermediacy of zinc carbenoids in the Clemmensen reduction arises from the observation that the relative yield of alkene to alkane increases with decreasing acid concentration.[87] Conclusive evidence, however, for the existence of a carbenoid is given by the reduction of medium ring cyclic ketones to give products of transannular insertion (*vide supra* section 1.2) (Scheme 1.41).[88]

46
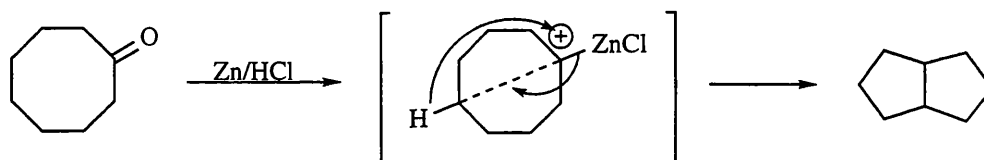
Scheme 1.41

A more recent study by Burden *et al.* finally provided overwhelming evidence for the derived zinc carbenoids.[89] Thus the reaction of 2- and 4-substituted acetophenones in 50% ethanolic hydrochloric acid gave the expected reduced alkanes along with styrenes and the self-coupled cyclopropanes, with the *syn* isomers predominating. In the presence of added styrene, *p*-bromoacetophenone gave primarily the cross-coupled cyclopropane with drastic reductions in the yields of other carbenoid or Clemmensen products. He proposed that all products had come from a zinc carbenoid intermediate (**25**) (Scheme 1.42).[89]

The use of deuterated acetophenones identified a second mechanism for the production of styrenes *via* a proton loss from the zinc carbenoid (**25**) and subsequent reprotonation of the intermediate vinyl zinc species (Scheme 1.42).[89] The reduction of 4-$ClC_6H_4COCD_3$ gave, among other products, $ArCH=CD_2$ (30%), and $ArCD=CD_2$ (< 2%), along with the self-coupled cyclopropane (38%). The longer chain $PhCOCD_2Me$ gives a less stable carbenoid. Rearrangement $PhCD=CDMe$ (40%) now predominates over the vinyl zinc pathway $PhCH=CDMe$ (17%) and no cyclopropane is formed.

Ar\ /CH₃
   ‖
///Zn///
(25)

—H⁺→

Ar_H /CH₃
   |
///Zn///

—H⁺→ Ar⌃CH₃

Ar\ /CH₂
   ‖
///Zn///

—H⁺→ Ar⌃

[1,2] shift Ar⌃

Ar⌃⌃Ar
      Me
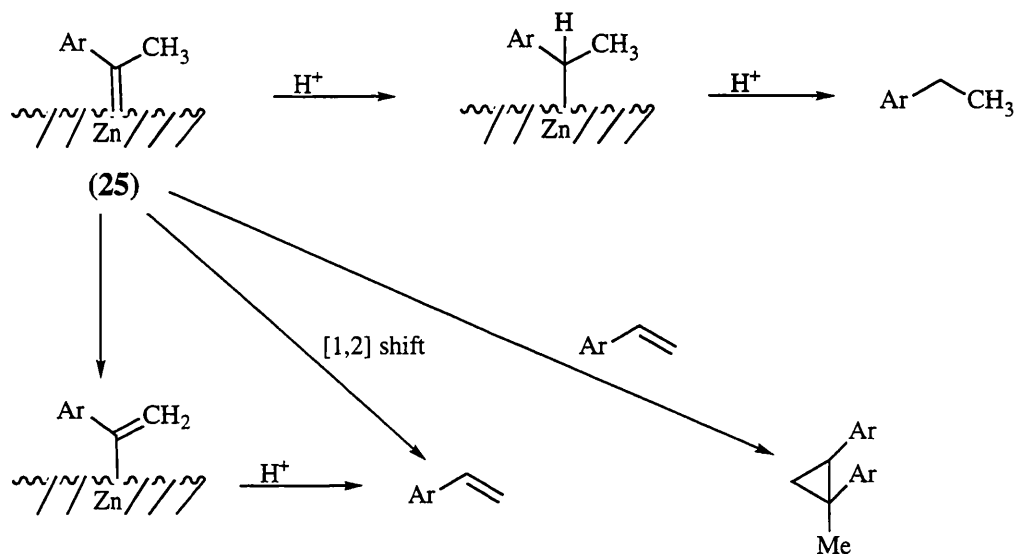
Scheme 1.42

These authors also noted that the rate of reduction was virtually independent of the nature of the group in the 4-position, but that it did affect the overall distribution of products. Interestingly, the 4-methoxy derivative gave no styrene or cyclopropane, while the 2-methoxy derivative did, although no further comment was made. They also proposed a mechanism for carbenoid formation where the reduction of the carbonyl takes place *via* sequential one electron reduction, with pinacol formation occurring at the zinc-bound radical stage (Scheme 1.43).[89]

>C=O
///Zn///

⟶

>Ċ–O
    |
///Zn///

>C'O
‖ ‖
/Zn–Zn/

⟵

>C–O
  | |
/Zn–Zn/
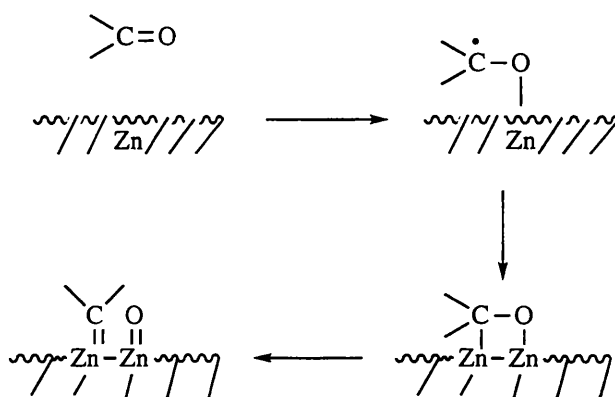
Scheme 1.43

The replacement of hydrochloric acid by boron trifluoride etherate allowed the conversion of aromatic aldehydes to carbenoids without further reduction.[90] The derived

zinc carbenoids readily cyclopropanated a range of neutral and electron-rich olefins in good

to moderate yield (Scheme 1.44).[90b]
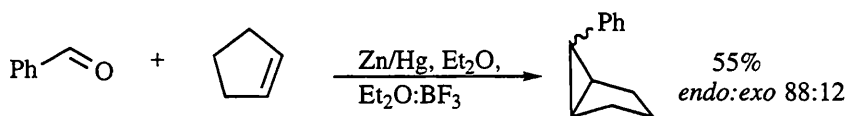
Scheme 1.44

Excluding transformations based on the Clemmensen reduction, direct routes to

metal carbenoids from carbonyl compounds are extremely rare. In a report by Bryan and

Mayer, a tungsten (II) complex $(Ph_2MeP)_4WCl_2$ was shown to react with a variety of

aliphatic aldehydes and ketones to give complexes with η^2 carbonyl ligands **(26)**. In the

case of cyclopentanone, the complex **(26)** decomposed at ambient temperature to generate

the oxo-alkylidene complex **(27)**, although no further reactions were reported for this

compound (Scheme 1.45).[91]

L = PMePh₂

(26)   **(27)**
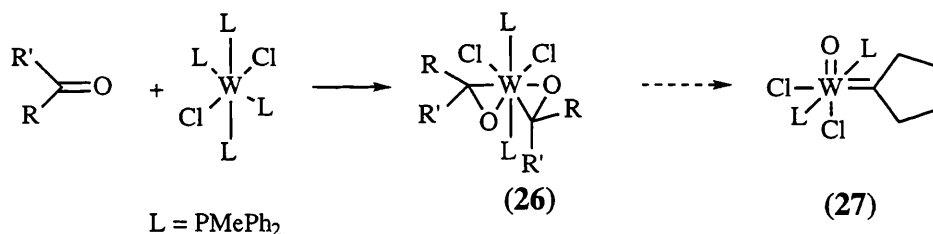
Scheme 1.45

A route by the Hegedus group involved the reaction of tertiary amides with

$Na_2Cr(CO)_5$ in the presence of Chlorotrimethylsilane to give amino-substituted Fischer

carbenes (Scheme 1.46).[92] Primary and secondary amides do not work, presumably due to

protonation of $Na_2Cr(CO)_5$. The reaction with esters, carbamates and carbonates also

failed to yield the corresponding complexes under these conditions.
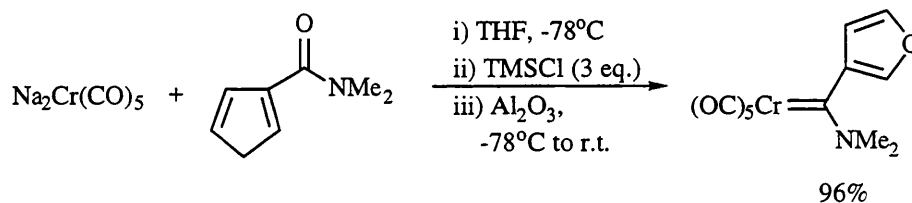
Scheme 1.46

A similar route was also employed by Hossain and co-workers to prepare precursors for cationic iron carbenes.[93] Treatment of the Fp anion with aldehydes in the presence of chlorotrimethylsilane gave the silylalkoxy iron complexes $Cp(CO)_2Fe$-$CHR(OTMS)$. Subsequent treatment of these silylalkoxy iron complexes with TMSOTf gave the cationic iron carbenes *in situ*. Sequential addition of the two silicon electrophiles to Fp anion and aldehyde gave a one-pot process for iron carbenoid generation (Scheme 1.47).[93b]
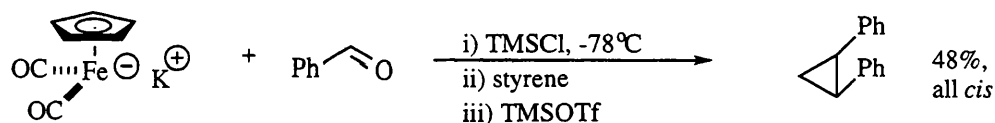
Scheme 1.47

1.4.3 Spectral Studies on Zinc Carbenoids

The carbenoid in the Simmons-Smith reaction, previously thought to be XCH_2ZnX,[62, 77c, 94] has recently been shown to exist primarily as a *bis*-halomethyl species $(XCH_2)_2Zn/ZnX_2$ from a variety of X-ray and NMR data.[75] While XCH_2ZnX may be the initial species formed, it slowly isomerises to $(XCH_2)_2Zn/ZnX_2$ in polar solvents.[75] However, the relatively short lifetime of substituted zinc carbenoids – the half-life of the carbenoid generated from $PhCH_2N_2$ and $ZnCl_2$ in ether was estimated to be about 10 seconds at room temperature[71a] – probably precludes such a rearrangement to a large extent. It has also been shown for the Simmons-Smith reagents $(XCH_2)_2Zn$ that the

remaining coordination sites on zinc are readily occupied by oxygenated functionality, and that the distorted tetrahedral geometry about zinc is very close to that found for coordinated dialkylzinc reagents.[75]

Following the publication of the carbenoid mechanism proposed by Burdon,[89] Billups and co-workers published a paper on the matrix isolation and characterisation of the zinc carbenoid $ZnCH_2$.[95] Zinc atoms were co-deposited with diazomethane and argon on a rhodium plated copper mirror at 12K. Photolysis of the zinc diazomethane complex (hv > 400 nm) gave a species $Zn=CH_2$, the identity of which was confirmed by FTIR spectroscopy. The measured frequencies for the adduct and isotopically labelled species agreed well with those calculated from a normal coordinate analysis for a planar adduct (**28**), and the authors concluded that the carbenoid exists as $Zn=CH_2$.

(**28**)
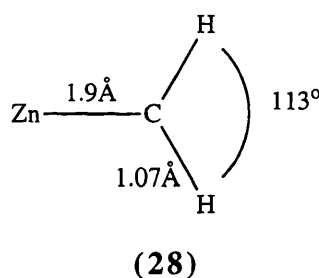
The frequency for the $Zn=C$ stretch (514 cm^{-1}) was also found to lie well between the values observed for $Zn-C$ (447 cm^{-1}) and $Zn\equiv C$ (648 cm^{-1}) bonds.

Later, *ab initio* quantum mechanical calculations predicted that the ground state is the planar triplet state (**29**), with the closed shell singlet state (**30**) lying only 49.6 kJ/mol higher,[96] an energy difference similar to the ground and excited states of methylene. The authors postulate that the closed shell singlet state is pyramidal about carbon, a structure that would be preferred by the interaction of zinc with the empty p-orbital of carbenes with singlet ground states.

H

Zn —1.961Å— C)112.5°

1.091Å

H

(29)

104.9°

103.7° H

H

Zn ——— C 1.107Å

1.974Å

(30)
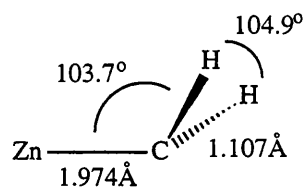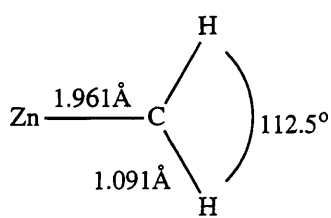
Bond distances and angles were calculated for these equilibrium geometries, and the authors suggested that the 'carbene' incorporates only a Zn-C single bond from comparison with zinc alkyls. Estimated Mulliken charges of +0.43 on zinc and -0.66 on carbon imply a degree of ionic charge. In parallel with observations on Fischer carbenes, however, (*vide supra*) organozinc carbenoids generally behave as electrophilic species.

1.5 Conclusion

The above introduction has hopefully given a broad overview of the general factors affecting the reactivity of carbenes and metallocarbenoids. Special attention has, of course, been drawn to the similarities between zinc and other transition metal carbenoids. The ability to generate zinc carbenoids from carbonyl compounds is, however, a distinct synthetic advantage over other metal carbenoids, especially with the difficulties of handling diazo compounds, *gem*-dihaloalkanes or metal complexes on a large scale.

The present thesis is concerned with the development of the use of carbonyl compounds, and related congeners as starting materials for zinc carbenoids.

2

The Conversion of Aldehydes

and Ketones to Alkenes

2.1 Historical Development of the Zinc/Silicon Electrophile Mediated Reduction of Carbonyl Compounds

2.1.1 Reduction using Chlorotrimethylsilane

This chapter is concerned with the reactions of carbonyl groups that have not been studied in the context of organozinc carbenoid chemistry within the group, i.e. simple alicyclic ketones, rigid cyclic ketones and aliphatic aldehydes. Before discussing our own results it is, however, important to place them in perspective by providing a brief outline of the history of the development of organozinc carbenoid chemistry within the group.

The diverse chemistry of the carbonyl group has proven, time and again, to be of fundamental importance in organic chemistry, and the transformation of ketones to olefins is a reaction which has often found widespread application. In 1973, however, Motherwell published a novel one-step method for the direct conversion of cyclic ketones to olefins by the action of zinc and chlorotrimethylsilane (Scheme 2.1).[97] The reaction conditions are very mild and chemoselective reduction takes place in the presence of remote ester and bromide functionality.

X	Yield
H	72%
OAc (36 hrs)	60%
Br	42%
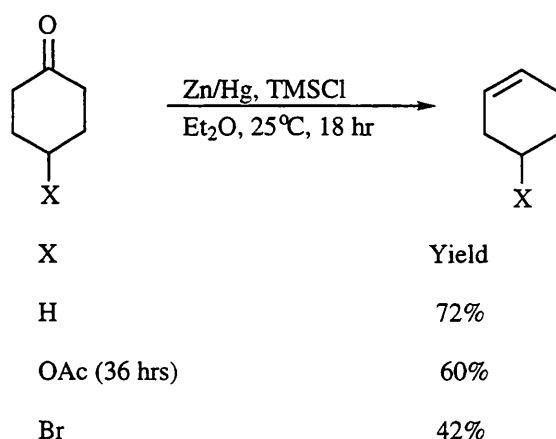
Scheme 2.1

A valuable mechanistic clue was found in the reduction of cyclooctanone which gave both cis-cyclooctene (37%) and bicyclo[3.3.0]octane (18%) *via* competing insertion in the 2- and 5-positions, a process typical of carbene reactivity. Both reactions were already seen in the Clemmensen reduction (*vide supra* chapter 1.8), under dilute acid conditions.

The mechanism was believed to be similar to the Clemmensen reduction, but the intermediate, depicted here as a Simmons-Smith like intermediate (31) did not undergo further reduction with zinc and the silicon electrophile, but rather inserted into a neighbouring C-H bond (Scheme 2.2). Subjecting trimethylsilyloxy cyclohexene to the reaction conditions gave no cyclohexene, dismissing the possibility of a silyl enol ether intermediate.[97]
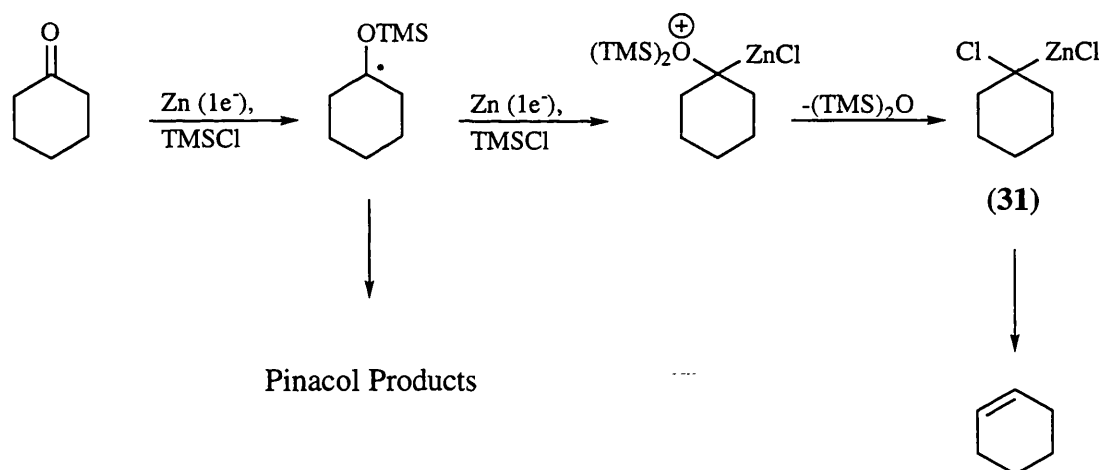
Scheme 2.2

Although the mechanism in Scheme 2.2 is somewhat simplistic, single electron reduction can be an important side reaction under certain conditions, especially where the intermediate radical is stabilised. Motherwell noted that acetophenone rapidly gave the pinacolic dimer, 2,3-diphenyl-butane-2,3-diol as the *bis*-trimethylsilyl ether in 82% yield, and no styrene was isolated.[97]

Modifications of the reaction conditions have enhanced the favourability of the one-electron process. Thus, Corey *et al.* have trapped the intermediate silyloxyalkyl
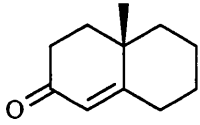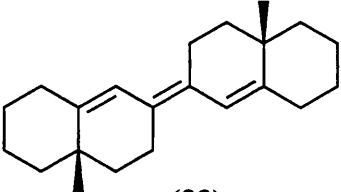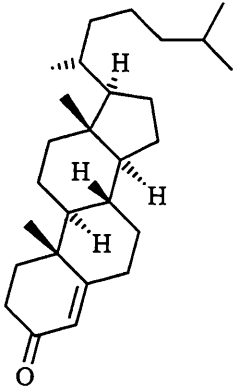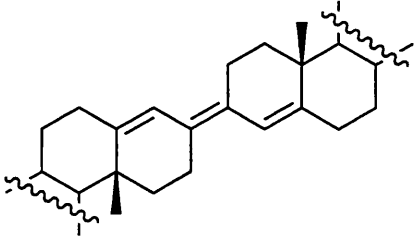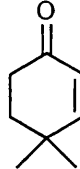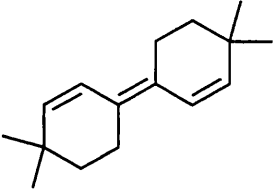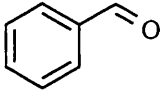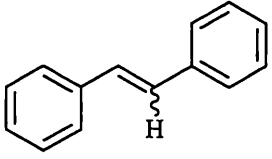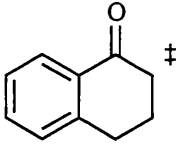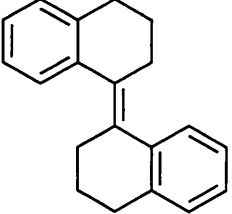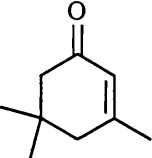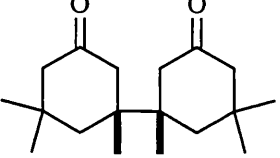
radical to give good yields of bicyclic products (Scheme 2.3.a)[98] and sonication has been used to give moderate yields of cross-coupled aromatic pinacols (Scheme 2.3.b).[99]

R, R' = Me : R, R' = OMe : R = OMe, R' = Me

0.73 : 0.76 : 1.0
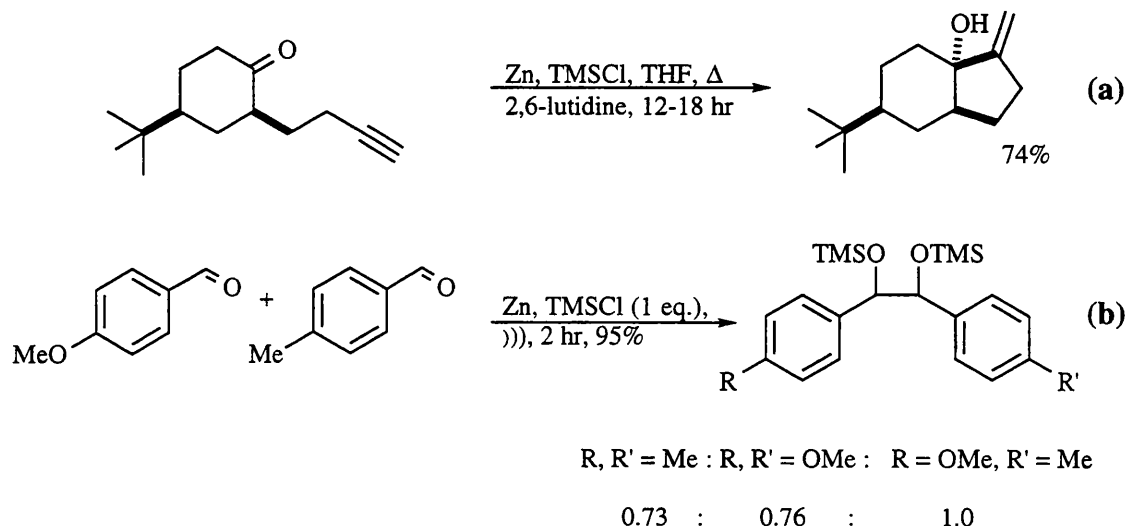
Scheme 2.3

Interest in the group then turned to the behaviour of unsaturated carbonyl compounds. Certain carbonyl substrates could undergo dicarbonyl coupling to give trienes by using a slow addition of the carbonyl compound to zinc and the silicon electrophile at -30°C (Table 2.1).[100] Thus the octalone (**32**) coupled to give the triene (**33**) in excellent yield. Other enones gave the oxygen-sensitive trienes in somewhat lower yields (entries 2, 3). Aromatic aldehydes and ketones also gave "dimers", but in rather lower yields, and pinacol coupling was a major side reaction. In the case of isophorone (entry 6), however, radical coupling occurred at the softer β carbon to give the diketone (**34**).

Entry	Substrate	Product	Yield
1	(32)	(33)	85%
2			43%
3			23%
4			15%
5	‡		20%
6		(34)	15%

‡ Reaction performed at -50°C

Table 2.1

57

Although many methods have been used to effect dicarbonyl coupling reactions, perhaps the most well-known is the McMurray reaction using low-valent titanium species.[101] Use of low temperatures will allow reduction to the diol, but complete deoxygenation takes place at 60°C to give the alkene. However, the zinc and silicon electrophile mediated coupling was shown not to proceed *via* the diol, nor *via* the derived *bis*-trimethylsilyl ether, as these groups failed to yield trienes when subjected to the reaction conditions.

However, reacting *trans*-stilbene oxide with zinc and chlorotrimethylsilane gave stilbene (83:17 *trans : cis*) suggesting capture of the intermediate organozinc carbenoid by a second molecule of carbonyl compound, and subsequent reduction to the alkene (Scheme 2.4).[100]
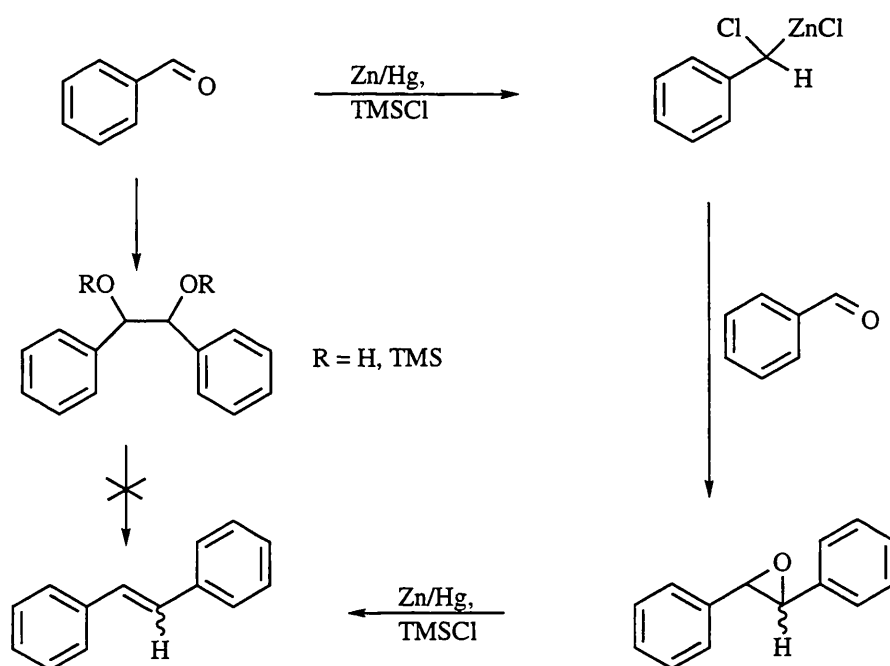
Scheme 2.4

2.1.2 The Development of an Intramolecular Silicon Electrophile

Efforts to extend this dicarbonyl coupling reaction, however, showed that dimerisation of the silyloxyalkyl radical was often the dominant process. It was therefore argued that since reduction of a carbonyl compound requires two electrons from zinc and

58

two equivalents of a silicon electrophile, the selection of the *bis*-silicon halide (**35**) could

lead to delivery of the second silicon electrophile in an intramolecular fashion (Scheme

2.5).
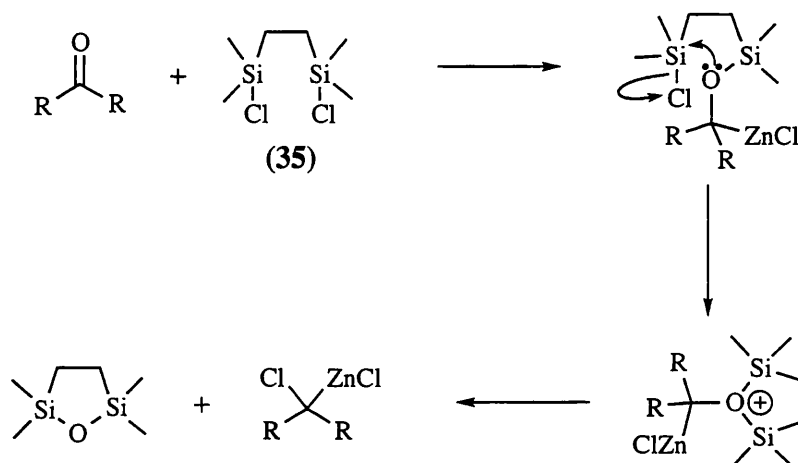
Scheme 2.5

This modification of the reaction conditions greatly improved the efficiency of

carbenoid generation, especially from aromatic aldehydes (Table 2.2).[102] Interestingly,

the yields of stilbenes obtained from *para*-substituted aromatic aldehydes (MeO> H> Cl)

parallel those obtained under classical Clemmensen reduction conditions. This may be

related to the ability of a donor group to expel the siloxane leaving group (Scheme 2.6).
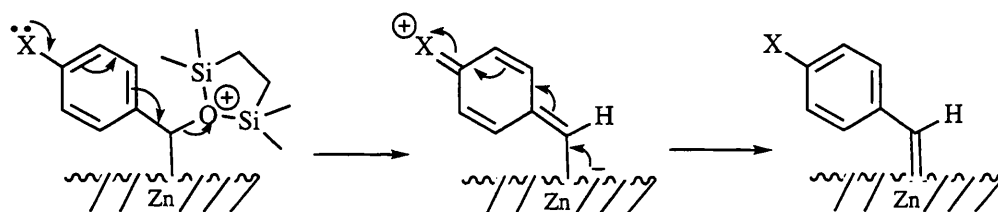
Scheme 2.6
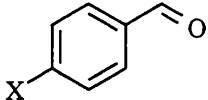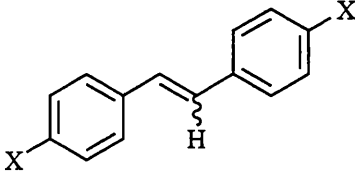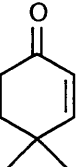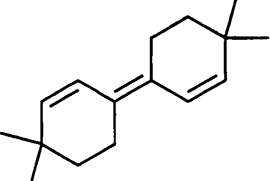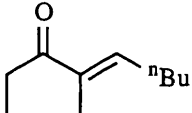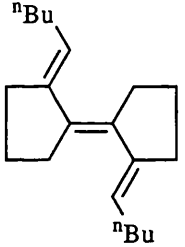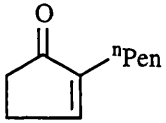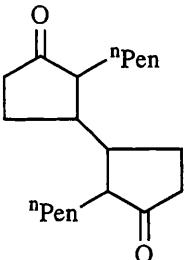
Entry	Substrate	Product	Yield	X
1			85%	OMe
2			86%	Me
3			69%	H
4			26%	Cl
5			76%	
6			72%	
7			18%	

Table 2.2

The mode of addition of substrate was found to be crucial for high yields of coupled product. Best results were obtained by slow addition of a solution of aldehyde to the silicon electrophile and zinc in THF.[102]

Attempts to perform intramolecular dicarbonyl coupling reactions, however, were not successful. Thus the diketone (36) gave dihydropyran (37) (31%), along with the open chain products of α-C-H insertion (38) (14%) and (39) (21%) (Scheme 2.7.a).[102] The homologated diketone (40), however, gave only the products of α-C-H insertion of the intermediate carbenoid, (41) (18%) and (42) (42%) (Scheme 2.7.b).[102]
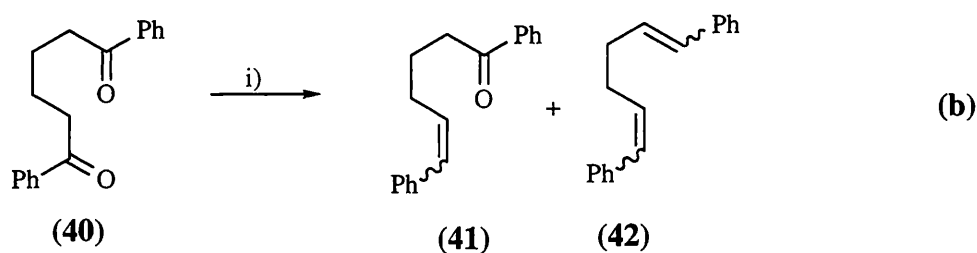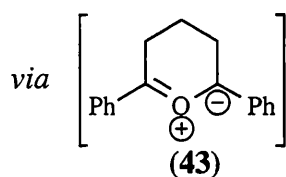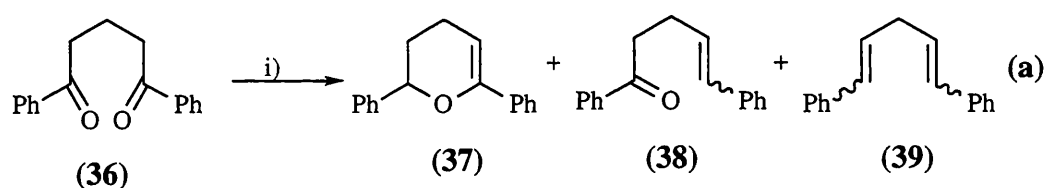
i) Zn/Hg, (ClMe$_2$SiCH$_2$)$_2$, THF, r.t.

Scheme 2.7

Nevertheless, the isolation of the dihydropyran provided a valuable mechanistic clue, since it is presumably formed from a carbonyl ylide intermediate (43), whose subsequent ring closure to the epoxide is retarded by a combination of ring strain and electronic effects. Carbonyl ylide formation is well known in rhodium carbenoid chemistry,[49c, 103] and the intermediate ylides readily undergo [3+2] cycloadditions (Scheme 2.8.a).[104] However, in certain cases, proton loss to give the enol ether can occur (Scheme 2.8.b).[105]

61

(a)

85%

(b)

60%
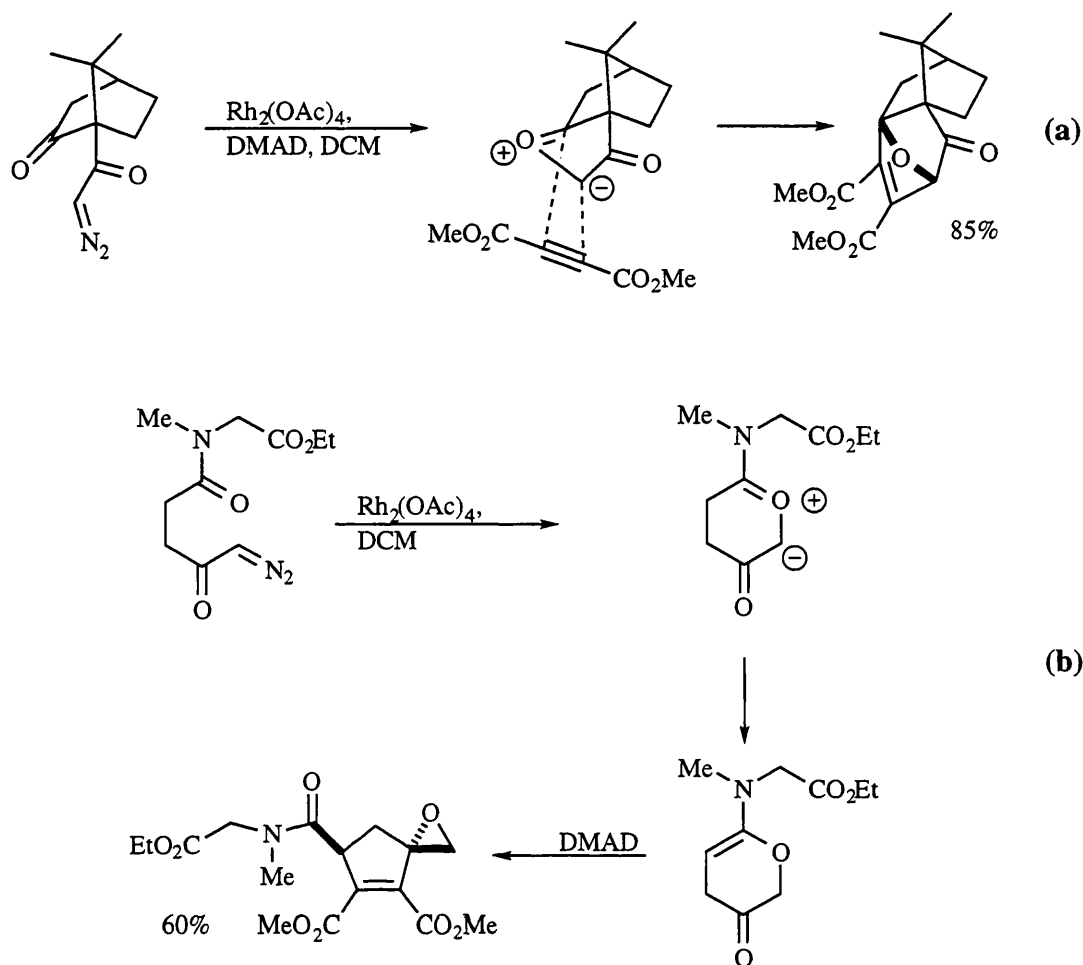
Scheme 2.8

At an earlier stage it had been thought that the zinc carbenoid could be considered as a Reformatsky-like reagent, and hence nucleophilic attack on the carbonyl would give the alkoxide with a subsequent Darzens-like ring closure then giving the observed epoxide (Scheme 2.9).[100] However, in the event, the reaction goes *via* the carbonyl ylide,[102] whose formation here is much more in keeping with the electrophilic nature of zinc carbenoids.
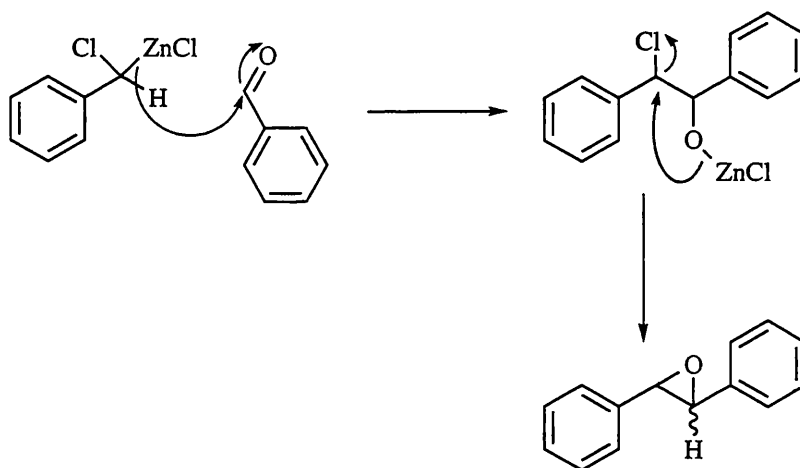
Scheme 2.9

The efficient generation of organozinc carbenoids from aromatic aldehydes has also lead to their use as cyclopropanation reagents. Once again, slow addition of the aldehyde to a stirred suspension of zinc, the silicon electrophile and the alkene in ether at reflux gives moderate to excellent yields of cyclopropanes. The more sterically hindered isomer is formed preferentially, and the yields decrease with decreasing electron donation from the *para*-substituent on the aromatic ring (Scheme 2.10).[106] The reasons for these observed selectivities will be discussed at a later stage (*vide infra* chapter 4.1).
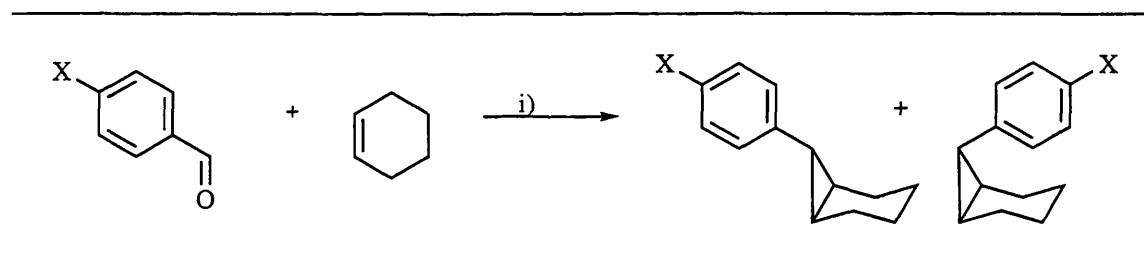
X	Yield	Ratio (endo:exo)
OMe	98%	15:1
Me	75%	8:1
H	68%	4:1
Cl	46%	3:1

i) Zn/Hg, $(ClMe_2SiCH_2)_2$, Et_2O, reflux, 36 hr

Scheme 2.10

The cyclopropanation reaction could also be extended to certain α,β-unsaturated aldehydes and ketones; primarily those which had been successful in the dicarbonyl coupling reaction, or bore close resemblance to the previously successful substrates.[106, 107]

2.2 A Mechanistic Reappraisal of the Possible Nature of Organozinc Carbenoid Intermediates

It is not surprising to record that, following on from the original work in the group on this zinc mediated reduction of carbonyl compounds, our understanding of the mechanism of formation and reactivity of organozinc carbenoids has undergone considerable change. Indeed, a better representation of the mechanism might be that shown in Scheme 2.11, rather than the simplistic electron count in Scheme 2.2.
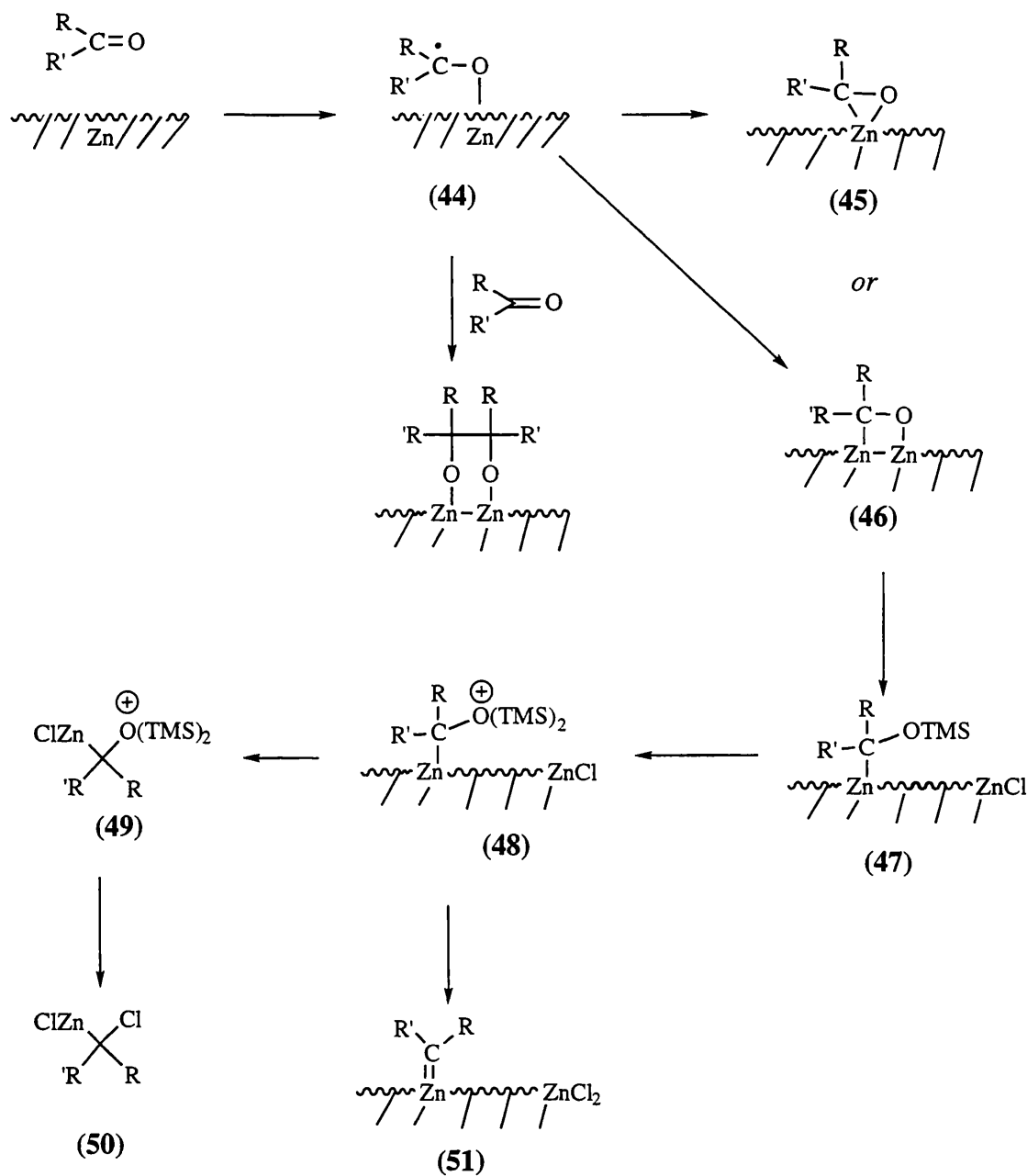
Scheme 2.11

Thus the coordination of the carbonyl group to the zinc surface and electron transfer gives the surface-bound ketyl radical (**44**). Such radicals could either undergo coupling to give pinacolic products, or accept a second electron from the zinc surface thereby forming an oxometallocycle (**45**) or (**46**). Subsequent cleavage of the initially formed zinc-oxygen bond by the silicon electrophile[68] can now occur to give (**47**), and reaction with a further silicon electrophile gives a carbenoid-like intermediate (**48**). This may be considered as a homogeneous species such as (**49**) or (**50**) by displacement with

65

chloride ion. Alternatively, direct loss of hexamethyldisiloxane may be thought to occur to give a surface bound heterogeneous carbenoid (**51**) with concomitant production of zinc chloride by electrochemical corrosion at another site on the zinc surface (Scheme 2.11).

At this moment in time, it might seem likely that the organozinc carbenoids derived from carbonyl compounds are heterogeneous. Nevertheless, comparison of the behaviour of our carbenoids with those prepared by other routes (*vide supra* chapter 1.4.1),[62, 71a, 72c, d] and known to be homogeneous, shows many similarities. Although the original Simmons-Smith procedure generated the carbenoid in heterogeneous medium, the carbenoid was shown to be homogeneous, as filtered solutions retained the ability to cyclopropanate alkenes.[79] Homologous Simmons-Smith reagents are much more short-lived and give products of intramolecular C-H insertion (*c.f.* chapter 1.4.1). Another similarity is that in the cyclopropanation of alkenes, the stereoselectivities of the homogeneous phenyl-zinc carbenoids, whether generated from *gem*-dihalides or phenyldiazomethane, increase with increasing electron density in the aromatic ring, with preference for the formation of the more hindered *syn* or *endo* isomer. This trend is also observed for our organozinc carbenoids (*vide supra*).

Comparison of the methods of formation and reactivity of other metal carbenoids shows that cationic intermediates could be important, and may be the transient reactive species. Studies on the catalytic decomposition of aryldiazomethanes by lithium salts, and especially with lithium perchlorate, suggested that a cationic ion pair species (**52**) was the reactive intermediate, and that the counter ion was of secondary importance here.[71a]
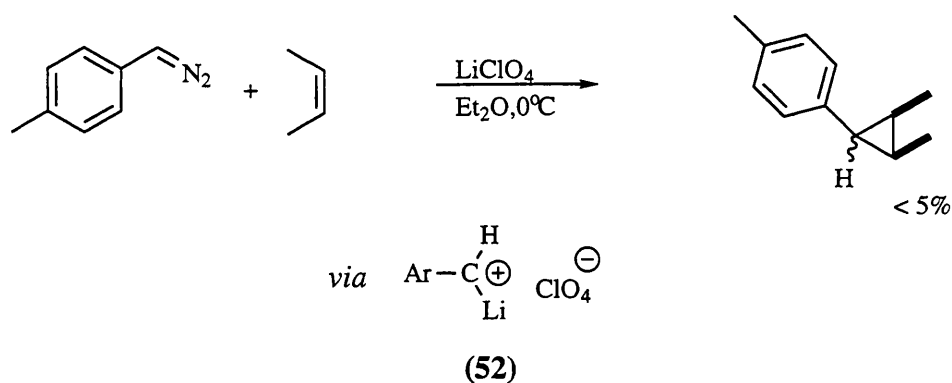
Scheme 2.12

In a similar vein, mechanistic studies on the cationic iron carbene complex **(53)** showed that ethylidene transfer occurred after loss of the thioether from **(53)**, suggesting that the species **(54)** is the reactive intermediate.[18] The rather forcing conditions required for carbene transfer from the complex **(53)** had led to the earlier suggestion that a bimolecular displacement mechanism might be responsible with the olefin acting as a nucleophile (Scheme 2.13).[108]
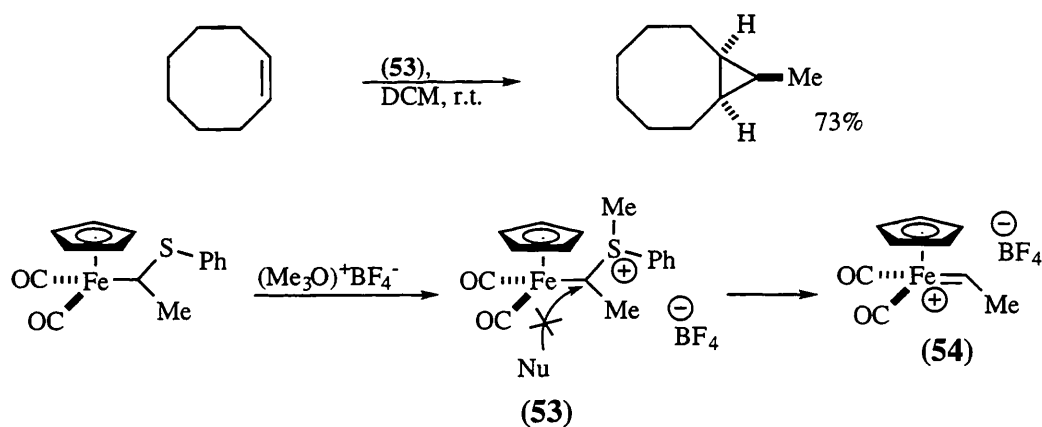
Scheme 2.13

Formation of our zinc carbenoids may proceed in a similar fashion. Disproportionation of the disiloxonium intermediate **(55)** would generate a cationic species **(56)** which could then react immediately or trap chloride to generate a Simmons-Smith-type intermediate **(57)** (Scheme 2.14).

$$ClZn \overset{\oplus}{\underset{R' \quad R}{\diagdown} O(TMS)_2} \qquad \longrightarrow \qquad \left[\; ClZn = \overset{\oplus}{\underset{R'}{\diagdown}} R \quad \longleftrightarrow \quad ClZn - \overset{R}{\underset{R'}{\diagdown}}_{\oplus} \; \right]$$

(55)   (56)

$$\big\downarrow \; Cl^{\ominus}$$

$$ClZn \overset{Cl}{\underset{R' \quad R}{\diagdown}}$$

(57)
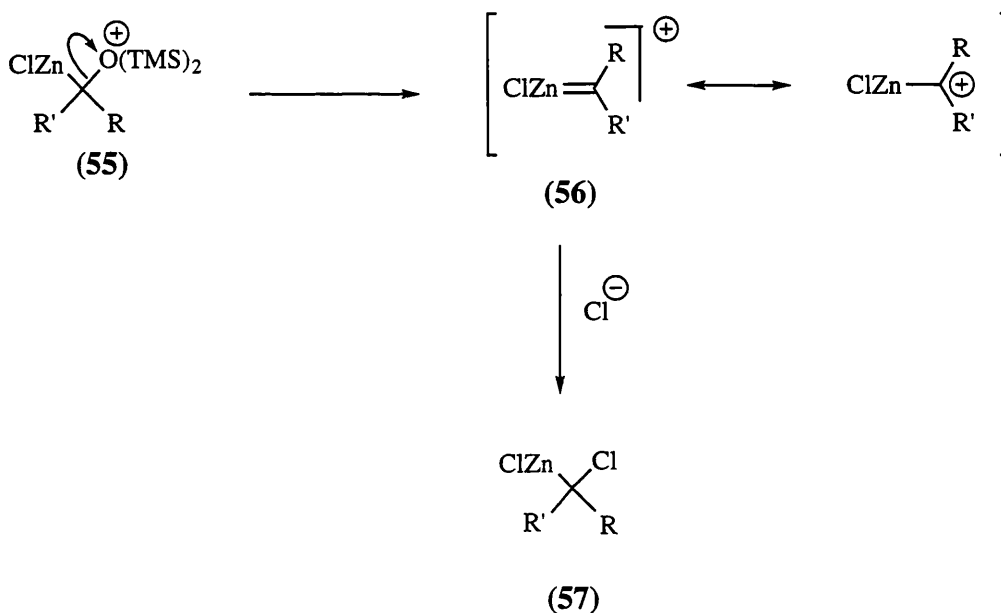
Scheme 2.14

A homogeneous metalloxirane has been proposed as the intermediate in the reduction of diaryl ketones with ytterbium metal. The metalloxirane generates benzhydrol when the electrophile is a proton, along with a small amount of diphenylmethane (Scheme 2.15).[109] It would be most interesting to see if carbenoid behaviour is exhibited in the presence of silicon electrophiles.

$$\underset{Ph \quad Ph}{\overset{O}{\big\|}} \xrightarrow{\text{i)}} \left[\underset{Ph}{Ph - \overset{O}{\diagdown} Yb} \right] \xrightarrow{H^+} \underset{Ph \quad Ph}{\overset{HO \quad H}{\diagdown}} + \underset{Ph \quad Ph}{\diagdown}$$

                                                         97%   3%

i) Yb metal, THF, HMPA, r.t., 10 min
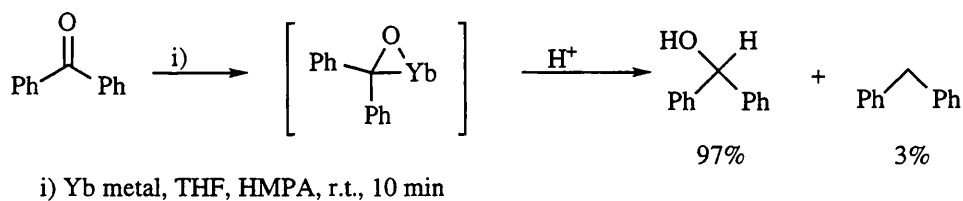
Scheme 2.15

Such an intermediate might also be envisaged in the case of zinc, with cleavage of the zinc-oxygen bond eventually leading to a zinc carbenoid species (55) (Scheme 2.16).

68

TMSCl

$$(55)$$
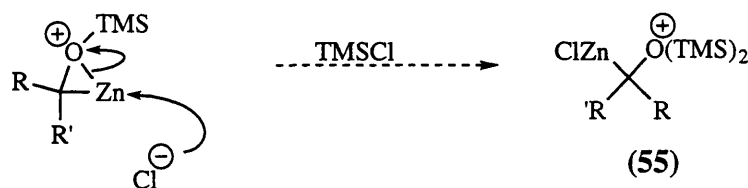
Scheme 2.16

2.3 Insertion Reactions of Organozinc Carbenoids

2.3.1 Possible Pathways of Insertion

The purpose of the above discussion has been to give a historical perspective to our use of the carbonyl group as a carbenoid synthon, although others have made use of our conceptual strategies (*c.f.* chapter 1.4.2).

The results detailed in this thesis, although not necessarily presented in strict chronological order, are intended to represent a progressively detailed picture of the generation, reactions and behaviour of organozinc carbenoids. In certain cases, reference will be made to results presented at a later stage in the thesis.

The initial report by Motherwell showed that organozinc carbenoids exhibit many of the characteristics shown by typical "free" carbenes generated from tosylhydrazone salts, but show a much greater preference for α-C-H insertion over other C-H insertions (1,3 and 1,5) (Scheme 2.17.a). The use of a crown ether with the potassium salt of cyclooctanone tosylhydrazone gave results virtually identical to the uncomplexed sodium salt, good evidence that these species are true free carbenes (Scheme 2.17.b).[110]

1	:	2	:	0	**(a)**

NaOMe, DEC, ↑↓ → 46 : 45 : 9

(b)

KH, 18-C-6, diglyme, ↑↓ → 45 : 47 : 8
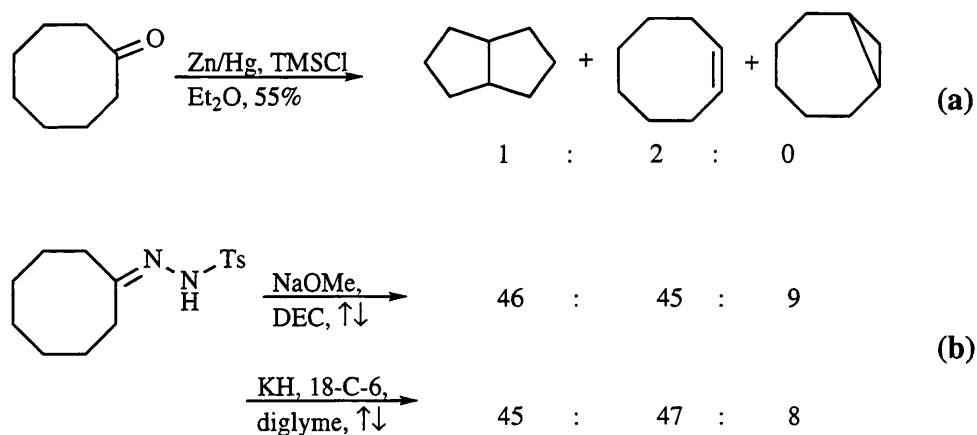
Scheme 2.17

The α-C-H insertion of free carbenes is believed to occur in a concerted fashion where the migrating hydrogen is coplanar with the empty p orbital of the singlet carbene (Scheme 2.18).[2b, 111]
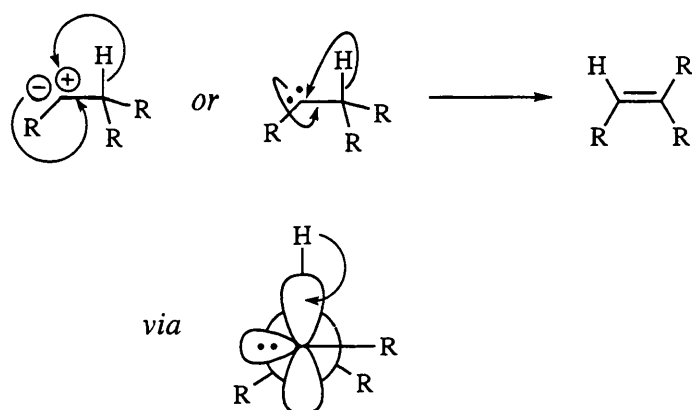
Scheme 2.18

However, transition metal carbenoids have been shown to give the products of formal α-C-H insertion *via* a variety of different mechanisms. In contrast to the intramolecular reactions of free carbenes, 1,3 or β-C-H insertion is not an important pathway. The insertion reactions of transition metal carbenoids though, are likely to proceed in a stepwise manner, due to the formal double bond between the metal and the carbene carbon. For such a stepwise process, the migrating hydrogen could migrate with hydride character, as for a free carbene to give the η^1 vinyl complex (**56**). Reductive

elimination then gives the alkene, the product of formal α-C-H insertion (Scheme 2.19.a).
The alternative is the removal of a proton with concomitant reduction of the metal centre,
followed by reprotonation of the η^1 vinyl complex (57) (Scheme 2.19.b).
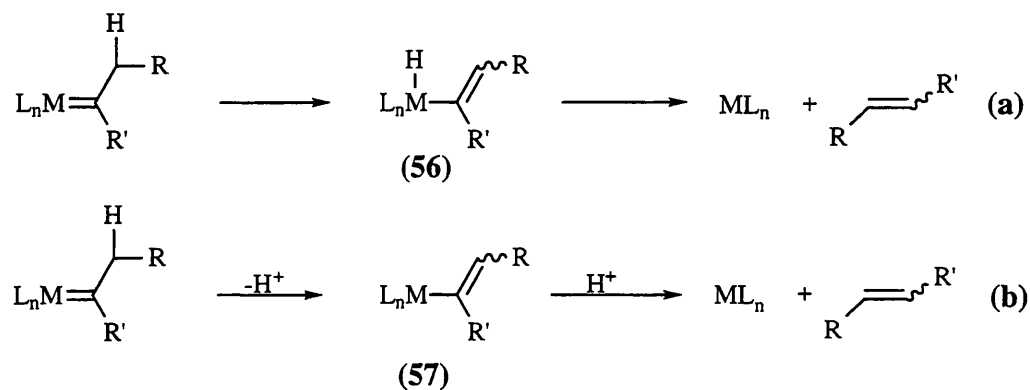
Scheme 2.19

Considerable evidence exists for both paths, but the hydride path is most
common. The existance of an intermediate of type (56) has been shown in the reaction of
the tungsten carbene complex $(CO)_5W=CPh(Me)$,[112] which gives the cyclopropane (58)
in situ but will not cyclopropanate added alkenes. Deuterium labelling showed that the
cyclopropane (58) was formed from the η^1 vinyl complex (59) attacking the carbene
complex (60) to give the cyclopropyl tungsten anion (61). Protonation of (61) gives the
cyclopropane (58) (Scheme 2.20).[112]

$(OC)_5W$=$\diagdown$ Ph / OMe $\xrightarrow[\text{ii) HCl}]{\text{i) D}_3\text{CLi}}$ $(OC)_5W$=$\diagdown$ Ph / CD_3 **(60)** *via* $\left[(OC)_5\overset{\ominus}{W}-\diagdown\begin{smallmatrix}Ph\\CD_3\\OMe\end{smallmatrix} \right]$ **(62)**

$(CO)_5\overset{\ominus}{W}$ Ph / CD_2 **(59)** $\xleftarrow{\text{base (62)}}$ $(CO)_5W$ D Ph / CD_2 $\longrightarrow$ $(OC)_5W$ D D / D Ph

>95% d₃ → $>95\%\ d_3$

$(OC)_5W$=$\diagdown$ Ph / CD_3

$(OC)_5W$= Ph $\ominus$ $W(CO)_5$ D D CD_3 Ph $\longrightarrow$ $(OC)_5W$ $\ominus$ D Me CD_3 Ar D **(61)** $\longrightarrow$ H D Me CD_3 Ar D **(58)**

Scheme 2.20

The importance of hydride character in the migrating hydrogen can also be seen in the reactions of iron and rhodium carbenoids (*c.f.* chapter 1.3.2 and 1.3.4). Primary hydrogens do not migrate as readily as secondary or tertiary hydrogens. The reactions in Scheme 2.21.a and 2.21.b are illustrative.[52b] The iron complex **(63)** can be deprotonated to the η^1 vinyl species **(64)** with pyridine (Scheme 2.21.c),[113] but higher homologues insert *via* the hydride pathway.[26b]

(a)

85 : 15

(b)

38 : 62

(c)

(63) (64)

Scheme 2.21

Both processes were observed by Burden and Price in the Clemmensen reduction of acetophenones (*c.f.* Scheme 1.42).[89] The deprotonation was favoured almost exclusively for a variety of *para*-substituted acetophenones. The homologous propiophenone, however, gives the alkene predominantly *via* the hydride route.

In the case of the Simmons-Smith-type intermediate, insertion may occur directly in a route comparable to the "butterfly" mechanism[60a,b, 62a,b] originally proposed for Simmons-Smith cyclopropanation (Scheme 2.22).
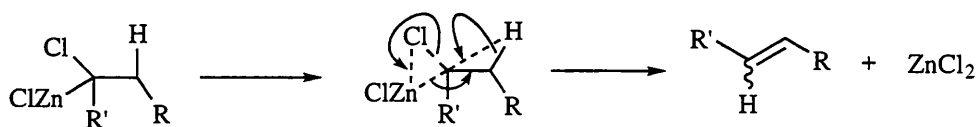
Scheme 2.22

2.3.2 Carbenoids derived from Aliphatic Ketones
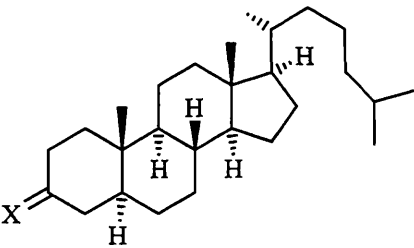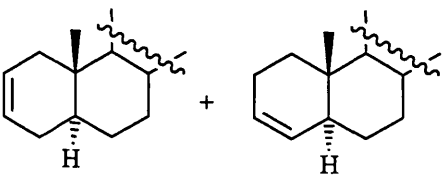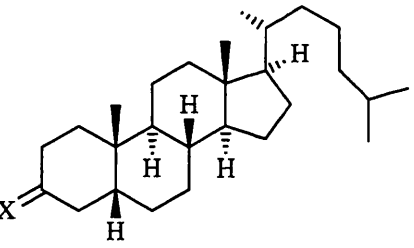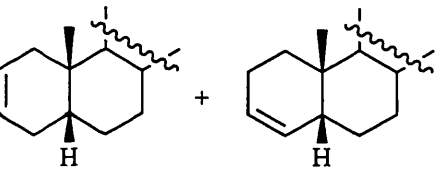
Since the original investigation had focused only on alicyclic systems, we elected in the first instance to study the behaviour of a simple symmetrical open chain ketone (**65**). However, we obtained a poor yield of alkenes (**66**) and (**67**), even after extended periods of reaction (Scheme 2.23.a). Thermolysis of the derived tosylhydrazone salts of analogous open chain ketones have been shown to form the thermodynamically more stable *trans* alkenes preferentially.[115] However, treatment of the tosylhydrazone (**68**) with sodium methoxide in diglyme gave a mixture of the *cis* and *trans* alkenes (**66**) and (**67**), along with the conjugated alkenes (**69**) and (**70**), resulting from base catalysed isomerisation, and a further unidentified isomer (**71**) (Scheme 2.23.b). Estimation of the ratios (**66**) to (**70**) in Scheme 2.23.b was precluded due to the overlap of the GC peaks for (**66**) with (**69**) and (**67**) with (**70**).

Ph—∕∖∕═∖—Ph

(66)

Ph—∕╲╱═╲—Ph   (65) → O

$$\frac{\text{Zn/Hg, TMSCl,}}{\text{Et}_2\text{O, ↑↓, 1 week}}$$

Ph—∕∖╱═╲—Ph

+ Ph—∕∖∕═╲—Ph

(67)

(a)

(66) : (67)
1.43 : 1   11%

Ph—∕∖∕═∖—Ph

(66)

Ph—∕╲╱═∖—Ph
    ‖
    N~NH
       |
       Ts

(68)

$$\frac{\text{NaOMe, ↑↓,}}{\text{diglyme, 58\%, 1 hr}}$$

+ Ph—∕∖∕═╲—Ph

(67)

(b)

+ Ph—∕∖∕═∖—Ph

(69)

+ Ph—∕╲╱═∖—Ph

(70)

+ **(71)** ?

(66) + (69) : (67) + (70) : (71)
  56   :   12   :   32
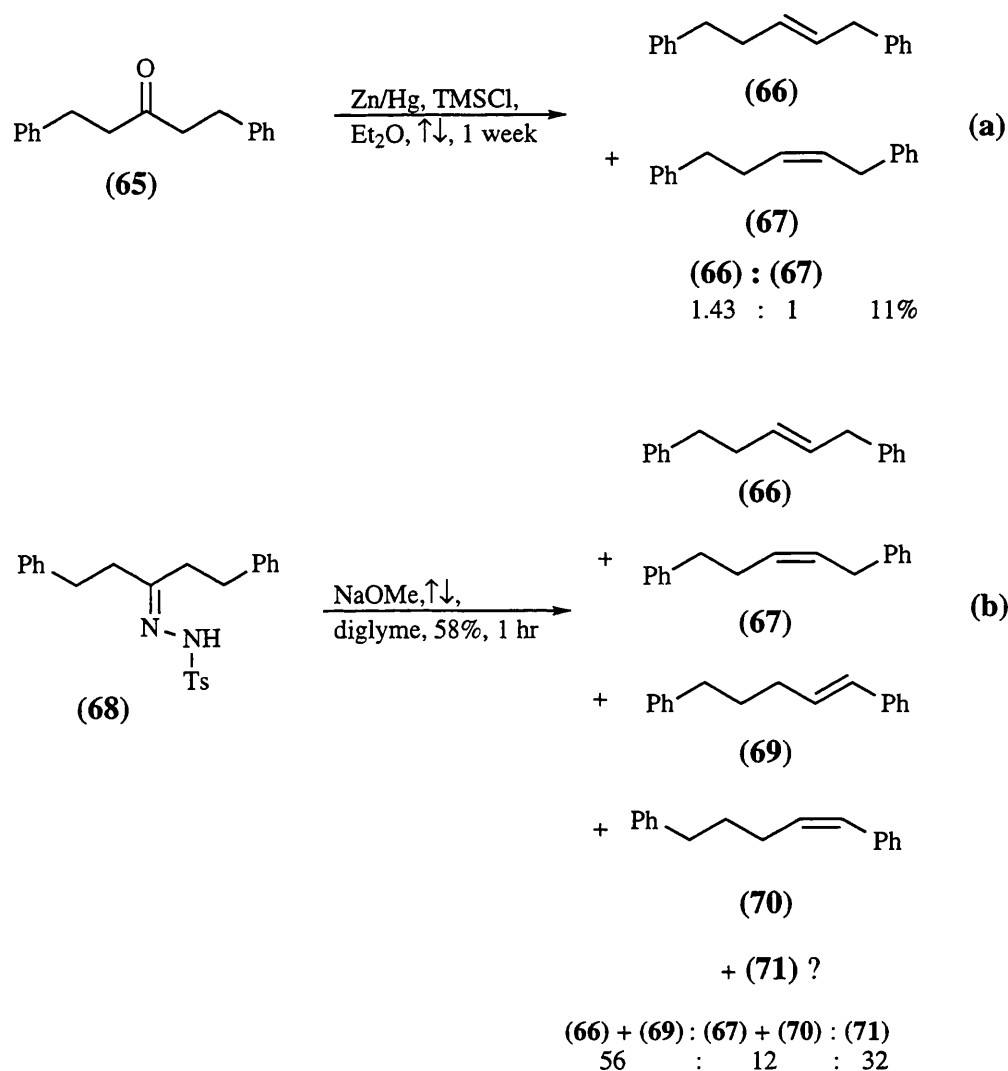
Scheme 2.23

In a further comparison of our organozinc carbenoids with free carbenes, the steroidal ketones 5α-cholestanone and 5β-cholestanone were selected to compare the relative regioselectivities in α-C-H insertion. The free carbene derived from *trans*-2-decalone tosylhydrazone shows a distinct preference for the formation of the less strained Δ2 alkene over the Δ1 alkene. This preference is even more pronounced in more rigid steroid skeletons,[115b] e.g. that of 5α-cholestan-3-one, and the Δ2 alkene is by far the major isomer. It can be seen from the results in Table 2.3 that the α-C-H insertion reaction of organozinc carbenoids is more sensitive to these strain factors. A similar trend is observed with the less rigid 5β-cholestan-3-one derivatives (Table 2.3), although here the preference for the less strained Δ3-5β alkene is less pronounced. These results show

the more selective behaviour of the organozinc carbenoids, and suggest a later transition state for hydrogen migration. Although the zinc/chlorotrimethylsilane reaction has been applied to a number of 3-oxo-steroids,[116] the products for 3-oxo-5α substrates were isolated by crystallisation of pure Δ2-5α alkenes, and hence exact ratios were not properly determined.

Substrate	Products	Yield

X = O   91   :   9   76%
X = NNHTs 84   :   16   40%

X = O   26.5   :   73.5   32%
X = NNHTs 27.4   :   72.6   21%

a) X = O; Zn/Hg, TMSCl, ZnCl$_2$, THF, ↑↓
b) X = NNHTs; NaOMe, diglyme, ↑↓

Table 2.3

2.3.3 Carbenoids derived from aliphatic Aldehydes

2.3.3.1 The Carbenoid derived from Hexadecanal

Our attention then turned to the deoxygenative chemistry of yet another carbonyl group which had never been studied; *viz.* the aldehyde. In comparison to the use of ketones, however, the use of aliphatic aldehydes as carbenoid precursors poses no problems of regio- and stereoselectivity, α-C-H insertion giving only the terminal alkene.

It is not, however, a trivial problem in the literature. The base-catalysed elimination of primary halides to give terminal alkenes is a reaction of fundamental importance in organic chemistry,[117] but direct routes from aldehydes without homologation of the carbon skeleton are unknown. A variety of indirect routes for this transformation do exist, including hydroboration of enamines,[118] and double deprotonation of the tosylhydrazone salt (the Shapiro reaction).[115b, 119] The free carbene route *via* the tosylhydrazone salt, however, gives significant quantities of cyclopropanes *via* 1,3 insertion.[115]

Subjecting hexadecanal to conditions similar to the original paper gave 1-hexadecene in 52% yield. A brief survey of solvents showed that the reaction gives best results in ether (Table 2.4), a trend generally observed in our generation of organozinc carbenoids from carbonyl compounds. Interestingly we also observed a significant amount of the cyclopropane product formed from 1,3-C-H insertion in the reaction in THF; some 10% of product isolated. This 1,3-C-H insertion is not without precedent in the reactions of zinc carbenoids, although Neuman had previously observed far lower amounts of this product (*c.f.* Scheme 1.33)

Me(CH$_2$)$_{13}$ —⟍⟍=O ⟶ Me(CH$_2$)$_{13}$ —⟍⟍
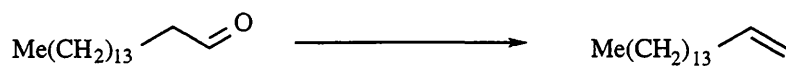
	Solvent	Temperature	Time (hr)	Yield
Method A*				
	Et$_2$O	20°C	18	52%
	Et$_2$O	reflux	9	85%
	THF	reflux	4.5	77%[‡]
	DCM	reflux	19	26%
Method B[§]				
	Et$_2$O	reflux	18	77%

* Method A: the aldehyde (1 mmol), zinc amalgam (10 eq.) and TMSCl (5eq.) stirred in the stated solvent.

[§] Method B: the aldehyde (1 mmol), zinc amalgam (10 eq.) and Me$_2$SiCl$_2$ (1.5 eq.) stirred in ether.

[‡]The product contains 10% of the cyclopropane: Me(CH$_2$)$_{12}$ —◁
formed *via* 1,3-C-H insertion.
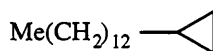
Table 2.4

It should be noted, however, that the use of the chelating *bis*-silicon electrophile, (35), while greatly improving the efficiency of carbenoid generation, is not without its drawbacks. The oligomeric siloxanes produced on work-up, (72), are often difficult to separate from the products, and require repeated chromatography to obtain pure materials (Scheme 2.24.a). In view of this difficulty, we decided to return to chlorotrimethylsilane, and also to investigate the efficiency of dichlorodimethylsilane as a replacement silicon electrophile. A simple reaction path for comparison with chlorotrimethylsilane is shown in Scheme 2.24.b. From a mechanistic standpoint, it could be argued that the silicon dihalide would be an intrinsically more powerful electrophile in each of the two successive halogen displacements. Thus, cleavage of the zinc-oxygen bond gives the species (73), and assisted expulsion of the second chloride gives a carbenoid-like intermediate (74). The high-energy intermediate, dimethylsilanone, has been postulated as an intermediate in the thermal and base catalysed decomposition of

polydimethylsiloxanes, has also been observed in a variety of cycloreversion reactions of siloxane bicyclic compounds,[120] and polymerises to more readily separated byproducts.
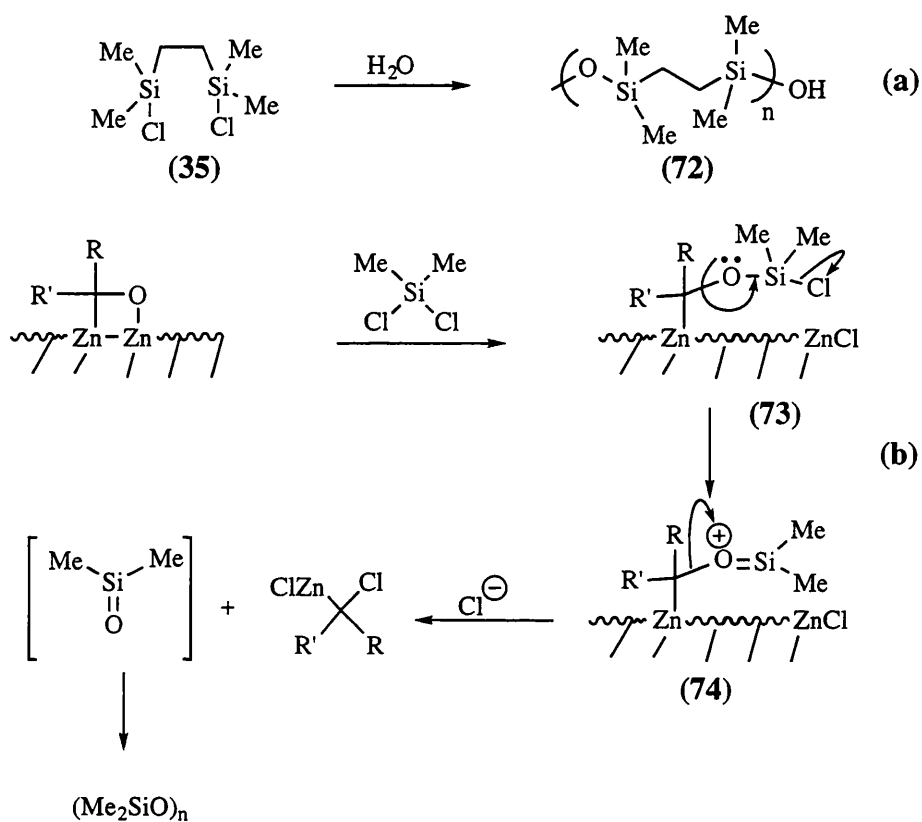
Scheme 2.24

An isolated report by Smith *et al.* had in fact described the use of dichlorodimethylsilane and zinc in our carbonyl deoxygenation chemistry.[121] Thus, as shown in Scheme 2.25, benzaldehyde gives a mixture of deoxybenzoin and diphenylacetaldehyde.[121]
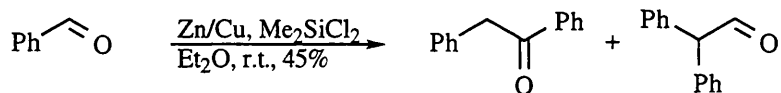
Scheme 2.25

2.3.3.2 The discovery of Lewis Acid Catalysis

However, the products formed in all but one case could be rationalised by pinacolic coupling followed by rearrangement. These authors had also shown that the reaction of benzaldehyde with zinc-copper couple, chlorotrimethylsilane and excess cyclohexene, in the presence of "a catalytic amount of zinc bromide" gave 7-phenylnorcarane, thereby proving the intermediacy of a carbenoid.[121] Accordingly, in the light of this statement, we additionally decided to investigate the effect of added Lewis acids on the rate and efficiency of conversion of aldehydes to alkenes.
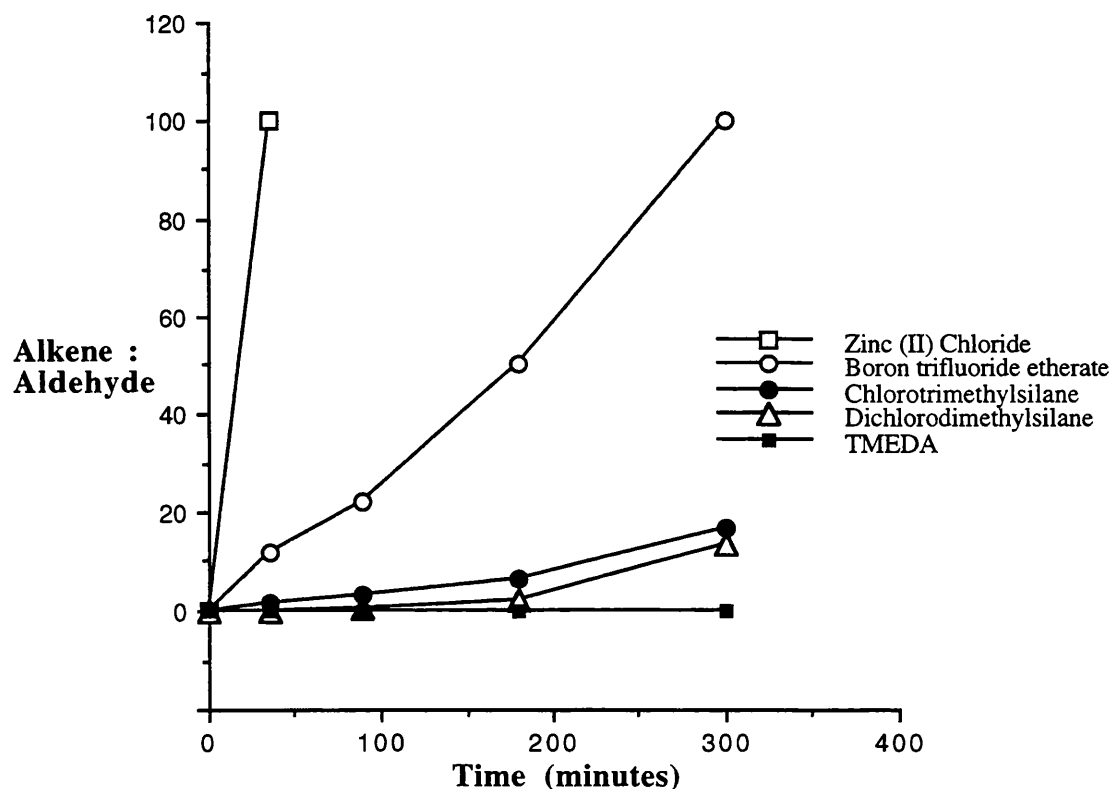
Figure 2.1

The graph in figure 2.1 shows the rate enhancement achieved by the addition of a Lewis acid in the conversion of hexadecanal to 1-hexadecene in ether using

chlorotrimethylsilane. Both zinc chloride and boron trifluoride etherate have a pronounced accelerating effect, reaction being essentially complete (> 98%) in 30 minutes and 3 hours respectively. Since zinc chloride is also generated in any normal reaction, its effect can therefore be considered as autocatalytic. Zinc chloride is also the strongest Lewis acid of the zinc halides in ether solution ($ZnCl_2 \approx ZnBr_2 > ZnI_2$).[122] Elphimoff-Felkin and Sarda have already shown that boron trifluoride etherate may be used in the reduction of aromatic aldehydes to zinc carbenoids,[90] and the acceleration in this instance can also probably have a component due to reduction by this potent oxophile.

Dichlorodimethylsilane is not as efficient as chlorotrimethylsilane, although only 1.3 equivalents were added to the reaction. A vast range of Lewis acids have, of course, been used to accelerate reactions in organic chemistry. However relatively few would be compatible with our reaction conditions, either inducing unwanted side reactions with the starting material, or by themselves being reduced to the metal by the very electropositive zinc (e.g. $TiCl_4$).

Although chloride ion has been shown to accelerate the Clemmensen reduction, Burden and Price have shown that a large excess of zinc chloride (45-fold molar excess over ketone) had a decelerating effect in acetophenone reduction (*c.f.* chapter 1.7.2). This they attributed to complexation of the ketone.[89] It should be emphasised, however, that our reaction conditions are significantly different from those traditionally employed in the Clemmensen reduction. A possible alternative explanation though is that the solvent molecules necessary to stabilise the forming zinc carbenoid are also complexed. These authors had also noted that the deprotonation of the derived carbenoids by the solvent molecules, ethanol and water, was completely eliminated, due presumably to their effective complexation by the added zinc chloride. Structural studies have shown that the coordination of aldehydes by zinc chloride is very poor, although the complexed species show some weakening of the C=O bond, and increasing positive character of the carbonyl carbon.[123] Such increased electrophilicity should render the donation of electrons more facile, and thus account for the increased rate.

The addition of a chelating Lewis base, N, N, N, N-tetramethylethylenediamine, however, inhibits reaction, complexing the Lewis base needed to promote reaction. Work-up after 24 hours afforded unchanged starting aldehyde.

In view of the autocatalytic effect of zinc chloride, we decided to optimise the yield of alkene by slow addition of a solution of hexadecanal to an ethereal suspension of zinc amalgam (10 equivalents), chlorotrimethylsilane (5 equivalents), and zinc chloride (2 equivalents) over 3 hours. However, the yield of alkene remained virtually unchanged at 84%.

2.3.3.3 The Carbenoid derived from 2-Methyl-undecanal

α-Branched aldehydes also react to yield olefins, by preferential α-C-H insertion to yield the *exo*-methylene alkenes (Scheme 2.26). The reaction times are a little longer due to the increased steric hindrance about the carbonyl group. However, in the presence of a trace of acid, isomerisation of the double bond takes place *via* the tertiary carbocation. It should be noted that it is always very difficult to remove adventitious HCl formed *via* partial hydrolysis of the silicon halide during reaction.
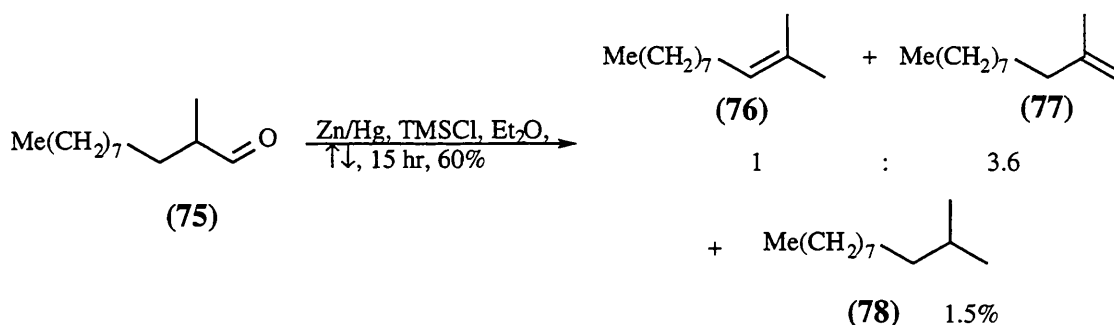
Scheme 2.26

The effect of adventitious HCl in our procedure has been noted previously.[100, 107, 124] Significant quantities of HCl promote pinacolic coupling of stabilised radicals, and smaller quantities lead to isomerisation of double bonds (Scheme 2.27.a)[124] and cleavage of cyclopropanols (Scheme 2.27.b),[107] and even in part to the

formation of full Clemmensen reduction products (Scheme 2.26). Previous work in the group had shown that the isomerisation of the steroidal alkene **(79)** is catalysed in the presence of zinc chloride.[124] No isomerisation to the more stable Δ2 **(80)** or Δ3 **(81)** alkene occurred with zinc chloride or chlorotrimethylsilane alone, but only when both are combined in ethereal solution.

(a)

(b)
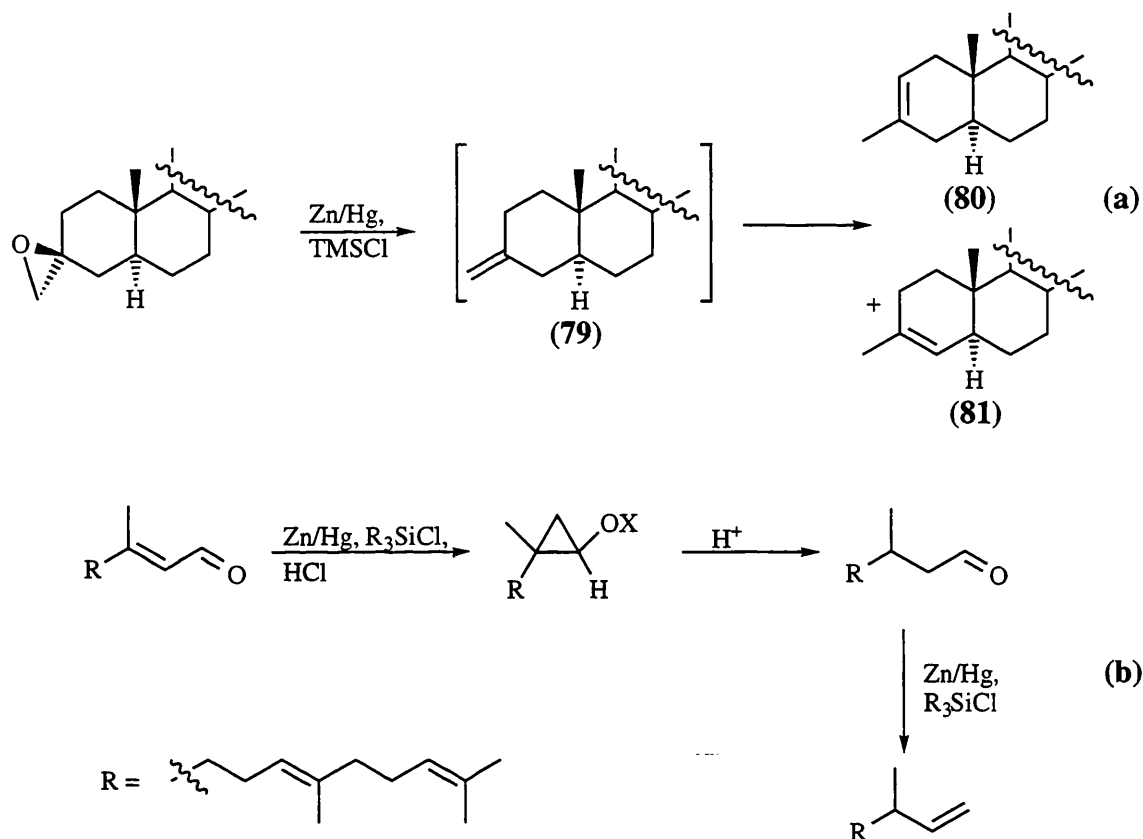
Scheme 2.27

In order to minimise or control the secondary isomerisation and Clemmensen reduction products, a systematic study involving addition of a variety of proton sponges to the reaction of 2-methyl-undecanal **(75)** was carried out. These, however, resulted in a much slower reaction, or had little effect on the isomer ratios (Table 2.5). While Corey *et al.* had used 2,6-lutidine to prevent elimination of the OTMS group (*c.f.* Scheme 2.3.a), we have found amines to have a significant decelerating effect on the reaction (*c.f.* Figure 2.1), and they give primarily the unwanted side products. In the case of propylene oxide

(entries 7 and 8), the additive has a significant beneficial effect, although it does not appear to be a reproducible method of tackling this problem.

Entry	Solvent	Additive	Time (hr)	Yield	(77) : (76)	(78)[†]
1	Et_2O	none	15	60%	1 : 3.6[†]	1.5%
2	THF	2,6 lutidine (3.0 eq.)	60	___	1 : 0[*][§]	___
3	Et_2O	2,6 lutidine (3.0 eq.)	96	___	1 : 0[*][‡]	___
4	Et_2O	2,6 lutidine (0.1 eq.)	42	___	1 : 3.6[†]	2.4%
5	Et_2O	2,6-di-[t]Bu-pyridine (0.1 eq.)	24	___	1 : 1.2[†]	1.4%
6	Et_2O	PVP (1.0 eq.)	18	___	1 : 1[*]	___
7	Et_2O	Propylene oxide (0.2 eq.)	20	68%	3.6 : 1[†]	<1.4%
8	Et_2O	Propylene oxide (1.0 eq.)	18	61%	2.3 : 1[†]	1.7%

[†] Ratios determined by GC

[*] Ratios determined by NMR

[§] Crude NMR shows (77): silyl enol ethers ca. 1 : 1, but major product is pinacol

[‡] Crude NMR shows (77): silyl enol ethers ca. 1 : 6, but mostly unreacted starting material

Table 2.5

2.3.3.4 Reduction of Aldehydes bearing Remote Functional Groups

It was also of interest to study the compatibility of a variety of other functional groups under the reaction conditions (Table 2.6). Thus, the ethyl ester (82) gives the ω-ene-ester (83), along with some Clemmensen reduced product (84) while the [t]butyl ester (85) gives both the ω-ene-acid (86) and the Clemmensen product (87). A primary bromide (88) survives intact to give the terminal alkene (89) in good yield, and more surprisingly, in the presence of zinc, a primary iodide (90) gives a moderate yield of olefin (91). In this instance, it was found that the yield of iodide (91) is significantly

improved by carrying out the reaction with added zinc chloride, giving a 37% yield in 45 minutes, although some Clemmensen product (ca. 8%) is formed. It is one of the inexplicable properties of aldehydes that although the bromo-aldehyde (**88**) and its iodo congener (**90**) differ only in the halogen atom, the iodide may be distilled to give the trimer, while the bromide is trimerised to only 40% after 36 hours in CDCl₃ solution.
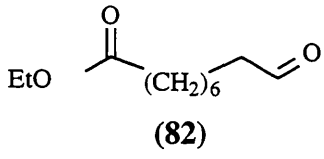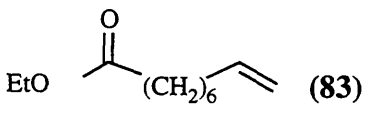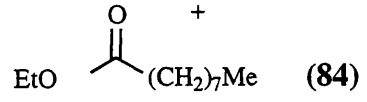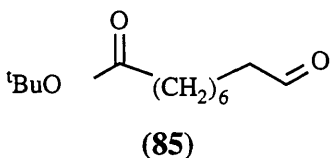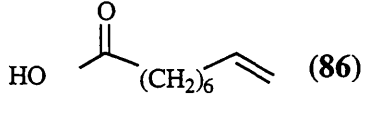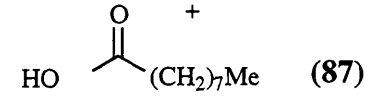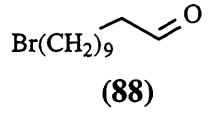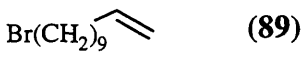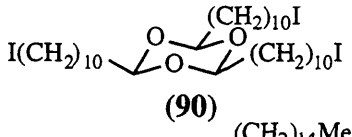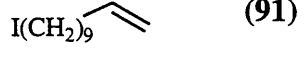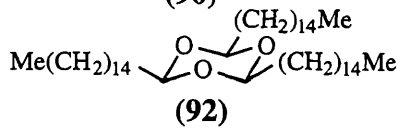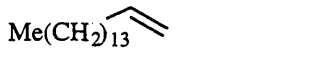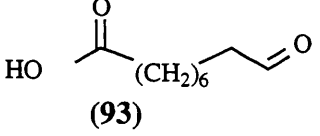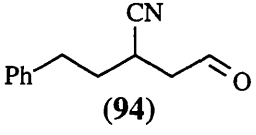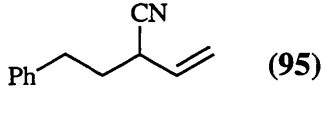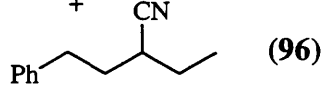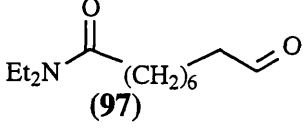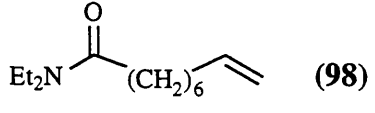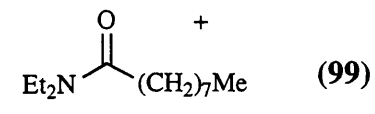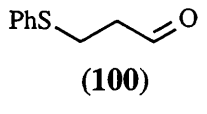
The trimeric could be transformed into hexadecanal trimer (**92**) using the alkyl copper reagents developed by Lipschutz *et al.*[125] (Scheme 2.28). This on subsequent reaction with zinc and chlorotrimethylsilane gave 1-hexadecene, but in a lower yield than the parent aldehyde. The suitability of aldehyde trimers alerted us to the possible use of acetals and ketals as precursors for organozinc carbenoids (*vide infra* chapter 3).

$$I(CH_2)_{10} \overset{(CH_2)_{10}I}{\diagdown O \diagup O \diagup} (CH_2)_{10}I \quad \xrightarrow[\text{THF, Et}_2\text{O, -78°C to r.t.}]{(^nC_5H_{11})_2Cu(CN)Li_2,} \quad Me(CH_2)_{14} \overset{(CH_2)_{14}Me}{\diagdown O \diagup O \diagup} (CH_2)_{14}Me$$

$$\textbf{(92)} \quad 40\%$$
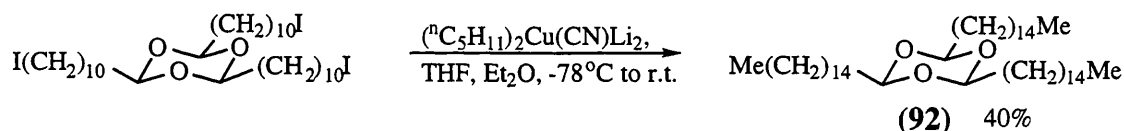
Scheme 2.28

Not surprisingly, the unstable acid (**93**), which is of course a proton source, gave a mixture of alkene (**86**) and fully reduced acid (**87**). The cyano-aldehyde (**94**) was inert under normal reaction conditions, but gave a mixture of carbenoid (**95**) and Clemmensen (**96**) products in a 1:1 ratio with 2 equivalents of added zinc chloride. Amide (**97**) reacted vigorously when added to the zinc amalgam and chlorotrimethylsilane, but a small amount of a mixture of amides (**98**) and (**99**) was recovered on work-up. A study by Hegedus *et al.* has shown that selected tertiary amides could be partially recovered from reaction with Na₂Cr(CO)₅ and chlorotrimethylsilane in THF.[92] It may be that Vilsmeir salt formation ($[R_2N=CRCl]^+.Cl^-$) is possible in our case, and subsequent reduction of this highly electrophilic species is not unlikely. Only phenylthio aldehyde (**100**) gave no alkene on reaction with zinc amalgam and chlorotrimethylsilane, yielding instead intractable material. However, this reaction may be an isolated case as sulfur functionality has been shown to be compatible with similar reaction conditions[126] (*c.f.* also chapter 3.3).

Entry	Substrate	Product(s)		Yield
1	EtO (CH$_2$)$_6$ (82)	EtO (CH$_2$)$_6$ (83) + EtO (CH$_2$)$_7$Me (84)		58% 9 : 1
2	^{t}BuO (CH$_2$)$_6$ (85)	HO (CH$_2$)$_6$ (86) + HO (CH$_2$)$_7$Me (87)		65% 85 : 15
3	Br(CH$_2$)$_9$ (88)	Br(CH$_2$)$_9$ (89)		62%
4	I(CH$_2$)$_{10}$ O O (CH$_2$)$_{10}$I (CH$_2$)$_{10}$I (90)	I(CH$_2$)$_9$ (91)		26% 37%*
5	Me(CH$_2$)$_{14}$ O O (CH$_2$)$_{14}$Me (CH$_2$)$_{14}$Me (92)	Me(CH$_2$)$_{13}$		47%
6	HO (CH$_2$)$_6$ (93)	(86) + (87) 86 : 14		25%
7	Ph CN (94)	Ph CN (95) + Ph CN (96)		23%* 1 : 1
8	Et$_2$N (CH$_2$)$_6$ (97)	Et$_2$N (CH$_2$)$_6$ (98) + Et$_2$N (CH$_2$)$_7$Me (99)		10% 3 : 1
9	PhS (100)	——		

* reaction performed with added zinc chloride (2 eq.)

Table 2.6

Although the reaction of 2-methyl-undecanal gave a minor amount of Clemmensen product (1.5%), many of the substrates containing polar groups yielded large amounts of fully reduced materials (14-50% of isolated product). It may well be that these substrates are somewhat hygroscopic, and the solvated water then liberates hydrogen chloride *in situ*. This adventitious acid is then responsible for the somewhat modest yields in such cases.

Although many additives e.g. $CaCO_3$, amines and propylene oxide have been tested in the present work, and previously, to neutralise the effect of acid, they do not eliminate the proton source. In retrospect, however, a possible solution to this problem may be found in the addition of an organometallic base. A compound with low nucleophilicity such as diethylzinc might be ideal, and would also allow the reduction of acid as their zinc salts, being readily hydrolysed on work-up.

From the results detailed above it is apparent that the reactions of organozinc carbenoids are more susceptible to strain influences than their free carbene counterparts, with much greater preferences for 1,2-C-H insertion over all other common free carbene modes, i.e. 1,3- and 1,5- insertion. We have also developed a general synthesis of terminal alkenes, although further work remains to be done to halt the isomerisation of *exo*-methylene alkenes, and full Clemmensen reduction in certain cases. Of further note is the rate enhancing effect of added Lewis acids, particularly zinc chloride, which has enabled the preparation of alkenes with sensitive halide functionality in increased yield.

3

The use of the Acetal Function

as a Carbenoid Synthon

3.1 Use of the Acetal Function as a Carbenoid Synthon

Although selected examples of the conversion of carbonyl groups to carbenoids have been published,[92, 93] the same authors have also realised the potential utility of the acetal function.[92, 93a] The groups of both Hegedus and Hossain have converted such compounds to metal carbenoids *via* their carboxonium salts (Scheme 3.1).[92, 93a] Both routes rely on the isolation of the metal carbene, or a precursor intermediate prior to carbene transfer.
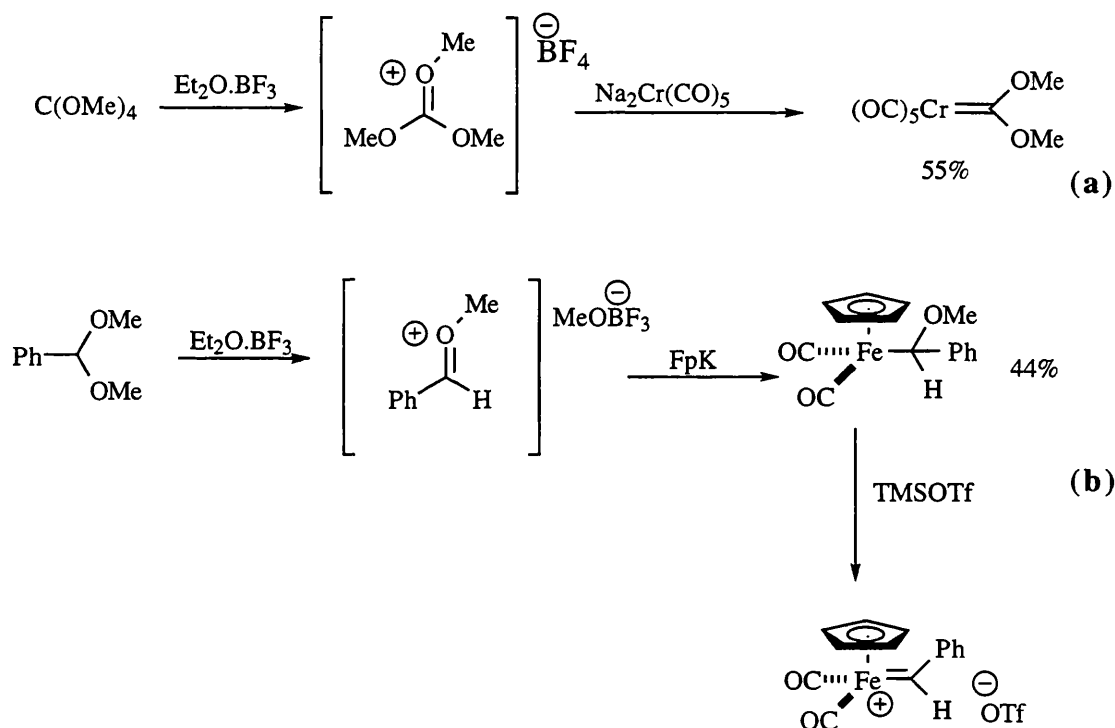
Scheme 3.1

As we have seen in chapter 2 during the course of investigations on the conversion of aldehydes into terminal alkenes, we had noted that trimeric acetal derivatives could also be used as carbenoid synthons. Although, in this case, the reduction may occur *via* the parent aldehyde, we were therefore alerted in a direct manner to the possible uses of acetals as suitable precursors for zinc carbenoid generation.

From a mechanistic standpoint, it could be considered that the oxonium ion **(101)**, generated *via* coordination of a Lewis acid to the acetal, should be readily reduced by the zinc (Scheme 3.2).

We reasoned that such an electrophilic species might also undergo direct two electron reduction by zinc to the carbenoid, without any necessity for passage through radical intermediates such as **(102)**, and without formation of the initial zinc-oxygen bond which has been postulated in the reactions of the carbonyl group.[89]
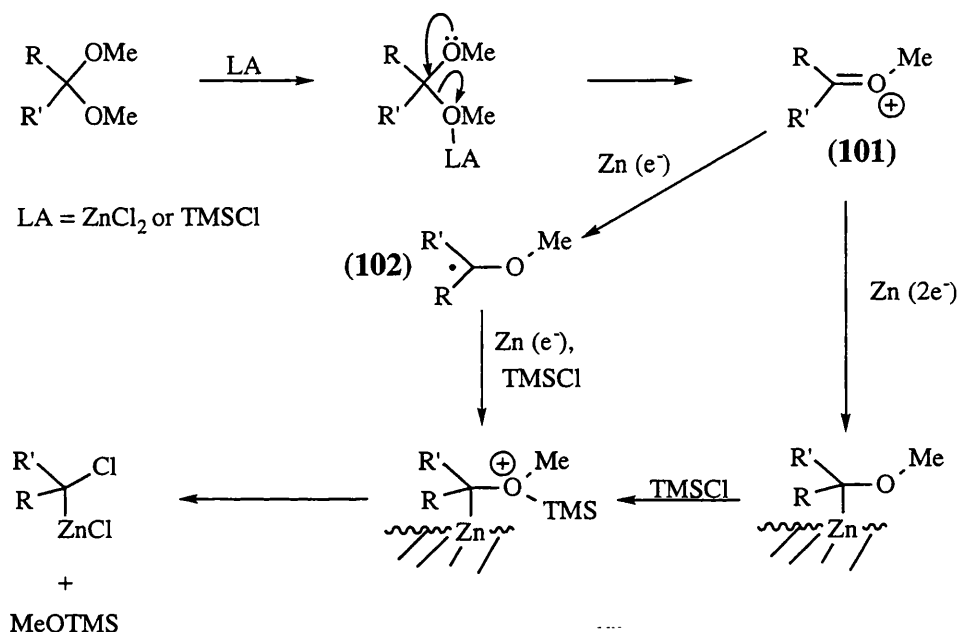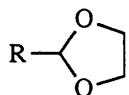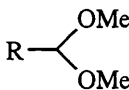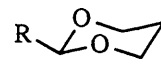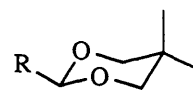
Scheme 3.2

3.2 Aldehyde Acetals

Armed with this mechanistic postulate, we decided to examine the behaviour of four of the more common acetal protecting groups using hexadecanal as substrate. Each of them was then reacted in turn with zinc amalgam and chlorotrimethylsilane under the standard conditions used for hexadecanal itself. The yields and reaction times are shown in Table 3.1.

Me(CH$_2$)$_{13}$ ┉ OR' $\xrightarrow[\text{Et}_2\text{O, reflux}]{\text{Zn/Hg, TMSCl}}$ Me(CH$_2$)$_{13}$ ┉
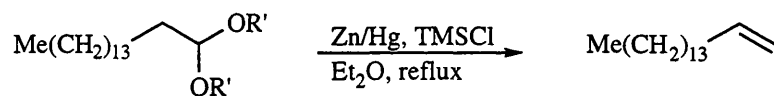
Entry	Substrate	Time (hr)	Yield
1	R—⟨O O⟩ (1,3-dioxolane)	17	86%
2	R—C(OMe)(OMe)	20	62%
3	R—(1,3-dioxane)	36	6% (84%)*
4	R—(1,3-dioxane, gem-dimethyl)	60	14% (80%)*

R = Me(CH$_2$)$_{13}$–

* figures in parentheses are yields of recovered starting material

Table 3.1

It was very encouraging to note that the reaction of the 1,3-dioxolane and dimethyl acetals gave good yields of terminal alkenes, which were comparable to the parent aldehyde itself. Of equal interest, however, was the considerable reluctance of the 1,3-dioxane acetals to undergo reaction to any extent. The relative rates of ring opening and stability of the acetals is of course of paramount importance to successful generation of a carbenoid, and we will return to this aspect later.

3.3 Ketals

92

Encouraged by the results from the aldehyde acetals, we decided to subject an identical series of ketals to the same conditions. 4-^{t}Butyl-cyclohexanone was selected as the parent compound and the rather volatile alkene product formed, 4-^{t}butyl-cyclohexene, was routinely isolated as the *trans* dibromide **(103)**. A control experiment, using an authentic sample of 4-^{t}butyl-cyclohexene gave the *trans* dibromide **(103)** in 93% yield (Scheme 3.3).

Br$_2$, Et$_2$O
r.t., 15 mins.

93%

(103)
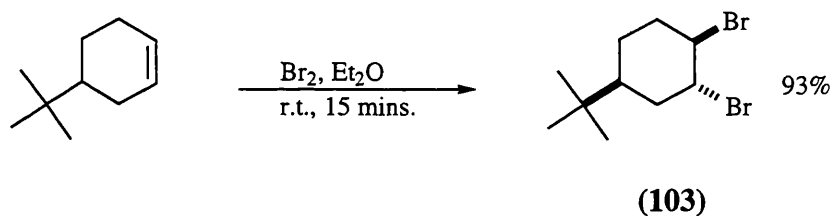
Scheme 3.3

The results for the four ketals are shown in Table 3.2 and display a marked contrast to those from the series of aldehyde acetals, inasmuch as all four derivatives gave acceptable yields of alkene in essentially comparable yield.
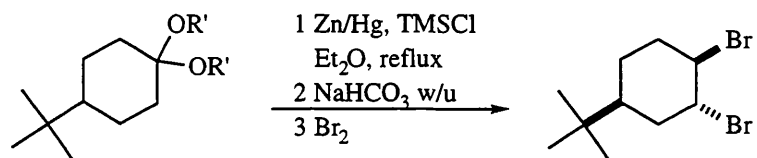
Entry	Substrate	Time (hr)	Yield
1		16	59%
2		16	56%
3		14	50%
4		17	52%

Table 3.2

3.4 A Mechanistic Rationale for the Observed Selectivities

At this stage it was important to verify that in the above reactions, the mechanistic pathway did not simply involve some form of acetal or ketal deprotection. In this respect, although Olah *et al.* have reported the deprotection of dimethyl acetals to the parent carbonyl compounds using sodium iodide and trichloromethylsilane in acetonitrile (Scheme 3.4),[127] we considered that in the absence of such a potent electrophile, this reaction was unlikely to occur in our own case.

i) NaI, MeSiCl$_3$, MeCN, r.t., 1 hr.
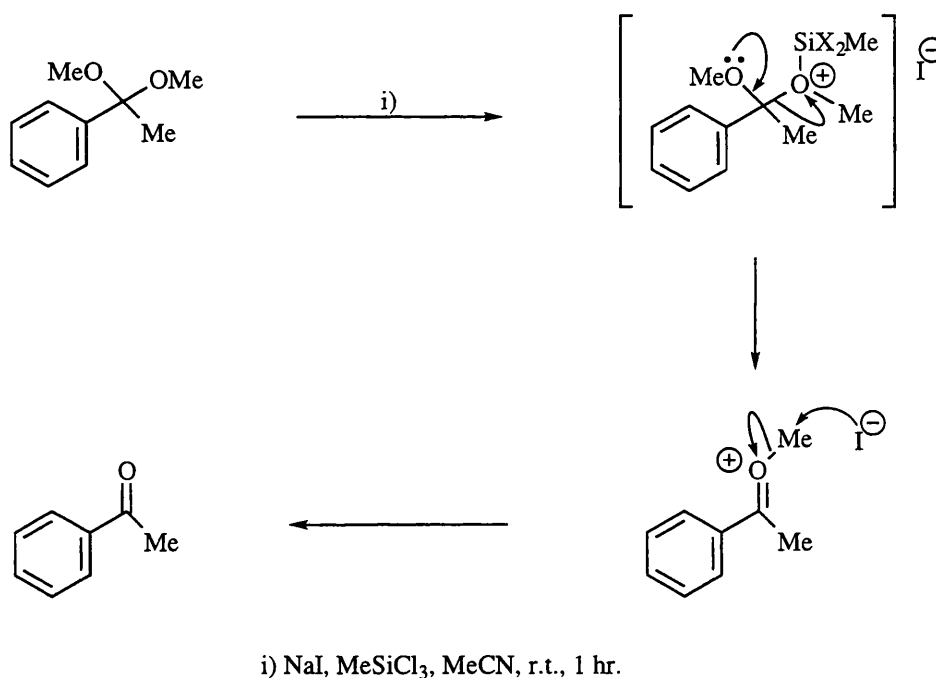
Scheme 3.4

However, in order to examine this possibility, a series of NMR experiments of the reaction of 2-pentadecyl-1,3-dioxolane **(104)** with chlorotrimethylsilane (22.5 hours) or with zinc chloride-chlorotrimethylsilane (15 hours) in THF-d$_8$ showed unchanged starting material, thereby indicating that the reaction does not proceed *via* conversion to the aldehyde or ketone prior to reduction (Scheme 3.5).

Me(CH₂)₁₃ —\/\— (O / O ring structure)

(104)

i) TMSCl, THF-d₈, r.t.
ii) ZnCl₂, r.t. ──────────→ No reaction
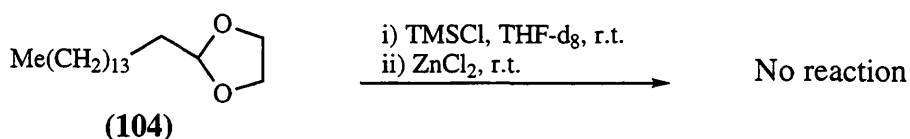
Scheme 3.5

The lower polarity of ether solvents, coupled with the lower nucleophilicity of chloride ion, and the decreased electrophilicity of chlorotrimethylsilane, particularly in the case of the *neo*-pentylic 5,5-dimethyl-1,3-dioxane acetals rendered such a pathway very unlikely indeed (Scheme 3.6).
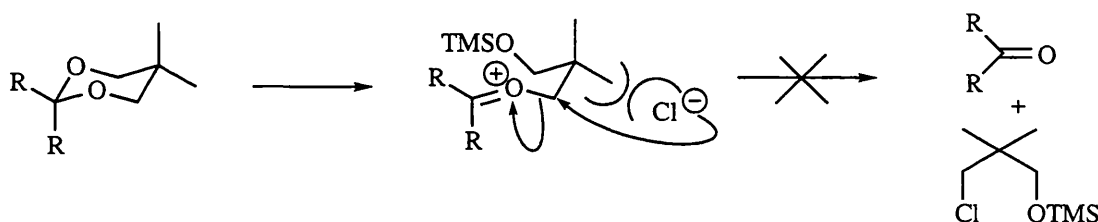
Scheme 3.6

The stark contrast between the behaviour of the aldehyde acetals and the ketal derivatives is certainly worthy of detailed comment. In the first instance, the more bulky ketone acetals are reduced more quickly. Such an observation is in keeping with the generally faster rates of hydrolysis of ketals relative to acetals.[128] This is due to the greater stabilisation of positive charge in the rate determining cleavage to the oxonium ion. Acid catalysed hydrolysis rates have been observed to be in the general order: $RC(OR')_3 > R_2C(OR')_2 > RCH(OR')_2 > H_2C(OR')_2$. The conversion of all ketal derivatives relative to the reluctance of certain acetals most probably involves similar phenomena.

The second difference is that the breakdown of the aldehyde dioxanes is very slow, especially compared to the other aldehyde acetals, and the ketal dioxane derivatives. It should be remembered, however, that aldehydes and ketones show different product preferences in the formation of cyclic acetals. Thus the reaction of ketones and aldehydes with 1,2,3-triols produce predominantly the 1,3-dioxolane **(105)**

and the 1,3-dioxane (106) derivatives respectively as shown for the simplest case of glycerol (Scheme 3.7).[129]

Examination of the steric requirements show that severe 1,3-diaxial interactions are present in the ketone dioxane (107) in chair conformations and a very unfavourable 1,4 interaction is present in the boat conformation (Scheme 3.7). The relief of ring strain in opening such derivatives is therefore considerable and accordingly such ketal derivatives can undergo reductive deoxygenation. Such severe interactions are not present in the analogous aldehyde acetal derivatives (106) or (108), and there is consequently less ring strain in the dioxane (106).

(107)

(105)   (106)   (108)
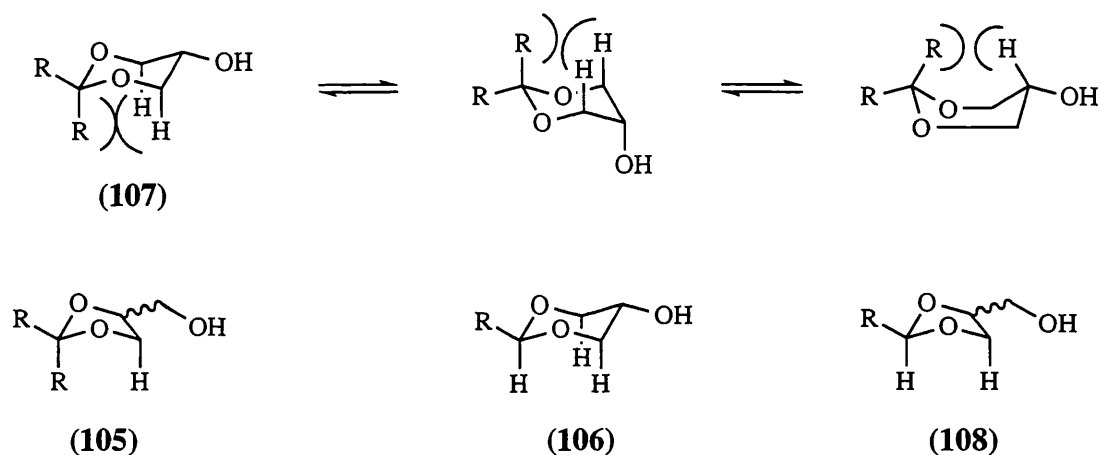
Scheme 3.7

The observed relative rates of reductive deoxygenation can be therefore correlated with the corresponding rates of cleavage which are a reflection of the relative stabilities of the acetal derivatives. The slower rate of cleavage of the ketone 5,5-dimethyl-dioxane compared to its nor-methyl derivative (Table 3.2, entries 3,4) can be attributed to the gem-dialkyl or Thorpe-Ingold effect,[130] and has also been observed for the acid catalysed hydrolysis of the respective cyclohexanone derivatives.[131]

The relative increase in the stability of the aldehyde dioxane acetals under reductive deoxygenation conditions may be due not only to the relative stability effects mentioned above, but also to the stereochemistry of coordination of the Lewis acid.[132] Since the more basic lone pairs of an acetal are those which are not in an antiperiplanar

relationship to the other C-OR bond, preferential protonation or coordination of Lewis acid may be expected on such lone pairs. However, in the dioxanes, the coordination to such axial lone pairs would introduce a severe 1,3-diaxial interaction, especially in the case of the *gem*-dimethyl derivative. This would of course be absent in the dioxolane acetal (Scheme 3.8). A combination of both effects – *viz.* the inherent stability of the six-membered ring and the preferred site of Lewis acid coordination on the less basic lone pair – may therefore both be responsible for the observed stability of the aldehyde dioxane acetals in the presence of silicon electrophiles and zinc chloride.
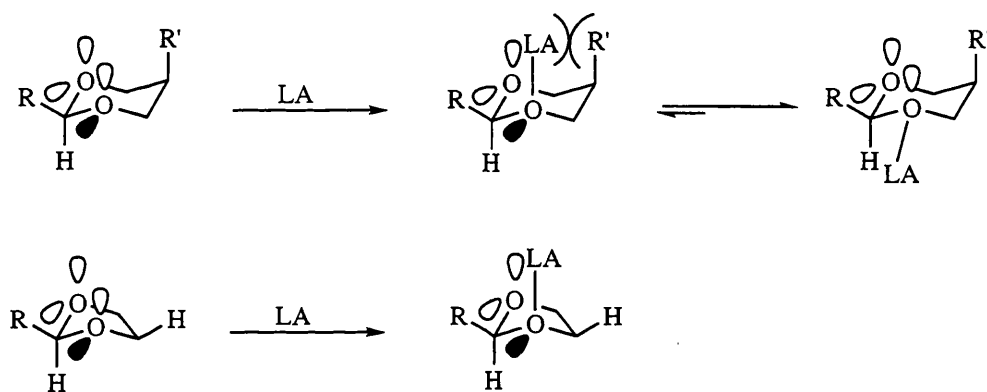
Scheme 3.8

The relatively slow rates and the lower yields observed in the case of the dimethyl acetals is somewhat surprising in view of the fact that the hydrolysis of dimethyl acetals is known to be more rapid than their cyclic congeners due to the positive contribution by the entropy factor.[133]

The virtually identical yields of alkene afforded by hexadecanal and the dioxolane acetal suggests that the cyclic acetal is a suitable substrate when the use of aldehydes is precluded due to their facile oxidation or propensity for aldol condensation.

Recognising that the selection of dichlorodimethylsilane and a cyclic acetal could lead to intramolecular delivery of the second silicon electrophile, (104) was subjected to the conditions shown in Scheme 3.9. Additionally, the presence of the second oxygen heteroatom in the silicon intermediate (109) should also make it more susceptible to

nucleophilic displacement.[134] The isolated yield of alkene is, however, identical to that using chlorotrimethylsilane (see Table 3.1).
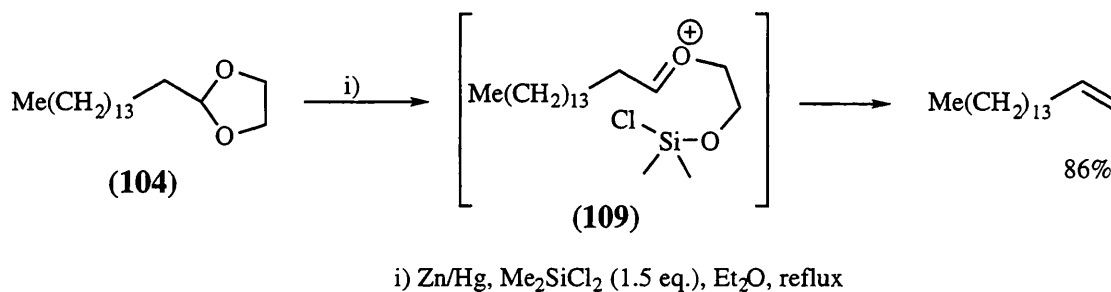
i) Zn/Hg, Me$_2$SiCl$_2$ (1.5 eq.), Et$_2$O, reflux

Scheme 3.9
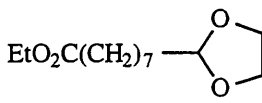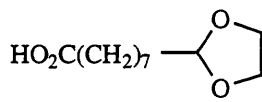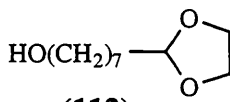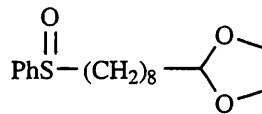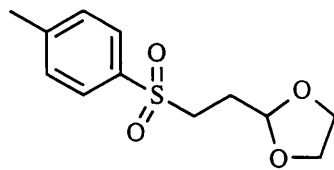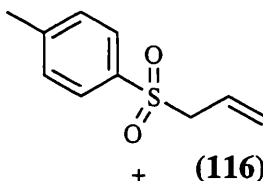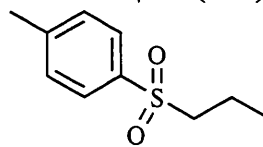
3.5 Remotely Functionalised Acetals

In view of the excellent yields shown with the parent aldehyde dioxolane acetal, we then decided to subject a variety of acetal substrates containing other remote functional groups to these conditions, especially those whose aldehyde derivatives were easily oxidised or difficult to purify. The results of this study are shown in Table 3.3.

In the first instance it was gratifying to note that both the ester **(110)** and the acid **(111)** derivatives (entries 1 and 2) gave better yields than their aldehyde counterparts (*c.f.* Table 2.6), and the ester now contained half the quantity of Clemmensen product seen with the aldehyde. The ω-hydroxy-dioxolane **(112)**, prepared from the easily oxidised aldehyde gave a rather modest yield of alkene and Clemmensen product. This modest yield (34%) may be due in part , however, to the volatility of the products.

The sulfoxide **(113)** gave the doubly reduced alkene thioether **(114)**,[126] and the rather unreactive sulfone **(115)** gave some terminal alkene **(116)** along with an abnormally large amount of fully reduced Clemmensen product **(117)**.

Entry	Substrate	Product(s)	Yield
1	$EtO_2C(CH_2)_7$ —[1,3-dioxolane] (110)	$EtO_2C(CH_2)_6$ (alkene) + $EtO_2C(CH_2)_7Me$	77% (58%)[§] 20 : 1
2	$HO_2C(CH_2)_7$ —[1,3-dioxolane] (111)	$HO_2C(CH_2)_6$ (alkene) + $HO_2C(CH_2)_7Me$	50% (25%)[§] 85 : 15
3	$HO(CH_2)_7$ —[1,3-dioxolane] (112)	$HO(CH_2)_6$ (alkene) + $HO(CH_2)_7Me$	34% 7 : 3
4	$PhS(=O)(CH_2)_8$ —[1,3-dioxolane] (113)	$PhS(CH_2)_7$ (alkene) (114)	23%
5	[tolyl-SO_2-(CH_2)_2-(1,3-dioxolane)] (115)	[tolyl-SO_2-allyl] (116) + [tolyl-SO_2-propyl] (117)	24% (68%)* 1 : 7

[§] figures in parentheses are yields for aldehyde congener

* figure in parenthesis is yield of recovered starting material

Table 3.3

In summary we have seen that the acetal group is an acceptable, and in some cases, superior precursor for the generation of organozinc carbenoids. This direct and straightforward route contrasts favourably with the multistep sequences using transition metal carbonyls. The mechanism of the reduction of acetals and ketals by zinc is also

significantly different from the postulated mechanistic pathway for the parent aldehydes

and ketones. Here the acetal or ketal is reduced without the formation of an initial zinc-

oxygen bond, and the identity of the carbenoid may indeed be somewhat different.

4

Cyclopropanation Reactions using

Organozinc Carbenoids

4.1 Cyclopropanation of Simple Alkenes

The development of 1,2-*bis*-chlorodimethylsilylethane as a bidentate silicon electrophile has led to the use of aromatic aldehydes for the cyclopropanation of alkenes (*vide supra* chapter 2.1.2). The reaction was compatible with a range of simple olefins and enol acetates.[106, 107] In common with the work carried out on the dicarbonyl coupling reaction, a similar variety of enones and enals could also be used as precursors to zinc carbenoids.

In parallel with the published work of my colleague,[106, 107] Dr. Lee Roberts, a fundamental study was undertaken to examine the inherent steric and electronic effects of the alkene component in the cyclopropanation reaction. Thus, subjecting a series of simple aliphatic alkenes to reaction with the carbenoid derived from *p*-anisaldehyde demonstrated a marked substrate selectivity as a result of steric and electronic factors (Scheme 4.1).
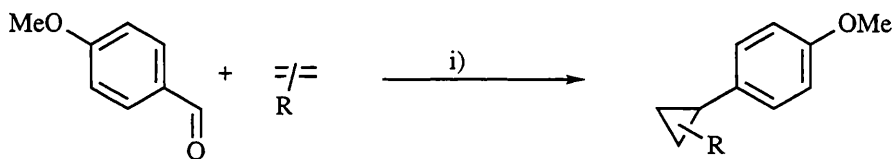
Substrate	Yield	Ratio (*syn* : *anti*)
^nBu $\diagup$ $\diagdown$ ^nBu	57%	44:1
^nBu $\diagdown$ $\diagup$ ^nBu	20%	—
$H_{13}C_6$ $\diagup\diagdown$ *	25%	5.0:1

i) Zn/Hg, $(ClMe_2SiCH_2)_2$, Et_2O, 36 hr, reflux, alkene (2 eqs.)
* Me_2SiCl_2 used as the silicon electrophile

Scheme 4.1

The marked difference in isolated yield between *cis*-5-decene and 1-octene may perhaps be attributed to the pronounced electrophilicity of our organozinc carbenoids, inasmuch as the *cis* disubstituted alkene is more electron rich, a pattern of behaviour in keeping with many transition metal carbenoids.[24, 49a,b] The greater efficiency of *cis* over *trans* alkenes observed here is also a general feature for transition metal carbenoids, and demonstrates the sterically sensitive nature of the transition state. GC analysis of the reaction of *cis*- and *trans*-5-decene revealed that no isomerisation about the original double bond had taken place, an indication of the essentially 'singlet' nature of our organozinc carbenoids.

Although the singlet/triplet nature of free carbenes is important in the cyclopropanation of alkenes, the loss of double bond geometry *via* a biradical intermediate is not an important pathway for metallocarbenoids.[49a] In comparing

transition metal carbenoids with free carbenes, the singlet/triplet distinction has been related to the bonding relationship with the metal: those with a donor-acceptor relationship, e.g. Fischer carbenes have sometimes been termed 'singlet' metal carbenes, while those with a more covalent bonding pattern, e.g. Schrock alkylidenes have occasionally been referred to as 'triplet' metallocarbenoids.[135]

However, isomerisation about a double bond can occur in the cyclopropanation reactions of some metallocarbenoids, especially where the carbenoid is very electrophilic and the alkene bears substituents that readily stabilise a positive charge. No detectable isomerisation (> 2%) occurs about the double bond, however, when the electrophilicity of the carbenoid is reduced as in (118), or the alkene is not so electron rich as in (119) (Scheme 4.2).[136]
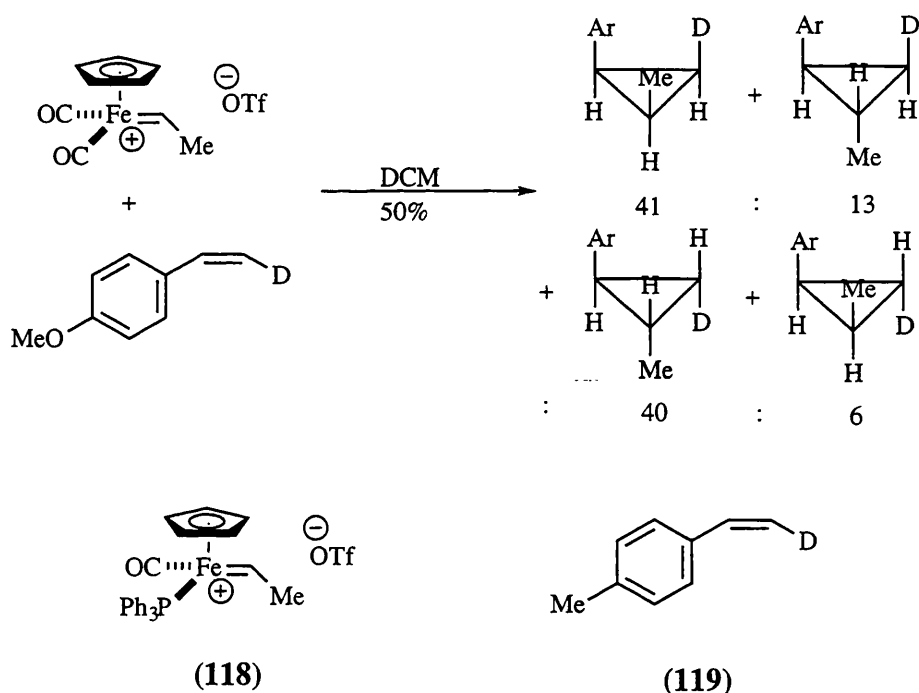
Scheme 4.2

The reaction of catalytic keto-carbenoids with electron rich alkenes can lead to a severe distortion of the cyclopropanation pathway,[49a, 137] giving dihydrofurans *via* a more polar transition state (Scheme 4.3).[137]

MeO

MeO

$+$ EtO$_2$C$\diagup\!\!\diagdown$N$_2$

$\xrightarrow[\text{DCM}]{\text{Rh}_2(\text{OAc})_4}$

MeO

MeO

O OEt

90%

ML$_n$,
-N$_2$

via

$\begin{bmatrix} \text{MeO} \quad \text{H} \quad \text{OMe} \\ \text{L}_n\text{M} \quad \delta+ \\ \text{H} \quad =\!\!\text{O} \\ \text{EtO} \end{bmatrix}$ $\longrightarrow$

MeO

MeO

$\overset{\ominus}{\text{ML}_n}$

O OEt

$\oplus$

-ML$_n$
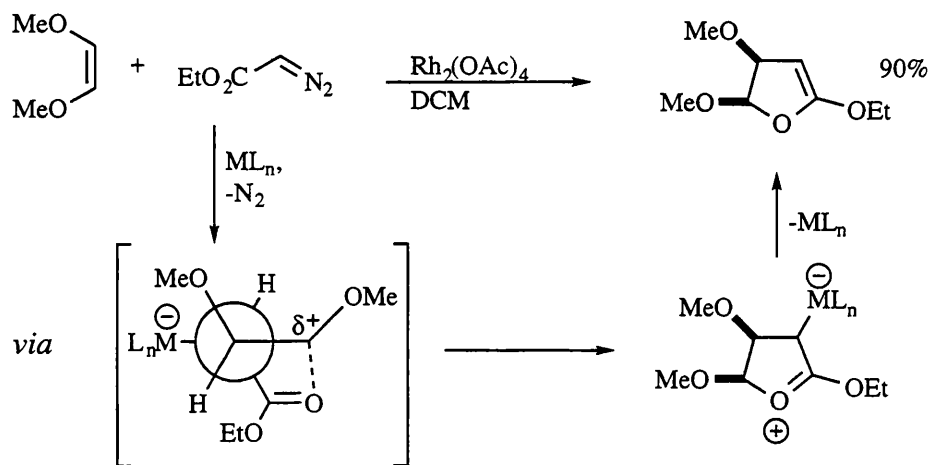
Scheme 4.3

In terms of stereoselectivity, examination of the reactions of a variety of stoichiometric metal carbenoids reveals a general preference for formation of the more hindered *cis* or *endo* isomer.[24] This observation is also true for zinc carbenoids formed from *gem*-dihaloalkanes and diethylzinc,[72] diazo compounds and zinc (II) salts,[71a] or aromatic aldehydes with zinc and boron trifluoride etherate.[90b] The reactivities of a variety of stoichiometric transition metal carbenoids suggest that a mechanism involving nucleophilic attack by the alkene on the carbene complex without formation of a metallocyclobutane but with substantial charge buildup in the transition state (120), and asynchronous bond formation, may be possible (Scheme 4.4).[24]

L$_n$M$=\!\!\!<^{\text{R}}_{\text{R}}$ $+$ $^{\text{H}}_{\text{R'}}\!\!>=\!\!<^{\text{H}}_{\text{H}}$ $\longrightarrow$

$\begin{array}{c} \overset{\ominus}{\text{L}_n\text{M}} \overset{\delta+}{\underset{\alpha}{-\text{C}}}\!\!-\!\text{R} \\ | \quad \text{H} \\ \delta+ \quad \text{C} \\ \text{H}\cdots\text{C}_2 \quad \text{H} \\ \text{R'} \end{array}$

(120)
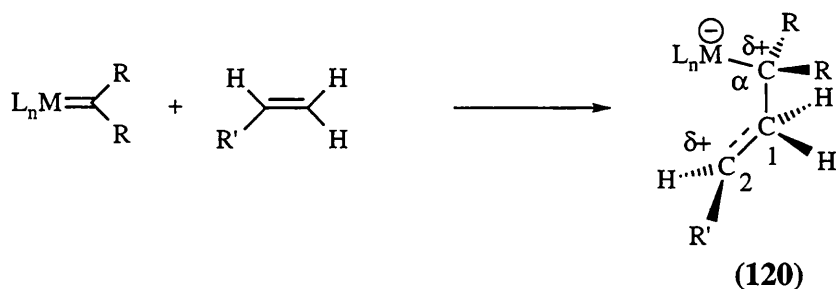
Scheme 4.4

Subsequent formation of cyclopropane from (120) must then involve formation of a carbon-carbon bond between C$_2$ and C$_\alpha$ with concomitant loss of the ML$_n$ fragment. Two stereochemically distinct modes of ring closure can be considered. In the first of

these (path A), a frontside attack on the developing electrophilic centre at C_2 on the M-C_α bond may occur to yield cyclopropane. The second route (path B), is a rearside closure inverting the stereochemistry at C_α (Scheme 4.5). For the symmetrical metallocarbenoid and the monosubstituted alkene shown, both routes lead to an identical cyclopropane.

Path A   Path B
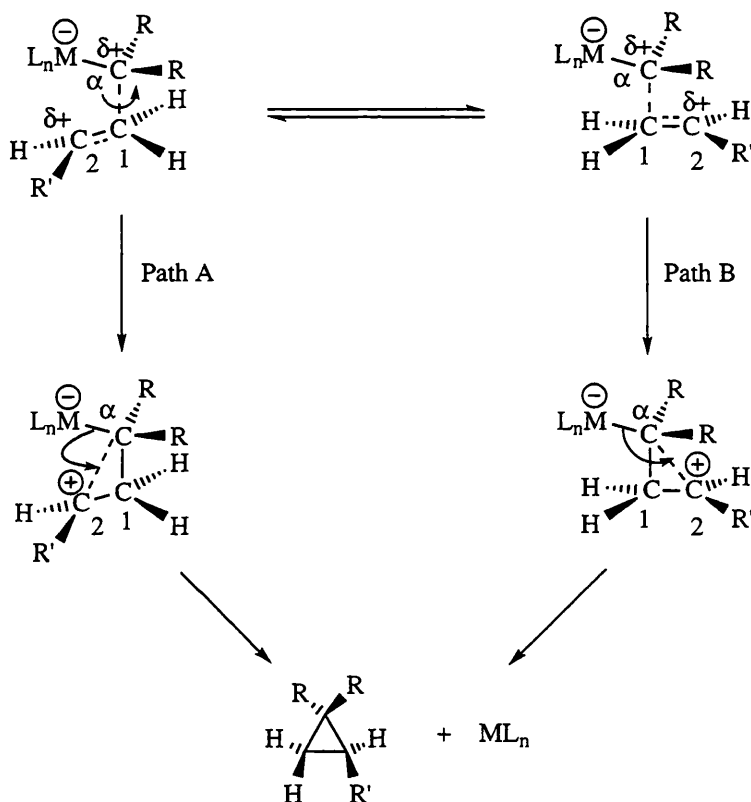
Scheme 4.5

The interpretation of such a model in our case leads to the four possible transition states shown for the reaction of an organozinc carbenoid with cyclohexene (figure 4.1). Unfortunately, however, predictions based on this model would seem to contradict the previously observed *endo* preference (*c.f.* chapter 2.1.2). Ring closure to the cyclopropane in either a frontside or rearside manner should then occur to place the aromatic substituent in the sterically more favourable *exo* position.

rearside

favoured ?

frontside

favoured ?
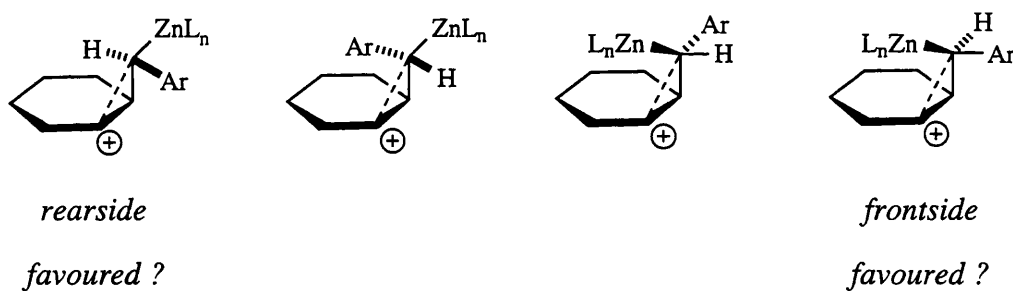
Figure 4.1

However, a mechanistic model advanced by Casey *et al.* for the preferential *syn* selectivity of a tungsten phenylcarbene complex neatly fits our observations, and relies on two competitive pathways where relative rates are determined by a combination of steric and electronic effects.[32] In the simplest case, that of a monosubstituted alkene, four possible transition states can be proposed (Figure 4.2).

A

B

C

D
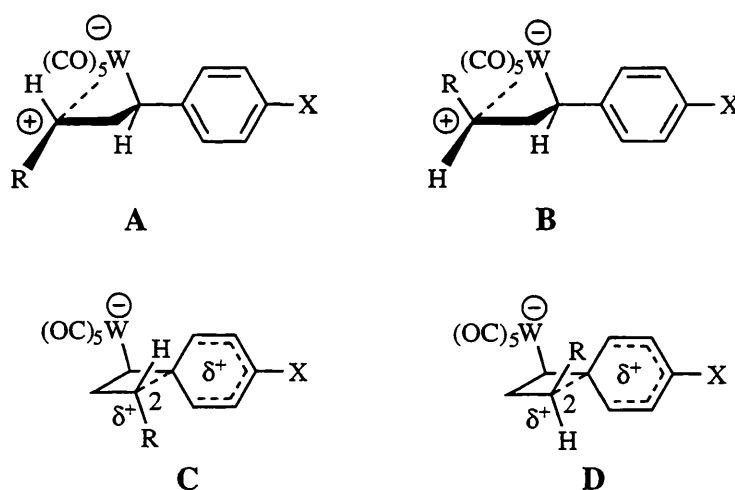
Figure 4.2

However, preferential approach of the alkene will occur to place the alkyl substituent away from the metal, and transition state **A** will be most favoured on steric grounds. Transition states **B** and **D** have the alkyl substituent *syn* to the metal, and are sufficiently high in energy to have little influence on the overall *cis/trans* ratio. As the bulk of the alkyl substituent increases, path B will become more dominant resulting in more formation of the *trans* isomer (Scheme 4.6). However, in less sterically demanding

107

cases, the developing positive charge on the alkene may be stabilised through electron donation from the aromatic ring *via* the *ipso* carbon **(121)**, resulting in the formation of the more hindered *syn* isomer (Scheme 4.6). Since this interaction becomes more important with increasing electron release from the aromatic ring (OMe > Me > H > Cl), this leads to preferential formation of the *cis* isomer in the pattern we have already seen (*vide supra* chapter 2.1.2). Once again, the cyclopropane may be formed *via* frontside attack, or through a discrete metallocycle which may be involved after the transition state. There is no evidence however, either for or against the existance of such intermediates.

Path A   Path B

+

(121)

Cis   Trans
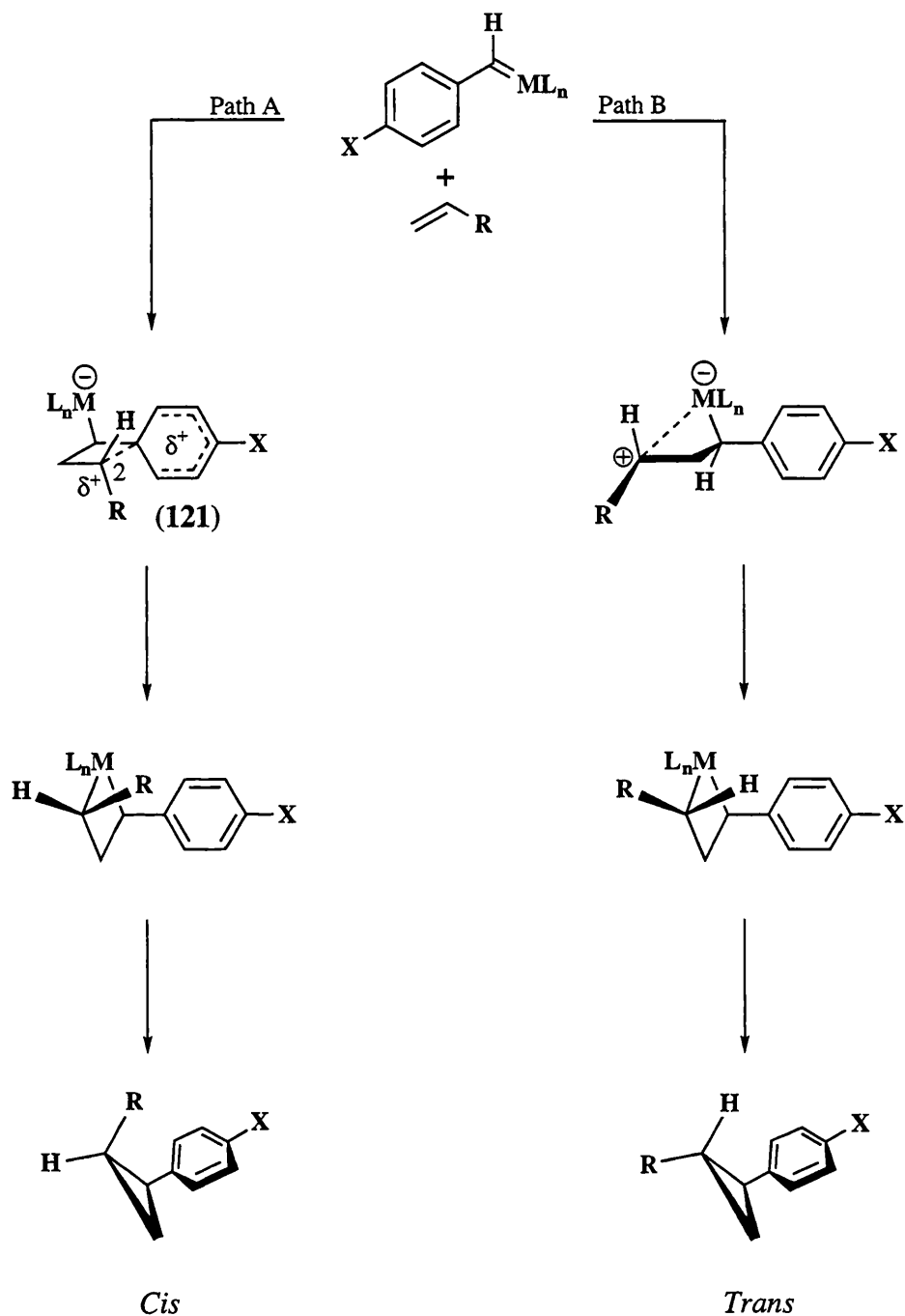
Scheme 4.6

This model also rationalises the observation that the *cis* alkene gives a greater yield than the *trans* as a result of the obligatory *syn* orientation of the alkyl groups with the metal of the transition state. Although a monosubstituted alkene will approach the carbene complex with the alkyl group preferentially *anti* to the metal, a stabilising *ipso* interaction is also available in the 1,3-*syn* position (Figure 4.1.**B**). A *cis* disubstituted

alkene would, however, suffer a far greater destabilising interaction in this conformation because of the extra prohibitive 1,2-*syn* interaction with the metal, (122), thus resulting in a much higher *syn* preference than that observed for the monosubstituted alkene.
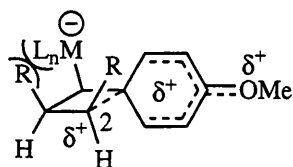
(122)

The very high *syn* selectivity exhibited for *cis*-5-decene (44:1) is the highest we have obtained so far for an aromatic aldehyde. Performing the reaction with *p*-chlorobenzaldehyde, however, gave a *syn:anti* ratio of 2.8:1, showing the overwhelming importance of *ipso* stabilisation.
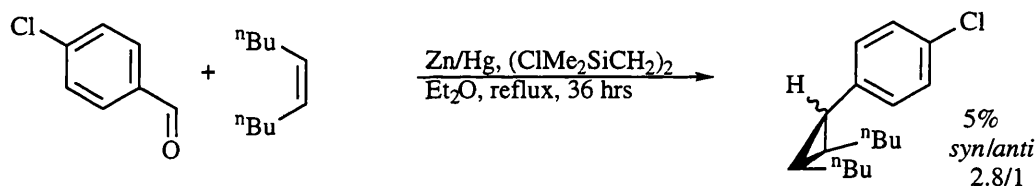
Scheme 4.7

Although the use of 1,2-*bis*-chlorodimethylsilylethane enabled the efficient generation of carbenoids from aromatic aldehydes, the resultant siloxane byproducts caused severe problems in the separation of pure cyclopropanes (*vide supra* chapter 2). The use of a variety of work-up procedures did not alleviate this problem. Again the use of dichlorodimethylsilane as a replacement *bis*-silicon electrophile allowed clean generation of the carbenoid with minimal loss of efficiency (Scheme 4.8), and much simpler purification procedures.
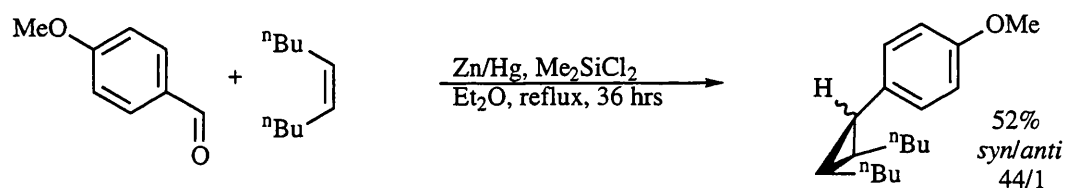
Scheme 4.8

In view of the long addition time required for optimal yields of cyclopropanes (36 hours), we attempted to shorten this period using added zinc chloride. However, addition of *p*-anisaldehyde over 9 hours to a solution of dichlorodimethylsilane, *cis*-5-decene and two equivalents of zinc chloride gave a much reduced yield of the desired cyclopropanes (30%).

It was also of interest to extend the range of alkene substrates to encompass silyl enol ethers. However, even although a simple enol acetate had been shown to perform well,[106] attempts to trap the carbenoid derived from *p*-anisaldehyde with silyl enol ethers **(123)** and **(124)** failed; presumably due to polymerisation or acid-catalysed ring-opening of the derived cyclopropanes (*vide supra* chapter 2.3.3.3).

(123)   **(124)**
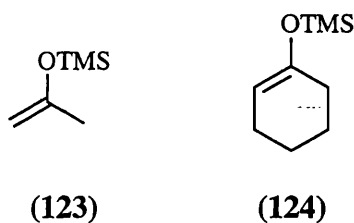
4.2 Cyclopropanation using Acetals

Our success in the use of aliphatic acetals as precursors for organozinc carbenoids prompted an exploration of their use in cyclopropanation. Coupled with this was the possibility that if the true carbenoid could be considered as (125), then the selection of the acetal precursor would lead to an entirely different steric environment around the crucial carbon atom to be delivered to an alkene (Scheme 4.9).
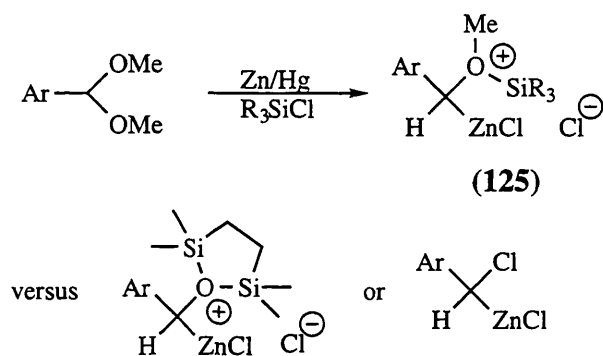
Scheme 4.9

Such a difference in the steric environment might be anticipated to have a significant effect on the *syn/anti* isomer ratios in the cyclopropanation of olefins. In the event, addition of *p*-anisaldehyde dimethyl acetal to styrene and dichlorodimethylsilane in ether at reflux under the usual conditions for cyclopropanation gave a mixture of *cis* and *trans* cyclopropanes in 40% yield (Scheme 4.10).

40% *cis/trans*
4.6/1
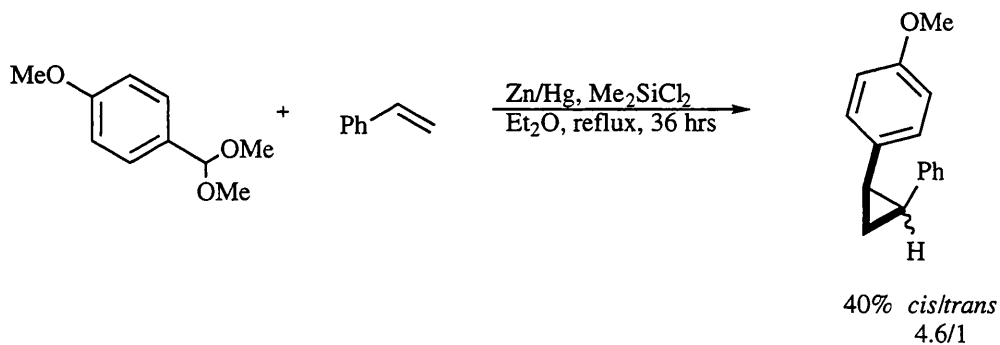
Scheme 4.10

We reasoned that the modest yield of cyclopropanes was due to the slower generation of the zinc carbenoid from the acetal, and that the addition of a Lewis acid should encourage more rapid formation of the oxonium ion. In the event, the addition of 2 equivalents of zinc chloride did lead to a significant improvement in yield (73%), and also to an enhancement in the *cis/trans* ratio of cyclopropanes (11.5:1). At the present time it is not clear why the stereoselectivity of this reaction is also enhanced by the addition of zinc chloride. However, the low selectivity in the initial cyclopropanation may be due to preferential chelation of the carbenoid by the silyl acetal **(126)** formed during the reaction.

<div align="center">

Me Me
\ /
Si
/ \
MeO OMe
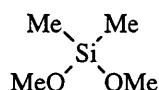
(126)

</div>

Lower yields and selectivities have previously been observed for THF and DME compared to diethyl ether for stoichiometric zinc phenyl carbenoids, due presumably both to a lowering of reactivity and increased steric congestion in the transition state. The added zinc chloride would also complex **(126)** resulting in a return to the higher levels of stereoselectivity previously seen with aromatic aldehydes.[106, 107] An alternative explanation is that the carbenoid may be converted by dismutation to a carbenoid of type **(127)** with increasing chloride concentration, when the initial siloxyalkyl ligand is displaced either in a uni- or in a bimolecular fashion (*c.f.* chapter 2.2).

<div align="center">

Ar   Cl
\ /
X
/ \
H   ZnCl
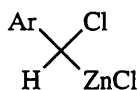
(127)

</div>

The much improved yield obtained with added zinc choride prompted us to explore the use of other alkenes. Cyclohexene has previously been shown to give good yields of cyclopropanes with aromatic aldehydes, and the same trends in yield and stereoselectivity are observed here using a series of the *p*-substituted dioxolane acetals

<div align="center">

113

</div>

with simple chlorotrimethylsilane as the electrophile (Scheme 4.11). A comparison reaction with *p*-anisaldehyde dimethyl acetal gave a marginally superior yield, a trend already seen for aliphatic acetals (*vide supra* chapter 3.2).
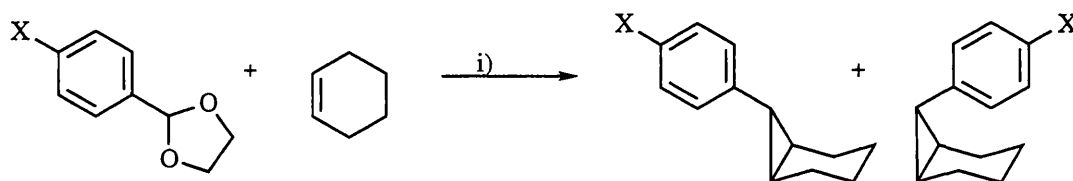
X	Yield	Ratio (*endo:exo*)
OMe	65%*	23.5:1
Me	38%	6.1:1
H	36%	3.3:1
Cl	30%	2.9:1

i) Zn/Hg, TMSCl, $ZnCl_2$ (1 eq.), Et_2O, reflux, 36 hrs
* 62% using the dimethyl acetal

Scheme 4.11

Although the initial experiments with anisaldehyde dimethyl acetal and styrene were carried out using dichlorodimethylsilane as the electrophile, this reagent could not now donate the second silicon electrophile in an intramolecular fashion, and had been selected in the heat of enthusiasm to extend the use of acetals to cyclopropanation. Nevertheless further attempts were also made to improve the efficiency of carbenoid generation. Again, the use of dichlorodimethylsilane as an intramolecular *bis*-silicon electrophile gave a yield virtually identical to that using chlorotrimethylsilane (Scheme 4.12). A reduction in the addition time to 18 hours also gave a yield comparable to that using the aldehyde and dichlorodimethylsilane (Scheme 4.12).
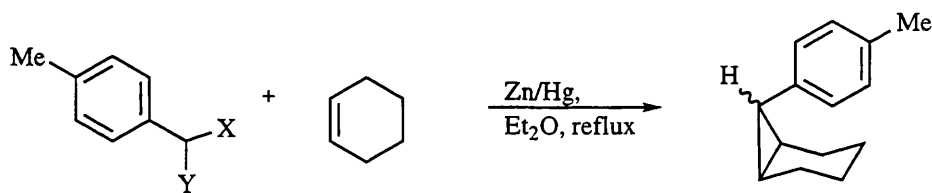
	Conditions	Yield	Ratio (*endo:exo*)
X,Y = -O(CH$_2$)$_2$O-	36 hr addition, ZnCl$_2$ (1 eq.), TMSCl	37%	6.1:1
"	18 hr addition, ZnCl$_2$ (1 eq.), TMSCl	33%	—
"	36 hr addition, ZnCl$_2$ (1 eq.), Me$_2$SiCl$_2$	38%	6.1:1
X = Y = O	36 hr addition, Me$_2$SiCl$_2$	34%	5.6:1

Scheme 4.12

The use of isopropenyl acetate, another successful substrate with aromatic aldehydes, however, gave extensive decomposition. Although cyclopropanes could be detected in the crude reaction mixture (< 20%), (Scheme 4.13), their chromatographic separation in pure form from decomposed polymeric material could not be achieved, and no quantitative study was therefore carried out on these substrates.

X = OMe, Me
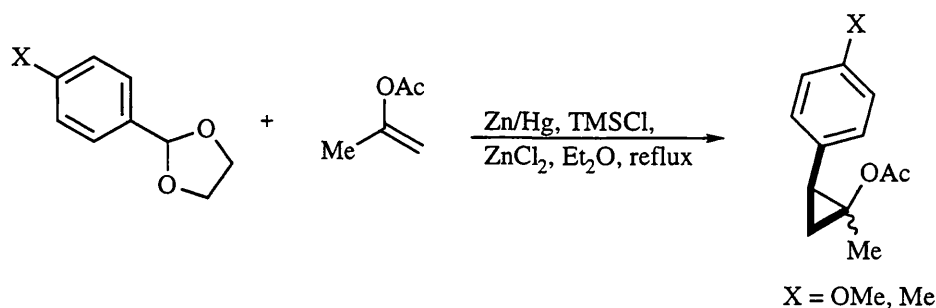
Scheme 4.13

Thus, as we have seen above, and in previous work, aromatic aldehydes and certain enones and enals, are useful precursors to zinc carbenoids and display many of the regio- and stereochemical features of other metallocarbenoids in the cyclopropanation of

115

olefins. This overall similarity to other metallocarbenoids would seem to lend a certain predictive power to the results expected when the cyclopropanation reaction is extended to other olefins. However, the present mechanistic model does not explain the differences in selectivity between chloro-, bromo-, or iodocarbenoids derived from aryldiazomethanes or *gem* -dihalides, *viz.* the increase in selectivity in the order Cl < Br < I. It may be that some level of pre-equilibrium occurs at a π-complex stage, as proposed by Doyle in the formation of cyclopropanes from catalytic carbenoid intermediates.[49a,b]

Our results show that aromatic acetals can also be used for the cyclopropanation of olefins. Although the isolated yields for the cyclopropanes prepared from acetal derivatives are not as high as those from the aldehydes and 1, 2-*bis*-chlorodimethylsilylethane (*c.f.* chapter 2.1), they are comparable to the yields obtained with dichlorodimethylsilane, and the use of the simpler silicon electrophiles makes purification much easier. An intriguing result though, is the difference in stereoselectivity observed with these acetal derivatives, especially in the presence or absence of added zinc chloride. This area warrants further investigation, and might lead to a deeper understanding of the environment around the carbenoid.

However, in the case of cyclopropanol derivatives, the highly Lewis acidic nature of the reaction mixture, coupled with the presence of adventitious proton sources, can bring about extensive decomposition of the product cyclopropanol ethers or esters. For these cyclopropanol derivatives, precedent already exists for their cleavage under Simmons-Smith conditions,[138] and care does need to be taken in the isolation of their trimethylsilyl ethers.[139] Again, the addition of an organometallic base such as diethylzinc might help to alleviate this problem.

5

Conclusions and Perspectives

The present work has extended the development of the carbonyl group as a carbenoid synthon, and developed the parallel use of the acetal function. These simple precursors possess many benefits over the more commonly used diazo or *gem*-dihalo compounds in terms of cost and safety, considerations which are paramount on a large scale. The ready conversion of aldehydes, or their trimeric derivatives, to terminal alkenes in a single step, a procedure not possible by any other means, and in the presence of much other base sensitive functionality, illustrates the usefulness of this direct approach.

The marked accelerating effect on the reduction of carbonyl compounds in the presence of added Lewis acids, particularly zinc chloride, opens up many routes to improve the selectivity of the reaction. Carbonyl compounds containing α-hydrogens could generate carbenoids at low temperatures and be trapped with olefins to give cyclopropanes. It has already been observed that the decomposition of aryldiazomethanes by zinc halides in the presence of alkenes gives highest *syn* selectivities with the iodide. Thus addition of zinc iodide or other iodide salts to the reaction could result in significant increases in the stereoselectivity of cyclopropanation. A moderate increase has already been noted by the addition of zinc chloride in the zinc/boron trifluoride mediated reduction of benzaldehyde in the presence of cyclohexene.[90b]

Although added Lewis acids have a significant beneficial effect on the reduction of carbonyl and acetal substrates, protic acid encourages many side reactions e.g. full Clemmensen reduction, pinacol formation and cyclopropanol cleavage. While efforts have been made in the past, and in the present work, to reduce or eliminate the effects of adventitious acid, diethylzinc or another organometallic base may serve as a panacea in this respect.

The direct one-pot conversion of acetals to carbenoids and their reaction *in situ* is, to the best of our knowledge, the first example of such a transformation. Our development of the use of acetals opens up a range of opportunities for cyclopropanation strategies based on zinc carbenoids. Among these are the development of the use of formaldehyde acetals as replacements for the expensive diiodomethane in the Simmons-

Smith reaction. Although preliminary experiments in this area have been unsuccessful, the alkene trap, 1-phenyl-cyclohexene, was completely consumed during the reaction. In view of the use of ethylene diiodide as an ethylidene transfer reagent in the Furukawa/Simmons-Smith reaction, it may also be possible to replace this with acetaldehyde. A group of other speculative acetal substrates are shown in Scheme 5.1.
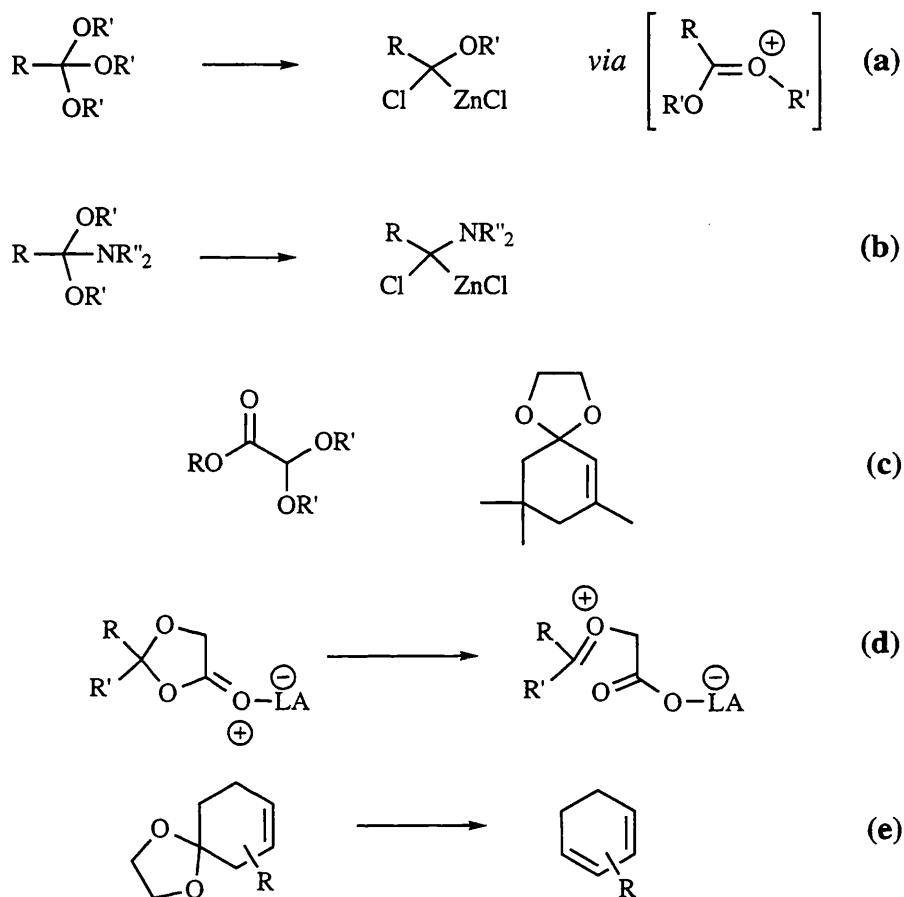
Scheme 5.1

These include the development of orthoesters and orthoamides as heteroatom stabilised carbenoids, possible replacements for the well-known Fischer carbenes (Scheme 5.1.a,b). The reduction of conjugated ketones and aldehydes under Clemmensen conditions frequently gives pinacol or rearrangement products. This pattern has also been observed in the zinc/silicon electrophile mediated reductions (*vide supra* chapter 2.1). However, the reduction of acetal derivatives with zinc and silicon electrophiles may avoid such pathways since reduction should lead directly to a zinc-carbon bond. Thus,

those substrates which had previously exhibited primarily radical coupling reactions, and others whose use as carbonyl compounds was precluded due to the stabilisation that would be afforded to radical intermediates, might also be developed as cyclopropanation reagents (Scheme 5.1.c). The decreased reactivity of the acetal substrates, relative to their parent carbonyl compounds, might be improved by the use of the 1,3-dioxolanone acetal function. The more nucleophilic lone pairs on the carbonyl oxygen should coordinate a Lewis acid more readily and give increased rates of oxonium ion formation (Scheme 5.1.d).

The protection of enones as their ketals often leads to deconjugation of the C=C bond under strong acid catalysis. Zinc and silicon electrophile mediated reduction of these deconjugated acetals should give conjugated dienes, *via* insertion into the activated C-H bond (Scheme 5.1.e).

Although zinc has been used as the reducing agent in this work, other metallocarbenoids should be accessible through the use of similar reduction strategies. Organometallic zinc reagents are well known to transmetallate with a variety of other metal salts of lower redox potential.[140] This reaction has been observed for the carbenoid ICH_2ZnI in selected cases,[141] and a cycling metal exchange has also been reported.[142] Thus, a wide variety of carbenoids could be accessible through the addition of a catalytic metal complex to the standard reaction. The use of other metals or metal anion complexes, and electrochemical techniques also provide novel, and unjustly neglected, routes to metallocarbenoid chemistry in general.

6

Experimental

^{1}H NMR spectra were recorded at 200 MHz on a Varian XL-200 instrument, at 270 MHz on a JEOL GSX 270 instrument, at 400 MHz on a Varian VXR-400 instrument, and at 500 MHz on a Bruker AM-500 instrument in the stated solvent, using residual protic solvent as the internal standard. [13]C spectra were recorded at 67.9 MHz on a JEOL GSX 270 instrument and at 100 MHz on a Varian VXR400 instrument using $\underline{C}DCl_3$ (δ_C = 77.0 ppm) as the internal standard. Infrared spectra were recorded on a Perkin Elmer 811, 983G or FT-IR 1600 spectrometer. Mass spectra and accurate mass measurements were recorded under electron impact conditions using VG 305, VG 7070, VG 7070B, VG 12-253, VG ZAB-E and VG ZAB-SE instruments, under chemical ionisation conditions using a VG-ZAB-SE or an AutospecQ instrument with the stated gas, and under fast atom bombardment conditions using a VG 7070, VG-ZAB-SE or AutospecQ instrument in the stated matrix. Gas chromatography coupled mass spectrometry was recorded on a VG 16F machine coupled to a Perkin Elmer series 204 chromatograph using helium as the carrier gas, and a BP1 25 m x 0.20 mm column (polydimethylsiloxane, 0.25 μm film). Gas chromatography was performed on a Hewlett-Packard 5780 machine (flame ionisation detector) with a 2.5 m APL column, or on a Hewlett-Packard 5890A machine (flame ionisation detector) with a 25 m x 0.32 mm BPX5 column (crosslinked 95% polydimethylsiloxane/5% polydiphenylsiloxane, 0.5 μm film) or with a 25 m x 0.10 mm BP5 column (95% polydimethylsiloxane/5% polydiphenylsiloxane, 0.1 μm film) using helium or hydrogen as the carrier gas. Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Boiling points for bulb to bulb or 'kugelrohr' distillations refer to uncorrected air temperatures. Optical rotations were recorded on an Optical Activity Polaar 2000 instrument. Microanalyses were performed in the Imperial College Chemistry Department or University College Chemistry Department microanalytical laboratories.

Petroleum ether (b.p. 40-60°C and 30-40°C) was distilled prior to use. Diethyl ether (ether), tetrahydrofuran and benzene were distilled from sodium-benzophenone ketyl, and dichloromethane from phosphorus pentoxide under an atmosphere of nitrogen or argon immediately prior to use. Dimethylformamide and dimethyl sulfoxide (calcium hydride at

reduced pressure), pyridine, triethylamine (potassium hydroxide) and 2,6-lutidine (aluminium trichloride), were distilled onto, and stored over, 4Å molecular sieves. Chlorotrimethylsilane (calcium hydride or sodium) and dichlorodimethylsilane (sodium) were distilled under an inert atmosphere immediately prior to use. 1,2-*Bis*-(chlorodimethylsilyl)ethane was prepared as a solution in dry ether and stored over polyvinylpyridine to remove any HCl. All other solvents were purified by standard means.

Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised under ultraviolet light (254 nm), iodine, acidic ethanolic vanillin, basic potassium permanganate [add 6.25 g of Na_2CO_3 in water (1.25 l) to 12.5 g of $KMnO_4$ in water (1.25 l)], and acidic ammonium (IV) molybdate [conc. H_2SO_4 (250 ml), ammonium molybdate tetrahydrate, water (2.25 l)] as appropriate. Preparative chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh). High pressure liquid chromatography was performed using a 250 mm x 10 mm Partisil 5 silica gel column on a Varian 5000 machine with UV (254 nm) detection.

Silver Nitrate-Silica.– Silica gel (100 g) was added to a stirred solution of silver nitrate (25 g) in water (100 ml) to give a slurry. Most of the water was removed on a rotary evaporator with protection from light, and the resulting powder was dried in an oven overnight at 150°C. The silica was stored in the dark in a tightly sealed container.

Zinc powder (> 90%) was purchased from FSA or BDH. Mercury (II) chloride (> 99.5%) was purchased from Aldrich.

Zinc Amalgam.– Mercuric chloride (2.00 g) was dissolved in conc. HCl (1 ml) and water (30 ml) in a 100 ml conical flask. To the solution was added zinc dust (10.0 g) and the suspension vigorously stirred exocentrically for 10 minutes. The zinc amalgam was then collected by filtration, washed with water (75 ml), acetone (75 ml), ethanol (75 ml),

and finally dry ether (75 ml) and dried under vacuum overnight. The activated zinc dust

was then stored under an atmosphere of argon or nitrogen.

The apparatus for all zinc carbenoid reactions was prepared as follows: the zinc

amalgam was preweighed into the flask, the apparatus assembled cold, teflon sealed, and

degassed with argon or nitrogen for 5 minutes before being flame dried under an argon or

nitrogen atmosphere which was maintained for the entire period of the reaction.

Preparation of 5-β-Cholestan-3-one (128).

(128)
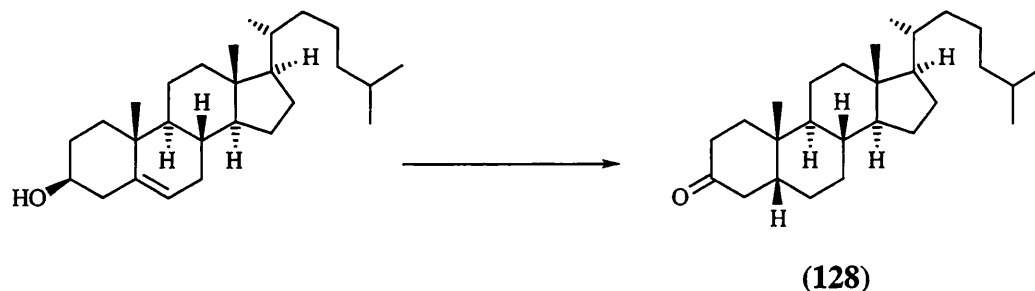
A solution of cholesterol (2.00 g, 5.17 mmol) and cyclohexanone (10 ml) in dry toluene (30 ml) were brought to reflux, and a cloudy solution of aluminium isopropoxide (588 mg, 2.87 mmol, 0.55 eq.) in dry toluene (10 ml) was added slowly over 20 minutes. Further dry toluene (10 ml) was added and the yellow solution heated for 2.5 hours to distil out the toluene (30 ml) using a Dean-Stark apparatus. The solution was poured into a saturated aqueous solution of potassium sodium tartarate (15 ml). The sludgy aqueous layer was extracted with ether (2 x 40 ml). The combined organic layers were dried (MgSO$_4$), filtered and concentrated to give a light yellow viscous oil which was filtered through a short pad of silica (0-25% ether in petrol (b.p. 40-60°C)) to give the crude enone as a white solid which was used directly in the next step.

A solution of the crude enone in dry pyridine (50 ml) was hydrogenated at a slight positive pressure in the presence of palladium on charcoal (10%, 2.50 g) until TLC indicated the absence of starting enone (3 hours). The solution was filtered, the catalyst washed with ether (40 ml), petrol (80 ml) and the combined solvents concentrated to give an oil. This was taken up in ether (60 ml) and washed with saturated aqueous copper sulphate (30 ml). The separated aqueous layer was extracted with ether (20 ml), the combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated to give a yellow oil which was chromatographed on silica twice (0-8% ether in petrol and 0-3% ethyl acetate in petrol (b.p. 40-60°C)) to give the ketone 128[143] (1.48 g, 74% for 2 steps) as a white solid. m.p. 61-62°C (plates from EtOH), (lit.[143] 63°C from MeOH); [α]^{18}$_D$ +36.4 (c. 0.96 in CHCl$_3$), lit.[143] [α]^{25}$_D$ +37 (CHCl$_3$).

v_{max} (NaCl, thin film)/cm^{-1} 2937, 2867, 1720, 1572, 1467, 1378, 1366, 1267, 1170; δ_H (270 MHz, CDCl$_3$) 2.69 (2H, t, J 14.0, H$_{2\alpha,4\alpha}$), 2.34 (2H, dt, J 5.4, 14.0, H$_{2\beta,4\beta}$), 2.22-0.88 (27H, m, alkyl H), 1.01 (3H, s, 19βCH$_3$), 0.91 (3H, d, J 7.1, 21αCH$_3$), 0.87 (6H, d, J 6.5, gem-26,27CH$_3$), 0.69 (3H, s, 18βCH$_3$); m/z (EI) 386 (M$^+$, 100%).

Preparation of 5-β-Cholestan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (129).

(129)
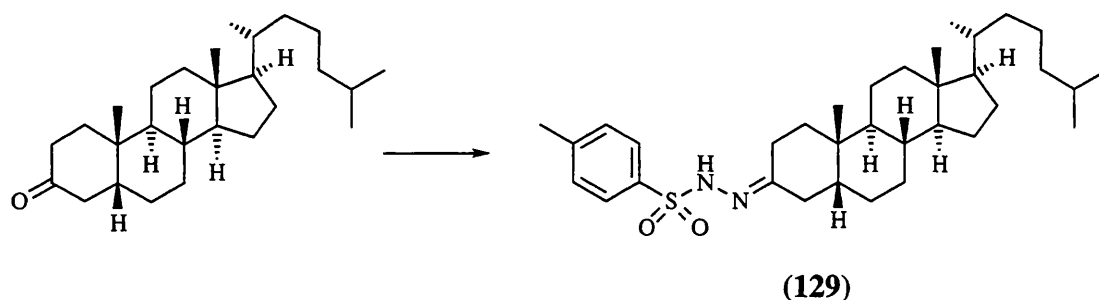
5-β-cholestan-3-one (406 mg, 1.05 mmol) and p-toluenesulfonyl hydrazone (215 mg, 1.16 mmol, 1.1 eq.) were dissolved in absolute ethanol (15 ml) with heating. After 24 hours the solution was concentrated *in vacuo*, and the residue taken up in ether, filtered and reconcentrated to give a white solid. Crystallisation from methanol gave the hydrazone **129**[144] (486 mg, 83%) as a white solid. m.p. 163-165.5°C (decomp.) (prisms from ether/petrol (b.p. 40-60°C)), lit.[144] 168°C, MeOH); [α]$^{18}_D$ +48.2 (c. 0.99 in EtOAc).

v_{max} (NaCl, thin film/neat)/cm^{-1} 3221, 2931, 2866, 1640, 1598, 1494, 1447, 1383, 1330, 1305, 1268, 1212, 1185, 1168, 1095, 1020, 969, 922, 813, 736, 705, 665; δ_H (270 MHz, CDCl$_3$) 7.83 (2H, d, J 8.2, H$_{2',6'}$), 7.40 (1H, br s, NH), 7.30 (2H, d, J 8.2, H$_{3',5'}$), 2.42 (3H, s, ArCH$_3$), 2.56-0.84 (31H, m, alkyl H), 0.91 (3H, d, J 7.6, 21αCH$_3$), 0.87 (3H, s, 19βCH$_3$), 0.85 (6H, d, J 6.6, gem-26,27CH$_3$), 0.64 (3H, s, 18βCH$_3$); m/z (FAB/MNOBA) 555 (M+H$^+$, 100%).

126

Preparation of 5-β-Cholest-2-ene (130) and 5-β-Cholest-3-ene (131).

(130)   **(131)**
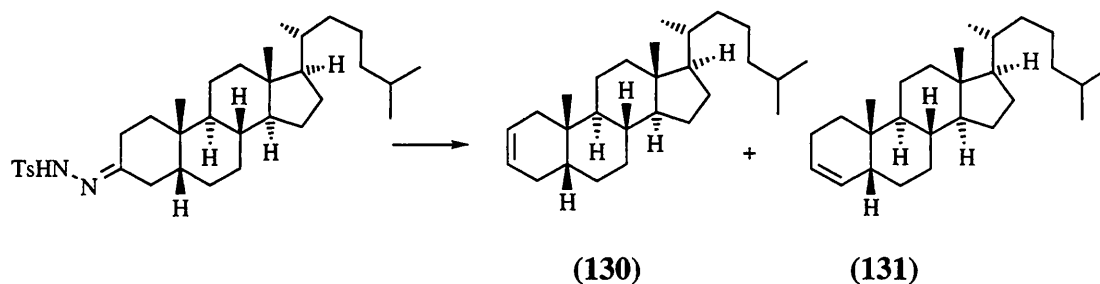
5-β-cholestan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (99 mg, 0.18 mmol) and sodium methoxide (48 mg, 0.9 mmol, 5.0 eq.) were dissolved in dry diglyme (5 ml) under nitrogen. The resultant solution was heated at reflux in a Woods metal bath for 1 hour, and then cooled to ambient temperature. The solution was poured into water (10 ml) and petrol (30 ml). The aqueous layer was extracted with petrol (2 x 30 ml) and the combined organic layers washed with water (20 ml), brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of 5-β-cholest-2-ene **130**[145] and 5-β-cholest-3-ene **131**[145b, 146] (72.6:27.4 by GC) as a clear colourless oil (13.7 mg, 21%).

v_{max} (NaCl, thin film)/cm⁻¹ 2935, 2867, 1465, 1382 δ_H (400 MHz, CDCl₃) *5-β-cholest-3-ene*: 5.68-5.59 (1H, m, H₃), 5.32 (1H, dd, *J* 1.8, 10.0, H₄), 2.19-0.94 (29H, m, alkyl H), 0.94 (3H, s, 19βCH₃), 0.88 (3H, d, *J* 6.5, 21αCH₃), 0.87 (6H, dd, *J* 1.7, 6.7, *gem*-26,27CH₃), 0.65 (3H, s, 18βCH₃); *5-β-cholest-2-ene*: 5.68-5.59 (1H, m, H₂, masked by other isomer), 5.48-5.58 (1H, m, H₃), 2.19-0.94 (29H, m, alkyl H, masked by other isomer), 0.96 (3H, s, 19βCH₃), 0.89 (3H, d, *J* 6.5, 21αCH₃), 0.87 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH₃, masked by other isomer), 0.65 (3H, s, 18βCH₃); m/z (EI/GCMS) t_R: 26.9 min.: *5-β-cholest-3-ene*: 370 (M⁺, 100%); t_R: 27.4 min.: *5-β-cholest-2-ene*: 370 (M⁺, 100%).

Preparation of 5-β-Cholest-2-ene (130) and 5-β-Cholest-3-ene (131).

(130)   (131)

A solution of chlorotrimethylsilane (280 μl, 2.24 mmol, 5 eq.) and zinc chloride (123 mg, 0.9 mmol, 2.0 eq.) in dry THF (5 ml) was added to flame dried zinc amalgam (290 mg, 4.5 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 5-β-cholestan-3-one (173 mg, 0.45 mmol) in dry THF (5 ml) was added. The reaction was vigorously stirred at reflux, and after 25 hours further chlorotrimethylsilane (290 μl, 2.3 mmol, 5 eq.) was added, and the suspension heated for a further 17 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (12 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a light yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of 5-β-cholest-2-ene **130**[145] and 5-β-cholest-3-ene **131**[145b, 146] (26.5:73.5 by GC) as a white solid (53 mg, 32%).

v_{max} (NaCl, thin film)/cm^{-1} 2935, 2867, 1465, 1382 δ$_H$ (400 MHz, CDCl$_3$) *5-β-cholest-3-ene*: 5.68-5.59 (1H, m, H$_3$), 5.32 (1H, dd, *J* 1.8, 10.0, H$_4$), 2.19-0.94 (29H, m, alkyl H), 0.94 (3H, s, 19βCH$_3$), 0.88 (3H, d, *J* 6.5, 21αCH$_3$), 0.87 (6H, dd, *J* 1.7, 6.7, *gem*-26,27CH$_3$), 0.65 (3H, s, 18βCH$_3$); *5-β-cholest-2-ene*: 5.68-5.59 (1H, m, H$_2$, masked by other isomer), 5.48-5.58 (1H, m, H$_3$), 2.19-0.94 (29H, m, alkyl H, masked by other isomer), 0.96 (3H, s, 19βCH$_3$), 0.89 (3H, d, *J* 6.5, 21αCH$_3$), 0.87 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH$_3$, masked by other isomer), 0.65 (3H, s, 18βCH$_3$); m/z (EI/GCMS) t$_R$: 26.9

min.: *5-β-cholest-3-ene*: 370 (M⁺, 100%); t_R: 27.4 min.: *5-β-cholest-2-ene*: 370 (M⁺, 100%).

Preparation of 5-α-Cholestan-3-one (132).

(132)

A solution of cholesterol (2.00 g, 5.17 mmol) was dissolved in warm glacial acetic acid (10 ml) with stirring in the presence of platinum oxide (42 mg). The flask was deoxygenated and placed under an atmosphere of hydrogen. The stirred suspension was heated in an oil bath, and hydrogenated at a slight positive pressure. After 1 hour further platinum oxide (25 mg) was added and hydrogenation continued for a further hour. The suspension was cooled to ambient temperature, filtered and concentrated to give a white oily solid. The residue was taken up in carbon tetrachloride (40 ml) and acetic anhydride (13 ml). Concentrated sulfuric acid (ca. 2 ml) was added dropwise with shaking until there was no further increase in colour. The blue/green solution was allowed to stand at ambient temperature for 20 minutes before water (3 ml) was added slowly and the solution formed into two layers. The upper layer was treated with dichloromethane (10 ml), ether (20 ml), further water (6 ml), and the layers again separated. The combined organic layers were concentrated *in vacuo* to a brown oil. This was taken up in ether (50 ml) and washed with aqueous sodium hydroxide (2M, 2 x 50 ml). The separated aqueous layers were extracted with ether (20 ml). The combined organic layers were washed with hydrochloric acid (2M, 100 ml), dried (MgSO₄), filtered and concentrated to give a brown solid. This solid was taken up in ethanol (40 ml) and heated to reflux with a solution of sodium hydroxide (2.5 g) in water (10 ml) for 2 hours. The solution was cooled to ambient temperature and concentrated *in vacuo* to small volume. Water (80 ml)

was added and the solution was extracted with ether (3 x 80 ml). The combined organic layers were washed with water (100 ml), hydrochloric acid (2M, 40 ml), brine (40 ml), dried ($MgSO_4$), filtered and concentrated to give the crude alcohol as a yellow/white solid (1.46 g). A solution of the crude alcohol in benzene (15 ml) was added dropwise to a stirred solution of potassium dichromate (1.93 g, 6.6 mmol) in a mixture of acetic acid (1.5 ml), water (9 ml) and concentrated sulfuric acid (2.7 ml) at 0°C over 5 minutes. The solution was allowed to attain ambient temperature and stirred for a further 1.5 hours. Water (30 ml), and ether (40 ml) were added and the separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (30 ml), aqueous sodium hydroxide (2M, 20 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated to give an off white solid which was chromatographed on silica (0-3.5% ethyl acetate in petrol (b.p. 40-60°C)) to give the ketone **132**[143] (1.06 g, 53% for 4 steps) as a white solid. m.p. 130-131.5°C (needles from EtOH), (lit.[143] 129-131°C from MeOH); $[\alpha]^{18}_D$ +40.5 (c. 0.86 in $CHCl_3$), lit.[143] $[\alpha]^{25}_D$ +41 ($CHCl_3$).

ν_{max} (NaCl, thin film)/cm^{-1} 2936, 2867, 2847, 1716, 1572, 1466, 1443, 1435, 1416, 1406, 1385, 1366, 1335, 1316, 1275, 1255, 1231, 1212, 1186, 1173, 1154, 1130, 1119, 1081, 1030, 1012, 1000, 956, 939, 922, 872, 803, 754, 732, 685; δ_H (270 MHz, $CDCl_3$) 2.46-2.21 (4H, m, $H_{2,4}$), 2.16-0.82 (27H, m, alkyl H), 0.99 (3H, s, 19βCH_3), 0.89 (3H, d, *J* 6.6, 21αCH_3), 0.85 (6H, d, *J* 6.6, *gem*-26,27CH_3), 0.67 (3H, s, 18βCH_3); m/z (EI) 386 (M^+, 85%), 231 (100%).

Preparation of 5-α-Cholestan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (133).

(133)
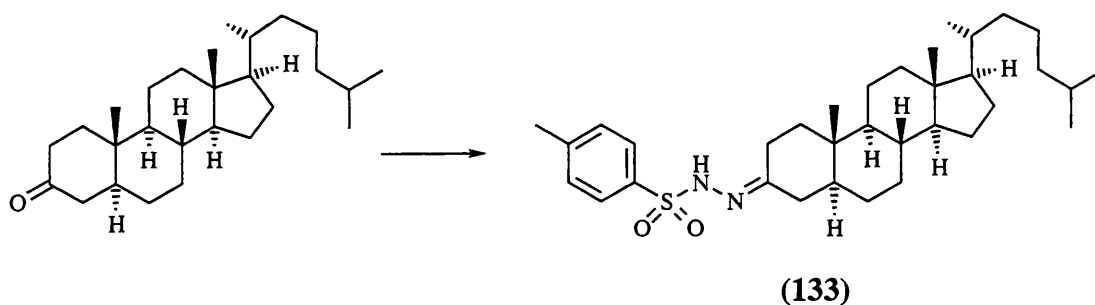
5-α-cholestan-3-one (226 mg, 0.59 mmol) and p-toluenesulfonyl hydrazone (120 mg, 0.64 mmol, 1.1 eq.) were dissolved in absolute ethanol (15 ml) with heating. After 24 hours the solution was concentrated *in vacuo*, and the residue taken up in ether, filtered and reconcentrated to give a white solid. Crystallisation from methanol gave the hydrazone **133**[144] (241 mg, 74%) as a white solid. m.p. 162-165°C (decomp.) (prisms from ether/petrol (b.p. 40-60°C)), lit.[144] 173-174°C, ether/heptane); $[\alpha]^{18}_D$ +30.3 (c. 1.01 in EtOAc).

ν_{max} (NaCl, thin film)/cm^{-1} 3218, 2930, 2867, 2635, 1599, 1495, 1445, 1385, 1366, 1330, 1212, 1186, 1168, 1094, 1020, 923, 813, 735, 706, 687, 667; δ_H (270 MHz, CDCl$_3$) 7.84 (2H, d, J 7.8, H$_{2',6'}$), 7.37 (1H, br s, NH), 7.27 (2H, d, J 7.8, H$_{3',5'}$), 2.42 (3H, s, ArCH$_3$), 2.60-0.75 (31H, m, alkyl H), 0.89 (3H, d, J 7.8, 21αCH$_3$), 0.87 (3H, s, 19βCH$_3$), 0.83 (6H, d, J 6.1, *gem*-26,27CH$_3$), 0.64 (3H, s, 18βCH$_3$); m/z (FAB/MNOBA) 555 (M+H$^+$, 100%).

131

Preparation of 5-α-Cholest-2-ene (134) and 5-α-Cholest-3-ene (135).

(134)   (135)
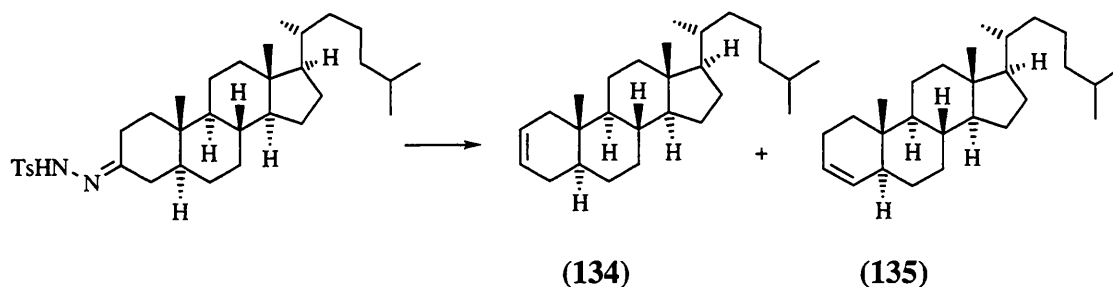
5-α-cholestan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (110 mg, 0.20 mmol) and sodium methoxide (54 mg, 1.0 mmol, 5.0 eq.) were dissolved in dry diglyme (5 ml) under nitrogen. The resultant solution was heated at reflux in a Woods metal bath for 1.3 hours, and then cooled to ambient temperature. The solution was poured into water (10 ml) and petrol (40 ml). The aqueous layer was extracted with petrol (2 x 30 ml) and the combined organic layers washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of 5-α-cholest-2-ene 134[145a, 147] and 5-α-cholest-3-ene 135[146, 147] (84:16 by GC) as an oily white solid (29 mg, 40%).

v_{max} (NaCl, thin film)/cm^{-1} 3020, 2929, 2870, 1656 (w), 1466, 1444, 1379, 1365; δ_H (400 MHz, CDCl$_3$) *5-α-cholest-2-ene*: 5.62-5.50 (2H, m, H$_{2,3}$), 1.98-0.86 (29H, m, alkyl H), 0.90 (3H, d, *J* 6.5, 21αCH$_3$), 0.86 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH$_3$), 0.75 (3H, s, 19βCH$_3$), 0.66 (3H, s, 18βCH$_3$); *5-α-cholest-3-ene*: 5.27-5.24 (2H, m, H$_{3,4}$), 1.98-0.86 (29H, m, alkyl H, masked by other isomer), 0.90 (3H, d, *J* 6.5, 21αCH$_3$, masked by other isomer), 0.86 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH$_3$, masked by other isomer), 0.77 (3H, s, 19βCH$_3$), 0.66 (3H, s, 18βCH$_3$, masked by other isomer); m/z (EI/GCMS) t$_R$: 29.1 min.: *5-α-cholest-2-ene*: 370 (M$^+$, 100%); t$_R$: 29.4 min.: *5-α-cholest-3-ene*: 370 (M$^+$, 100%).

Preparation of 5-α-Cholest-2-ene (134) and 5-α-Cholest-3-ene (135).

(134)   (135)

A solution of chlorotrimethylsilane (290 μl, 2.3 mmol, 5 eq.) and zinc chloride (125 mg, 0.9 mmol, 2.0 eq.) in dry THF (5 ml) was added to flame dried zinc amalgam (300 mg, 4.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 5-α-cholestan-3-one (177 mg, 0.46 mmol) in dry THF (5 ml) was added. The reaction was vigorously stirred at reflux, and after 25 hours further chlorotrimethylsilane (290 μl, 2.3 mmol, 5 eq.) was added, and the suspension heated for a further 20 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (12 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a light yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of 5-α-cholest-2-ene **134**[145a, 147] and 5-α-cholest-3-ene **135**[146, 147] (91:9 by GC) as a white solid (122 mg, 72%).

v_{max} (NaCl, thin film)/cm^{-1} 3020, 2929, 2870, 1656 (w), 1466, 1444, 1379, 1365; δ_H (400 MHz, CDCl$_3$) *5-α-cholest-2-ene*: 5.62-5.50 (2H, m, H$_{2,3}$), 1.98-0.86 (29H, m, alkyl H), 0.90 (3H, d, *J* 6.5, 21αCH$_3$), 0.86 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH$_3$), 0.75 (3H, s, 19βCH$_3$), 0.66 (3H, s, 18βCH$_3$); *5-α-cholest-3-ene*: 5.27-5.24 (2H, m, H$_{3,4}$), 1.98-0.86 (29H, m, alkyl H, masked by other isomer), 0.90 (3H, d, *J* 6.5, 21αCH$_3$, masked by other isomer), 0.86 (6H, dd, *J* 1.7, 6.5, *gem*-26,27CH$_3$, masked by other isomer), 0.77 (3H, s,

19βCH₃), 0.66 (3H, s, 18βCH₃, masked by other isomer); m/z (EI/GCMS) t_R:29.1 min.:

5-α-cholest-2-ene: 370 (M⁺, 100%); t_R:29.4 min.: *5-α-cholest-3-ene*: 370 (M⁺, 100%).

Preparation of 1,5-Diphenyl-pentan-3-one (65).

(65)

A stirred suspension of dibenzylidene acetone (3.86 g, 16.5 mmol) and palladium on charcoal (10%, 190 mg) in ethyl acetate (35 ml) was hydrogenated at slight positive pressure for 3 hours. The suspension was filtered through a pad of celite and concentrated *in vacuo* to a light yellow oil. Bulb to bulb distillation (200°C/1 mbar) and filtration through a pad of silica (10% ether in petrol (b.p. 40-60°C)) gave the ketone 65[148] as a clear colourless oil (1.57 g, 40%).

ν_{max} (NaCl, thin film)/cm^{-1} 3085, 3062, 3028, 2925, 1712, 1604, 1495, 1453, 1406, 1371, 1092, 1078, 1031, 980, 774, 749, 699; δ_H (270 MHz, CDCl$_3$) 7.14-7.31 (10H, m, ArH), 2.89 (4H, t, *J* 7.6, -CH$_2$CO), 2.71 (4H, t, *J* 7.6, -CH$_2$Ar); m/z (EI) 238 (M$^+$, 13%), 91 (100%).

Preparation of 1,5-Diphenyl-pentan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (68).

(68)
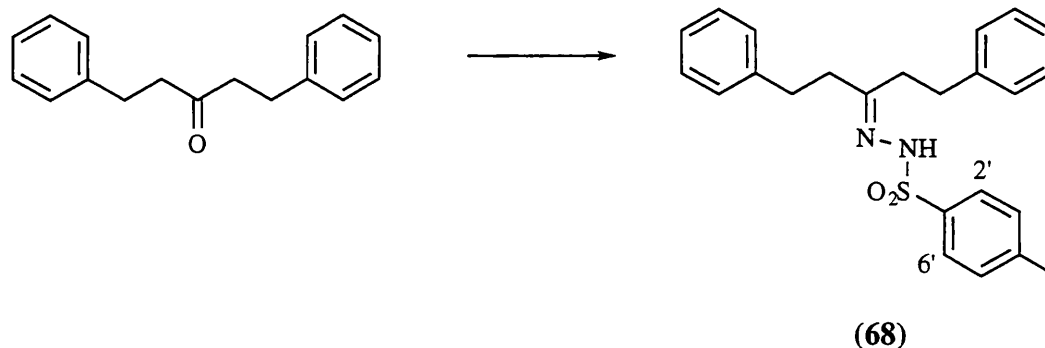
1,5-diphenyl-pentan-3-one (549 mg, 2.31 mmol) and *p*-toluenesulfonyl hydrazone (420 mg, 2.18 mmol, 0.95 eq.) were dissolved in absolute ethanol (10 ml). After 24 hours the solution was concentrated *in vacuo* to give a very light yellow oil. Crystallisation from ether/petrol gave the hydrazone **68** (750 mg, 85%) as a white solid. m.p. 86.5-88°C (plates from ether/petrol (b.p. 40-60°C))

v_{max} (NaCl, thin film)/cm^{-1} 3222, 3061, 3026, 2924, 1635, 1600, 1495, 1453, 1385, 1335, 1306, 1186, 1166, 1093, 1045, 914, 814, 749, 700, 670; δ_H (270 MHz, CDCl$_3$) 7.71 (2H, d, J 8.1, H$_{2',6'}$), 7.30 (2H, d, J 8.1, H$_{3',5'}$), 7.22-7.14 (6H, m, *m*-, *p*-PhH), 7.02 (2H, dd, 1.5, 7.3, *o*-PhH$_A$), 6.94 (2H, dd, 1.7, 7.6, *o*-PhH$_B$), 6.72 (1H, s, NH), 2.78 (2H, t, J 7.5, -CH$_{2A}$C=N), 2.69 (2H, t, J 7.3, -CH$_{2B}$C=N), 2.47 (2H, t, J 7.5, -CH$_{2A}$Ph), 2.45 (3H, s, -CH$_3$), 2.43 (2H, t, J 7.3, -CH$_{2B}$Ph); m/z (CI/NH$_3$) 407 (M+H$^+$, 39%), 253, 238, 222, 189, 151, 131, 124, 91 (100%); (Found: M+H$^+$, 407.1793. C$_{24}$H$_{27}$N$_2$O$_2$S requires *M*, 407.1793); (Found: C, 70.6. H, 6.38. N, 6.94. C$_{24}$H$_{27}$N$_2$O$_2$S requires C, 70.9. H, 6.45. N, 6.89.).

Preparation of 1,5-Diphenyl-pent-2-ene (*trans* (66) and *cis* (67)) and 1,5-Diphenyl-pent-1-ene (*trans* (69) and *trans cis* (70)).
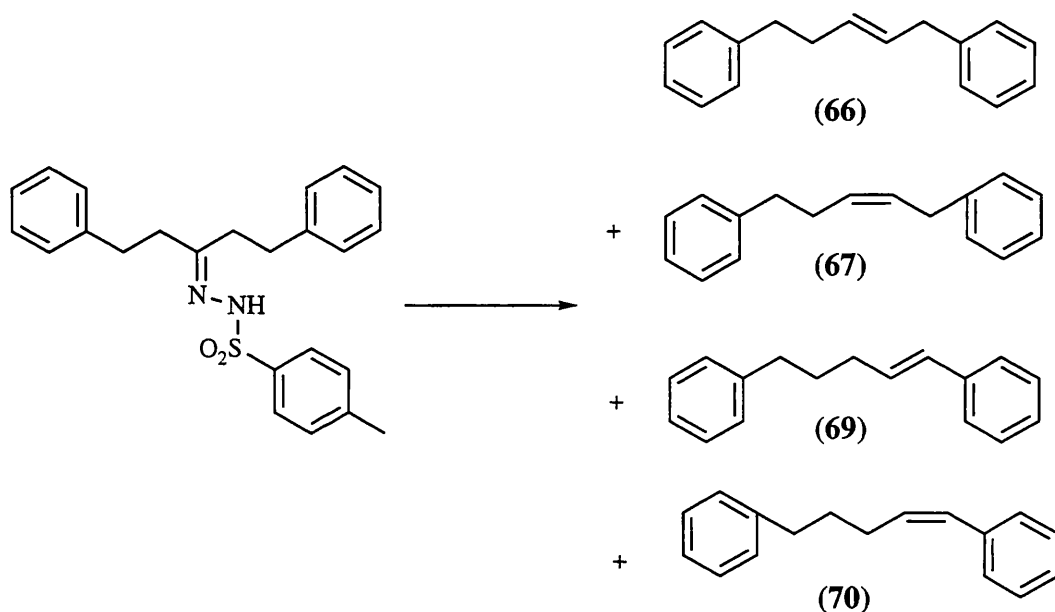
1,5-diphenyl-pentan-3-one-(4-methyl-benzene-sulfonyl)-hydrazone (450 mg, 1.11 mmol) and sodium methoxide (299 mg, 5.5 mmol, 5.0 eq.) were dissolved in dry diglyme (10 ml) under nitrogen. The resultant solution was heated at reflux in a Woods metal bath for 25 minutes, and then cooled to ambient temperature. The solution was poured into water (10 ml) and petrol (40 ml). The aqueous layer was extracted with petrol (2 x 30 ml) and the combined organic layers washed with water (3 x 20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a yellow oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60°C)) furnished an inseparable mixture of 1,5-diphenyl-pent-2-ene (*cis* 67 and *trans* 66), 1,5-diphenyl-pent-1-ene[149] (*cis* 70 and *trans* 69), along with an unidentified material (62 : 38 alkenes : unknown by GC; *trans* alkenes : *cis* alkenes: 82 : 18) as a clear colourless oil (143 mg, 58%). HPLC gave enriched samples of *cis* and *trans* 1,5-diphenyl-pent-1-ene[149].

v_{max} (NaCl, thin film)/cm^{-1} *alkenes + unknown mixture*: 3084, 3062, 2923, 2854, 1603, 1584, 1495, 1453, 1434, 1181, 1157, 1109, 1074, 1030, 969, 931, 910, 743, 698; *cis-1,5-diphenyl-pent-1-ene*: 3082, 3060, 2924, 2854, 1601, 1495, 1452, 1406, 1263, 1109, 1076, 1029, 914, 799, 771, 750, 698; *trans-1,5-diphenyl-pent-2-ene*: 3083, 3061, 3026, 2958,

2854, 1602, 1495, 1452, 1333, 1073, 1030, 965, 909, 734, 698; δ_H (400 MHz, CDCl$_3$)

trans-1,5-diphenyl-pent-1-ene: 7.36-7.10 (10H, m, ArH), 6.39 (1H, d, J 15.9, -CH=C*H*Ph), 6.23 (1H, dt, J 15.9, 6.9, -C*H*=CHPh), 2.67 (2H, t, J 8.0, -CH$_2$C*H$_2$*Ph), 2.24 (2H, q, J 6.9, -C*H$_2$*CH=CPh), 1.80 (2H, tt, J 6.9, 8.0, -C*H$_2$*CH$_2$Ph); *cis-1,5-diphenyl-pent-1-ene*: 7.34-7.12 (10H, m, ArH), 6.44 (1H, dd, J 1.7, 11.7, -CH=C*H*Ph), 5.69 (1H, dt, J 11.7, 7.3, -C*H*=CHPh), 2.64 (2H, t, J 7.7, -CH$_2$C*H$_2$*Ph), 2.38 (2H, dq, J 1.7, 7.3, -C*H$_2$*CH=CHPh), 1.78 (2H, tt, J 7.3, 7.7, -C*H$_2$*CH$_2$Ph); *trans-1,5-diphenyl-pent-2-ene*: 7.34-7.09 (10H, m, ArH), 5.64-5.50 (2H, m, C=CH), 3.34 (2H, d, J 6.2, C=CH-C*H$_2$*Ph), 2.71 (2H, t, J 8.0, -CH$_2$Ph), 2.51-2.44 (2H, m, -C*H$_2$*CH$_2$Ph); *cis-1,5-diphenyl-pent-2-ene*: 7.34-7.09 (10H, m, ArH, masked by other isomer), 5.64-5.50 (2H, m, C=CH, masked by other isomer), 3.35 (2H, d, J 5.6, C=CH-C*H$_2$*Ph), 2.73 (2H, t, J 8.0, -CH$_2$Ph), 2.38-2.30 (2H, m, -C*H$_2$*CH$_2$Ph); m/z (EI/GCMS) t$_R$: 11.3 min.: *trans- alkenes*: 222 (M$^+$, 17%), 207, 131, 117, 116, 115, 104, 92, 91 (100%), 77, 65, 52, 50; t$_R$: 11.6 min.: *cis-alkenes*: 222 (M$^+$, 22%), 207, 131, 118, 117, 116, 115, 105, 104, 92, 91 (100%), 77, 65; t$_R$: 15.5 min.: *unknown*: 222 (M$^+$, 45%), 207, 131, 129, 118, 117, 116, 115, 105, 104, 92, 91 (100%), 77, 65

Preparation of 1,5-Diphenyl-pent-2-ene (*trans* (66) and *cis* (67)).
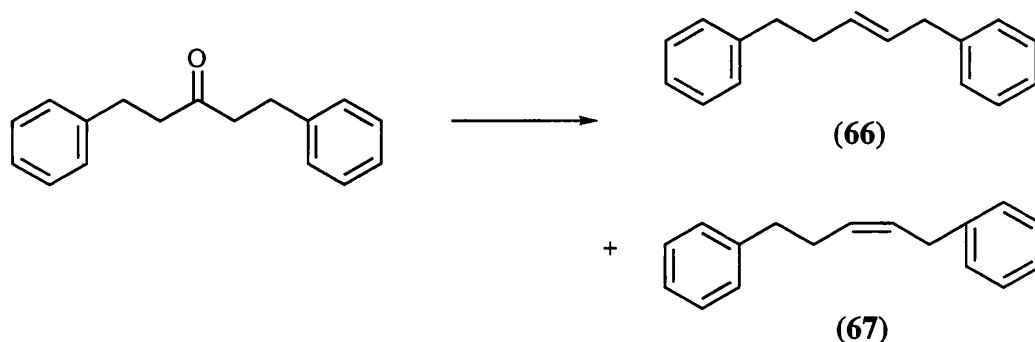
A solution of chlorotrimethylsilane (550 μl, 4.34 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (570 mg, 8.7 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 1,5-diphenyl-pentan-3-one (207 mg, 0.87 mmol) in dry ether (4 ml) was added. The reaction was vigorously stirred at reflux for a further 120 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (12 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to a light yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) gave in order of elution: an inseparable mixture of 1,5-diphenyl-pent-2-ene *trans*-66 and *cis* 67 (38:62 by GC) as a clear colourless oil (22 mg, 11%), and recovered 1,5-diphenyl-pentan-3-one 65 (49 mg, 24%).

v_{max} (NaCl, thin film)/cm^{-1} 3084, 3062, 2923, 2854, 1603, 1584, 1495, 1453, 1434, 1181, 1157, 1109, 1074, 1030, 969, 931, 910, 743, 698; δ_H (400 MHz, $CDCl_3$) *trans-1,5-diphenyl-pent-2-ene*: 7.34-7.09 (10H, m, ArH), 5.64-5.50 (2H, m, C=CH), 3.34 (2H, d, *J* 6.2, C=CH-C*H*$_2$Ph), 2.71 (2H, t, *J* 8.0, -CH$_2$Ph), 2.51-2.44 (2H, m, -C*H*$_2$CH$_2$Ph); *cis-1,5-diphenyl-pent-2-ene*: 7.34-7.09 (10H, m, ArH, masked by other isomer), 5.64-5.50 (2H, m, C=CH, masked by other isomer), 3.35 (2H, d, *J* 5.6, C=CH-C*H*$_2$Ph), 2.73 (2H, t, *J* 8.0, -CH$_2$Ph), 2.38-2.30 (2H, m, -C*H*$_2$CH$_2$Ph); m/z (EI/GCMS) t_R: 11.2 min.: *trans-1,5-diphenyl-pent-2-ene*: 222 (M$^+$, 17%), 131, 117, 116, 115, 104, 92, 91 (100%),

77, 65, 53, 51, 49; t_R: 11.6 min.: *cis-1,5-diphenyl-pent-2-ene*: 222 (M⁺, 16%), 131, 117, 116, 115, 104, 92, 91 (100%), 77, 65, 53, 51, 49; (Found: M⁺, 222.1404. $C_{17}H_{18}$ requires *M*, 222.1409).

Preparation of Hexadecanal (136).

$$^nH_{27}C_{13}\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown OH \longrightarrow {}^nH_{27}C_{13}\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown O$$

(136)
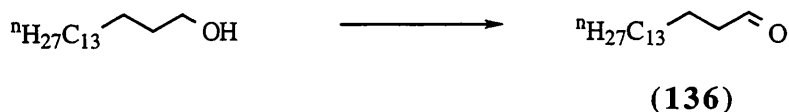
To a solution of 1-hexadecanol (6.00 g, 24.8 mmol) in dry dichloromethane (180 ml) under argon was added pyridinium chlorochromate (8.01 g, 37.2 mmol 1.5 eq.) in a single portion. After 3.75 hours ether (200 ml) was added and the suspension filtered through a pad of silica. Concentration *in vacuo* gave a green semi-solid oil. Bulb to bulb distillation (150°C/0.2 mm Hg) furnished the aldehyde **136**[150] (4.16 g, 17.3 mmol, 71%) as a white solid m.p. 36-38°C (petrol (b.p. 40-60°C)/ether), (lit.[150] 34°C).

ν_{max} (NaCl, thin film)/cm^{-1} 2922, 2851, 2710, 1724, 1463, 1409, 1387, 1048, 721; δ_H (270 MHz, CDCl$_3$) 9.76 (1H, t, J 1.7, CHO), 2.41 (2H, dt, J 1.7, 8.3, CH_2CHO), 1.62 (2H, m, CH_2CH$_2$CHO), 1.18-1.35 (24H, m, alkyl chain), 0.87 (3H, t, J 6.5, CH$_3$); m/z (EI) 240 (M$^+$, 0.4%), 43 (100%).

Preparation of 1-Hexadecene (137).

$$^nH_{27}C_{13}\diagup\!\!\diagdown\!\!\diagup\!\!\diagdown O \longrightarrow {}^nH_{27}C_{13}\diagup\!\!\diagdown\!\!\diagup\!\!\diagup$$

(137)

Method A:– To flame dried zinc amalgam (561 mg, 8.6 mmol, 10 eq.) under argon was added a solution of chlorotrimethylsilane (4 ml, 5 mmol, 6 eq., 1.25M in ether). To the resultant stirred suspension was added a solution of 1-hexadecanal (207 mg, 0.86 mmol) in dry ether (8 ml) over 9.5 hours via syringe pump. The reaction mixture was stirred at ambient temperature for a further 8.5 hours and then quenched by addition of saturated aqueous sodium bicarbonate (10 ml). The resultant suspension was filtered through celite, and the filter cake washed with ether (20 ml). The aqueous layer was extracted with ether (20 ml) and the combined organic layers washed with water (10 ml), brine (10 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto

141

silica. Column chromatography (1-2% ether in petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (102 mg, 0.45 mmol, 52%).

Method B:– A solution of chlorotrimethylsilane (320 μl, 2.5 mmol, 6 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (270 g, 4.1 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of hexadecanal (101 mg, 0.41 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 14 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene **137**[151]as a clear colourless oil (79 mg, 85%).

Method C:– To flame dried zinc amalgam (561 mg, 8.6 mmol, 10 eq.) under argon was added a solution (stored over poly-4-vinyl-pyridine for 1 hour) of chlorotrimethylsilane (1.6 ml, 12.5 mmol, 10 eq.) in dry dichloromethane (4 ml) . To the resultant vigorously stirred suspension was added a solution of 1-hexadecanal (300 mg, 1.25 mmol) in dry dichloromethane (8 ml) in a single portion. The reaction mixture was stirred at reflux for 19 hours and then quenched by addition of saturated aqueous sodium bicarbonate (10 ml). The resultant suspension was filtered, and the filter cake washed with dichloromethane (20 ml). The aqueous layer was extracted with dichloromethane (10 ml) and the combined organic layers washed with water (20 ml), sat. brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear colourless oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (72 mg, 0.32 mmol, 26%).

Method D:– A solution of dichlorodimethylsilane (110 μl, 0.92 mmol, 1.5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (400 mg, 6.1 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of hexadecanal (150 mg, 0.61 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 23 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (105 mg, 77%).

Method E:– A solution of chlorotrimethylsilane (0.55 ml, 4.3 mmol, 5 eq.) in dry ether (8 ml) was added to flame dried zinc amalgam (560 mg, 8.6 mmol, 10 eq.), and zinc chloride (234 mg, 1.7 mmol, 2 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 30 minutes a solution of hexadecanal (200 mg, 0.83 mmol) in dry ether (2.5 ml) was added *via* syringe pump over 3 hours. The reaction mixture was vigorously stirred at reflux for a further 13 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (157 mg, 84%).

v_{max} (NaCl, thin film)/cm^{-1} 3074, 2925, 2851, 2710, 1637, 1463, 1376, 1302, 991, 909, 721; δ_H (270 MHz, CDCl$_3$) 5.82 (1H, ddt, J 10.3, 17.1, 6.6, RCH=CHH), 5.00 (1H, ddt, J 1.2, 17.1, 0.5, RCH=CHH), 4.94 (1H, ddt, J 1.2, 10.3, 1.0, RCH=CHH), 2.05 (2H, ddq, J 0.5, 1.0, 6.6, CH_2CH=CHH), 1.08-1.30 (24H, m, alkyl chain), 0.86 (3H, t, J 6.5, CMe); m/z (EI) 224 (M$^+$, 6%), 43 (100%).

Preparation of 1-Hexadecene (137) and *n*-Tridecylcyclopropane (138).

(137)   (138)
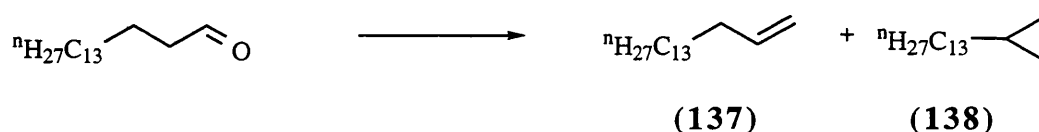
To flame dried zinc amalgam (704 mg, 10.8 mmol, 10 eq.) under nitrogen was added a solution of chlorotrimethylsilane (680 µl, 5.4 mmol, 5 eq.) in dry THF (5 ml) . To the resultant vigorously stirred suspension was added a solution of 1-hexadecanal (259 mg, 1.08 mmol) in dry THF (5 ml) in a single portion. The reaction mixture was stirred at reflux for 4.5 hours and then quenched by addition of saturated aqueous sodium bicarbonate (11 ml). The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 15 ml) and the combined organic layers washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give an oily solid which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of hexadecene 137[151] and *tridecyl-cyclopropane* 138 (9:1 by GC) as a clear colourless oil (184 mg, 0.82 mmol, 77%).

v_{max} (NaCl, thin film)/cm^{-1} 3074, 2925, 2851, 2710, 1637, 1463, 1376, 1302, 991, 909, 721; δ_H (400 MHz, CDCl$_3$) *hexadecene*: 5.82 (1H, ddt, J 10.3, 17.1, 6.6, RCH=CHH), 5.00 (1H, ddt, J 1.2, 17.1, 0.5, RCH=CHH), 4.94 (1H, ddt, J 1.2, 10.3, 1.0, RCH=CHH), 2.05 (2H, ddq, J 0.5, 1.0, 6.6, -CH_2CH=CHH), 1.08-1.30 (24H, m, alkyl chain), 0.86 (3H, t, J 6.5, -CH$_3$); *tridecyl-cyclopropane*: 1.40-1.20 (24H, m, alkyl H, masked by alkene), 0.94-0.82 (3H, t, -CH$_3$, masked by alkene), 0.70-0.60 (1H, m, H$_1$), 0.38 (2H, ddd, J 4.1, 5.6, 8.1, H$_{2\alpha,3\alpha}$), -0.01 (2H, ddd, J 4.1, 4.9, 5.6, H$_{2\beta,3\beta}$); *m/z*

(EI/GCMS) t_R: 8.4 min.: *hexadecene*: 224 (M+, 7%), 196, 183, 168, 154, 140, 125, 111, 97, 83, 69, 57, 55, 43 (100%), 29; t_R: 9.45 min.: *tridecyl-cyclopropane*: 224 (M+, 1%), 196, 168, 154, 140, 125, 111, 97, 83, 69, 55 (100%), 43, 41, 29.

Preparation of 1-Hexadecene (137).

$$^nH_{27}C_{13}\diagdown\diagup\diagdown O \longrightarrow {}^nH_{27}C_{13}\diagdown\diagup\diagdown$$

(137)

Method A: A solution of chlorotrimethylsilane (0.55 ml, 4.3 mmol, 5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (0.56 g, 8.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of additive (2.0 eq.) in dry ether (4 ml) was added. After a further 5 minutes at reflux a solution of hexadecanal (200 mg, 0.86 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux, and aliquots (ca. 200 µl) were removed at 35 minutes, 1.5 hours, 3 hours and 5 hours. The reaction mixture was heated at reflux for a further 18 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. NMR analysis of the crude mixture showed that hexadecene **137**[151] was the major product, except for the case of N,N,N,N-tetramethylethylenediamine, where hexadecanal **136**[150] was recovered unchanged.

Method B: A solution of dichlorodimethylsilane (135 µl, 1.12 mmol, 1.3 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (0.56 g, 8.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. After 5 minutes at reflux a solution of hexadecanal (200 mg, 0.86 mmol) in dry ether (5 ml) was added. The reaction

mixture was vigorously stirred at reflux, and aliquots (ca. 200 μl) were removed at 35 minutes, 1.5 hours, 3 hours and 5 hours. The reaction mixture was heated at reflux for a further 18 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. NMR analysis of the crude mixture showed that hexadecene 137[151] was the major product.

Additive	Ratio (alkene/aldehyde)			
	35 min.	1.5 hr.	3 hr.	5 hr.
None	1.7	3.4	6.5	17.0
$ZnCl_2$	>100	>200		
$Et_2O{:}BF_3$	11.8	22	>50	>100
Me_2SiCl_2	0.17	0.68	2.05	13.3
TMEDA	0	0	0	0

Preparation of and 2-Methyl-undec-2-ene (76) 2-Methyl-undec-1-ene (77) and 2-Methylundecane (78).

Method A:– A solution of chlorotrimethylsilane (1.07 ml, 8.4 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.10 g, 16.8 mmol, 10 eq.), in a 25 ml

conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-methyl-undecanal (370 μl, 1.68 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 15 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (15 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and washed through with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Silica gel column chromatography (petrol, b.p. 30-40°C) furnished a mixture of the alkenes 2-methyl-2-undecene 76[152] and 2-methyl-1-undecene 77[153] (3.6:1 by GC) as a clear colourless oil (178 mg, 60%), containing some 2-methyl-undecane 78[154] (1.5% by GC).

Method B:– A solution of chlorotrimethylsilane (1.38 ml, 10.9 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.42 g, 21.7 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of propylene oxide (30 μl, 0.43 mmol, 0.2 eq.) in dry ether (2 ml) was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (480 μl, 2.17 mmol) in dry ether (3 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 20 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Silica gel column chromatography (petrol, b.p. 30-40°C) furnished a mixture of the alkenes 2-methyl-2-undecene 76[152] and 2-methyl-1-undecene 77[153] (1:3.6 by GC) as a clear colourless oil (248 mg, 68%), containing some 2-methyl-undecane 78[154] (< 1.4% by GC).

Method C:– A solution of chlorotrimethylsilane (1.38 ml, 10.9 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.42 g, 21.7 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of propylene oxide (150 μl, 2.17 mmol, 1.0 eq.) in dry ether (2 ml)was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (480 μl, 2.17 mmol) in dry ether (3 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 20 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Silica gel column chromatography (petrol, b.p. 30-40°C) furnished a mixture of the alkenes 2-methyl-2-undecene **76**[152] and 2-methyl-1-undecene **77**[153] (1:2.3 by GC) as a clear colourless oil (223 mg, 61%), containing some 2-methyl-undecane **78**[154] (1.7% by GC).

v_{max} (NaCl, thin film)/cm^{-1} major isomer *2-methyl-1-undecene*: 3075, 2958, 2926, 2855, 1650, 1467, 1456, 1377, 887, 721; 2957, major isomer *2-methyl-2-undecene*: 2925, 2855, 1467, 1378, 1252, 909, 846, 736; δH (400 MHz, $CDCl_3$) *2-methyl-1-undecene*: 4.68 (1H, br s, RCMe=CH_AH$_B$), 4.66 (1H, br s, RCMe=CH$_A$$H_B$), 2.00 (2H, t, *J* 7.6 -CH_2CMe=CH$_2$), 1.71 (3H, s, RCCH_3=CH$_2$), 1.46-1.38 (2H, m, -CH_2CH$_2$CMe=CH$_2$), 1.34-1.22 (12H, m, alkyl chain), 0.89 (3H, t, *J* 7.3, -CH$_2$CH_3); *2-methyl-2-undecene*: 5.12 (1H, tt, *J* 1.4, 7.1, RCH=CMe$_2$), 2.02-1.92 (2H, m, -CH_2CH=CMe$_2$), 1.68 (3H, br s, RCH=CCH_3CH$_3$), 1.60 (3H, br s, RCH=CCH$_3$CH_3), 1.45-1.20 (12H, m, alkyl chain), 0.88 (3H, t, *J* 6.5, -CH$_2$CH_3); *m/z* (EI/GCMS) t_R: 9.65 min.: *2-methyl-1-undecene*: 168 (M^+, 3%), 112, 97, 83, 69, 57 (100%), 44; t_R: 10.1 min.: *2-methyl-2-undecene*: 168 (M^+, 14%), 140, 125, 112, 97, 83, 69 (100%), 57, 44; t_R: 12.6 min.: *2-methyl-undecane*: 170 (M^+, 3%), 155, 127, 112, 85, 71, 59 (100%), 45.

Preparation of 2-Methyl-undec-1-ene (77) and 1-Trimethylsilyloxy-2-methyl-undec-1-ene (139).

Me(CH₂)₇ ⟍⟍⟋⟍₌O   ⟶   Me(CH₂)₇ ⟍⟍⟋⟍   +   Me(CH₂)₇ ⟍⟍⟋⟍⟍OTMS

                                                                   H

                            (77)   **(139)**

Method A:– A solution of chlorotrimethylsilane (4.1 ml, 32.6 mmol, 10 eq.) in dry THF (6 ml) was added to flame dried zinc amalgam (2.13 g, 32.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,6 lutidine (1.14 ml, 9.8 mmol, 3.0 eq.) in dry THF (2 ml) was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (720 μl, 3.26 mmol) in dry THF (2 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 60 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and washed through with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Crude NMR showed the major products to be pinacols, with a small amount of the alkenes, 1-trimethylsilyloxy-2-methyl-undec-1-ene **139** and 2-methyl-1-undecene **77**[153] (1:1).

Method B:– A solution of chlorotrimethylsilane (4.1 ml, 32.6 mmol, 10 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (2.13 g, 32.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,6 lutidine (1.14 ml, 9.8 mmol, 3.0 eq.) in dry ether (2 ml) was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (720 μl, 3.26 mmol) in dry ether (2 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 96 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium

bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Crude NMR showed the major products to be the trimethylsilyl enol ether **139** and 2-methyl-1-undecene **77**[153] (6:1), along with unreacted starting material (ca. 50%).

Preparation of 2-Methyl-undec-2-ene (76), 2-Methyl-undec-1-ene (77), 1-Trimethylsilyloxy-2-methyl-undec-1-ene (139) and 2-Methyl-undecane (78).
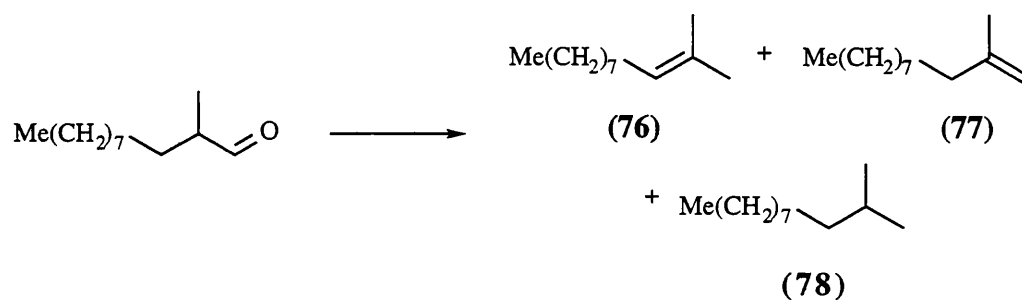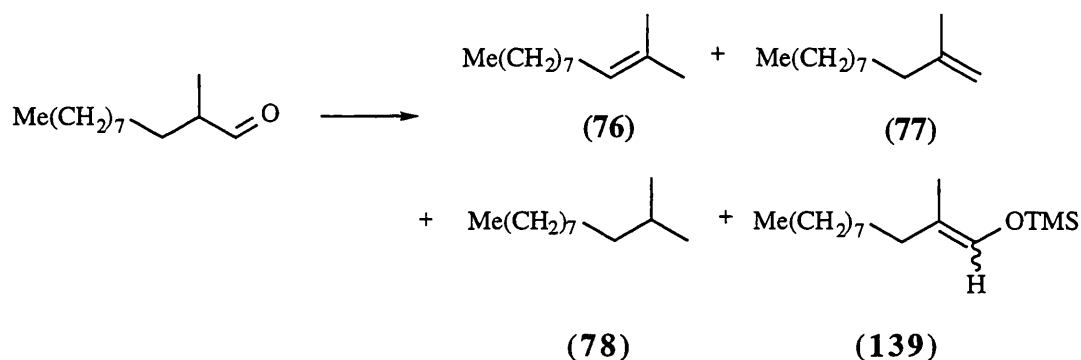

Method A:– A solution of chlorotrimethylsilane (1.38 ml, 10.9 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.42 g, 21.7 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,6 lutidine (25 µl, 0.22 mmol, 0.1 eq.) in dry ether (2 ml) was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (480 µl, 2.17 mmol) in dry ether (2 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 42 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Crude NMR showed the major

products to be the trimethylsilyl enol ether **139**, 2-methyl-2-undecene **76**[153] and 2-methyl-1-undecene **77**[154], along with unreacted starting material (ca. 30%). GC showed the ratio of alkenes 2-methyl-2-undecene **76**[153] and 2-methyl-1-undecene **77**[154], to be 3.6:1, with 2.4% of 2-methyl-undecane **78**[155].

Method B:– A solution of chlorotrimethylsilane (1.38 ml, 10.9 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.42 g, 21.7 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,6 di-^{t}butyl-pyridine (50 μl, 0.22 mmol, 0.1 eq.) in dry ether (2 ml) was added. After a further 5 minutes at reflux a solution of 2-methyl-undecanal (480 μl, 2.17 mmol) in dry ether (2 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 24 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Crude NMR showed the major products to be the trimethylsilyl enol ether **139**, 2-methyl-2-undecene **76**[152] and 2-methyl-1-undecene **77**[153], along with unreacted starting material (ca. 30%). GC showed the ratio of alkenes 2-methyl-2-undecene **76**[152] and 2-methyl-1-undecene **77**[153] to be 1.2:1, with 1.4% of 2-methyl-undecane **78**[154].

Preparation of 2-Methyl-undec-2-ene (76) and 2-Methyl-undec-1-ene (77).

(76)   (77)

A solution of chlorotrimethylsilane (1.38 ml, 10.9 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (1.42 g, 21.7 mmol, 10 eq.) and poly-4-vinylpyridine (225 mg, 2.17 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under
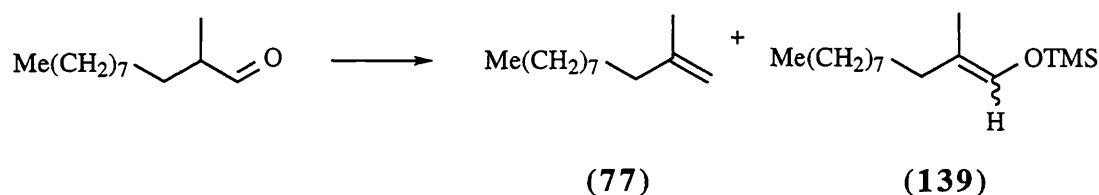
nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-methyl-undecanal (480 µl, 2.17 mmol) in dry ether (2 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 18 hours and then cooled to ambient temperature. The reaction mixture was poured into saturated aqueous sodium bicarbonate (20 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a colourless oil. Crude NMR showed the major products to be 2-methyl-2-undecene 76[152] and 2-methyl-1-undecene 77[153] (ca. 1:1), along with unreacted starting material (ca. 50%).

Preparation of Ethyl-Z-octadec-9-enoate (141).

(141)
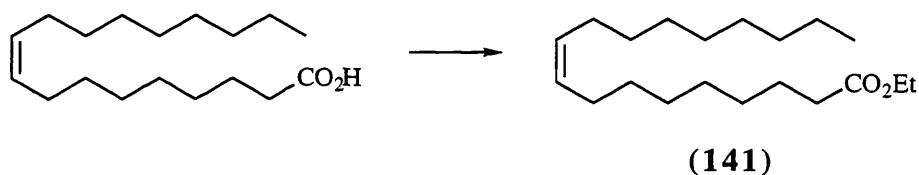
Oxalyl chloride (6.66 ml, 76.4 mmol, 1.1 eq.) was added to a solution of oleic acid (19.97 g, 70.7 mmol) in dry dichloromethane (150 ml). After 1.25 hours the solvent was removed *in vacuo* and the brown oil taken up in dry benzene (100 ml). A solution of dry pyridine (7.7 ml, 76.4 mmol, 1.1 eq.) was added followed by a solution of dry ethanol (4.5 ml, 76.4 mmol, 1.1 eq.). The solution turned cloudy instantly and was left to stir at ambient temperature overnight. The suspension was poured into hydrochloric acid (50 ml, 2M), and the aqueous phase extracted with ether (3 x 50 ml). The combined organic layers were washed with saturated aqueous copper sulphate (50 ml), water (50 ml), saturated aqueous sodium bicarbonate (50 ml), brine (100 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a dark brown oil which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the ester 141[155] (20.95 g, 95%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2925, 2854, 1739, 1466, 1372, 1179, 1117, 1037; δH (400 MHz, CDCl$_3$) 5.34 (2H, t, *J* 6.2, C=CH), 4.12 (2H, q, *J* 7.1, CH$_2$O), 2.28 (2H, t, *J* 7.6,

CH$_2$CO$_2$R), 1.92-2.06 (4H, m, C=CHC*H*$_2$), 1.66-1.54 (2H, m, C*H*$_2$CH$_2$CO$_2$R), 1.48-1.18 (23 H, m, alkyl H, OCH$_2$C*H*$_3$), 0.87 (3H, t, *J* 7.1, CH$_2$CH$_2$C*H*$_3$); *m/z* (EI) 310 (M$^+$, 2.5%), 88 (100%).

Preparation of Ethyl 9-oxo-nonanoate (82).

(82)
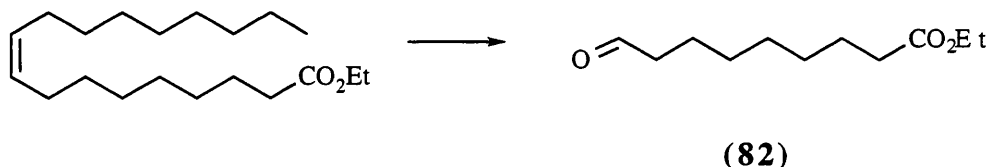
A stirred solution of the alkene (20.77 g, 66.9 mmol) in dry dichloromethane (200 ml) was cooled to -78°C under a continuous flow of oxygen. Ozonized oxygen was passed through the solution (oxygen flow rate of 2 l/minute) at -78°C until the blue colour of ozone appeared in the solution. The reaction mixture was then purged with oxygen, and triphenylphosphine (19.3 g, 73.6 mmol, 1.1 eq.) added at -78°C in a single portion, and the solution warmed slowly to ambient temperature and left overnight under an atmosphere of nitrogen. The solution was concentrated *in vacuo* to give a yellow slurry. Bulb to bulb distillation gave a fraction (b.p.< 140°C/12 mm Hg) which was rejected and a second fraction (b.p.< 150°C/0.8 mbar) which was chromatographed on silica (0-10% ether in petrol (b.p. 40-60°C)) to give the aldehyde 82[156] (3.08 g, 23%) as a clear colourless oil. ν_{max} (NaCl, thin film)/cm^{-1} 2932, 2857, 2719, 1732, 1464, 1418, 1373, 1246, 1178, 1098, 1035, 857, 727; δ_H (400 MHz, CDCl$_3$) 9.37 (1H, t, *J* 1.8, CHO), 4.10 (2H, q, *J* 7.1, CH$_2$O), 2.40 (2H, dt, *J* 1.8, 7.3, CH$_2$CHO), 2.27 (2H, t, *J* 7.6, CH$_2$CO$_2$R), 1.64-1.54 (4H, m, C*H*$_2$CH$_2$CO$_2$R), 1.34-1.26 (6 H, m, alkyl H), 1.23 (3H, t, *J* 7.1, CH$_3$); *m/z* (EI) 200 (M$^+$, 17%), 29 (100%).

## Preparation of Ethyl non-8-enoate (83) and Ethyl nonanoate (84).
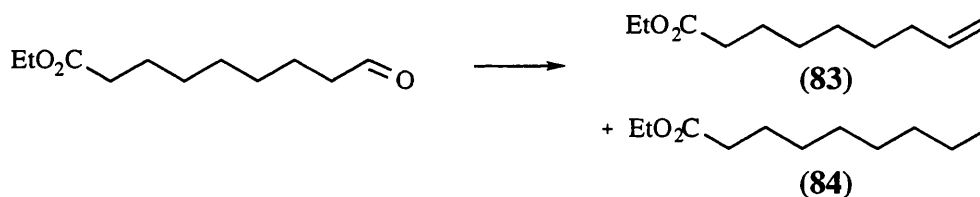
A solution of chlorotrimethylsilane (1.12 ml, 9.0 mmol, 5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (1.18 g, 18 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of ethyl 9-oxo-nonanoate (360 mg, 1.80 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 14 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C)) furnished a mixture of ethyl non-8-enoate **83**[157] and ethyl nonaoate **84**[158] (9:1 by GC) as a clear colourless oil (193 mg, 58%).

v_{max} (NaCl/KBr disc, thin film/neat)/cm^{-1} ; δ_H (400 MHz, CDCl$_3$) *ethyl non-9-enoate*: 5.79 (1H, ddt, *J* 10.3, 17.1, 6.7, RC*H*=CHH), 4.98 (1H, ddt, *J* 2.2, 17.1, 1.5, RCH=C*H*H), 4.92 (1H, ddt, *J* 2.2, 10.3, 1.7, RCH=CH*H*), 4.10 (2H, q, *J* 7.1, CH$_2$O), 2.28, (2H, t, *J* 7.4, CH$_2$CO$_2$R), 2.03 (2H, ddq, *J* 1.5, 1.7, 6.7, C*H$_2$*CH=CHH), 1.66-1.56 (2H, m, CH$_2$CO$_2$R), 1.42-1.22 (6H, m, alkyl H), 1.24 (3H, t, *J* 7.1, CH$_3$); *ethyl nonaoate*: 4.12-1.22 (17H, signals masked by ene-ester), 0.87 (3H, t, *J* 7.0, CH$_3$), ; *m/z* (EI/GCMS) *ethyl non-9-enoate*: 184 (M$^+$, 0.3%), 56 (100%)*ethyl nonaoate*: 186 (M$^+$, 4%), 88 (100%).

Preparation of 2-Methyl-2-propyl-*Z*-octadec-9-enoate (140).

(140)

Oxalyl chloride (1.04 ml, 11.9 mmol, 1.5 eq.) was added to a solution of oleic acid (2.50 g, 7.97 mmol) in dry dichloromethane (20 ml), along with 1 drop of dry N,N-dimethyl formamide. After 20 minutes the solvent was removed *in vacuo* and the brown oil taken up in dry benzene (16 ml). A solution of dry pyridine (970 μl, 11.9 mmol, 1.5 eq.) in dry benzene (2 ml) was added followed by a solution of dry t-butanol (900 μl, 9.56 mmol, 1.2 eq.) in dry benzene (2 ml). The solution turned cloudy instantly and was left to stir at ambient temperature overnight. The suspension was poured into water (30 ml), and the aqueous phase extracted with ether (2 x 20 ml). The combined organic layers were washed with saturated aqueous copper sulphate (30 ml), water (25 ml), saturated aqueous sodium bicarbonate (25 ml), brine (25 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to a light brown oil which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the ester **140**[159] (1.87 g, 69%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm⁻¹ 3005, 2926, 2854, 1734, 1458, 1391, 1366, 1254, 1153, 952, 894, 722; δ_H (400 MHz, CDCl₃) 5.32 (2H, t, *J* 6.2, C=CH), 2.17 (2H, t, *J* 7.4, CH₂CO₂R), 2.02-1.92 (4H, m, C=CHC*H₂*), 1.58-1.50 (2H, m, C*H₂*CH₂CO₂R), 1.42 (9H, s, C(CH₃)₃), 1.34-1.20 (20 H, m, alkyl H), 0.86 (3H, t, *J* 7.0, CH₂C*H₃*); *m/z* (FAB/MNOBA) 339 (M+H⁺, 0.1%), 57 (100%).

Preparation of (2-Methyl-2-propyl) 9-oxo-nonanoate (85).

(85)
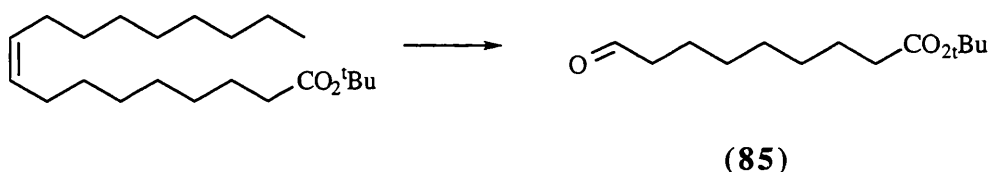
A stirred solution of the alkene (1.51 g, 4.46 mmol) in dry dichloromethane (20 ml) was cooled to -78°C under a continuous flow of oxygen. Ozonized oxygen was passed through

the solution (oxygen flow rate of 2 l/minute) at -78°C until the blue colour of ozone appeared in the solution (10 minutes). The reaction mixture was then purged with oxygen, and dimethyl sulfide (1.0 ml, 13.4 mmol, 3.0 eq.) added at -78°C in a single portion, and the solution stirred at -78°C under an atmosphere of nitrogen for 45 minutes. The reaction mixture was then warmed to ambient temperature and left overnight under nitrogen. NMR analysis of an aliquot showed the presence of much unreacted ozonide. Triphenylphosphine (1.40 g, 5.35 mmol, 1.2 eq.) was added and the solution left at ambient temperature for 24 hours, and then concentrated *in vacuo* to give a light brown oil which was chromatographed on silica (0-15% ether in petrol (b.p. 40-60°C)) to give the aldehyde **85**[159] (613 mg, 60%) as a clear colourless oil.

ν_{max} (NaCl, thin film)/cm[-1] 2932, 2857, 2716, 1727, 1458, 1420, 1392, 1367, 1255, 1156, 1105, 1039, 974, 848, 754, 726; δ_H (400 MHz, CDCl$_3$) 9.72 (1H, t, J 1.1, CHO), 2.39 (2H, dt, J 1.1, 7.3, CH_2CHO), 2.16 (2H, t, J 7.5, CH_2CO$_2$R), 1.64-1.50 (4H, m, CH_2CH$_2$COX), 1.41 (9H, s, C(CH$_3$)$_3$), 1.32-1.22 (6H, m, alkyl H), ; m/z (FAB/MNOBA) 229 (M+H^{+}, 7.4%), 57 (100%).

Preparation of 8-Nonenoic acid (86) and Nonanoic acid (87).
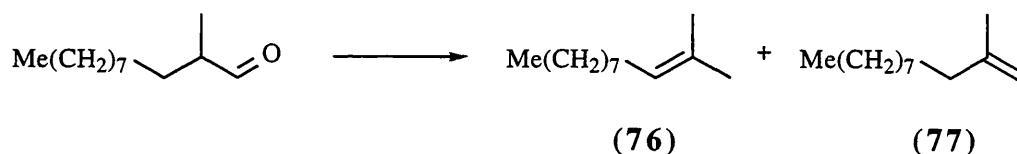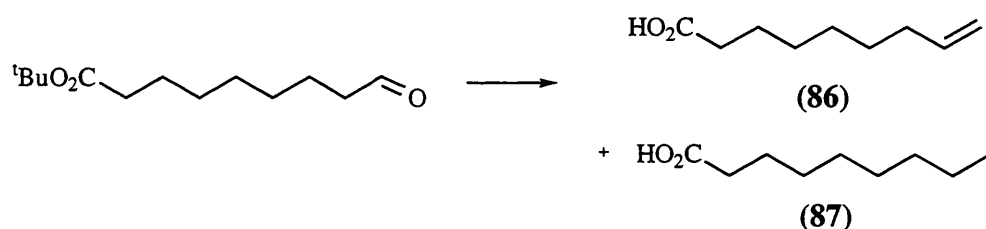

A solution of chlorotrimethylsilane (875 μl, 6.9 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (900 mg, 13.8 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 9-oxo-(2-methyl-2-propyl) nonanoate (315 mg, 1.38 mmol) in dry ether (6 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 15 hours and then cooled to ambient temperature. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate

(10 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was acidified with hydrochloric acid (5 ml, 2M), and extracted with ether (2 x 20 ml). The combined organic layers were washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (10-35% ether in petrol (b.p. 40-60°C)) furnished a mixture of the acids 8-nonenoic acid **86**[157] and nonanoic acid **87**[160] (85:15 by GC as their trimethylsilyl esters) as a clear colourless oil (141 mg, 65%).

v_{max} (NaCl, thin film)/cm^{-1} 3500-2500 (br, OH), 3078, 2926, 2857, 2677, 1720, 1641, 1464, 1438, 1414, 1289, 1235, 1114, 994, 910; δ_H (400 MHz, $CDCl_3$) *Nonenoic acid*: 9.50 (1H, br CO_2H), 5.80 (1H, ddt, *J* 17.1, 10.3, 6.7, RC*H*=CHH), 4.99 (1H, ddt, *J* 2.3, 17.1, 2.3, RCH=C*H*H), 4.93 (1H, ddt, *J* 2.3, 10.3, 1.7, RCH=CH*H*), 2.34(2H, t, *J* 7.6, C*H*$_2$CO$_2$R), 2.03 (2H, dddt, *J* 1.5, 1.7, 6.7, 6.7, C*H*$_2$CH=CHH), 1.63 (2H, tt, *J* 7.3, 7.6, C*H*$_2$CH$_2$CO$_2$R), 1.44-1.24 (6H, m, alkyl chain): *nonanoic acid*: 1.24-2.36 (14H, masked by ene-acid), 0.86 (3H, t, *J* 7.0, C*Me*); *m/z* (EI/GCMS as trimethylsilyl esters) *Nonenoic acid* t_R 9.9 min; 213 (40%, M-Me$^+$), 75 (100%); *nonanoic acid* t_R 10.2 min; 215 (40%, M-Me$^+$), 73 (100%).

Preparation of 11-Bromo-undecanal (88).

$Br(CH_2)_8$ ~~~~ OH $\longrightarrow$ $Br(CH_2)_8$ ~~~~ O

(88)
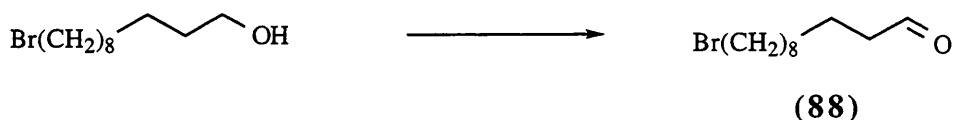
To a solution of 11-bromo-undecanol (2.00 g, 7.8 mmol) in dry dichloromethane (30 ml) under nitrogen was added pyridinium chlorochromate (2.52 g, 11.7 mmol 1.5 eq.) in a single portion. After 2.5 hours, ether (40 ml), was added and the suspension filtered through a pad of silica and concentrated *in vacuo* to give a green semi-solid oil. Bulb to bulb distillation (200°C/1.5 mbar) furnished the aldehyde **88**[161] (1.54 g, 79%) as a white solid. m.p. 39-41°C (needles from EtOH).

v_{max} (NaCl, thin film)/cm^{-1} 2975, 2854, 2716, 1725, 1464, 1408, 1390, 1354, 1254, 1125, 1050, 722; δ_H (400 MHz, CDCl$_3$) 9.76 (1H, t, 1.8, CHO), 3.40 (2H, t, J 6.8, CH$_2$Br), 2.42 (2H, dt, 1.8,7.3, CH_2CHO), 1.85 (2H, tt, J 6.8, 7.5, CH_2CH$_2$Br), 1.60-1.58 (2H, m, CH_2CH$_2$CHO), 1.47-1.25 (12H, m, alkyl chain); m/z (FAB/MNOBA) 251 (M+H$^+$(^{81}Br), 4.2%), 249 (M+H$^+$(^{79}Br)/M-H$^+$(^{81}Br), 13.16%), 247 (M-H$^+$(^{79}Br), 7.2%), 55 (100%).

Preparation of 11-Bromo-undecene (89).

$Br(CH_2)_8$ ~~~~ O $\longrightarrow$ $Br(CH_2)_8$ ~~~~

(89)
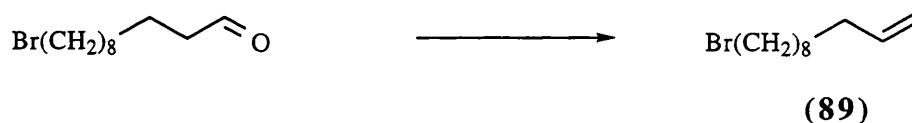
A solution of chlorotrimethylsilane (1.03 ml, 8.1 mmol, 5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (1.06 g, 16.2 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 11-bromo-undecanal (404 mg, 1.62 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 14 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (20 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed

with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene 89[162] as a clear colourless oil (234 mg, 62%).

v_{max} (NaCl, thin film)/cm^{-1} 3075, 2926, 2854, 1640, 1463, 1246, 992, 909; δ_H (400 MHz, CDCl$_3$) 5.81 (1H, ddt, J 10.3, 17.1, 6.6, RC*H*=CHH), 4.99 (1H, dq, J 17.1, 1.2, RCH=C*H*H), 4.93 (1H, dq, J 10.3, 1.2, RCH=CH*H*), 3.42 (2H, t, J 6.9, C*H*$_2$Br), 2.05 (2H, dtt, J 6.6, 1.2, 6.1, C*H*$_2$CH=CHH), 1.85 (2H, tt, J 6.9, 7.4, C*H*$_2$CH$_2$Br), 1.44-1.25 (12H, m, alkyl chain); m/z (EI) 234 (M$^+$(^{81}Br), 3.7%), 232 (M$^+$(^{79}Br), 3.9%), 69 (100%).

Preparation of 2,4,6-Tri-(10-iododecyl)-1,3,5-trioxane (90).

(90)
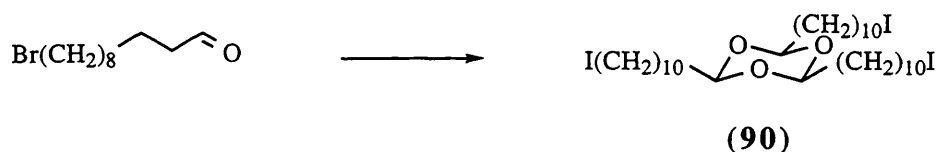
A solution of 11-bromo-undecanal (522 mg, 2.09 mmol) and sodium iodide (1.67 g, 11.1 mmol, 5 eq.) in dry acetone was heated to reflux with stirring for 2 hours. The cooled suspension was concentrated *in vacuo*, and the residue partitioned between ether/dichloromethane (4/1, 50 ml) and water (20 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with 10% aqueous sodium thiosulphate (5 ml), brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a white solid which was chromatographed on silica (1% ether in petrol (b.p. 40-60°C)) to give the *trioxane* 90 (546 mg, 88%) as a white solid. m.p. 67-68°C (needles from ether/petrol (b.p. 40-60°C)).

v_{max} (KBr disc)/cm^{-1} 2997, 2923, 2848, 1466, 1422, 1400, 1382, 1358, 1344, 1294, 1237, 1230, 1202, 1166, 1133, 1101, 1076, 1058, 1043, 961, 920, 722, 600; δ_H (400 MHz, CDCl$_3$) 4.80 (3H, t, J 5.2, OC*H*RO), 3.16 (6H, t, J 7.0, C*H*$_2$I), 1.79, 6H, tt, J 7.0, 7.5, C*H*$_2$CH$_2$I), 1.63 (6H, dt, J 5.2, 7.6, C*H*$_2$CHRO$_2$), 1.45-1.18 (42H, m, alkyl

H); *m/z* (EI) 297 (M+H$^+$ (C$_{11}$H$_{21}$IO), 5%); (Found: C, 44.4; H, 6.90. C$_{33}$H$_{63}$I$_3$O$_3$ requires C, 44.6; H, 7.14%).

Preparation of 11-Iodo-undecene (91).

$$I(CH_2)_{10}\text{—O—}\overset{O\text{—}(CH_2)_{10}I}{\underset{(CH_2)_{10}I}{\diamond}} \longrightarrow I(CH_2)_8\diagup\diagup$$

(91)
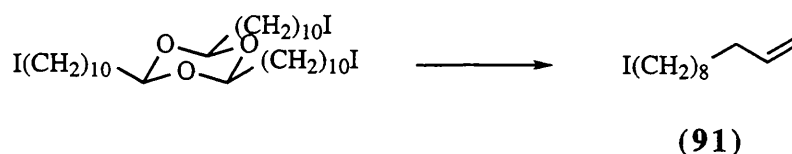
A solution of chlorotrimethylsilane (400 µl, 3.1 mmol, 15 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (410 mg, 6.3 mmol, 30 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,4,6-tri-(10-iododecyl)-1,3,5-trioxane (170 mg, 0.21 mmol) in dry ether (7 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 14 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene **91**[162] as a clear colourless oil (42 mg, 26%).

v_{max} (NaCl, thin film)/cm^{-1} 3075, 2996, 2853, 1640, 1464, 1394, 1220, 1183, 1168, 993, 909, 721; δ_H (400 MHz, CDCl$_3$) 5.81 (1H, ddt, *J* 10.3, 17.1, 6.7, RC*H*=CHH), 4.99 (1H, ddt, *J* 2.0, 17.1, 1.7, RCH=C*H*H), 4.93 (1H, ddt, *J* 2.0, 10.3, 1.1, RCH=CH*H*), 3.19 (2H, t, *J* 7.1, CH$_2$I), 2.04 (2H, dddt, *J* 1.1, 1.7, 6.7, 7.0, C*H*$_2$CH=CHH), 1.82 (2H, tt, *J* 7.1, 7.3, C*H*$_2$CH$_2$I), 1.38-1.27 (12H, m, alkyl chain); *m/z* (CI/^{i}C$_4$H$_{10}$) 281 (M+H$^+$, 18%), 280 (M$^+$, 12%), 57 (100%).

Preparation of 11-Iodo-undecene (91) and 1-Iodoundecane (147).

$$I(CH_2)_{10} \underset{O}{\overset{O}{\diagdown}}\!\!\!\diagup\!\!\!\overset{(CH_2)_{10}I}{\underset{O}{\diagdown}} \!\!\!\diagup (CH_2)_{10}I \longrightarrow I(CH_2)_8\diagup\!\!\!\diagup + I(CH_2)_8\diagup\!\!\!\diagdown$$

$$(91) \qquad\qquad (147)$$
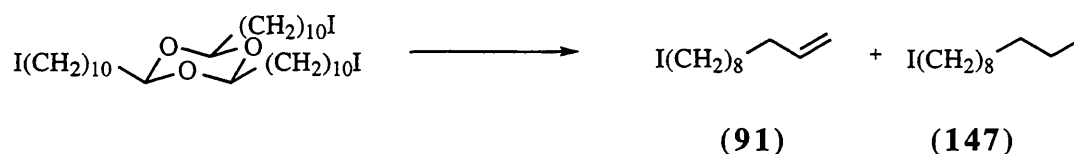
A solution of chlorotrimethylsilane (473 μl, 3.7 mmol, 15 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (490 mg, 6.9 mmol, 30 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,4,6-tri-(10-iododecyl)-1,3,5-trioxane (201 mg, 0.23 mmol) in dry ether/dichloromethane (10/1 7 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 14 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished a mixture of 11-iodo-undecene **91**[162] and 1-iodoundecane **147**[163] (10:1 by NMR) as a clear colourless oil (70 mg, 37%).

v_{max} (NaCl, thin film)/cm^{-1} 3075, 2996, 2853, 1640, 1464, 1394, 1220, 1183, 1168, 993, 909, 721; δ_H (400 MHz, $CDCl_3$) *11-iodo-undecene*: 5.81 (1H, ddt, *J* 10.3, 17.1, 6.7, RC*H*=CHH), 4.99 (1H, ddt, *J* 2.0, 17.1, 1.7, RCH=C*H*H), 4.93 (1H, ddt, *J* 2.0, 10.3, 1.1, RCH=CH*H*), 3.19 (2H, t, *J* 7.1, CH_2I), 2.04 (2H, dddt, *J* 1.1, 1.7, 6.7, 7.0, C*H₂*CH=CHH), 1.82 (2H, tt, *J* 7.1, 7.3, C*H₂*CH_2I), 1.38-1.27 (12H, m, alkyl chain); *1-iodoundecane*: 3.19 (2H, t, *J* 7.1, CH_2I, masked by alkene), 1.82 (2H, tt, *J* 7.1, 7.3, C*H₂*CH_2I, masked by alkene), 1.38-1.27 (12H, m, alkyl chain, masked by alkene), 0.89 (3H, t, *J* 6.5, -CH_3); m/z (CI/^{i}C_4H_{10}) 282 (M^+, 2%, 1-iodoundecane), 281 (M+H^+, 18%), 280 (M^+, 12%), 57 (100%).

Preparation of 2,4,6-Tri-pentadecyl-1,3,5-trioxane (92).

(92)

A suspension of lithium (694 mg, 100 mmol) in dry ether (7 ml) was sonicated for 15 minutes in a Sonicor cleaning bath. The suspension was cooled to -20°C and a solution of bromopentane (2.48 ml, 20.0 mmol) in dry ether (8 ml) was added with stirring over 1 hour. The solution was stirred at -10°C for a further hour. Titration of 2 aliquots with *o*-tolyl-pivalamide in dry tetrahydrofuran indicated a pentyllithium concentration of 1.0M.

Copper (1) cyanide (242 mg, 2.7 mmol) was placed in a dried 50 ml 3 neck flask, and dried by azeotroping with dry toluene (2 x 3 ml) under vacuum at ambient temperature. Dry tetrahydrofuran (4 ml) was added and the stirred suspension cooled to -78°C. A solution of pentyllithium in dry ether (5.4 ml, 1M, 5.4 mmol, 2 eq.) was added dropwise and after 5 minutes the solution was allowed to warm to 0°C. After 5 minutes at 0°C the tan-coloured suspension was recooled to -78°C, and a solution of 2,4,6-tri-(10-iododecyl)-1,3,5-trioxane (400 mg, 0.45 mmol) in dry tetrahydrofuran (4 ml) added. The suspension was maintained at -78°C for 1 hour, and then slowly warmed to -20°C over 1 hour before warming to ambient temperature. The reaction was quenched by addition of 20% ammonium hydroxide in saturated aqueous ammonium chloride (30 ml) and stirred at ambient temperature for 10 minutes to complex the copper salts. The separated aqueous layer was extracted with ether (3 x 30 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered through celite and concentrated *in vacuo* to give an oily solid which was chromatographed on silica (0-20% dichloromethane in petrol (b.p. 40-60°C)) to give the trioxane **92**[164] (132 mg, 41%) as a white solid. m.p. 66-71°C (ether), (lit.[164] 73°C, ether).

v_{max} (KBr disc)/cm^{-1} 2916, 2849, 1470, 1400, 1381, 1362, 1328, 1159, 1134, 1116, 1101, 1066, 1030, 988, 966, 718; δ_H (400 MHz, CDCl$_3$) 4.83 (3H, t, *J* 5.3, OCHRO), 1.63 (6H, dt, *J* 5.3, 7.4, C*H*$_2$CHRO$_2$), 1.42-1.36 (6H, m, C*H*$_2$CH$_2$CHRO$_2$), 1.34-1.20 (36H, m, alkyl H), 0.88 (9H, t, *J* 6.5, CH$_3$); δ_C (100 MHz, CDCl$_3$), 101.7, 34.4, 31.9,

29.71, 29.67, 29.61, 29.58, 29.51, 29.38, 23.6, 22.7, 14.1; *m/z* (EI) 241 (M+H$^+$ (C$_{16}$H$_{32}$O), 44%).

**Preparation of Hexadecene (137).**

(137)
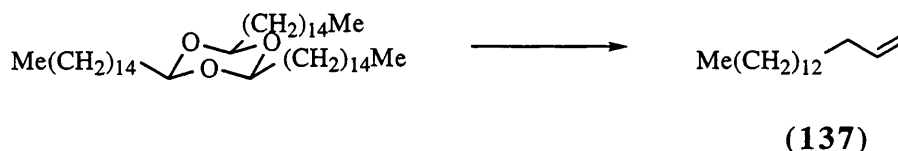
A solution of chlorotrimethylsilane (180 μl, 1.45 mmol, 15 eq.) in dry ether (2 ml) was added to flame dried zinc amalgam (190 mg, 2.9 mmol, 30 eq.), in a 10 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2,4,6-tripentadecyl-1,3,5-trioxane (170 mg, 96 μmol) in dry ether/dichloromethane (4/1, 5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 20 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (5 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene 137[151] as a clear colourless oil (30 mg, 47%), spectroscopically identical to material already prepared.

Preparation of 2-(7-Ethoxycarbonyl-heptyl)-1,3-dioxolane (142).

(142)
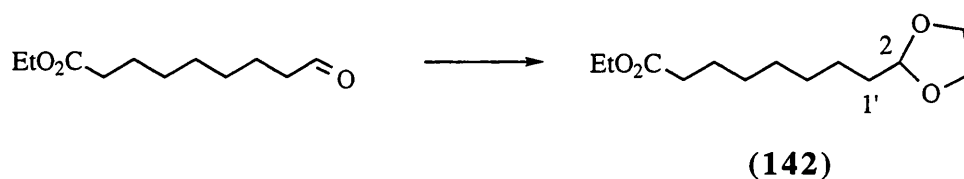
A solution of 9-oxo-ethyl nonanoate (2.19 g, 10.9 mmol), ethylene glycol (1.23 ml, 21.8 mmol, 2.0 eq.) and *p*-toluenesulfonic acid monohydrate (150 mg) were heated to reflux in

benzene (60 ml), and the water formed removed by azeotropic distillation using a Dean-Stark apparatus, for 2 hours. The reaction mixture was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (20 ml) and extracted with ether (3 x 30 ml). The combined organic layers were washed with water (2 x 20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which upon bulb to bulb distillation (160°C/0.9 mbar), and filtration through a silica pad (35% ether in petrol (b.p. 40-60°C)) gave the *dioxolane* 142 (1.61 g, 60%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2932, 2858, 2766, 1736, 1464, 1410, 1373, 1301, 1142, 1036, 943, 858, 727; δ_H (400 MHz, CDCl$_3$) 4.73 (1H, t, *J* 4.8, RCHO$_2$), 4.03 (2H, q, *J* 7.1, CH$_2$O), 3.72-3.87 (4H, m, O(CH$_2$)$_2$O), 2.18, (2H, t, *J* 7.4, CH$_2$CO$_2$R), 1.56-1.50 (4H, m, H$_{1',6'}$), 1.36-1.18 (8H, m, alkyl H), 1.15 (3H, t, *J* 7.1, CH$_3$); *m/z* (FAB/MNOBA) 245 (M+H$^+$, 45%), 244 (M$^+$, 10%), 239 (M-H$^+$, 71%), 73 (100%); (Found: M+H$^+$, 243.1596. C$_{13}$H$_{24}$O$_4$, requires *M*, 243.1593).

Preparation of 2-(7-Hydroxycarbonyl-heptyl)-1,3-dioxolane (143).

(143)
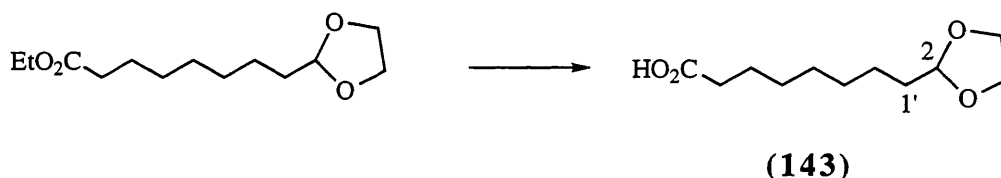
A solution of potassium hydroxide (348 mg, 6.2 mmol, 1.5 eq.) in methanol (10 ml) was added to neat 2-(7-ethoxycarbonyl-heptyl)-1,3-dioxolane (1.01 g, 4.13 mmol) with stirring at ambient temperature. Water (2 ml) was added, and the resultant solution was stirred for 2 hours. Aqueous acetic acid (1M) was added until the solution reached pH6. The solution was extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the acid 143[165] (882 mg, 98%) as a white solid. m.p. 58-63°C (prisms from dichloromethane).

v_{max} (KBr disc)/cm^{-1} 3037 (br, OH), 2916, 2849, 1694, 1466, 1422, 1339, 1302, 1265, 1227, 1196, 1168, 1132, 1096, 1035, 933, 728, 679, 558; δ_H (400 MHz, CDCl$_3$) 9.30

1H, br, OH), 4.84 (1H, t, J 4.8, RCHO$_2$), 4.01-3.80 (4H, m, O(CH$_2$)$_2$O), 2.33, (2H, t, J 7.4, CH_2CO$_2$H), 1.74-1.50 (4H, m, H$_{1',6'}$), 1.50-1.14 (8H, m, alkyl H); m/z (FAB/MNOBA) 217 (M+H$^+$, 35%), 216 (M$^+$, 9%), 215 (M-H$^+$, 69%), 73 (100%).

Preparation of 9-Oxo-nonanoic acid (93).

(93)
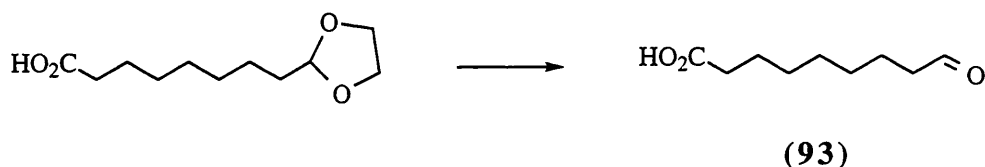
2-(7-Hydroxycarbonyl-heptyl)-1,3-dioxolane (381 mg, 1.74 mmol) and p-toluenesulfonic acid monohydrate were dissolved in acetone (15 ml), and water (1.5 ml) was added. The resultant solution was heated to reflux under nitrogen for 3 days. The cooled solution was poured into hydrochloric acid (15 ml, 1M), and the aqueous layer extracted with ether (3 x 20 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (50-75% ether in petrol (b.p. 40-60°C)) to give the acid 93[166] (296 mg, 95%) as a light yellow oil.

v_{max} (NaCl, thin film)/cm^{-1} 3097 (br, OH), 2932, 2857, 2722, 1707, 1457, 1412, 1284, 1244, 1102, 1042, 943, 762; δ_H (400 MHz, CDCl$_3$) 9.75 (1H, t, J 1.8, CHO), 7.50 (1H, br, OH), 2.42, (2H, t, J 1.8, 7.3, CH_2CHO), 2.34 (2H, t, J 7.5, CH_2CO$_2$H), 1.69-1.52 (4H, m, CH_2CH$_2$COX), 1.46-1.20 (6H, m, alkyl H); m/z (FAB/MNOBA) 173 (M+H$^+$, 19%), 172 (M$^+$, 6%), 171 (M-H$^+$, 23%), 136 (100%).

Preparation of 8-Nonenoic acid (86) and Nonanoic acid (87).

HO$_2$C$\diagdown\diagup\diagdown\diagup\diagdown\diagup\diagdown$O $\longrightarrow$

HO$_2$C$\diagdown\diagup\diagdown\diagup\diagdown\diagup=$
(86)

+ HO$_2$C$\diagdown\diagup\diagdown\diagup\diagdown\diagup\diagdown$
(87)
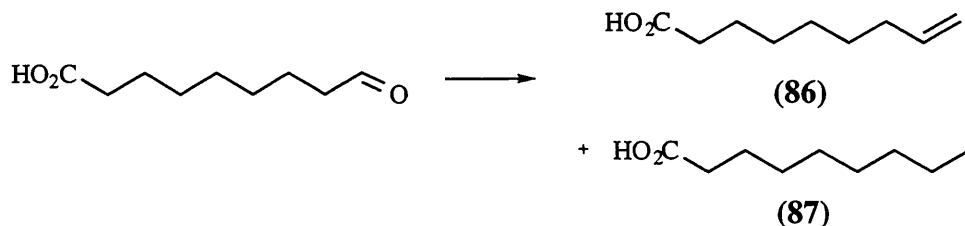
A solution of chlorotrimethylsilane (840 μl, 6.65 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (870 mg, 13.3 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 9-oxo-nonanoic acid (229 mg, 1.33 mmol) in dry ether (6 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 3 hours and then cooled to ambient temperature. The reaction was quenched by addition of water (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (10% ether in petrol (b.p. 40-60°C)) furnished a mixture of the acids 8-nonenoic acid 86[157] and nonanoic acid 87[160] (86:14 by GC as their trimethylsilyl esters) as a clear colourless oil (52 mg, 25%). Data as already described above.

Preparation of 2-(2-Phenyl-ethyl)-but-3-enenitrile (145).

CN $\longrightarrow$

CN
(145)
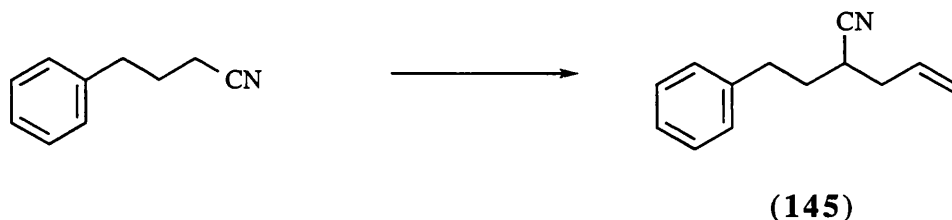
n-Butyllithium (2.72 ml, 7.00 mmol, 1.0 eq., 2.57 M in hexanes) was added to a solution of diisopropylamine (1.09 ml, 7.7 mmol, 1.1 eq.) in tetrahydrofuran (10 ml) at -78°C. 4-Phenyl-butyronitrile (1.04 ml, 7.00 mmol) was added dropwise to the solution at -78°C

166

to give a yellow suspension. Further tetrahydrofuran (10 ml) was added and the suspension warmed to ambient temperature whereupon the precipitate dissolved. The light brown solution was recooled to -78°C and allyl bromide (575 ml, 6.65 mol, 0.95 eq.) added in a single portion. After 1.7 hours at -78°C the solution was warmed rapidly to ambient temperature and poured into hydrochloric acid (2M, 10 ml), and ether (40 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (10 ml), brine (20 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the *nitrile* **145** (1.17 g, 95%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 3084, 3028, 2982, 2928, 2863, 2239 (C≡N), 1643 (C=C), 1604, 1497, 1455, 1418, 1349, 1031, 994, 924, 750, 700; δ_H (400 MHz, CDCl₃) 7.32-7.17 (5H, m, ArH), 5.80 (1H, ddt, *J* 9.9, 17.3, 7.1, RC*H*=CHH), 5.20-5.14 (2H, m, C=CH₂), 2.89 (1H, ddd, *J* 5.2, 8.8, 14.0, ArC*H*$_A$H$_B$), 2.73 (1H, ddd, *J* 7.9, 8.4, 14.0, ArCH$_A$*H*$_B$), 2.56 (1H, dddd, *J* 2.9, 4.9, 6.7, 8.4, CHCN), 2.32-2.26 (2H, m, CH₂C=C), 1.99-1.82 (2H, m, ArCH₂C*H*₂); *m/z* (FAB/MNOBA) 186 (M+H⁺, 395), 185 (M⁺, 11%), 158, 143, 129, 117, 115, 105, 91 (100%), 81, 77, 65, 51; (Found: M⁺, 185.1204. C₁₄H₁₅N requires *M*, 185.1200).

Preparation of 3-Cyano-5-phenyl-pentanal (94).

(94)
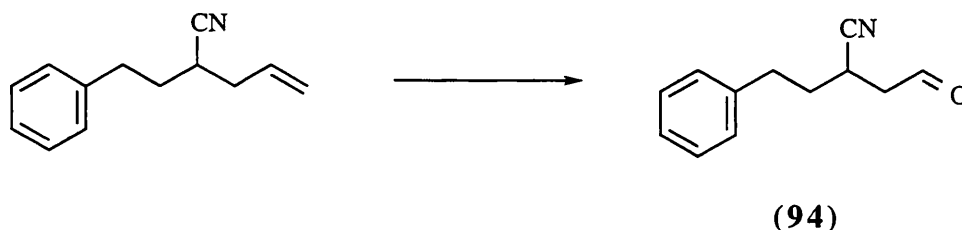
A stirred solution of 2-(2-phenyl-ethyl)-but-3-enenitrile (1.115 g, 6.02 mmol) in dry dichloromethane (20 ml) was cooled to -78°C under a continuous flow of oxygen. Ozonized oxygen was passed through the solution (oxygen flow rate of 2 l/minute) at -78°C until the blue colour of ozone appeared in the solution (17 minutes). The reaction mixture was then purged with oxygen, and dimethyl sulfide (1.32 ml, 18.0 mmol, 3.0 eq.)

added at -78°C in a single portion, and the solution stirred at -78°C under nitrogen for 1 hour before warming to ambient temperature. After 4.5 hours triphenylphosphine (1.57 g, 6.0 mmol, 1.0 eq.) was added and the solution left at ambient temperature overnight. Concentration *in vacuo* gave a light brown oil which was chromatographed on silica (10-60% ether in petrol (b.p. 40-60°C)) to give the *aldehyde* **94** (865 mg, 76%) as a light yellow oil.

v_{max} (NaCl, thin film)/cm^{-1} 3062, 3028, 2930, 2857, 2734, 2242 (C≡N), 1725, 1603, 1496, 1453, 1404, 1354, 1151, 1080, 907, 752, 702; δ_H (400 MHz, CDCl$_3$) 9.68 (1H, br s, CHO), 7.45-7.15 (5H, m, ArH), 3.05-2.62 (5H, m, ArCH$_2$CH$_2$CHCNCH$_2$CHO), 2.05-1.80 (2H, m, ArCH$_2$CH$_2$); m/z (FAB/MNOBA) 188 (M+H$^+$, 16%), 165, 154, 143, 136, 129, 117, 115, 105, 91 (100%), 77; (Found: M$^+$ 188.1075. C$_{12}$H$_{14}$NO requires M, 188.1070).

Preparation of 2-(2-Phenyl-ethyl)-pent-4-enenitrile (95) and 2-Ethyl-5-phenyl-pentanenitrile (96).
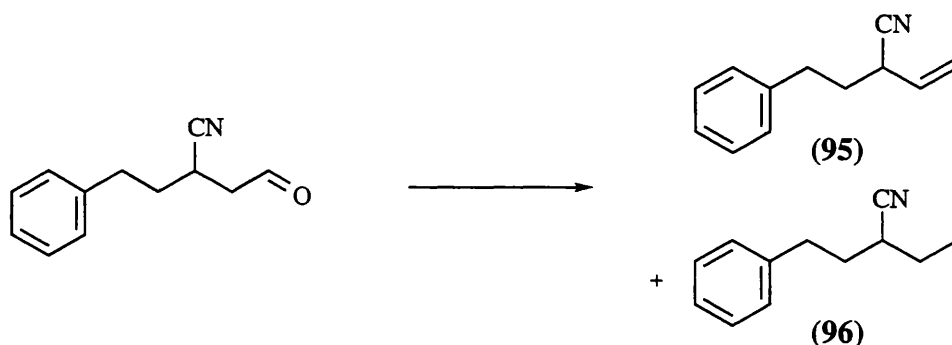
A solution of chlorotrimethylsilane (1.11 ml, 8.7 mmol, 5 eq.) in dry ether (3 ml) was added to flame dried zinc amalgam (1.14 g, 17.5 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. A solution of zinc chloride (3.5 ml, 3.5 mmol, 1M in ether) was added and the resultant vigorously stirred suspension was brought to reflux. After 5 minutes at reflux a solution of 3-cyano-5-phenyl-pentanal (327 mg, 1.75 mmol) in dry ether (7 ml) was added. The resultant cloudy reaction mixture was vigorously stirred at reflux for a further 1.5 hours and then cooled to ambient temperature. The

reaction mixture was poured into saturated aqueous sodium bicarbonate (70 ml), and stirred for 30 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil which was absorbed onto silica. Column chromatography (3-5% ether in petrol (b.p. 40-60°C)) furnished a mixture of *2-(2-phenyl-ethyl)-pent-4-enenitrile* **95** and *2-ethyl-5-phenyl-pentanenitrile* **96** (1:1 by GC) as a clear colourless oil (68 mg, 23%).

v_{max} (NaCl, thin film)/cm^{-1} 3087, 3064, 3028, 2968, 2933, 2864, 2238 (C≡N), 1643 (C=C), 1604, 1497, 1455, 1413, 1112, 1030, 989, 936, 751, 700; δ_H (400 MHz, CDCl$_3$) *2-(2-phenyl-ethyl)-pent-4-enenitrile*: 7.32-7.15 (5H, m, ArH), 5.71 (1H, ddd, *J* 5.9, 10.4, 17.4, RC*H*=CHH), 5.44 (1H, dd, *J* 1.4, 17.4, RCH=C*H*H), 5.30 (1H, dd, *J* 1.4, 10.4, RCH=CH*H*), 3.22 (1H, dtt, *J* 1.4, 5.9, 7.2, CHCN), 2.94-2.79 (2H, m, ArCH$_2$), 2.08-1.81 (2H, m, ArCH$_2$*H*$_2$); *2-ethyl-5-phenyl-pentanenitrile*: 7.32-7.15 (5H, m, ArH, masked by ene-nitrile), 2.94-2.79 (2H, m, ArCH$_2$, masked by ene-nitrile), 2.42-2.49 (1H, m, CHCN), 2.08-1.81 (2H, m, ArCH$_2$*H*$_2$, masked by ene-nitrile), 1.65 (2H, p, *J* 7.4, C*H*$_2$CH$_3$), 1.08 (3H, t, *J* 7.4, CH$_3$); *m/z* (EI/GCMS) *2-(2-phenyl-ethyl)-pent-4-enenitrile*: 171 (M$^+$, 22%), 105, 103, 92, 91 (100%), 80, 77, 65; (Found: M$^+$, 171.1043. C$_{12}$H$_{13}$N requires *M*, 171.1048); *2-ethyl-5-phenyl-pentanenitrile*: 173 (M$^+$, 14%), 105, 103, 92, 91 (100%), 82, 77, 65; (Found M$^+$, 173.1200. C$_{12}$H$_{15}$N requires *M*, 173.1204).

Preparation of N,N Diethyl-Z-octadec-9-enamide (144).
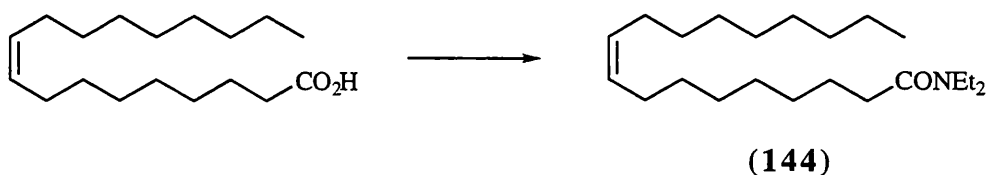
(144)

Oxalyl chloride (1.04 ml, 11.9 mmol, 1.5 eq.) was added to a solution of oleic acid (2.50 g, 7.97 mmol) in dry dichloromethane (20 ml), along with 1 drop of dry

dimethylformamide. After 30 minutes the solvent was removed *in vacuo* and the brown oil taken up in dry benzene (20 ml). A solution of dry diethylamine (2.06 ml, 19.9 mmol, 2.5 eq.). The solution turned cloudy instantly and was stirred at ambient for a further 2 hours before being poured into hydrochloric acid (10 ml, 2M), and the aqueous phase extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a light brown oil which was chromatographed on silica (50% ether in petrol (b.p. 40-60°C)) to give the amide **144**[167] (2.26 g, 84%) as a clear colourless oil.

ν_{max} (NaCl, thin film)/cm^{-1} 2923, 2851, 1648, 1460, 1427, 1379, 1363, 1261, 1224, 1141, 1096; δ_H (400 MHz, CDCl$_3$) 5.28 (2H, m, C=CH), 3.31 (2H, q, *J* 7.1, CH$_{2A}$N), 3.24 (2H, q, *J* 7.1, CH$_{2B}$N), 2.22 (2H, t, *J* 7.6, CH$_2$CO$_2$R), 2.02-1.90 (4H, m, C=CHC*H*$_2$), 1.64-1.56 (2H, m, C*H*$_2$CH$_2$CONR$_2$), 1.35-1.20 (24 H, m, alkyl H), 1.11 (3H, t, *J* 7.1, NCH$_2$C*H*$_{3A}$), 1.04 (3H, t, *J* 7.1, NCH$_2$C*H*$_{3B}$), 0.82 (3H, t, *J* 6.7, CH$_2$CH$_2$C*H*$_3$); *m/z* (FAB/MNOBA) 338 (M+H$^+$, 10%), 337 (M$^+$, 10%), 336 (M-H$^+$, 36%), 72 (100%).

Preparation of N,N-Diethyl-9-oxo-nonamide (97).

(97)
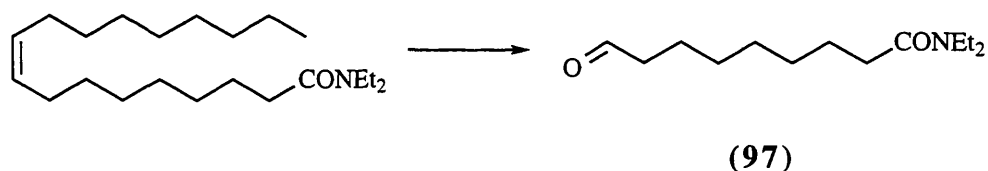
A stirred solution of N,N-diethyl cis octadec-9-enamide (1.065 g, 3.15 mmol) in dry dichloromethane (20 ml) was cooled to -78°C under a continuous flow of oxygen. Ozonized oxygen was passed through the solution (oxygen flow rate of 2 l/minute) at -78°C until the blue colour of ozone appeared in the solution (20 minutes). The blue colour was then purged with oxygen, and dimethyl sulfide (460 µl, 6.3 mmol, 2.0 eq.) added at -78°C in a single portion. After 20 minutes at -78°C the solution was warmed rapidly to ambient temperature. A further aliquot of dimethyl sulfide (460 µl, 6.3 mmol, 2.0 eq.) was added, and the solution left overnight under an atmosphere of nitrogen. The solution was

concentrated *in vacuo* to give a light brown oil which was chromatographed on silica (35-75% ether in petrol (b.p. 40-60°C)) to give the *aldehyde* **97** (171 mg, 24%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2930, 2856, 2717, 1725, 1643, 1462, 1430, 1380, 1363, 1310, 1263, 1223, 1140, 1097, 946, 794; δ_H (400 MHz, CDCl$_3$) 9.74 (1H, t, *J* 1.8, CHO), 3.35 (2H, q, *J* 7.1, CH$_2$N), 3.28 (2H, q, *J* 7.2, CH$_2$N), 2.40 (2H, dt, *J* 1.8, 7.4, C*H*$_2$CHO), 2.27 (2H, t, *J* 7.6, C*H*$_2$CO$_2$R), 1.64-1.54 (4H, m, C*H*$_2$CH$_2$COX), 1.32-1.22 (6H, m, alkyl H), 1.15 (3H, t, *J* 7.2, NCH$_2$C*H*$_3$), 1.09 (3H, t, *J* 7.1, NCH$_2$C*H*$_3$); *m/z* (FAB/MNOBA) 228 (M+H$^+$, 100%), 226 (M-H$^+$, 10%), 184, 170, 142, 136, 128, 115, 100, 72, 69, 55, 43, 41; (Found: M+H$^+$, 228.1964. C$_{13}$H$_{25}$NO requires *M*, 228.1958).

Preparation of N,N-Diethyl-non-8-enamide (98) and N,N-Diethyl-nonamide (99).

A solution of chlorotrimethylsilane (420 µl, 3.3 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (430 g, 6.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. To the resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 9-oxo-N,N-diethyl-nonamide (151 mg, 0.66 mmol) in dry ether (4 ml) was added. The solution rapidly turned cloudy. The cloudy suspension was vigorously stirred at reflux, and after 45 minutes the zinc amalgam had coagulated. The supernatant solution was added *via* cannula to fresh zinc amalgam (430 g, 6.6 mmol, 10 eq.). The suspension was vigorously stirred at reflux for a further 10 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (8 ml), and stirred for 5 minutes. The

resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (20-50% ether in petrol (b.p. 40-60°C)) furnished a mixture of *N,N-diethyl non-8-enamide* **98** and N,N-diethyl nonamide **99**[158] (3:1 by GC) as a clear colourless oil (18 mg, 10%).

v_{max} (NaCl, thin film)/cm^{-1} 3077, 2931, 2856, 1652, 1635, 1456, 1379, 1363, 1314, 1266, 1223, 1143, 1098, 994, 948, 908, 795, 724; δ_H (400 MHz, $CDCl_3$) *N,N-diethyl non-8-enamide*: 5.79 (1H, ddt, *J* 10.3, 17.0, 6.7, RC*H*=CHH), 4.98 (1H, ddt, *J* 2.6, 17.0, 1.7, RCH=C*H*H), 4.94 (1H, ddt, *J* 2.6, 10.3, 1.7, RCH=CH*H*), 3.36 (2H, q, *J* 7.1, CH_2N), 3.29 (2H, q, *J* 7.2, CH_2N), 2.28 (2H, t, *J* 7.6, CH_2CONR_2), 2.03 (2H, dtt, *J* 6.7, 1.7, 7.0, C*H$_2$*CH=CHH), 1.46-1.22 (6H, m, alkyl H), 1.16 (3H, t, *J* 7.2, NCH$_2$C*H$_3$*), 1.10 (3H, t, *J* 7.1, NCH$_2$C*H$_3$*); *N,N-diethyl nonamide*: 3.38-1.08 (24H, masked by enamide), 0.86 (3H, t, *J* 6.9, $CH_2CH_2CH_3$); *m/z* (EI/GCMS) *N,N-diethyl non-8-enamide:* 211 (M$^+$, 1.1%), 170, 128, 115, 100, 87, 72, 58 (100%), 44, 42; *N,N-diethyl nonamide*: 213 (M$^+$, 0.8%), 115 (100%).

Preparation of 3-Phenylthio-1-propanol (148).

(148)

Thiophenol (1.40 ml, 13.2 mmol) was added dropwise to a suspension of sodium hydride (634 mg, 15.8 mmol, 1.2 eq.) in dry N,N-dimethylformamide (5 ml). After 15 minutes the solution was added *via* cannula to a stirred suspension of sodium iodide (1.69 g) and 3-bromo-propanol (1.31 ml, 14.5 mmol, 1.1 eq.) in dry N,N-dimethylformamide (10 ml), and washed in with a further portion of dry N,N-dimethylformamide (5 ml). The reaction mixture was stirred at ambient temperature for 1.3 hours and then poured into water (60 ml) and extracted with ether (3 x 50 ml). The combined organic layers were washed with

aqueous sodium hydroxide (1M, 40 ml), water (50 ml), brine (50 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a clear colourless oil which was purified by bulb to bulb distillation (140°C/0.5 mbar) to give the alcohol **148**[168] (2.22g, 99%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 3355 (OH), 3058, 2935, 2878, 1584, 1480, 1439, 1350, 1264, 1156, 1092, 1054, 1026, 909, 738, 692; δ_H (400 MHz, CDCl$_3$) 7.39-7.16 (5H, m, ArH), 3.75 (2H, t, *J* 7.0, CH$_2$O), 3.02 (2H, t, *J* 7.0, CH$_2$S), 1.87 (2H, p, *J* 7.0, SCH$_2$C*H$_2$*CH$_2$O), 1.60 (1H, br, OH); *m/z* (FAB/MNOBA) 169 (M+H$^+$, 24%), 168 (M$^+$, 49%), 41 (100%).

Preparation of 3-Phenylthio-propanal (100).

(100)

Dimethyl sulfoxide (2.37 ml, 33.5 mmol, 2.4 eq.) was added to a solution of oxalyl chloride (1.46 ml, 16.75 mmol, 1.2 eq.) in dry dichloromethane (30 ml) at -78°C. After 30 minutes at -78°C, a solution of the alcohol in dry dichloromethane (10 ml) was added. After a further 20 minutes, triethylamine (4.86 ml, 34.9 mmol, 2.5 eq.) was added and the suspension stirred at -78°C for a further 1.5 hours. Hydrochloric acid (2M, 15 ml) was added and the solution allowed to attain ambient temperature overnight. The aqueous phase was extracted with dichloromethane (2 x 15 ml), and the combined organic layers were washed with saturated aqueous sodium bicarbonate (15 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to a light yellow oil which was purified by bulb to bulb distillation (120°C/0.8 mbar) and chromatography on silica (5-10% ether in petrol (b.p. 40-60°C)) to give the aldehyde **100**[169] (1.11 g, 47%) as a clear very light yellow oil.

v_{max} (NaCl, thin film)/cm^{-1} 3058, 3019, 2931, 2894, 2829, 2730, 1723, 1583, 1481, 1438, 1408, 1387, 1333, 1279, 1172, 1092, 1071, 1-25, 1001, 896, 850, 741, 692; δ_H (400 MHz, CDCl$_3$) 9.75 (1H, t, *J* 1.0, CHO), 7.38-7.16 (5H, m, ArH), 3.16 (2H, t, *J*

7.1, CH$_2$S), 2.75 (2H, dt, *J* 1.0, 7.1, SCH$_2$C*H*$_2$CHO); *m/z* (EI) 166 (M$^+$, 35%), 110 (100%).

Preparation of Hexadecanal dimethyl acetal (148).

(148)
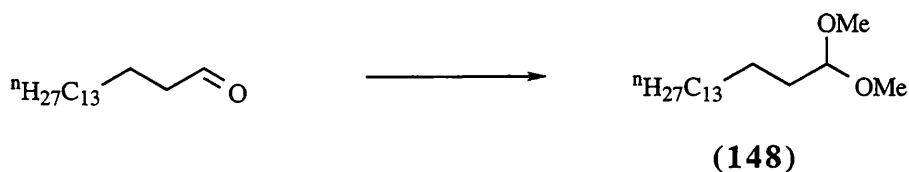
Hexadecanal (490 mg, 2.04 mmol), trimethyl orthoformate (6.0 ml, 55 mmol, 27 eq.) methanol (10 ml) and *p*-toluenesulfonic acid monohydrate (30 mg) were heated to reflux for 24 hours. The reaction mixture was cooled to ambient temperature, poured into sodium hydroxide (1M, 10 ml) and ether. The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine(20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (0-35% dichloromethane in petrol (b.p. 40-60°C)) to give the acetal **148**[164] (490 mg, 84%) as a clear colourless oil.

v_{max} (NaCl neat)/cm^{-1} 2925, 2854, 2829 (C-H), 1467, 1385, 1192, 1124, 1057 and 959; δ_H (400 MHz, CDCl$_3$) 4.36 (1H, t, *J* 5.7, H$_1$), 3.31 (6H, s, -OCH$_3$), 1.58 (2H, dt, *J* 5.7, 6.8, H$_2$), 1.20-1.35 (26H, m, alkyl chain), 0.88 (3H, t, *J* 6.7, -CH$_3$); m/z (FAB/MNOBA) 285 (M-H$^+$, 14%), (75, 100%).

Preparation of 1-Hexadecene (137).

(137)

A solution of chlorotrimethylsilane (410 μl, 3.2 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (420 mg, 6.4 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of hexadecanal dimethyl acetal (183 mg, 0.64 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 20 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml),

and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a colourless oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (89 mg, 62%), spectroscopically identical to material already prepared.

Preparation of 2-n-Pentadecyl-1,3-dioxolane (104).

(104)

Hexadecanal (846 mg, 3.52 mmol), ethylene glycol (400 µl, 7.0 mmol, 2.0 eq.) and *p*-toluenesulfonic acid monohydrate (90 mg) were heated to reflux in benzene (40 ml) for 2 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with ether (2 x 15 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a white solid which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the acetal **104**[170] (895 mg, 90%) as a white solid. m.p. 35-36°C (prisms from ether/petrol (b.p. 40-60°C)).

v_{max} (KBr disc)/cm^{-1} 2916, 2856 (C-H), 1472, 1414, 1376, 1222, 1159, 1124, 1099, 1064, 1054, 1033, 1019, 982, 959, 943, 906, 871, 836, 804 and 717; δ_H (400 MHz, CDCl$_3$) 4.82 (1H, t, J 4.9, H$_2$), 3.95-3.90 (2H, m, H$_{4\alpha,5\alpha}$), 3.87-3.78 (2H, m, H$_{4\beta,5\beta}$), 1.63 (2H, dt, J 4.9, 7, H$_{1'}$), 1.42-1.35 (2H, m, H$_{2'}$) 1.34-1.20 (24H, m, alkyl chain), 0.85 (3H, t, J 6.7 -CH$_3$); m/z (FAB/MNOBA), 285 (M+H$^+$, 20.4%), 284 (M$^+$, 5.8%), 283 (M-H$^+$, 29.7%), 73 (100%).

Preparation of 1-Hexadecene (137).

(137)

A solution of chlorotrimethylsilane (640 μl, 5.03 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (660 g, 10.1 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-pentadecyl-1,3-dioxolane (286 mg, 1.01 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 17 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene 137[151] as a clear colourless oil (193 mg, 86%), spectroscopically identical to material already prepared.

Preparation of 2-n-Pentadecyl-1,3-dioxane (149).

(149)
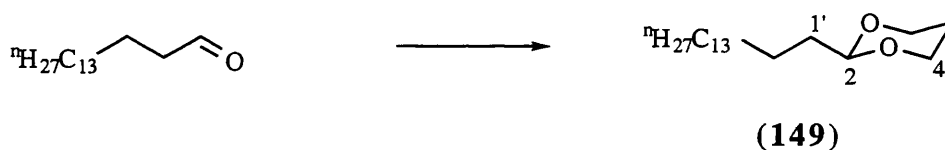
Hexadecanal (603 mg, 2.51 mmol), propane-1,3-diol (360 ml, 5.0 mmol, 2.0 eq.) and *p*-toluenesulfonic acid monohydrate (200 mg) were heated to reflux in benzene (60 ml) for 2 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (20 ml) and ether. The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml),

brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the acetal **149**[170] (659 mg, 88%) as a white solid. m.p. 31-32.5°C (prisms from ether/petrol (b.p. 40-60°C)).

ν_{max} (NaCl melt)/cm^{-1} 2924, 2854 (C-H), 1468, 1405, 1378, 1282, 1241, 1217, 1147, 1118, 1085, 1056, 1000, 941, 927, 893 and 722; δ_H (400 MHz, CDCl$_3$) 4.48 (1H, t, *J* 5.2, H$_2$), 4.07 (2H, ddd, 1.3, 4.9, 11.8, H$_{4\beta}$, H$_{6\beta}$), 3.73 (2H, ddd, *J* 1.9, 11.8, 12.4, H$_{4\alpha}$, H$_{6\alpha}$), 2.03 (1H, dtt, *J* 17, 1.9, 4.9, H$_{5\alpha}$), 1.55 (2H, dt, *J* 5.2, 7, H$_{1'}$), 1.40-1.25 (27H, m, alkyl chain and H$_{5\beta}$), 0.85 (3H, t, *J* 6.8, -CH$_3$); m/z (FAB/MNOBA) 299 (M+H$^+$, 24.8%), 298 (M$^+$, 7.6%), 297 (M-H$^+$, 37.1%), 57 (100%).

Preparation of 1-Hexadecene (137).

$^nH_{27}C_{13}$ ⟍⟋⟍⟋⟍⟋O⟍⟋O⟍⟋ ⟶ $^nH_{27}C_{13}$ ⟋⟍⟋⟍⟍

(137)

A solution of chlorotrimethylsilane (420 μl, 3.3 mmol, 5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (430 mg, 6.6 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-pentadecyl-1,3-dioxane (197 mg, 0.66 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 36 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C)) furnished the alkene **137**[151] as a clear colourless oil (9 mg, 6%), and recovered 2-pentadecyl-1,3-dioxane **149**[170] (166 mg, 84%), both spectroscopically identical to material already prepared.

Preparation of 2-n-Pentadecyl-5,5-dimethyl-1,3-dioxane (150).

$^nH_{27}C_{13}$ ⟋⟍⟋⟍⟍O ⟶ $^nH_{27}C_{13}$ ⟍⟋⟍⟋$^{1'}$⟍O⟍⟋O$_4$⟍

(150)
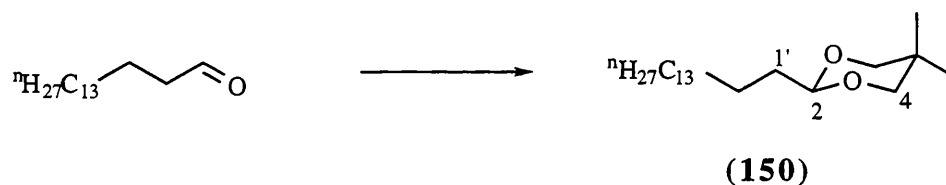
Hexadecanal (808 mg, 3.36 mmol), 2,2-dimethyl-propane-diol (700 mg, 6.7 mmol, 2.0 eq.) and *p*-toluenesulfonic acid monohydrate (70 mg) were heated to reflux in benzene (40 ml) for 2 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction mixture was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with ether (2 x 15 ml). The

combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a white solid which was chromatographed on silica (5% ether in petrol (b.p. 40-60°C)) to give the *acetal* **150** (985 mg, 90%) as a white solid. m.p. 32-35°C (prisms from ether/petrol (b.p. 40-60°C)).

v_{max} (KBr disc)/cm^{-1} 2954, 2920, 2850 (C-H), 1473, 1406, 1395, 1361, 1314, 1158, 1123, 1101, 1079, 1044, 1022, 984, 966, 945, 923, 907, 870, 718, 668; δ_H (400 MHz, CDCl$_3$) 4.37 (1H, t, *J* 5.1, H$_2$), 3.57 (2H, d, *J* 10.9, H$_{4\alpha}$, H$_{6\alpha}$), 3.89 (2H, d, *J* 10.9, H$_{4\beta}$, H$_{6\beta}$), 1.58 (2H, dt, *J* 5.1, 7.5, H$_{1'}$), 1.36 (2H, m, H$_{2'}$), 1.30-1.20 (24H, m, alkyl chain), 1.16 (3H, s, -CH$_{3\alpha}$), 0.85 (3H, t, *J* 6.9, -CH$_2$CH$_3$), 0.68 (3H, s, -CH$_{3\beta}$); m/z (FAB/MNOBA) 327 (M+H$^+$, 11.7%), 326 (M$^+$, 10%), 325 (M-H$^+$, 43%), 69 (100%); (Found M$^+$ 326.3185, C$_{21}$H$_{42}$O$_2$ requires *M* 326.3189.

Preparation of 1-Hexadecene (137).

(137)

A solution of chlorotrimethylsilane (475 μl, 3.75 mmol, 4.5 eq.) in dry ether (6 ml) was added to flame dried zinc amalgam (490 mg, 7.5 mmol, 9 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-pentadecyl-5,5-dimethyl-1,3-dioxane (272 mg, 0.83 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 60 hours and then cooled to ambient temperature. The reaction was quenched by a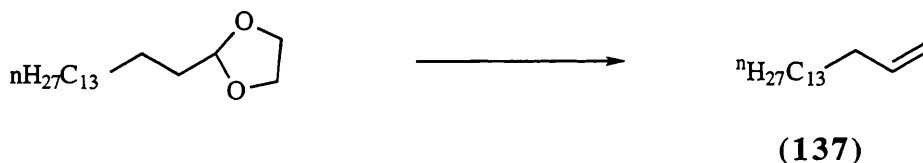ddition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a colourless oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C))

furnished the alkene **137**[151] as a clear colourless oil (27 mg, 14%), and recovered 2-pentadecyl-5,5-dimethyl-1,3-dioxane **149** (218 mg, 80%), both spectroscopically identical to material already prepared.

Preparation of 1-Hexadecene (137).

$nH_{27}C_{13}$ ⌐⌐⌐ (2-pentadecyl-1,3-dioxolane) $\longrightarrow$ $^nH_{27}C_{13}$ ⌐⌐⌐ (alkene)

(137)
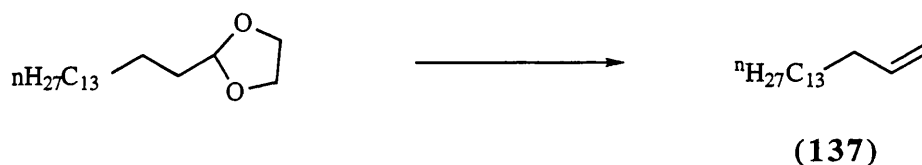
A solution of dichlorodimethylsilane (160 μl, 1.3 mmol, 1.5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (556 mg, 8.8 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-pentadecyl-1,3-dioxolane (249 mg, 0.88 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 22 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (7 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil which was absorbed onto silica. Column chromatography (petrol (b.p. 40-60°C)) furnished the alkene as a clear colourless oil (169 mg, 86%), spectroscopically identical to material already prepared.

Preparation of 4-(2-Methyl-2-propyl)-cyclohexene (151).

(151)
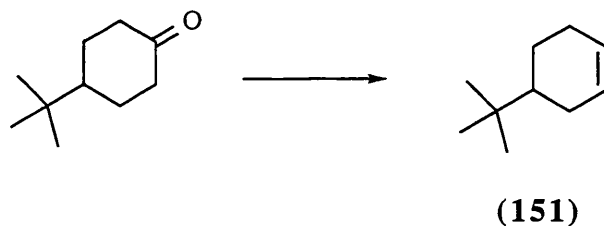
Dry ether (60 ml) and chlorotrimethylsilane (35.6 ml, 0.28 mol, 5 eq.) were added to flame-dried zinc (36.68 g, 0.56 mol, 10 eq.) in a 250 ml conical flask, fitted with a reflux condenser, under nitrogen. The stirred suspension was brought to reflux and a solution of 4-^{t}butyl cyclohexanone (8.66 g, 56.1 mmol) in dry ether (40 ml) was added via cannula. The suspension was heated at reflux for 22 hours and the cooled to ambient temperature and poured into saturated aqueous sodium bicarbonate (500 ml).The resultant suspension was stirred for 5 minutes, filtered through celite, and the filter cake washed with ether (100 ml). The separated aqueous layer was extracted with ether (2 x 100 ml). The combined organic layers were washed with brine (100 ml), dried (MgSO$_4$), filtered and concentrated at 0°C to give a light yellow oil, which was distilled under vacuum (b.p. 108-110°C/140 mm Hg, lit.[171] b.p. 70-72°C/15 mm Hg))to give the alkene 151[171] (2.51g, 32%) as a clear colourless oil.

ν_{max} (NaCl, thin film)/cm^{-1} 3023 (C=C-H), 2963, 2839 (C-H), 1656 (C=C), 1477, 1468, 1436, 1394, 1364, 1304, 1244, 1230, 1172, 1147, 1046, 978, 924, 910, 873, 772, 702 and 655; δ_H (200 MHz, CDCl3) 5.66 (2H, br s, H$_1$, H$_2$), 2.16-1.85 (2H, m, H$_{3eq}$, H$_{6eq}$), 1.85-1.60 (2H, m, H$_{3ax}$, H$_{6ax}$), 1.35-0.85 (3H, m, H$_4$, H$_5$), 0.85 (9H, s, C(CH$_3$)$_3$); m/z (EI) 138 (M+, 4%), 57 (100%).

Preparation of *trans*-1,2-Dibromo-*cis*-4-(2-methyl-2-propyl)-cyclohexane (103).

(103)

Excess bromine was added to a solution of 4-(2-methyl-2-propyl)-cyclohexene (243 mg, 1.78 mmol) in ether (30 ml). The flask was swirled once and left at ambient temperature for 15 minutes. Aqueous sodium thiosulphate (10%, 10 ml) was then added to remove unreacted bromine, and the separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo* to give a very light yellow oil which was chromatographed on silica (petrol (b.p. 40-60°C)) to give the dibromide **103**[172] (432 mg, 93%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2960, 2907 (C-H), 1478, 1452, 1433, 1395, 1367, 1265, 1240, 1207, 1191, 1180, 1135, 1018, 979, 933, 906, 878, 848, 771, 674 (axial C-Br) and 647; δ_H (400 MHz, CDCl₃) 4.78 (1H, ddd, *J* 2.5, 2.7, 5.0 Hz, H₁), 4.66 (1H, m, H₂), 2.44 (1H, dddd, *J* 3.3, 4.5, 12.0, 13.0 Hz, H₃α), 2.17 (1H, ddd, *J* 3.2, 11.6, 14,7 Hz, H₆α), 1.97 (2H, m, H₃β, H₆β), 1.69-1.52 (3H, m, H₄, H₅), 0.89 (9H, s, C(CH₃)₃), δ_C (100 MHz, CDCl3) 54.83 (CBr), 53.70 (CBr), 41.15, 32.05 (C(CH₃)₃), 29.38, 28.89, 27.33 (C(CH₃)₃), 21.14; m/z (CI/^{i}C₄H₁₀) 299 / 297 / 295 (M-H⁺, 0.3% (^{81}Br + ^{81}Br) / 0.6% (^{81}Br + ^{79}Br) / 0.3% (^{79}Br + ^{79}Br)), 219 / 217 (M-HBr, 42.5% (^{81}Br) / 44.9% (^{79}Br)), 137 (100%).

Preparation of 1,1-Dimethoxy-4-(2 methyl-2 propyl)-cyclohexane (152).

(152)
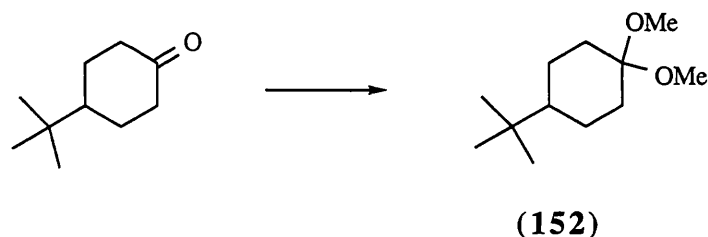
A solution of 4-^{t}butyl-cyclohexanone (1.68 g, 10.9 mmol), trimethyl orthoformate (6 ml, 0.05 mol, 5 eq.), and *p*-toluenesulfonic acid monohydrate (180 mg) in dry methanol (10 ml) were heated to reflux for 1.5 hours. The reaction was cooled to ambient temperature, and poured into sodium hydroxide solution (1 M, 10 ml) and ether (30 ml). The separated aqueous layer was extracted with ether (2 x 30 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by bulb to bulb distillation (100°C/2 mbar), (lit.[173] b.p. 115/15 mm Hg) to give the ketal 152[173] (2.10 g, 96%) as a white solid. m.p. 35-37°C, (prisms from ether/petrol (b.p. 40-60°C)).

ν$_{max}$ (KBr disc)/cm^{-1} 2957, 2869, 2830 (C-H), 1470, 1447, 1431, 1393, 1367, 1343, 1316, 1281, 1249, 1223, 1197, 1162, 1134, 1124, 1101, 1056, 1039, 968, 950, 933, 904, 820, 778, 761, 625, 556 and 535; δ$_H$ (400 MHz, CDCl$_3$) 3.15 (3H, s, OCH$_{3\beta}$), 3.10 (3H, s, OCH$_{3\alpha}$), 2.02-1.97 (2H, m, H$_{2\beta}$, H$_{6\beta}$), 1.62-1.56 (2H, m, H$_{2\alpha}$, H$_{6\alpha}$), 1.22 (2H, ddd, *J* 3.1, 3.7, 13.4 Hz, H$_{3\alpha}$, H$_{5\alpha}$), 1.10 (2H, dddd, *J* 2.5, 3.2, 11.8, 13.4 Hz, H$_{3\beta}$, H$_{5\beta}$), 0.95 (1H, tt, *J* 3.1, 11.8 Hz, H$_4$), 0.81 (9H, s, C(CH$_3$)$_3$); m/z (EI) 200 (M$^+$, 0.4%), 101 (100%).

Preparation of *trans*-1,2-Dibromo-*cis*-4-(2-methyl-2-propyl)-cyclohexane (103).

OMe
OMe
→
Br
Br

(103)
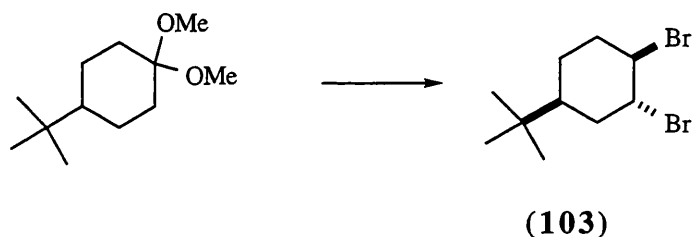
Dry ether (6 ml) and chlorotrimethylsilane (720 µl, 5.67 mmol, 5 eq.)were added to flame-dried zinc amalgam (741 mg, 11.3 mmol, 10 eq) in a 25 ml conical flask, fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and a solution of 1,1-dimethoxy-4-(2-methyl-2-propyl)-cyclohexane (227 mg, 1.13 mmol) in dry ether (4 ml) added via cannula. The suspension was vigorously stirred at reflux for 16 hours, and then cooled to ambient temperature. The suspension was poured into saturated aqueous sodium bicarbonate (15 ml), stirred for 5 minutes and then filtered through celite. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and treated with excess bromine for 20 minutes. Saturated aqueous sodium bicarbonate (10 ml), and sodium thiosulphate solution (10%, 20 ml) were added, the layers shaken and separated, and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a light brown oily solid which was chromatographed on silica (petrol (b.p. 40-60°C)) to give the dibromide 103[172] (190 mg, 56%) as a clear colourless oil, spectroscopically identical to material already prepared.

Preparation of 8-(2 Methyl-2-propyl)-1,4-dioxaspiro-[4,5]-decane (153).

(153)
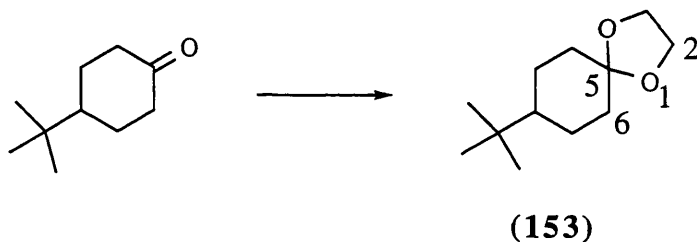
A solution of 4-^{t}butyl-cyclohexanone (1.54 g, 10.0 mmol), ethylene glycol (1.13 ml, 20.0 mmol, 2 eq.), and p-toluenesulfonic acid monohydrate (180 mg) in benzene (60 ml) were heated to reflux for 1 hour, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction was cooled to ambient temperature, and poured into saturated aqueous sodium bicarbonate solution (20 ml) and ether (30 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by bulb to bulb distillation (110°C/2 mbar) to give the ketal **153**[173] (1.875 g, 95%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2948, 2870(C-H), 1480, 1469, 1447, 1413, 1394, 1375, 1366, 1340, 1311, 1286, 1252, 1195, 1125, 1105, 1041, 962, 937, 928, 906 and 821; δ_H (400 MHz, CDCl$_3$) 3.91 (4H, s, H$_2$, H$_3$), 1.78-1.67 (4H, m, H$_6$, H$_{10}$), 1.42-1.51 (2H, m, H$_{7\beta}$, H$_{9\beta}$), 1.31-1.18 (2H, m, H$_{7\alpha}$, H$_{9\alpha}$), 1.10 (2H, dddd, J 2.5, 3.2, 11.8, 13.4 Hz, H$_{3\beta}$, H$_{5\beta}$), 0.99 (1H, tt, J 2.8, 12.1 Hz, H$_8$), 0.83 (9H, s, C(CH$_3$)$_3$); m/z (FAB/MNOBA) 199 (M+H$^+$, 12.9 %), 198 (M$^+$, 5.5%), 197 (M-H$^+$, 10.5%), 99 (100%).

Preparation of *trans*-1,2-Dibromo-*cis*-4-(2-methyl-2-propyl)-cyclohexane (103).

(103)
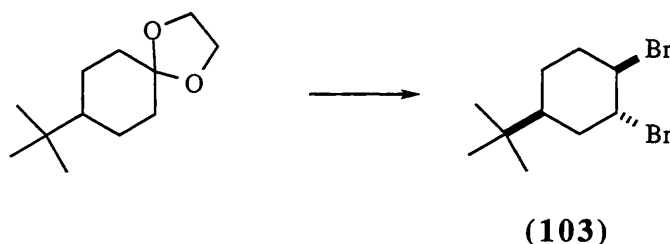
Dry ether (6 ml) and chlorotrimethylsilane (740 µl, 5.8 mmol, 5 eq.)were added to flame-dried zinc amalgam (761 mg, 11.6 mmol, 10 eq) in a 25 ml conical flask, fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and a solution of 8-(2-methyl-2-propyl)-1,4-dioxaspiro-[4,5]-decane (231 mg, 1.16 mmol) in dry ether (4 ml) added via cannula. The suspension was vigorously stirred at reflux for 16 hours, and then cooled to ambient temperature. The suspension was poured into saturated aqueous sodium bicarbonate (15 ml), stirred for 5 minutes and then filtered through celite. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and treated with excess bromine for 20 minutes. Saturated aqueous sodium bicarbonate (10 ml), and sodium thiosulphate solution (10%, 20 ml) were added, the layers shaken and separated, and the organic layer dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (petrol (b.p. 40-60°C)) to give the dibromide 103[172] (205 mg, 59%) as a clear colourless oil, spectroscopically identical to material already prepared.

Preparation of 9-(2 Methyl-2 propyl)-1,5-dioxaspiro-[5,5]-undecane (154).
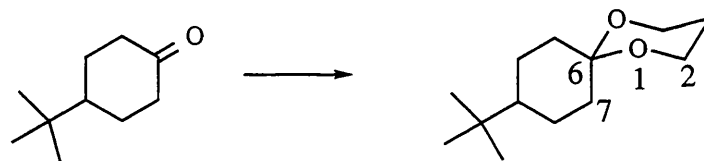
(154)

A solution of 4-^{t}butyl-cyclohexanone (1.54 g, 10.0 mmol), propane 1,3 diol (1.45 ml, 20.0 mmol, 2 eq.), and p-toluenesulfonic acid monohydrate (225 mg) in benzene (50 ml) were heated to reflux for 1 hour, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction was cooled to ambient temperature, and poured into saturated aqueous sodium bicarbonate solution (20 ml) and ether (30 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was purified by bulb to bulb distillation (130°C/0.4 mbar) to give the ketal **154**[174] (2.04 g, 96%) as a clear colourless oil.

ν_{max} (NaCl, thin film)/cm^{-1} 2952, 2865 (C-H), 1480, 1446, 1378, 1366, 1336, 1280, 1243, 1219, 1192, 1145, 1130, 1111, 1057, 982, 931 and 898; δ_H (400 MHz, CDCl$_3$) 3.90 (2H, t, J 5.6 Hz, H$_{2\beta}$, H$_{4\beta}$), 3.83 (2H, t, J 5.6 Hz, H$_{2\alpha}$, H$_{4\alpha}$), 2.25-2.33 (2H, m, H$_3$), 1.65-1.72 (2H, m, H$_{7\alpha}$, H$_{11\alpha}$), 1.63-1.55 (2h, m, H$_{7\beta}$, H$_{11\beta}$), 1.40-1.22 (4H, m, H$_8$, H$_{10}$), 0.99 (1H, tt, J 2.5, 12.2 Hz, H$_9$), 0.82 (9H, s, C(CH$_3$)$_3$); m/z (FAB/MNOBA) 213 (M+H$^+$, 25.1%), 212 (M$^+$, 10.1%), 211 (M-H$^+$, 20.1%), 113 (100%).

Preparation of *trans*-1,2-Dibromo-*cis*-4-(2-methyl-2-propyl)-cyclohexane (103).

(103)

Dry ether (6 ml) and chlorotrimethylsilane (700 μl, 5.48 mmol, 5 eq.)were added to flame-dried zinc amalgam (717 mg, 11.3 mmol, 10 eq) in a 25 ml conical flask, fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and a solution of 9-(2-methyl-2-propyl)-1,5-dioxaspiro-[5,5]-undecane (233 mg, 1.10 mmol) in dry ether (4 ml) added via cannula. The suspension was vigorously stirred at reflux for 16 hours, and then cooled to ambient temperature. The suspension was poured into saturated aqueous sodium bicarbonate (15 ml), stirred for 5 minutes and then filtered through celite. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$), filtered and treated with excess bromine for 20 minutes. Saturated aqueous sodium bicarbonate (10 ml), and sodium thiosulphate solution (10%, 20 ml) were added, the layers shaken and separated, and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil, which was chromatographed on silica (petrol (b.p. 40-60°C)) to give the dibromide **103**[172] (164 mg, 50%) as a clear colourless oil, spectroscopically identical to material already prepared.

## Preparation of 3,3-Dimethyl-9-(2-methyl-2-propyl)-1,4-dioxaspiro-[4,5]-undecane (155).

(155)
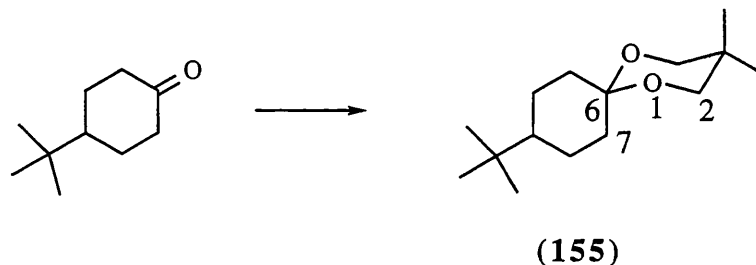
A solution of 4-^{t}butyl-cyclohexanone (1.54 g, 10.0 mmol), neopentyl glycol (2.08 ml, 20.0 mmol, 2 eq.), and p-toluenesulfonic acid monohydrate (200 mg) in benzene (50 ml) were heated to reflux for 1 hour, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction was cooled to ambient temperature, and poured into aqueous sodium hydroxide solution (1 M, 10 ml) and ether (30 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (2 x 25 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a white solid which was purified by bulb to bulb distillation (190°C/6 mbar) to give the ketal 155[175] (2.35 g, 98%) as a white solid. m.p. 85-86°C (prisms from ether/petrol (b.p. 40-60°C)), (lit.[175] 84-85°C)

v_{max} (KBr disc)/cm^{-1} 2957, 2910, 2867 (C-H), 1485, 1468, 1441, 1397, 1390, 1374, 1362, 1349, 1341, 1312, 1288, 1251, 1192, 1173, 1109, 1058, 1043, 1028, 1016, 1009, 961, 946, 924, 909, 898, 821 and 665; δ_H (400 MHz, CDCl$_3$) 3.51 (2H, s, H$_{1\beta}$, H$_{4\beta}$), 3.46 (2H, s, H$_{1\alpha}$,H$_{4\alpha}$), 2.33-2.26 (2H, m, H$_{7\alpha}$, H$_{11\alpha}$), 1.64-1.58 (2H, m, H$_{7\beta}$, H$_{11\beta}$), 1.30-1.17 (4H, m, H$_8$, H$_{10}$), 1.01 (1H, tt, J 3.0, 11.7 Hz, H$_9$), 0.95 (6H, s, 2 x C$_3$-CH$_3$), 0.84 (9H, s, C(CH$_3$)$_3$); m/z (FAB/MNOBA) 241 (M+H$^+$, 9.3%), 240 (M$^+$, 2.6%), 239 (M-H$^+$, 6.1%), 41 (100%).

Preparation of *trans*-1,2-Dibromo-*cis*-4-(2-methyl-2-propyl)-cyclohexane (103).

(103)

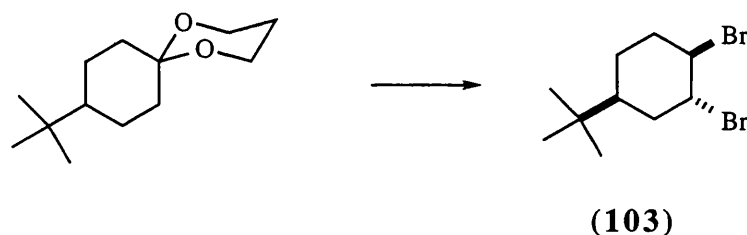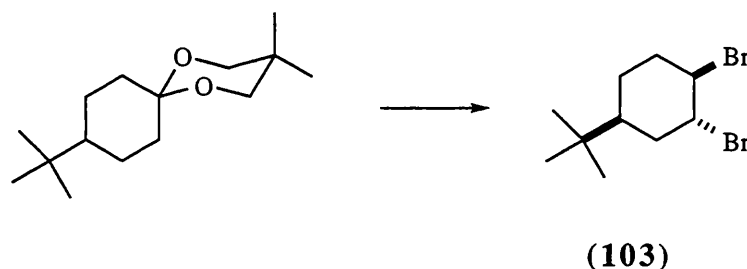Dry ether (6 ml) and chlorotrimethylsilane (670 μl, 5.28 mmol, 5 eq.)were added to flame-dried zinc amalgam (690 mg, 10.6 mmol, 10 eq) in a 25 ml conical flask, fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and a solution of 3,3-dimethyl-9-(2-methyl-2-propyl)-1,4-dioxaspiro-[4,5]-undecane (254 mg, 1.06 mmol) in dry ether (4 ml) added via cannula. The suspension was vigorously stirred at reflux for 16 hours, and then cooled to ambient temperature. The suspension was poured into saturated aqueous sodium bicarbonate (15 ml), stirred for 5 minutes and then filtered through celite. The aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and treated with excess bromine for 20 minutes. Saturated aqueous sodium bicarbonate (10 ml), and sodium thiosulphate solution (10%, 20 ml) were added, the layers shaken and separated, and the organic layer dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oily solid which was chromatographed on silica (100% petrol (b.p. 40-60°C)) to give the dibromide **103**[172] (190 mg, 56%) as a clear colourless oil, spectroscopically identical to material already prepared.

191

Reaction of 2-Pentadecyl-1,3-dioxolane with Chlorotrimethylsilane and Zinc chloride.

Chlorotrimethylsilane (45 µl, 0.7 mmol, 20 eq.) was added to a solution of 2-pentadecyl-1,3-dioxolane (9.9 mg, 35 µmol) in THF-d_8 (0.6 ml) at ambient temperature. After 22.5 hours at ambient temperature NMR analysis showed the reaction to contain only unreacted starting material. Zinc chloride (3 mg, 22 µmol, 0.6 eq.) in THF-d_8 (0.2 ml) was added. After 14.5 hours at ambient temperature NMR analysis showed the reaction to contain only unreacted starting material.

Preparation of Ethyl non-8-enoate (83) and Ethyl nonanoate (84).

EtO$_2$C

O
O

→

EtO$_2$C

(83)

+ EtO$_2$C

(84)
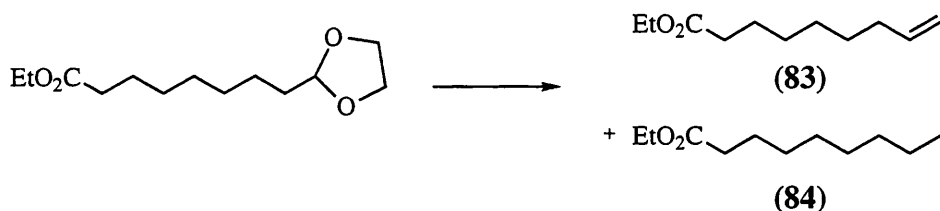
A solution of chlorotrimethylsilane (610 ml, 4.8 mmol, 5 eq.) in dry ether (5 ml) was added to flame dried zinc amalgam (620 mg, 9.5 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-(7-ethoxycarbonyl-heptyl)-1,3-dioxolane (232 mg, 0.95 mmol) in dry ether (5 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 15 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and washed through with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C)) furnished a mixture of ethyl non-8-enoate 83[157] and ethyl nonaoate 84[160] (20:1 by NMR) as a clear colourless oil (136 mg, 77%). Data as already described above.

Preparation of 8-Nonenoic acid (86) and Nonanoic acid (87).

HO$_2$C

O
O

→

HO$_2$C

(86)

+ HO$_2$C

(87)
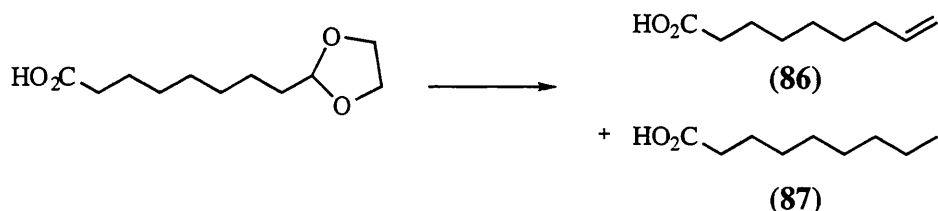
A solution of chlorotrimethylsilane (480 μl, 3.75 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (490 mg, 7.5 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension

was brought to reflux and after 5 minutes a solution of 2-(7-hydroxycarbonyl-heptyl)-1,3-dioxolane (162 mg, 0.75 mmol) in dry ether (4 ml) was added. The reaction mixture was vigorously stirred at reflux for a further 2.5 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (6 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with dichloromethane (40 ml). The aqueous layer was extracted with dichloromethane (2 x 15 ml). The aqueous layer was acidified with hydrochloric acid (5 ml, 2M), and extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (10% ether in petrol (b.p. 40-60°C)) furnished a mixture of the acids 8-nonenoic acid **86**[157] and nonanoic acid **87**[160] (86:14 by GC as their trimethylsilyl esters) as a clear colourless oil (59 mg, 50%).

v_{max} (NaCl, thin film)/cm^{-1} 3500-2500 (br, OH), 3078, 2926, 2857, 2677, 1720, 1641, 1464, 1438, 1414, 1289, 1235, 1114, 994, 910; δH (400 MHz, CDCl$_3$) *8-nonenoic acid* 5.80 (1H, ddt, *J* 17.1, 10.3, 6.7 Hz RC*H*=CHH), 4.99 (1H, ddt, *J* 2.3, 17.1, 2.3 Hz RCH=C*H*H), 4.93 (1H, ddt, *J* 2.3, 10.3, 1.7 Hz RCH=CH*H*), 2.34(2H, t, *J* 7.6 Hz, C*H$_2$*CO$_2$R), 2.03 (2H, dddt, *J* 1.5, 1.7, 6.7, 6.7 Hz C*H$_2$*CH=CHH), 1.63 (2H, tt, *J* 7.3, 7.6 Hz C*H$_2$*CH$_2$CO$_2$R), 1.44-1.24 (6H, m, alkyl chain); *nonanoic acid* 2.36-1.24 (14H, masked by ene-acid), 0.86 (3H, t, *J* 7.0 Hz, CH$_3$); m/z (EI/GCMS as trimethylsilyl esters) *8-nonenoic acid* t$_R$: 9.9 min; 213 (M-Me$^+$, 40%), 75 (100%); *nonanoic acid* t$_R$: 10.2 min; 215 (M-Me$^+$, 40%), 73 (100%).

Preparation of 2-(7-Hydroxy-heptyl)-1,3-dioxolane (156).

(156)
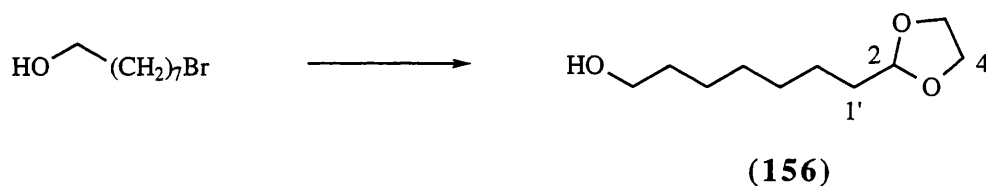
8-Bromo-1-octanol (5.00 g, 22.7 mmol) and sodium iodide were dissolved in dry acetone and the resultant solution heated to reflux overnight. The cooled suspension was

concentrated *in vacuo* and the residue taken up in ether (70 ml) and water (30 ml). The aqueous layer was extracted with ether (2 x 30 ml), and the combined organic layers washed with 10% aqueous sodium thiosulphate (10 ml), water (30 ml), brine (40 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was used directly in the next step.

The crude iodide in dry dimethyl sulfoxide (10 ml) was added to a suspension of sodium bicarbonate in dry dimethyl sulfoxide (80 ml) and washed in with further solvent (10 ml). The vigorously stirred suspension was heated in a Woods metal bath at 155°C and nitrogen bubbled through the mixture for 8 minutes.[176] The cooled suspension was poured into water (200 ml) and extracted with ether (4 x 80 ml). The combined organic layers were washed with water (2 x 70 ml), brine (100 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which solidified overnight. The resultant oily solid was subjected to bulb to bulb distillation (140°C/1 mbar) to give the unstable aldehyde (v_{max}/cm^{-1} 3356, 1724) as a clear colourless oil (1.17 g, 36% for 2 steps) which readily resolidified, and was directly converted to the dioxolane.

The aldehyde (1.16 g, 8.04 mmol), ethylene glycol (900 µl, 16 mmol, 2.0 eq.) and p-toluene-sulphonic acid monohydrate (220 mg) were heated to reflux in benzene (60 ml) for 2.75 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with ether (3 x 30 ml). The combined organic layers were washed with water (2 x 20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was chromatographed on silica (35-60% ether in petrol (b.p. 40-60°C)) to give the *dioxolane* **156** (819 mg, 54%) as a clear colourless oil.

v_{max} (NaCl thin film)/cm^{-1} 3405, 2932, 2858, 1465, 1436, 1410, 1362, 1215, 1141, 1051, 945, 898; δ_H (400 MHz, CDCl$_3$) 4.83 (1H, t, J 4.9, OCHRO), 3.80-3.96 (4H, m, O(CH$_2$)$_2$O), 3.61 (2H, t, J 6.6, -CH$_2$O), 1.68-1.61 (2H, m, H$_{1'}$), 1.59-1.52 (2H, m, H$_{6'}$), 1.50 (1H, br, OH), 1.45-1.28 (6H, m, alkyl H); m/z (FAB/MNOBA) 189 (M+H$^+$, 27%), 188 (M$^+$, 5%), 187 (M-H$^+$, 33%), 167, 149, 139, 138, 137, 127, 123, 109, 95,

81, 69, 55 (100%), 43, 29; (Found: M-H$^+$, 187.1334. $C_{10}H_{19}O_3$ requires M-H 187.1330).

**Preparation of 7-Octen-1-ol (157) and Octanol (158).**
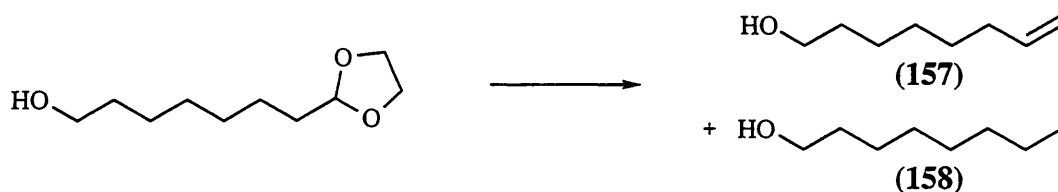
A solution of chlorotrimethylsilane (720 µl, 5.65 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (740 mg, 11.3 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-(7-hydroxy-heptyl)-1,3-dioxolane (213 mg, 1.13 mmol) in dry ether (6 ml) was added. The reaction was vigorously stirred at reflux for a further 1.5 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (12 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* at 0°C to a yellow oil which was absorbed onto silica. Column chromatography (20-35% ether in petrol b.p. 30-40°C) furnished a mixture of 7-octen-1-ol 157[177] and 1-octanol 158[178] (7:3 by GC) as a clear colourless oil (49 mg, 34%).

ν_{max} (NaCl thin film)/cm^{-1} 3341, 3078, 2924, 2857, 1642, 1465, 1437, 1420, 1379, 1251, 1120, 1057, 995, 910, 843, 725; δ_H (400 MHz, CDCl$_3$) *7-octen-1-ol* 5.77 (1H, ddt, J 10.2, 17.0, 6.6, RCH=CHH), 4.95 (1H, ddt, J 2.3, 17.0, 1.7, RCH=CHH), 4.89 (1H, ddt, J 2.3, 10.2, 1.5, RCH=CHH), 3.59 (2H, t, J 6.5, -CH$_2$O), 2.01 (2H, dddt, J 1.5, 1.7, 6.6, 7.4, CH_2CH=CHH), 1.83 (1H, br, OH), 1.52 (2H, tt, J 6.5, 7.0, -CH_2CH$_2$OH), 1.39-1.20 (6H, m, alkyl H); *1-octanol* 3.59 (2H, t, J 6.5, -CH$_2$O, masked by alkene), 1.83 (1H, br, OH, masked by alkene), 1.52 (2H, tt, J 6.5, 7.0, -CH_2CH$_2$OH, masked by alkene), 1.39-1.20 (10H, m, alkyl H, masked by alkene), 0.84

(3H, t *J* 6.5, -CH$_3$); m/z (EI/GCMS/14eV) *7-octen-1-ol* t$_R$: 9.9 min; 110 (M-H$_2$O$^+$, 12%), 95, 82, 81, 68 (100%), 67, 54; *1-octanol* t$_R$: 10.2 min; 112 (M-H$_2$O$^+$, 12%), 97, 84 (100%), 83, 70, 69, 56, 55.

Preparation of 2-(7-(4-Methyl-benzenesulfonyloxy)-heptyl)-1,3-dioxolane (159).

(159)
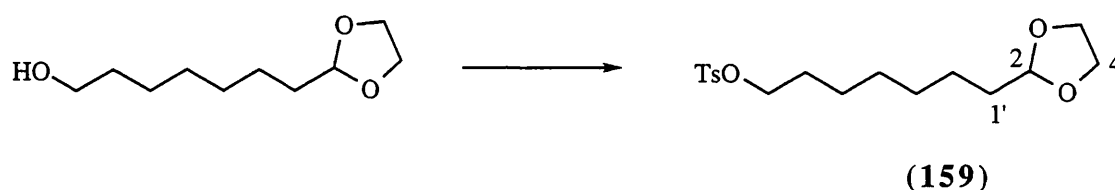
Dry pyridine (178 ml, 2.2 mmol, 1.4 eq.) was added to a stirred solution of *p*-toluenesulfonyl chloride (367 mg, 1.89 mmol, 1.2 eq.) and 2-(7-hydroxy-heptyl)-1,3-dioxolane (296 mg, 1.57 mmol) in dry dichloromethane (5 ml) under nitrogen. After 64 hours at ambient temperature the solution was poured into water (10 ml) and the aqueous layer extracted with ether (3 x 10 ml). The combined organic layers were washed with saturate aqueous copper sulphate (2 x 10 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a very light brown oil which was chromatographed on silica (20-35% ether in petrol (b.p. 40-60°C)) to give the *tosylate* **159** (415 mg, 77%) as a viscous clear colourless oil.

v$_{max}$ (NaCl thin film)/cm^{-1} 2935, 2859, 1598, 1496, 1466, 1402, 1360, 1307, 1292, 1189, 1175, 1143, 1121, 1098, 1036, 945, 911, 816, 769, 725, 665; δ$_H$ (400 MHz, CDCl$_3$) 7.76 (2H, d, *J* 8.2, ArH$_{2,6}$), 7.33 (2H, d, *J* 8.2, ArH$_{3,5}$), 4.80 (1H, t, *J* 4.8, OCHRO), 3.99 (2H, t, *J* 6.5, CH$_2$OTs), 3.98-3.81 (4H, m, O(CH$_2$)$_2$O), 2.43 (3H, s, -CH$_3$), 1.70-1.57 (4H, m, H$_{1',6'}$), 1.37-1.19 (8H, m, alkyl H); δ$_C$ (100 MHz, CDCl$_3$) 144.6, 133.1, 129.8, 127.8, 104.5, 70.6, 64.8, 33.7, 29.2, 28.74, 28.69, 25.1, 23.8, 21.6; m/z (FAB/MNOBA) 343 (M+H$^+$, 65%), 342 (M$^+$, 20%), 341 (M-H$^+$, 85%), 299, 199, 185, 173, 169, 155, 151, 139, 127, 109 (100%), 99, 91; (Found: M$^+$, 342.1501. C$_{17}$H$_{28}$O$_5$S requires *M*, 342.1506).

Preparation of 2-(8-Benzenesulfinyl-octyl)-1,3-dioxolane (113).

(113)
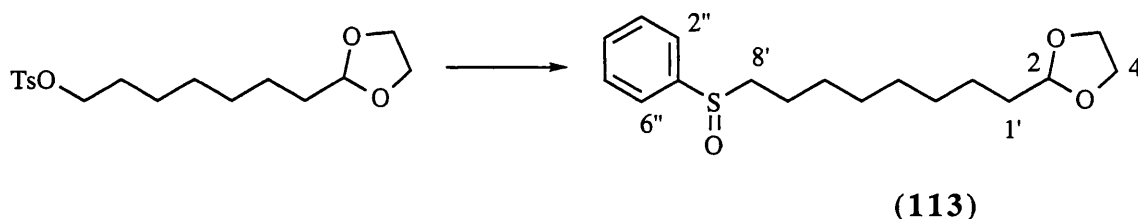
Butyllithium (760 ml, 1.95 mmol, 1.7 eq., 2.57M in hexanes) was added to a solution of phenyl methyl sulfoxide (283 mg, 1.95 mmol, 1.7 eq.) in dry tetrahydrofuran (5 ml) at -78°C. After 5 minutes at -78°C the solution was warmed to ambient temperature and then recooled to -78°C. A solution of 2-(7-(4-methyl-benzenesulfonyloxy)-heptyl)-1,3-dioxolane in dry tetrahydrofuran (5 ml) was added *via* cannula. The solution was allowed to attain ambient temperature and after 12 hours water (10 ml), was added. The solution was concentrated *in vacuo* and neutralised with saturated aqueous ammonium chloride (10 ml). The aqueous layer was extracted with ether (3 x 30 ml) and the combined organic layers were washed with brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil which was chromatographed on silica (80-100% ether in petrol (b.p. 40-60°C)) to give the *sulfoxide* 113 (163 mg, 46%) as a pale yellow oil.

ν_{max} (NaCl thin film)/cm^{-1} 3055, 2927, 2856, 1583, 1466, 1444, 1409, 1364, 1302, 1210, 1127, 1089, 1044, 944, 749, 693; δ_H (400 MHz, CDCl$_3$) 7.65-7.57 (2H, m, H2'',6''), 7.33 (3H, m, H3'',4'',5''), 4.82 (1H, t, J 4.8, OCHRO), 3.98-3.81 (4H, m, O(CH$_2$)$_2$O), 2.77 (2H, t, J 7.8, CH$_2$SO), 1.82-1.54 (4H, m, H2',7'), 1.46-1.22 (10H, m, alkyl H); δ_C (100 MHz, CDCl$_3$) 144.0, 130.9, 129.1, 124.0, 104.6, 64.8, 57.3, 33.8, 29.33, 29.18, 28.98, 28.60, 23.93, 22.1; m/z (FAB/MNOBA) 311 (M+H$^+$, 73%), 267, 149, 137, 123, 109, 95, 81, 73, 69, 55 (100%), 41; (Found: M+H$^+$, 311.1681. C$_{17}$H$_{26}$O$_3$S requires $M+H$ 311.1685).

## Preparation of 9-Phenylthio-1-nonene (114).

(114)
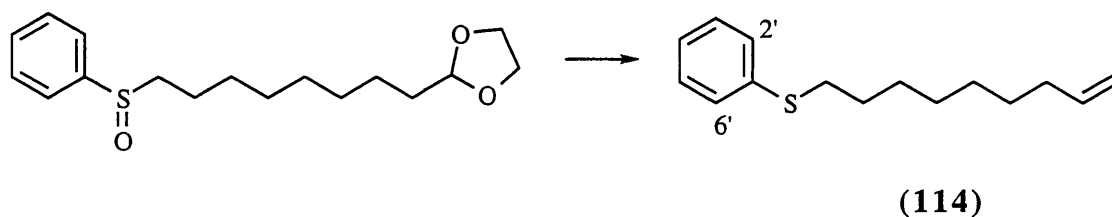
A solution of chlorotrimethylsilane (320 μl, 2.5 mmol, 5 eq.) in dry ether (2 ml) was added to flame dried zinc amalgam (325 mg, 5.0 mmol, 10 eq.), in a 10 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-(8-benzenesulfinyl-octyl)-1,3-dioxolane (143 mg, 0.46 mmol) in dry ether (3 ml) was added. The reaction was vigorously stirred at reflux for a further 7.25 hours and then cooled to ambient temperature. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (6 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and washed through with ether (40 ml). The aqueous layer was extracted with ether (2 x 15 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-25% dichloromethane in petrol (b.p. 40-60°C)) furnished the *alkene* **114** as a clear colourless oil (24 mg, 23%).

v_{max} (NaCl thin film)/cm⁻¹ 3075, 2975, 2927, 2854, 1640, 1586, 1480, 1464, 1438, 1368, 1301, 1156, 1092, 1069, 1026, 995, 910, 737, 690; δ_H (400 MHz, CDCl₃) 7.29 (2H, dd, *J* 1.4, 7.7, H₂′,₆′), 7.27 (2H, dd, *J* 7.1, 7.7, H₃′,₅′), 7.16 (1H, tt, *J* 1.4, 7.1, H₄′), 5.81 (1H, ddt, *J* 10.3, 16.5, 6.7, RC*H*=CHH), 5.00 (1H, ddt, *J* 2.3, 16.5, 1.5, RCH=C*H*H), 5.01 (1H, ddt, *J* 2.3, 10.3, 1.8, RCH=CH*H*), 2.92 (2H, t, *J* 7.3, -CH₂SPh), 2.43 (2H, dddt, *J* 1.5, 1.8, 6.7, 7.0, C*H*₂CH=CHH), 1.65 (2H, tt, *J* 7.3, 7.6, -C*H*₂CH₂SPh), 1.46-1.26 (8H, m, alkyl H); *m/z* (EI) 234 (M⁺, 11%), 123, 110 (100%), 95, 82, 69, 55, 41; (Found: M⁺, 234.1442. C₁₅H₂₂S requires *M* 234.1446).

Preparation of 4-(4-Methyl-benzenesulfonyl)-but-1-ene (160).

(160)
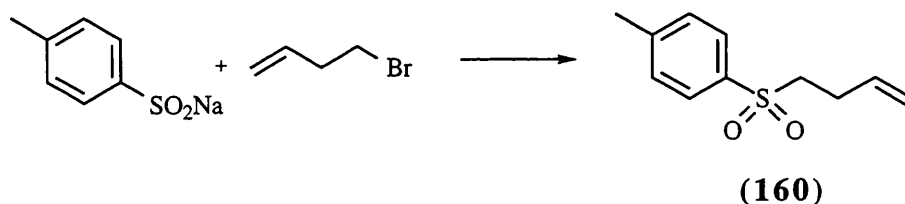
4-Bromo-1-butene (945 ml, 9.3 mmol, 1.1 eq.) was added to a suspension of sodium iodide (1.42 g, 18.6 mmol, 2.2 eq.) and sodium p-toluenesulfinate (1.81 g, 8.45 mmol) in dry N,N dimethylformamide (15 ml). The resultant suspension was vigorously stirred in the dark at ambient temperature for 49 hours and then poured into water (50 ml). The aqueous layer was extracted with dichloromethane (3 x 40 ml). The combined organic layers were washed with 10% aqueous sodium thiosulphate (10 ml), brine (40 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give an orange oil which was chromatographed on silica (0-35% ether in petrol (b.p. 40-60°C)) to give the *sulfone* **160** (1.51 g, 78%) as a clear colourless oil.

v_{max} (NaCl thin film)/cm^{-1} 3081, 2982, 2924, 1642, 1598, 1495, 1446, 1406, 1315, 1302, 1233, 1185, 1144, 1087, 1018, 997, 922, 818, 778, 728, 665; δ_H (400 MHz, CDCl$_3$) 7.78 (2H, d, J 8.3, H$_{2',6'}$), 7.35 (2H, d, J 8.3, H$_{3',5'}$), 5.71 (1H, ddt, J 10.4, 17.0, 6.5, RCH=CHH), 5.04 (1H, ddt, J 2.3, 17.0, 1.5, RCH=CHH), 5.01 (1H, ddt, J 2.3, 10.4, 1.4, RCH=CHH), 3.13 (2H, t, J 8.1, CH_2Ts), 2.44 (3H, s, -CH$_3$), 2.43 (2H, dddt, J 1.4, 1.5, 6.5, 8.1, CH_2CH=CHH); m/z (CI/^{i}C$_4$H$_{10}$) 281 (M+H$^+$, 18%), 280 (M$^+$, 12%), 57 (100%); (Found: M$^+$ 211.0790, C$_{11}$H$_{25}$O$_2$S requires M 211.0793

Preparation of 2-(2-(4-Methyl-benzenesulfonyl)-ethyl)-1,3-dioxolane (115).

(115)
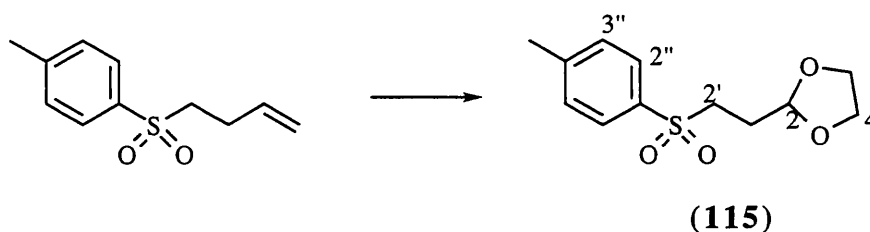
A stirred solution of the alkene (1.43 g, 6.27 mmol) in dry dichloromethane (20 ml) was cooled to -78°C under a continuous flow of oxygen. Ozonized oxygen was passed through the solution (oxygen flow rate of 2 l/minute) at -78°C until the blue colour of ozone appeared in the solution. The reaction mixture was then warmed to ambient temperature and left overnight under nitrogen. The reaction mixture was then purged with oxygen, and dimethyl sulfide (1.15 ml, 15.7 mmol, 2.5 eq.) added at -78°C in a single portion. The solution was stirred at -78°C under an atmosphere of nitrogen for 1 hour before warming to ambient temperature and left overnight under nitrogen. The solution was poured into water (15 ml) and the aqueous layer extracted with dichloromethane (2 x 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a light yellow viscous oil which was chromatographed on silica (0-35% ethyl acetate in petrol (b.p. 40-60°C)) to give the impure aldehyde (1.01 g) as a light yellow oil.

The impure aldehyde (909 mg, < 3.9 mmol), ethylene glycol (450 ml, 7.9 mmol, ca. 2 eq.) and *p*-toluenesulphonic acid monohydrate (130 mg) were heated to reflux in benzene (40 ml) for 2.5 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The reaction was cooled to ambient temperature, poured into saturated aqueous sodium bicarbonate (10 ml) and extracted with ether (3 x 20 ml). The combined organic layers were washed with water (2 x 20 ml), brine (20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a light yellow oily solid. Chromatography on silica (50-65% ether in petrol (b.p. 40-60°C)) gave the acetal 115[179] (666 mg, 46% for 2 steps) as a white solid. m.p. 82-85°C (needles from ether/hexane) (lit.[179] 83-85°C, ether/hexane).

v_{max} (KBr disc)/cm^{-1} 3056, 2968, 2941, 2922, 2895, 1596, 1495, 1443, 1406, 1382, 1298, 1228, 1177, 1144, 1087, 1055, 1033, 969, 945, 878, 826, 811, 778, 707, 698, 632; δ_H (400 MHz, CDCl$_3$) 7.77 (2H, d, J 8.1, H2'',6''), 7.34 (2H, d, J 8.1, H3'',5''), 4.94 (1H, t, J 3.9, OCHRO), 3.93-3.79 (4H, m, O(CH$_2$)$_2$O), 3.19 (2H, t, J 8.2, -CH$_2$Ts), 2.44 (3H, s, -CH$_3$), 2.05 (2H, dt, J 3.9, 8.2, -CH_2CH$_2$Ts); m/z (FAB/MNOBA) 257 (M+H$^+$, 95%), 101 (100%).

Preparation of 1-(4-Methyl-benzenesulfonyl)-prop-2-ene (116) and 1-(4-Methyl-benzenesulfonyl)propane (117).

(116)   (117)
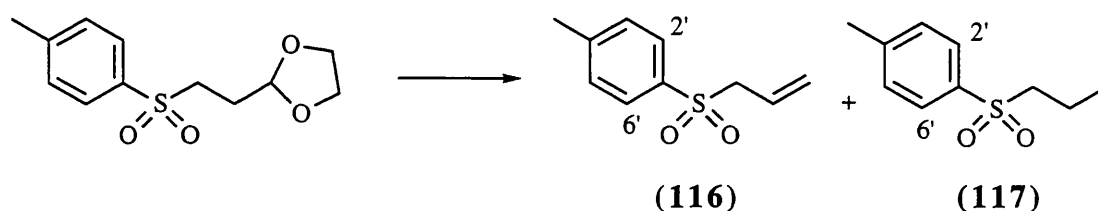
A solution of chlorotrimethylsilane (0.64 ml, 5.0 mmol, 5 eq.) in dry ether (4 ml) was added to flame dried zinc amalgam (660 mg, 10.1 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant vigorously stirred suspension was brought to reflux and after 5 minutes a solution of 2-(2-(4-methyl-benzenesulfonyl)-ethyl)-1,3-dioxolane (258 mg, 1.01 mmol) in dry ether/THF (4/1, 7.5 ml) was added. The reaction was vigorously stirred at reflux for a further 18 hours. Further chlorotrimethylsilane (0.64 ml, 5.0 mmol, 5 eq.) was added and after 24 hours, further chlorotrimethylsilane (1.28 ml, 10.0 mmol, 10 eq.) was added. After 39 hours the suspension was cooled to ambient temperature. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (45 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (20-50% ethyl acetate in petrol (b.p. 40-60°C)) furnished a mixture of 1-(4-Methyl-benzenesulfonyl)-propane 117[180] and 1-(4-Methyl-benzenesulfonyl)-2-propene 116[181] (7:1 by NMR) as a clear

colourless oil (48 mg, 24%), and recovered 2-(2-(4-methyl-benzenesulfonyl)-ethyl)-1,3-dioxolane **115**[179] (177 mg, 69%).

v_{max} (NaCl, thin film)/cm^{-1} 3067, 2969, 2927, 2879, 1636, 1597, 1496, 1456 1405, 1381, 1341, 1316, 1287, 1249, 1212, 1184, 1144, 1087, 1041, 1018, 937, 859, 846, 819, 802, 772, 739, 720, 706, 692, 666, 645, 630; δ_H (400 MHz, CDCl$_3$) *1-(4-Methyl-benzenesulfonyl)-propane* 7.76 (2H, d, *J* 8.4, H$_{2',6'}$), 7.34 (2H, d, *J* 8.4, H$_{3',5'}$), 3.03 (2H, t, *J* 8.0, -CH$_2$Ts), 2.44 (3H, s, ArCH$_3$), 1.72 (2H, tt, *J* 7.5, 8.0, -C*H$_2$*CH$_2$Ts), 0.97 (3H, t, *J* 7.5, -CH$_2$C*H$_3$*); *1-(4-Methyl-benzenesulfonyl)-3-propene* 7.76 (2H, d, *J* 8.4, H$_{2',6'}$, masked by Clemmensen product), 7.34 (2H, d, *J* 8.4, H$_{3',5'}$, masked by Clemmensen product), 5.77 (1H, ddt, *J* 10.1, 17.1, 7.4, RC*H*=CHH), 5.31 (1H, d, *J* 10.1, RCH=C*H*H), 5.13 (1H, dt, *J* 17.1, 1.2, RCH=CH*H*), 3.78 (2H, dd, *J* 1.2, 7.4, -CH$_2$Ts), 2.44 (3H, s, ArCH$_3$, masked by Clemmensen product); m/z (EI) 198 (M$^+$, 60%, *1-(4-Methyl-benzenesulfonyl)-propane*), 196 (M$^+$, 2%, *1-(4-Methyl-benzenesulfonyl)-propane*); (EI/GCMS) t$_R$:21.7 min.: *1-(4-Methyl-benzenesulfonyl)-propane* 198 (M$^+$, 15%), 156, 155, 139, 107, 92 (100%), 91, 65, 45.

Preparation of 1-(4-Methoxy-phenyl)-2,3-*cis*-di-*n*-butyl-cyclopropane (161) (*syn* and *anti*).

(161)
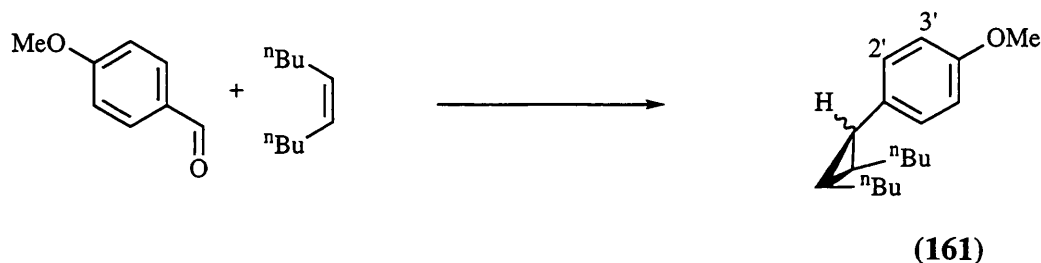
Method A:– A solution of 1,2-*bis*-(chlorodimethylsilyl)ethane (2.2 ml, 2.2 mmol, 1.1 eq., 1.0 M in ether) and *cis*-5-decene (760 μl, 4.0 mmol, 2.0 eq.) in dry ether (16 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.), in a 50 ml conical flask fitted with a reflux condenser, under argon. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxybenzaldehyde (229 μl, 2.0 mmol) in dry ether (6 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a clear yellow oil which was absorbed onto silica. Column chromatography (0-20% and 0-3% ether in petrol (b.p. 40-60°C)) furnished the *cyclopropane* **161** (inseparable mixture of diastereomers, 44:1; *syn:anti* by GC) as a clear colourless oil (295 mg, 57%).

Method B:– A solution of dichlorodimethylsilane (315 μl, 2.6 mmol, 1.5 eq.) and *cis*-5-decene (760 μl, 4.0 mmol, 2.3 eq.) in dry ether (15 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 11.4 eq.), in a 50 ml conical flask fitted with a reflux condenser, under argon. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxybenzaldehyde (202 μl, 1.76 mmol) in dry ether (9 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant

suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-2.5% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane inseparable mixture of diastereomers, **161** (inseparable mixture of diastereomers, 44:1; *syn:anti* by GC) as a clear colourless oil (240 mg, 52%).

Method C:– A solution of dichlorodimethylsilane (315 µl, 2.6 mmol, 1.3 eq.), zinc chloride (4.0 ml, 4.0 mmol, 1.0 M in ether) and *cis*-5-decene (760 µl, 4.0 mmol, 2.0 eq.) in dry ether (15 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.), in a 50 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxybenzaldehyde (229 µl, 2.0 mmol) in dry ether (9 ml) was added over 9 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (30 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oily solid which was absorbed onto silica. Column chromatography (0-2.5% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane **161** (inseparable mixture of diastereomers) as a clear colourless oil (155 mg, 30%).

Method D:– A solution of dichlorodimethylsilane (315 µl, 2.6 mmol, 1.5 eq.) and *cis*-5-decene (760 µl, 4.0 mmol, 2.0 eq.) in dry ether (15 ml) was added to zinc chloride (550 mg, 4.0 mmol, 2.0 eq.) and flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.), in a 50 ml conical flask fitted with a reflux condenser, under argon. To the resultant vigorously stirred suspension at reflux was added a solution of 4-methoxybenzaldehyde (229 µl, 2.0 mmol) in dry ether (9 ml) over 36 hours *via* syringe pump. The reaction was quenched by

addition of saturated aqueous sodium bicarbonate (15 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-2.5% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane **161** (inseparable mixture of diastereomers) as a clear colourless oil (230 mg, 44%).

v_{max} (NaCl, thin film)/cm^{-1} 2956, 2927, 2857, 1611, 1576, 1511, 1464, 1377, 1356, 1289, 1244, 1174, 1109, 1042, 832, 799; δ_H (500 MHz, CDCl$_3$) *syn-1-(4-methoxy-phenyl)-2,3-cis-di-n-butyl-cyclopropane*: 7.17 (2H, d, *J* 8.5, H$_{2',6'}$), 6.83 (2H, d, *J* 8.5, H$_{3',5'}$), 3.80 (3H, s, -OCH$_3$), 1.98 (1H, t, *J* 8.6, -CHAr), 1.50-1.28 (10H, m, alkyl H), 1.16-1.02 (4H, m, H$_{2,3}$, alkyl H), 0.90 (6H, t, *J* 7.2, -CH$_2$C*H*$_3$); m/z (EI) 260 (M$^+$, 27%), 217, 203, 189, 161, 147 (100%), 121, 115, 108, 103, 91, 77, 67, 55, 41; (Found: M$^+$, 260.2153. C$_{18}$H$_{28}$O requires *M* 260.2140).

Preparation of 1-(4-Methoxy-phenyl)-2,3-*trans*-di-*n*-butyl-cyclopropane (162).

(162)
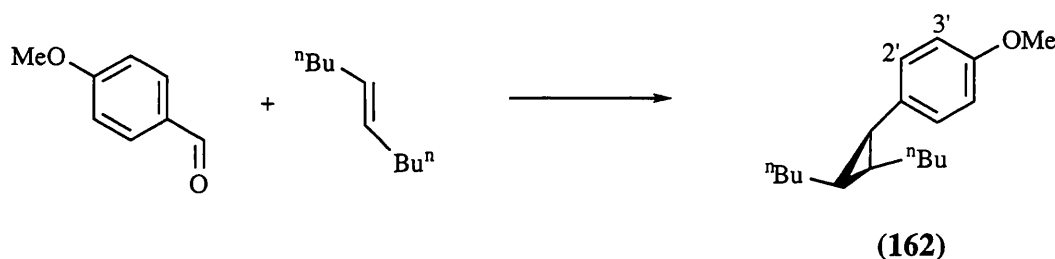
A solution of 1,2-*bis*-(chlorodimethylsilyl)ethane (1.1 ml, 1.1 mmol, 1.1 eq., 1.0 M in ether) and *trans*-5-decene (380 µl, 2.0 mmol, 2.0 eq.) in dry ether (13 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.), in a 25 ml conical flask fitted with a reflux condenser, under argon. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxybenzaldehyde (114 µl, 1.0 mmol) in dry ether (3 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The

resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a clear yellow oil which was absorbed onto silica. Column chromatography (0-20% and 0-2% ether in petrol (b.p. 40-60°C)) furnished the *cyclopropane* **162** as a clear colourless oil (51 mg, 20%).

v_{max} (NaCl, thin film)/cm^{-1} 2957, 2924, 2854, 1612, 1578, 1511, 1464, 1441, 1377, 1293, 1247, 1178, 1107, 1042, 937, 909, 829, 803, 731, 700; δ_H (500 MHz, CDCl$_3$) 7.08 (2H, d, *J* 8.6, H$_{2',6'}$), 6.80 (2H, dd, *J* 8.6, H$_{3',5'}$), 3.79 (3H, s, -OCH$_3$), 1.74 (1H, dd, *J* 5.2, 8.8, -CHAr), 1.48-1.38 (6H, m, alkyl H), 1.30-1.12 (6H, m, alkyl H), 0.98-0.74 (2H, m, H$_{2,3}$), 0.91 (3H, t, *J* 7.1, -CH$_2$CH_3), 0.79 (3H, t, *J* 7.0, -CH$_2$CH_3); m/z (EI) 260 (M$^+$, 33%), 217, 203, 189, 147 (100%), 121, 115, 108, 91, 77, 55, 41; (Found: M$^+$, 260.2150. C$_{18}$H$_{28}$O requires *M* 260.2140).

Preparation of 1-(4-Methoxy-phenyl)-2-*n*-hexyl-cyclopropane (163) (*cis* and *trans*).

(163)
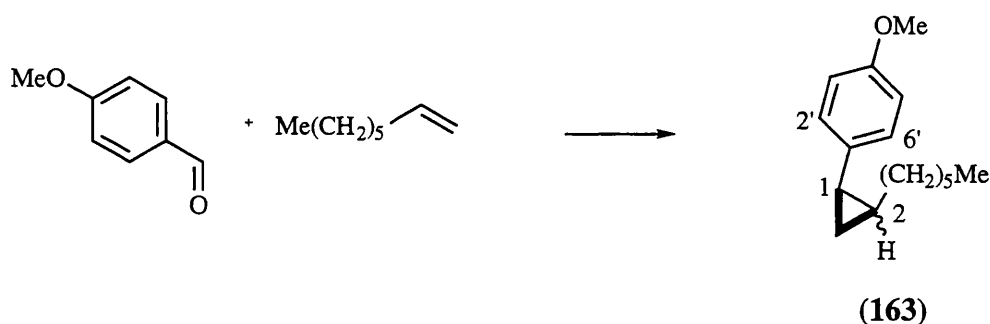
A solution of dichlorodimethylsilane (390 µl, 3.2 mmol, 1.6 eq.), 1-octene (630 µl, 4.0 mmol, 2.0 eq.) in dry ether (12 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 11.4 eq.), in a 50 ml conical flask fitted with a reflux condenser, under argon. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxybenzaldehyde (229 µl, 2.0 mmol) in dry ether (9 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer

was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-5% ether in petrol (b.p. 40-60°C)) furnished the *cyclopropane* **163** (inseparable mixture of diastereomers, 5.0:1 *cis*: *trans* by GC) as a clear colourless oil (116 mg, 25%).

ν_{max} (NaCl, thin film)/cm^{-1} 3065, 2998, 2956, 2927, 2855, 1614, 1581, 1515, 1467, 1456, 1442, 1303, 1248, 1180, 1113, 1040, 830, 801; δ_H (400 MHz, $CDCl_3$) *cis-1-(4-methoxy-phenyl)-2-n-hexyl-cyclopropane*: 7.11 (2H, d, *J* 8.5, $H_{2',6'}$), 6.82 (2H, d, *J* 8.5, $H_{3',5'}$), 3.80 (3H, s, $-OCH_3$), 2.04 (1H, ddd, *J* 6.0, 8.6, 12.9, -CHAr), 1.64-1.08 (8H, m, alkyl H), 1.04-0.66 (4H, m, $H_{2,3\alpha}$, alkyl H), 0.84 (6H, t, *J* 7.0, $-CH_2CH_3$), 0.55 (1H, dt, *J* 6.0, 5.1, $H_{3\beta}$); *trans-1-(4-methoxy-phenyl)-2-n-hexyl-cyclopropane*: 6.99 (2H, d, *J* 8.7, $H_{2',6'}$), 6.81 (2H, d, *J* 8.7, $H_{3',5'}$), 3.78 (3H, s, $-OCH_3$), 1.82 (1H, ddd, *J* 6.0, 8.1, 17.5, -CHAr), 1.64-0.66 (12H, m, alkyl H, masked by other isomer); m/z (EI/GCMS) t_R:9.8 min.: *cis-1-(4-methoxy-phenyl)-2-n-hexyl-cyclopropane*: 232 (M^+, 37%), 161, 148, 147 (100%), 134, 121, 108, 91, 77; t_R:10.9 min.: *trans-1-(4-methoxy-phenyl)-2-n-hexyl-cyclopropane*: 232 (M^+, 29%), 161, 148, 147 (100%), 134, 121, 108, 91; (Found: M^+, 232.1827. $C_{16}H_{24}O$ requires *M* 232.1829).

Preparation of 1-(4-Chloro-phenyl)-2,3-*cis*-di-*n*-butyl-cyclopropane (164) (*syn* and *anti*).


(164)
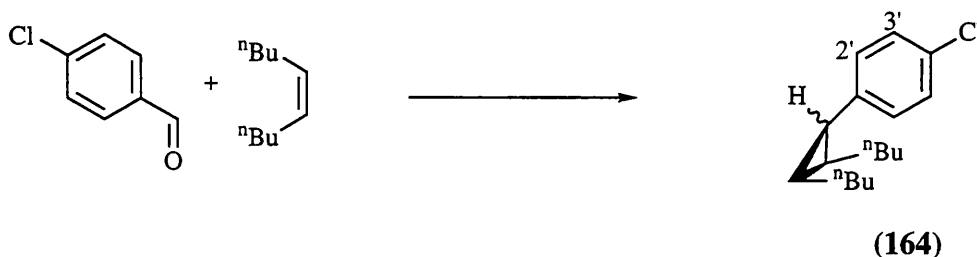
A solution of 1,2-*bis*-(chlorodimethylsilyl)ethane (2.4 ml, 2.4 mmol, 1.2 eq., 1.0 M in ether) and *cis*-5-decene (760 μl, 4.0 mmol, 2.0 eq.) in dry ether (16 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.), in a 50 ml conical flask fitted with a reflux condenser, under argon. The resultant suspension was vigorously stirred at reflux

and a solution of 4-chlorobenzaldehyde (281 mg, 2.0 mmol) in dry ether (6 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a clear yellow oil which was absorbed onto silica. Column chromatography (silica/petrol (b.p. 40-60°C), and 25%w/w $AgNO_3$ silica, 0-4% ether in petrol (b.p. 40-60°C)) furnished the *cyclopropane* **164** (inseparable mixture of diastereomers, 2.9:1 by GC) as a clear colourless oil (29 mg, 5%).

v_{max} (NaCl, thin film)/cm^{-1} 2957, 2926, 2827, 2859, 1494, 1467, 1397, 1378, 1251, 1108, 1093, 1074, 1014, 832, 790, 759; δ_H (400 MHz, $CDCl_3$) *syn-1-(4-chloro-phenyl)-2,3-cis-di-n-butyl-cyclopropane*: 7.23 (2H, d, *J* 8.6, H$_{3',5'}$), 7.16 (2H, d, *J* 8.6, H$_{2',6'}$), 1.98 (1H, t, *J* 8.5, -CHAr), 1.56-1.20 (10H, m, alkyl H), 1.14-1.02 (4H, m, alkyl H), 0.88 (6H, t, *J* 7.3, -CH$_3$); *anti-1-(4-chloro-phenyl)-2,3-cis-di-n-butyl-cyclopropane*: 7.17 (2H, d, *J* 8.4, H$_{3',5'}$), 6.81 (2H, d, *J* 8.7, H$_{2',6'}$), 1.56-1.02 (12H, m, alkyl H, masked by other isomer); m/z (EI/GCMS) t$_R$: 13.5 min.: *anti-1-(4-chloro-phenyl)-2,3-cis-di-n-butyl-cyclopropane*: 266/264 (M$^+$, (^{37}Cl) 6% / (^{35}Cl) 33%), 209, 207, 194, 165, 151 (100%), 153 (32%), 138, 127, 125, 116, 115, 95, 83, 69; t$_R$: 13.7 min.: *syn-1-(4-chloro-phenyl)-2,3-cis-di-n-butyl-cyclopropane*: 266/264 (M$^+$, 8% (^{37}Cl) / 28% (^{35}Cl)), 209, 207, 194, 165, 151 (100%), 153 (33%), 138, 127, 125, 116, 115, 97, 83, 69; (Found: M$^+$, 264.1640. $C_{17}H_{25}Cl$ requires *M* 264.1645).

Preparation of 2-Trimethylsilyloxy-propene (123).

(123)

A solution of oven-dried sodium iodide (9.29 g, 62 mmol, 1.25 eq.) in dry acetonitrile (62 ml) was added to a stirred solution of acetone (3.7 ml, 50 mmol), triethylamine (8.6 ml, 62 mmol, 1.25 eq.) and chlorotrimethylsilane (7.87 ml, 62 mmol, 1.25 eq.) over 10 minutes, and the resultant suspension stirred for a further 15 minutes at ambient temperature. The reaction mixture was then poured into ice-water (200 ml), and extracted with pentane (200 ml). The organic layer was dried (MgSO$_4$), filtered and concentrated by distillation. The crude product was distilled to give the silylenol ether **123**[182] (2.64 g, 40%) as a clear colourless oil b.p. 90-93°C/760 mmHg (lit.[182].92°C/760 mmHg).

v_{max} (NaCl, thin film)/cm^{-1} 3115, 2961, 2922, 2902, 1636, 1447, 1373, 1283, 1254, 1047, 990, 899, 845, 756, 687; δ_H (400 MHz, CDCl$_3$) 4.03 (2H, br s, C=CH), 1.74 (3H, s, -CH$_3$), 0.18 (9H, s, Si(CH$_3$)$_3$); m/z (EI) 130 (M$^+$, 18%), 75 (100%).

Preparation of 1-Trimethylsilyloxy-cyclohexene (124).
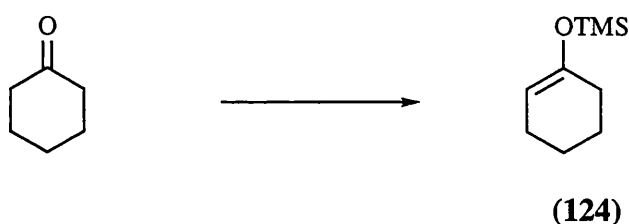
(124)

A solution of oven-dried sodium iodide (9.29 g, 62 mmol, 1.25 eq.) in dry acetonitrile (62 ml) was added to a stirred solution of cyclohexanone (5.18 ml, 50 mmol), triethylamine (8.6 ml, 62 mmol, 1.25 eq.) and chlorotrimethylsilane (7.87 ml, 62 mmol, 1.25 eq.) over 10 minutes, and the resultant suspension stirred for a further 20 minutes at ambient temperature. The reaction mixture was then poured into ice-water (200 ml), and extracted with pentane (200 ml). The organic layer was dried (MgSO$_4$), filtered and concentrated

in vacuo at 0°C to a light yellow oil. The crude product was distilled to give the silylenol

ether **124**[183] (5.31 g, 62%) as a clear colourless oil b.p. 100-104°C/70 mmHg.

v_{max} (NaCl, thin film)/cm^{-1} 3054, 3023, 29313, 2859, 2841, 1669, 1440, 1423, 1367,

1340, 1267, 1252, 1188, 1171, 1138, 1082, 1048, 987, 926, 896, 844, 794, 755, 690, 629;

δ_H (400 MHz, CDCl$_3$) 4.86 (1H, m, C=CH), 2.04-1.93 (4H, m, H$_{3,6}$), 1.68-1.62 (2H, m,

H$_4$), 1.54-1.46 (2H, m, H$_5$), 0.17 (9H, s, Si(CH$_3$)$_3$); m/z (EI) 170 (M$^+$, 59%), 75 (100%).

Preparation of 4-Methoxy-benzaldehyde dimethyl acetal (165).

(165)
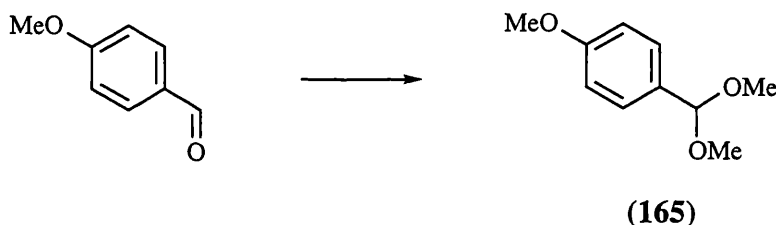
A solution of *p*-methoxy-benzaldehyde (10.0 g, 73.5 mmol), methanol (10 ml), trimethyl

orthoformate (16 ml, 147 mmol, 2.0 eq.) and *p*-toluenesulfonic acid monohydrate (190

mg) was heated at reflux for 1.75 hours. The solution was cooled to ambient temperature

and poured into saturated aqueous sodium bicarbonate (20 ml) and ether (40 ml). The

separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic

layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and

concentrated *in vacuo* to give a light yellow oil which was distilled under vacuum (154-

157°C/13 mmHg) to give the acetal **165**[184] (8.23 g, 59%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2994, 2938, 2902, 2833 (C-H), 1614, 1587, 1513, 1466,

1443, 1353, 1303, 1250, 1209, 1171, 1102, 1075, 1052, 1036, 983, 912, 824 and 786; δ_H

(400 MHz, CDCl$_3$) 7.34 (2H, d, *J* 8.5, H$_{2,6}$), 6.90 (2H, d, *J* 8.5, H$_{3,5}$), 5.36 (1H, s, H$_2$),

3.81 (3H, s, ArOCH$_3$), 3.31 (6H, s, ArCH(OC*H*$_3$)$_2$); m/z (EI) 182 (M$^+$, 8.6%), 151 (M-

OMe$^+$, 100%).

Preparation of 1-(4-Methoxy-phenyl)-2-phenyl-cyclopropane (166) (*cis and trans*).

(166)

Method A:– A solution of dichlorodimethylsilane (485 μl, 4.0 mmol, 2.0 eq.) and styrene (460 μl, 4.0 mmol, 2.0 eq.) in dry ether (15 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 11.4 eq.), in a 50 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxy-benzaldehyde dimethyl acetal (364 mg, 2.00 mmol) in dry ether (9 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (20 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-3% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane 166[185] (inseparable mixture of diastereomers, 4.6:1 *cis:trans* by GC) as a clear colourless oil (178 mg, 40%).

Method B:– A solution of dichlorodimethylsilane (485 μl, 4.0 mmol, 2.0 eq.) and styrene (460 μl, 4.0 mmol, 2.0 eq.) in dry ether (15 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 11.4 eq.) and zinc chloride (550 mg, 4.0 mmol, 2.0 eq.) in a 50 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxy-benzaldehyde dimethyl acetal (364 mg, 2.00 mmol) in dry ether (9 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (20 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite,

and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-3% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane 166[185] (inseparable mixture of diastereomers, 11.5:1 *cis:trans* by GC) as a clear colourless oil (178 mg, 40%).

v_{max} (NaCl, thin film)/cm^{-1} 3063, 3027, 3005, 2956. 2934, 2834, 2603, 1582, 1515, 1498, 1456, 1441, 1365, 1302, 1249, 1179, 1113, 1073, 1036, 829, 801, 769, 731, 698; δH (400 MHz, CDCl$_3$) *cis-1-(4-methoxy-phenyl)-2-phenyl-cyclopropane*: 7.32-6.90 (5H, m, PhH), 6.87 (2H, d, *J* 8.6, H$_{2',6'}$), 6.65 (2H, d, *J* 8.6, H$_{3',5'}$), 3.71 (3H, s, -OCH$_3$), 2.44 (2H, ddd, *J* 2.5, 6.3, 8.6, -CHAr), 1.45 (1H, dt, *J* 5.3, 8.6, H$_{3\alpha}$), 1.31 (1H, q, *J* 6.3,, H$_{3\beta}$); *trans 1-(4-methoxy-phenyl)-2-phenyl-cyclopropane*: 7.32-6.90 (9H, m, ArH, masked by *cis* isomer), 3.81 (3H, s, -OCH$_3$), 2.19-2.07 (2H, m, -CHAr), 1.45-1.38 (2H, m, H$_{3\alpha,3\beta}$, masked by *cis* isomer); m/z (EI/GCMS) t$_R$: 12.1 min.;*cis-1-(4-methoxy-phenyl)-2-phenyl-cyclopropane*: 224 (M$^+$, 100%); t$_R$: 17.2 min.; *trans 1-(4-methoxy-phenyl)-2-phenyl-cyclopropane*: 224 (M$^+$, 100%).

Preparation of 7-(4-Methoxy-phenyl)bicyclo[4.1.0]heptane (167) (*endo* and *exo*).

(167)
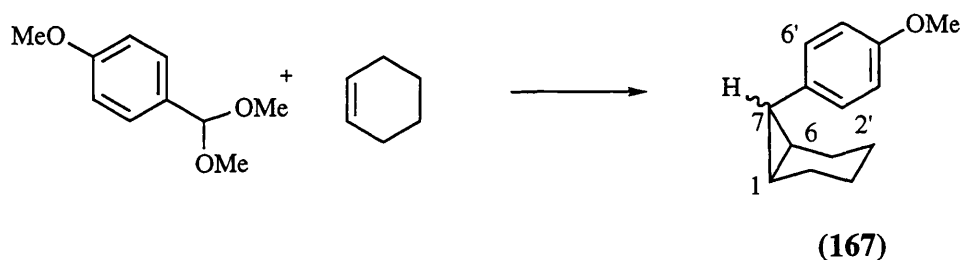
A solution of chlorotrimethylsilane (1.27 ml, 10.0 mmol, 5.0 eq.) and cyclohexene (405 µl, 4.0 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.) and zinc chloride (273 mg, 2.0 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 4-methoxy-benzaldehyde dimethyl acetal (364 mg, 2.00

mmol) in dry ether (4.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (25 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-3% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane 167[90b] (inseparable mixture of diastereomers, 23.5:1 *end:exo* by GC) as a clear colourless oil (253 mg, 62%).

v_{max} (NaCl, thin film)/cm^{-1} 3001, 2932, 2863, 2834, 1610, 1577, 1511, 1462, 1449, 1358, 1340, 1289, 1242, 1180, 1171, 1109, 1039, 968, 928, 902, 831, 810, 799, 773, 745, 729; δ_H (400 MHz, $CDCl_3$) 7.21 (2H, dd, J 1.0, 8.8, $H_{3',5'}$), 6.87 (2H, dd, J 2.1, 8.8, $H_{2',6'}$),3.80 (3H, s, CH_3), 1.88 (1H, t, J 9.0, -CHAr), 1.92-1.82 (2H, m, alkyl H), 1.69-1.60 (2H, m, alkyl H), 1.26-1.16 (2H, m, alkyl H), 1.12-1.01 (2H, m, alkyl H), 0.71-0.61 (2H, m, $H_{1,6}$); m/z (EI/GCMS) *endo-7-(4-Methoxy-phenyl)bicyclo[4.1.0]heptane* :t_R: 8.9 min. 202 (M^+, 100%), 121 (100%); t_R: 9.4 min. *exo 7-(4-Methoxy-phenyl)bicyclo[4.1.0]heptane*: 202 (M^+, 78%), 121(100%).

Preparation of 2-(4-Methoxy-phenyl)-1,3-dioxolane (168).

(168)
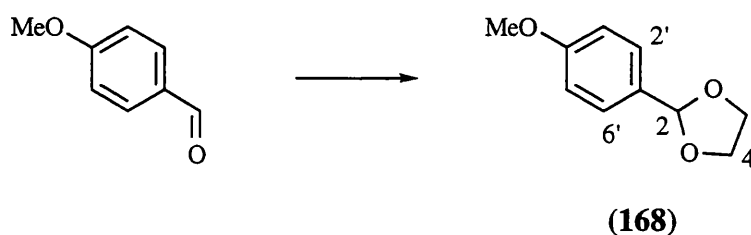
A solution of distilled *p*-methoxy-benzaldehyde (4.29g, 31.5 mmol), ethylene glycol (2.7 ml, 47 mmol, 1.5 eq.), and *p*-toluenesulfonic acid monohydrate (415 mg) in benzene (30 ml), was heated to reflux for 18 hours, and the water formed removed by azeotropic distillation using a reverse Dean-Stark apparatus filled with dried 4Å molecular sieves. The solution was cooled to ambient temperature and poured into aqueous sodium

hydroxide (1M, 10 ml) and ether (40 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (2 x 30 ml), brine (30 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a light yellow oil. This oil was treated with a solution of sodium borohydride (1.5 g) in ethanol (20 ml) for 2 hours and then poured into a saturated solution of sodium carbonate (40 ml), and extracted with ether (3 x 40 ml). The combined organic layers were washed with brine (2 x 80 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give an orange oil which was distilled under vacuum (142-148°C/11 mmHg, lit.[133] 97-98°C/1.5 mmHg) to give the acetal **168**[133] (3.12 g, 55%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2954, 2887, 2838, 1614, 1589, 1520, 1464, 1433, 1392, 1304, 1248, 1170, 1112, 1078, 103, 1012, 967, 943, 831, 779, 728, 668 and 632; δ_H (200 MHz; CDCl$_3$) 7.39 (2H, d, J 8.5, H$_{2',6'}$), 6.89 (2H, d, J 8.5, H$_{3',5'}$), 5.74 (1H, s, H$_2$), 4.15-4.06 (2H, m, H$_{4\beta,5\beta}$), 4.03-3.95 (2H, m, H$_{4\alpha,5\alpha}$), 3.79 (3H, s, -CH$_3$); m/z (EI) 180 (M$^+$, 61%), 135 (100%).

## Preparation of 7-(4-Methoxy-phenyl)bicyclo[4.1.0]heptane (167) (*endo* and *exo*).

(167)
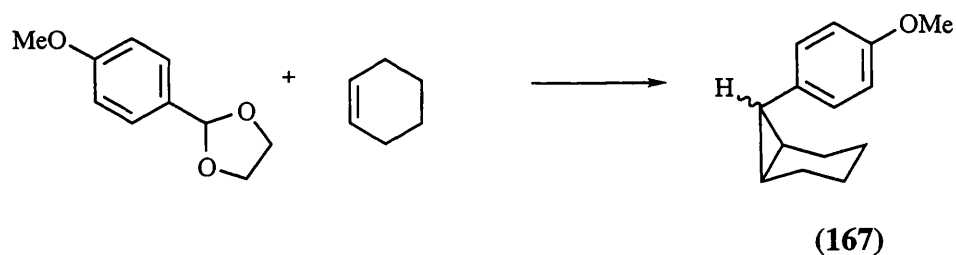
A solution of chlorotrimethylsilane (1.18 ml, 9.3 mmol, 5.0 eq.) and cyclohexene (375 µl, 3.7 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.22 g, 18.6 mmol, 10 eq.) and zinc chloride (253 mg, 1.9 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. To the resultant vigorously stirred suspension at reflux was added a solution of 2-(4-methoxy-phenyl)-1,3-dioxolane (364 mg, 2.00 mmol) in dry ether (4.5 ml) over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (25 ml), and stirred for 5 minutes. The resultant suspension was filtered through celite, and washed through with

ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (0-2% ether in petrol (b.p. 40-60°C)) furnished the cyclopropane 167[90b] (inseparable mixture of diastereomers, 23.5:1 *endo:exo* by GC) as a clear colourless oil (244 mg, 65%), spectroscopically identical to material already prepared.

## Preparation of 2-(4-Methyl-phenyl)-1,3-dioxolane (169).

(169)
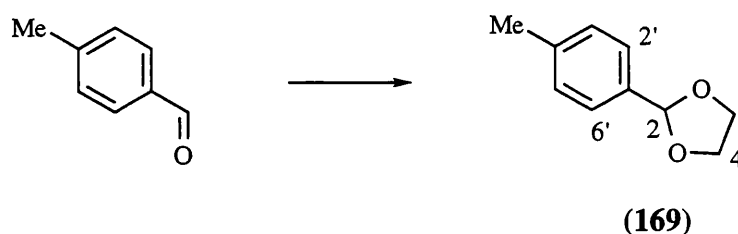
A solution of distilled *p*-methyl-benzaldehyde (4.43g, 36.9 mmol), ethylene glycol (3.1 ml, 55 mmol, 1.5 eq.), and *p*-toluenesulfonic acid monohydrate (335 mg) in benzene (35 ml), was heated to reflux for 18 hours, and the water formed removed by azeotropic distillation using a reverse Dean-Stark apparatus filled with dried 4Å molecular sieves. The solution was cooled to ambient temperature and poured into aqueous sodium hydroxide (1M, 10 ml) and ether (40 ml). The separated aqueous layer was extracted with ether (2 x 20 ml). The combined organic layers were washed with water (20 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give an orange oil which was distilled under vacuum (118-122°C/12 mmHg, lit.[133] 88°C/2.4 mmHg) to give the acetal 169[133] (2.95 g, 49%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm^{-1} 2954, 2886 (C-H), 1619, 1516, 1424, 1389, 1308, 1224, 1209, 1178, 1082, 1022, 968 and 942; δ_H (200 MHz; CDCl$_3$) 7.35 (2H, d, J 8.2, H$_{2',6'}$), 7.17 (2H, d, J 8.2, H$_{3',5'}$), 5.77 (1H, s, H$_2$), 4.15-4.05 (2H, m, H$_{4\beta,5\beta}$), 4.04-3.94 (2H, m, H$_{4\alpha,5\alpha}$), 2.33 (3H, s, -CH$_3$); m/z (EI) 164 (M$^+$, 37%), 163 (M-H$^+$, 100%).

Preparation of 7-(4-Methyl-phenyl)bicyclo[4.1.0]heptane (*endo* (170) and *exo* (171)).

(171)   (170)
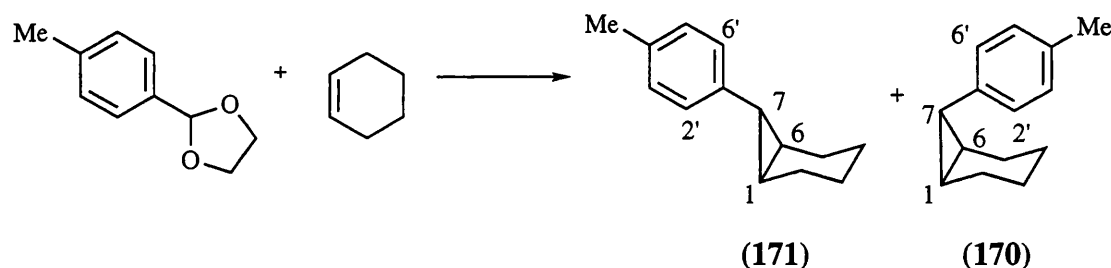
Method A:– A solution of chlorotrimethylsilane (1.34 ml, 10.5 mmol, 5.0 eq.) and cyclohexene (425 μl, 4.2 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.37 g, 21 mmol, 10 eq.) and zinc chloride (290 mg, 2.12 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-methyl-phenyl)-1,3-dioxolane (348 mg, 2.12 mmol) in dry ether (2.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (22 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give an off white oily solid which was absorbed onto silica. Column chromatography (silica, 0-10% dichloromethane in petrol (b.p. 40-60°C)) gave the cyclopropanes[90b] (6.05:1 *endo : exo* by GC) as clear colourless oils (155 mg, 37%), in order of elution, the *endo* cyclopropane **170**, and the *exo* cyclopropane **171**.

Method B:– A solution of chlorotrimethylsilane (1.17 ml, 9.3 mmol, 5.0 eq.) and cyclohexene (375 μl, 3.7 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.21 g, 18.5 mmol, 10 eq.) and zinc chloride (252 mg, 1.85 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-methyl-phenyl)-1,3-dioxolane (303 mg, 1.85 mmol) in dry ether (2.5 ml) was added over 18 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate

217

(22 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow/green oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60°C)) gave the cyclopropanes[90b] (6.05:1 *endo* : *exo* by GC) as clear colourless oils(115 mg, 33%), in order of elution, the *endo* cyclopropane **170** and the *exo* cyclopropane **171**.

Method C:– A solution of dichlorodimethylsilane (365 µl, 3.0 mmol, 1.5 eq.) and cyclohexene (400 µl, 4.0 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.30 g, 20 mmol, 10 eq.) and zinc chloride (270 mg, 2.0 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-methyl-phenyl)-1,3-dioxolane (326 mg, 1.99 mmol) in dry ether (2.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (16 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60°C)) gave the cyclopropanes[90b] (6.07:1 *endo : exo* by GC) as clear colourless oils (139 mg, 38%), in order of elution, the *endo* cyclopropane **170** and the *exo* cyclopropane **171**.

endo-7-(4-Methyl-phenyl)bicyclo[4.1.0]heptane **170**: v_{max} (NaCl, thin film)/cm^{-1} 3087, 3048, 3006, 2933, 2865, 1515, 1462, 1448, 1358, 1249, 1181, 1112, 1023, 969, 928, 850, 820, 772, 737; δ_H (400 MHz, $CDCl_3$) 7.19 (2H, d, J 7.7, $H_{3',5'}$), 7.13 (2H, d, J 7.7, $H_{2',6'}$), 2.34 (3H, s, CH_3), 1.95-1.82 (3H, m, -CHAr, alkyl H), 1.73-1.62 (2H, m, alkyl H), 1.28-1.20 (2H, m, alkyl H), 1.13-1.02 (2H, m, alkyl H), 0.74-0.62 (2H, m, $H_{1,6}$); m/z (EI) 186 (M^+, 53%), 105 (100%).

exo-7-(4-Methyl-phenyl)bicyclo[4.1.0]heptane **171**: v_{max} (NaCl, thin film)/cm^{-1} 3010, 2925, 2854, 1619, 1518. 1448, 1377, 1355, 1255, 1223, 1200, 1150, 1111, 1077, 1019, 973, 850, 802, 771; δ_H (400 MHz, $CDCl_3$) 7.05 (2H, d, J 7.9, $H_{3',5'}$), 6.90 (2H, d, J 7.9, $H_{2',6'}$), 1.98-1.88 (2H, m, alkyl H), 1.79-1.71 (2H, m, alkyl H), 1.54 (1H, t, J 4.7, -CHAr), 1.34-1.18 (6H, m, alkyl H); m/z (EI) 186 (M^+, 56%), 105 (100%).

Preparation of 2-Phenyl-1,3-dioxolane (172).

(172)
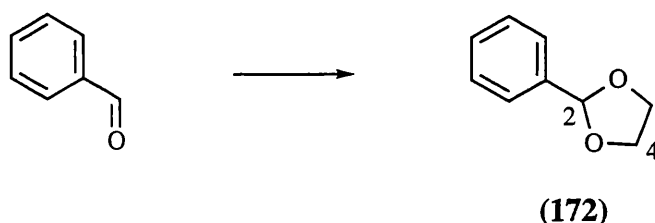
A solution of distilled benzaldehyde (4.67 g, 43.9 mmol), ethylene glycol (5.6 ml, 66 mmol, 1.5 eq.), and p-toluenesulfonic acid monohydrate (610 mg) in benzene (70 ml), was heated to reflux for 3.5 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The solution was cooled to ambient temperature and poured into aqueous sodium hydroxide (1M, 10 ml) and ether (40 ml). The separated aqueous layer was extracted with ether (2 x 30 ml). The combined organic layers were washed with water (2 x 30 ml), brine (30 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was distilled under vacuum (108-110°C/17 mmHg, lit.[133] 61-62°C/1 mmHg) to give the acetal **172**[133] (5.36 g, 81%) as a clear colourless oil.

v_{max} (NaCl, thin film)/cm⁻¹ 3066, 3045, 2955, 2887, 1458, 1395, 1312, 1293, 1220, 1174, 1094, 1070, 1028, 967, 944, 915, 849, 759, 699 and 639; δ_H (200 MHz; $CDCl_3$) 7.51-7.35 (5H, m, -Ph), 5.81 (1H, s, H2), 4.17-4.08 (2H, m $H_{4\alpha,5\alpha}$), 4.06-3.98 (2H, m, $H_{4\beta,5\beta}$); m/z (EI) 150 (16%, M⁺), 149 (M-H⁺, 57%), 51 (100%).

Preparation of 7-Phenylbicyclo[4.1.0]heptane (*endo* (173) and *exo* (174)).

(174)   **(173)**
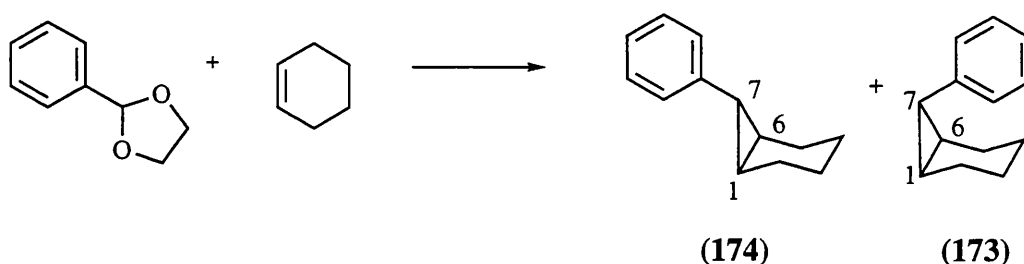
A solution of chlorotrimethylsilane (1.30 ml, 10.2 mmol, 5.0 eq.) and cyclohexene (415 μl, 4.1 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.34 g,

20.5 mmol, 10 eq.) and zinc chloride (280 mg, 2.05 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. To the resultant suspension was vigorously stirred at reflux and a solution of 2-phenyl-1,3-dioxolane (308 mg, 2.05 mmol) in dry ether (4.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (30 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60°C)) gave the cyclopropanes[90b] (3.3:1 *endo* : *exo* by GC) as clear colourless oils (129 mg, 37%), in order of elution, the *endo* cyclopropane **173** and the *exo* cyclopropane **174**.

endo-7-Phenylbicyclo[4.1.0]heptane **173**: v_{max} (NaCl, thin film)/cm^{-1} 3080, 3057, 2932, 2865, 1602, 1497, 1462, 1449, 1358, 1348, 1340, 1246, 1184, 1132, 1073, 1030, 966, 912, 848, 810, 777, 730, 718, 701, 668, 658; δ_H (400 MHz, CDCl$_3$) 7.34-7.16 (5H, m, ArH), 1.96-1.84 (2H, m, alkyl H), 1.95 (1H, t, *J* 9.4, -CHAr), 1.72-1.63 (2H, m, alkyl H), 1.31-1.22 (2H, m, alkyl H), 1.12-1.01 (2H, m, alkyl H), 0.71-0.60 (2H, m, H$_{1,6}$); m/z (EI) 172 (M$^+$, 18%), 39 (100%).

exo-7-Phenylbicyclo[4.1.0]heptane **174**: v_{max} (NaCl, thin film)/cm^{-1} 3085, 3062, 3010, 2927, 2852, 1606, 1581, 1500, 1486, 1456, 1448, 1355, 1348, 1280, 1255, 1220, 1200, 1174, 1150, 1098, 108, 1064, 1032, 1015, 972, 908, 845, 788, 727, 696; δ_H (400 MHz, CDCl$_3$) 7.27-7.21 (2H, m, H$_{3',5}$), 7.14-7.07 (2H, H$_4$), 7.02-6.97 (2H, H$_{2',6'}$), 2.02-1.91 (2H, m, alkyl H), 1.82-1.72 (2H, m, alkyl H), 1.57 (1H, t, *J* 4.6, -CHAr), 1.38-1.24 (6H, m, alkyl H); m/z (EI) 172 (M$^+$, 38%), 91 (100%).

Preparation of 2-(4-Chloro-phenyl)-1,3-dioxolane (175).

(175)
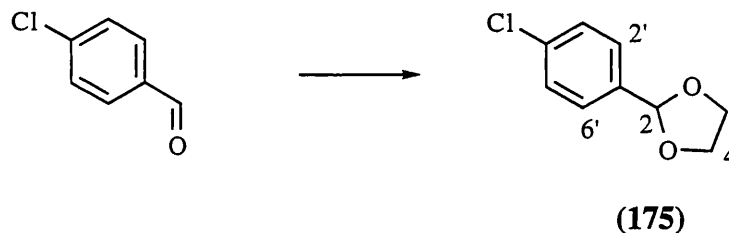
A solution of distilled *p*-chloro-benzaldehyde (5.15 g, 36.6 mmol), ethylene glycol (3.1 ml, 55 mmol, 1.5 eq.), and *p*-toluenesulfonic acid monohydrate (430 mg) in benzene (70 ml), was heated to reflux for 2 hours, and the water formed removed by azeotropic distillation using a Dean-Stark apparatus. The solution was cooled to ambient temperature and poured into aqueous sodium hydroxide (1M, 10 ml) and ether (40 ml). The separated aqueous layer was extracted with ether (2 x 30 ml). The combined organic layers were washed with water (2 x 30 ml), brine (20 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was distilled under vacuum (136-139°C/15 mmHg, lit.[133] 123.5°C/11.5 mmHg) to give the acetal **175**[133] (4.82 g, 71%) as a clear colourless oil.

ν_{max} (NaCl, thin film)/cm^{-1} 3057, 2954, 2887, 1602, 1491, 1423, 1385, 1349, 1298, 1280, 1218, 1172, 1108, 1089, 1028, 1016, 971, 942, 854, 821, 717 and 668; δ_H (200 MHz; CDCl$_3$) 7.37 (2H, d, J 6.3, H$_{3',5'}$), 7.36 (2H, d, J 6.3, H$_{2',6'}$), 5.76 (1H, s, H$_2$), 4.10-3.96 (4H, m H$_{4,5}$); m/z (EI) 186/184 (M$^+$, 11.3% (^{37}Cl) / 38.7% (^{35}Cl)), 185/183 (M-H$^+$, 38.1% (^{37}Cl) / 100% (^{35}Cl)).

Preparation of 7-(4-Chloro-phenyl)bicyclo[4.1.0]heptane (*endo* (176) and *exo* (177)).
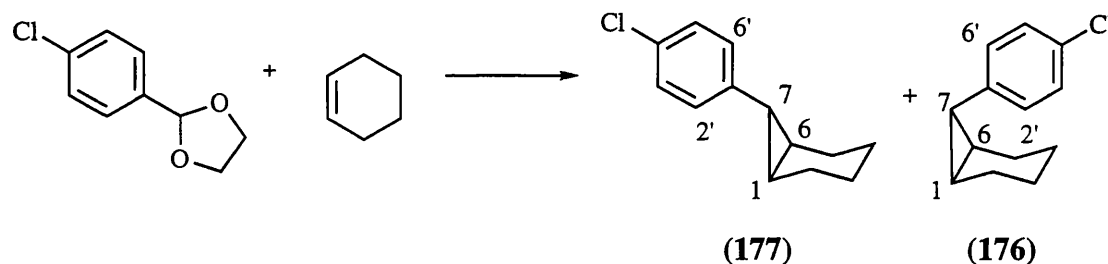
A solution of chlorotrimethylsilane (1.28 ml, 10.1 mmol, 5.0 eq.) and cyclohexene (410 μl, 4.04 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.32g, 20 mmol, 10 eq.) and zinc chloride (275 mg, 2.0 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-chloro-phenyl)-1,3-dioxolane (373 mg, 2.02 mmol) in dry ether (4.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (30 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60°C)) gave the cyclopropanes[90b] (2.89:1 *endo* : *exo* by GC) (125 mg, 30%), in order of elution, the *endo* cyclopropane **176** as a clear colourless oil and the *exo* cyclopropane **177** as a semi-crystalline solid.

endo-7-(4-Chloro-phenyl)bicyclo[4.1.0]heptane **176**: v_{max} (NaCl, thin film)/cm^{-1} 3008, 2932, 2864, 1596, 1498, 1462, 1449, 1394, 1358, 1348, 1340, 1248, 1181, 1132, 1091, 1019, 968, 928, 902, 849, 829, 806, 776, 756, 724, 664; δ_H (400 MHz, CDCl$_3$) 7.26 (2H, d, *J* 8.7, H$_{3',5'}$), 7.19 (2H, d, *J* 8.7, H$_{2',6'}$), 1.94-1.82 (2H, m, alkyl H), 1.87 (1H, t, *J* 9.0, -CHAr), 1.64-1.55 (2H, m, alkyl H), 1.29-1.21 (2H, m, alkyl H), 1.11-1.01 (2H, m, alkyl H), 0.69-0.58 (2H, m, H$_{1,6}$); m/z (EI) 208/206 (M$^+$, 4% (^{37}Cl) /14% (^{35}Cl)), 81 (100%).

223

exo-7-(4-Chloro-phenyl)bicyclo[4.1.0]heptane **177**: v_{max} (NaCl, thin film)/cm^{-1} 3005, 2930, 2855, 1598, 1494, 1462, 1445, 1433, 1392, 1264, 1198, 1150, 1105, 1090, 1078, 1064, 1012, 972, 854, 844, 810, 794, 772, 740, 705; δ_H (400 MHz, CDCl$_3$) 7.18 (2H, d, *J* 8.5, H$_{3',5'}$), 6.91 (2H, d, *J* 8.5, H$_{2',6'}$), 1.98-1.88 (2H, m, alkyl H), 1.78-1.69 (2H, m, alkyl H), 1.53 (1H, t, *J* 4.6, -CHAr), 1.36-1.17 (6H, m, alkyl H); m/z (EI) 208/206 (M$^+$, 8%(^{37}Cl) / 25% (^{35}Cl)), 39 (100%).

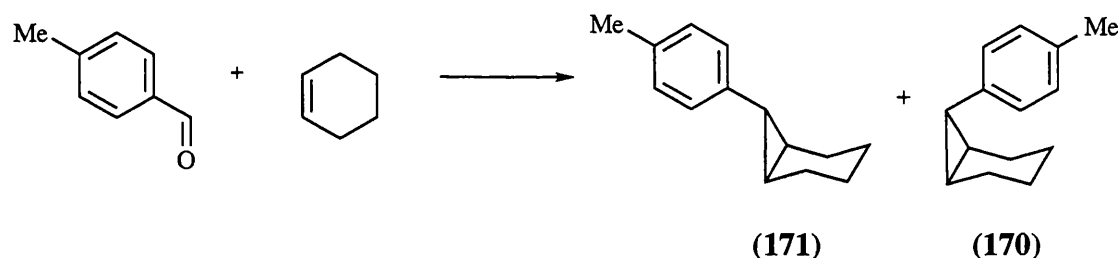**Preparation of 7-(4-Methyl-phenyl)bicyclo[4.1.0]heptane (*endo* (170) and *exo* (171)).**

A solution of dichlorodimethylsilane (315 μl, 2.6 mmol, 1.3 eq.) and cyclohexene (405 μl, 4.0 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.31 g, 20 mmol, 10 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 4-methyl-benzaldehyde (235 μl, 2.0 mmol) in dry ether (2.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (11 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil which was absorbed onto silica. Column chromatography (silica, petrol (b.p. 40-60ºC)) gave the cyclopropanes[90b] (5.6:1 *endo* : *exo* by GC) as clear colourless oils (128 mg, 34%), in order of elution, the *endo* cyclopropane **170** and the *exo* cyclopropane **171**, spectroscopically identical to materials already prepared.

Preparation of 2-(4-Methoxy-phenyl)-1-methyl-cyclopropan-1-ol acetate (178) (*syn* and *anti*).
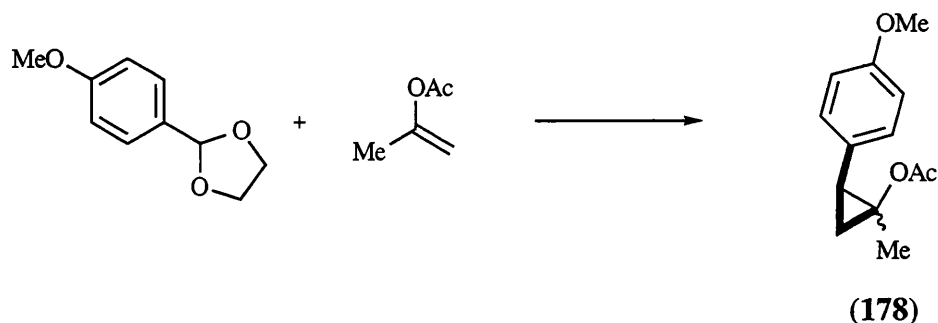
(178)

A solution of chlorotrimethylsilane (1.26 ml, 10 mmol, 5.0 eq.) and isopropenyl acetate (445 µl, 4.06 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.31g, 20 mmol, 10 eq.) and zinc chloride (271 mg, 2.0 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-methoxy-phenyl)-1,3-dioxolane (366 mg, 2.03 mmol) in dry ether (4.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (30 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil. NMR analysis of the crude reaction mixture confirmed the presence of *syn*- and *anti*-2-(4-methoxy-phenyl)-1-methyl-cyclopropan-1-ol acetate **178**[107] (< 20%).

225

Preparation of 2-(4-Methyl-phenyl)-1-methyl-cyclopropan-1-ol acetate (179) (*syn* and *anti*).
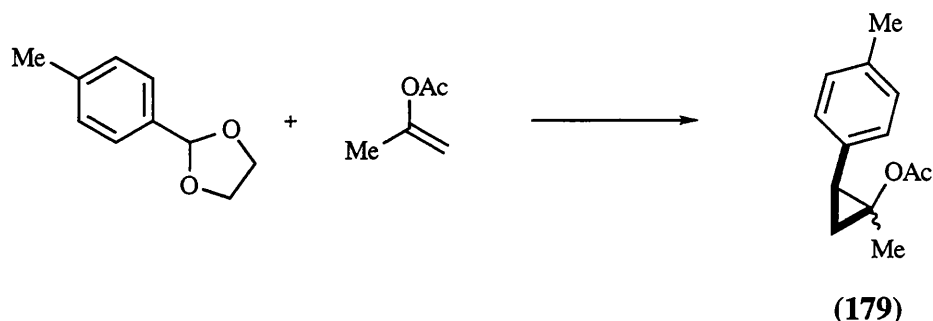
(179)

A solution of chlorotrimethylsilane (1.26 ml, 10 mmol, 5.0 eq.) and isopropenyl acetate (445 μl, 4.06 mmol, 2.0 eq.) in dry ether (9 ml) was added to flame dried zinc amalgam (1.31g, 20 mmol, 10 eq.) and zinc chloride (271 mg, 2.0 mmol, 1.0 eq.) in a 25 ml conical flask fitted with a reflux condenser, under nitrogen. The resultant suspension was vigorously stirred at reflux and a solution of 2-(4-methyl-phenyl)-1,3-dioxolane (327 mg, 1.99 mmol) in dry ether (4.5 ml) was added over 36 hours *via* syringe pump. The reaction was quenched by addition to saturated aqueous sodium bicarbonate (30 ml), and the mixture stirred for 5 minutes. The resultant suspension was filtered through celite, and the filter cake washed with ether (40 ml). The aqueous layer was extracted with ether (2 x 20 ml) and the combined organic layers washed with brine (15 ml), dried (MgSO$_4$), filtered and concentrated *in vacuo* to give a yellow oil. NMR analysis of the crude reaction mixture confirmed the presence of *syn*- and *anti*-2-(4-methyl-phenyl)-1-methyl-cyclopropan-1-ol acetate **179**[107] (< 20%).

226

References

1. *Carbene Chemistry*, 2nd edn., ed. W. Kirmse, Academic Press, New York, 1973; J.F. Harrison , ch. 5, p. 159.

2. a) *Transition Metal Carbene Complexes*, ed. D. Seyferth, Verlag, Weinheim, 1983; P. Hoffman, ch. 4, p. 113; b) T.H. Lowry, K. Schueller Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd. edn., Harper and Row, New York, 1987, ch. 6, p. 517, and references cited therein.

3. *Carbene Chemistry*, 2nd edn., ed. W. Kirmse, Academic Press, New York, 1973; W. Kirmse, ch. 4, p. 129.

4. *Carbene Chemistry*, 2nd edn., ed. W. Kirmse, Academic Press, New York, 1973; W. Kirmse, ch. 3, p. 85.

5. *Carbenes*, eds. R.A. Moss, M. Jones Jr., Wiley, New York, 1973; D. Seyferth, vol. 2, ch. 3, p.101.

6. G.L. Closs, R.A. Moss, *J. Am. Chem. Soc.*, **1964**, *86*, 4042.

7. L. Friedman, H. Schechter, *J. Am. Chem. Soc.*, **1961**, *83*, 3159.

8. W. Kirmse, M. Buschoff, *Chem. Ber.*, **1967**, *100*, 1491.

9. a) G.L. Closs, R.A. Moss, *J. Am. Chem. Soc.*, **1964**, *86*, 4042; b) *Carbenes*, eds. R.A. Moss, M. Jones Jr., W.J. Barron, M.E. Hendrick, M. Jones Jr., Wiley, New York, 1973; R.H. Levin, M.B. Sohn, vol. 1, ch. 1, p. 1; c) V. Franzen, H.I. Joschek, *Ann.*, **1960**, *633*, 7.

10. G.L. Closs, L.E. Closs, *J. Am. Chem. Soc.*, **1961**, *83*, 2015.

11. a) H. Wanzlick, E. Schikova, *Angew. Chem.*, **1960**, *73*, 494; b) E. Chinoporos, *Chem. Rev.*, **1963**, *63*, 253.

12. D.M. Lemal, E.P. Gosselink, S.D. McGregor, *J. Am. Chem. Soc.*, **1966**, *88*, 582.

13. R.J. Crawford, R. Raap, *Can. J. Chem.*, **1965**, *43*, 356.

14. U. Schollkopf, E .Wiscott, *Ann.*, **1966**, *694*, 44.

15. a) G.L. Closs, J.J. Coyle, *J. Am. Chem. Soc.*, **1965**, *87*, 4270; b) *Carbenes*, eds. R.A. Moss, M. Jones Jr., W.J. Barron, M.E. Hendrick, M. Jones Jr., Wiley, New York, 1973; R.A. Moss, vol. 1, ch. 2, p. 153.

16. a) J.C. Horrison, *J. Am. Chem. Soc.*, **1971**, *93*, 4112; b) *Carbene Chemistry*, 2nd edn., ed. W. Kirmse, Academic Press, New York, 1973; W. Kirmse, ch. 8, p. 267.

17. E. Ciganek, *J. Am. Chem. Soc.*, **1966**, *88*, 1979.

18. E.K. Barefield, P.C. McCarter, M.C. Hillhouse, *Organometallics*, **1985**, *4*, 1682.

19. E.O. Fischer, A. Massböl, *Angew. Chem. Int. Ed. Engl.*, **1964**, *3*, 580.

20. *Comprehensive Organic Synthesis*, eds. B.M. Trost, I. Fleming, Pergamon press, Oxford, 1991; R.H. Grubbs, S.H. Pine, vol. 5, ch. 9.3, p. 1115.

21. a) H. Nakatsuji, J. Ushio, S. Han, T. Yonezawa, *J. Am. Chem. Soc.*, **1983**, *105*, 426; b) J. Ushio, H. Nakatsuji, T. Yonezawa, *J. Am. Chem. Soc.*, **1984**, *106*, 5892.

22. W.A. Nugent, R.J. McKinney, R.V. Kasowski, F.A. Van Catledge, *Inorg. Chim. Acta*, **1982**, *65*, L91.

23. a) A. Aguero, J.A. Osborn, *New J. Chem.*, **1982**, *12*, 111; b) *Comprehensive Organic Synthesis*, eds. B.M. Trost, I. Fleming, Pergamon press, Oxford, 1991; P. Helquist, vol. 4.6, p. 951; c) *Advances in Metal-Organic Chemistry*, ed. L.S. Liebeskind, JAI Press, Greenwich, 1989; W.D. Wulff, vol. 1, p. 209.

24. M. Brookhart, W.B. Studabaker, *Chem. Rev.*, **1987**, *87*, 411.

25. J.E. Bäckwall, C. Löfström, S.K. Juntunen, M. Mattson, *Tetrahedron Lett.*, **1993**, *34*, 2007.

26. a) M. Brookhart, J.R. Tucker, G.R. Husk, *J. Am. Chem. Soc.*, **1981**, *103*, 979; b) M. Brookhart, J.R. Tucker, G.R. Husk, *J. Am. Chem. Soc.*, **1983**, *105*, 258.

27. M. Brookhart, J.R. Tucker, G.R. Husk, *J. Am. Chem. Soc.*, **1983**, *105*, 258.

28. a) K.A.M. Kremer, G.H. Kuo, E.J. O'Connor, P. Helquist, R.C. Kerber, *J. Am. Chem. Soc.*, **1982**, *104*, 6119; b) R.S. Iyer, G.H. Kuo, P. Helquist, *J. Org. Chem.*, **1985**, *50*, 5898.

29. C.P. Casey, W.H. Miles, H. Tukada, J.M. O'Connor, *J. Am. Chem. Soc.*, **1982**, *104*, 3761.

30 a) E.O. Fischer, K.H. Dötz, *Chem. Ber.*, **1972**, *105*, 3966; b) K.H. Dötz, E.O. Fischer, *Chem. Ber.*, **1972**, *105*, 1356.

31. C.P. Casey, T.J. Burkhardt, *J. Am. Chem. Soc.*, **1974**, *96*, 7808.

32. C.P. Casey, S.W. Polchinowski, A.J. Schusterman, C.R. Jones, *J. Am. Chem. Soc.*, **1979**, *101*, 7282.

33. a) M. Brookhart, G.O. Nelson, *J. Am. Chem. Soc.*, **1977**, *99*, 6099; b) M. Brookhart, M.B. Humphrey, H.J Kratzer, G.O. Nelson, *J. Am. Chem. Soc.*, **1980**, *102*, 7802.

34. C.P. Casey, A.J. Schusterman, *Organometallics*, **1985**, *4*, 736.

35. W.A. Nugent, J.M. Mayer, *Metal-Ligand Multiple Bonds*, Wiley, New York, 1988, ch. 3, p. 52.

36. a) L.F. Canizzo, R.H. Grubbs, *J. Org. Chem.*, **1985**, *50*, 2386; b) W.A. Nugent, J.M. Mayer, *Metal-Ligand Multiple Bonds*, Wiley, New York, 1988, ch. 6, p. 220.

37. a) S.M. Clift, J. Schwartz, *J. Am. Chem. Soc.*, **1984**, *106*, 8300; b) F.W. Hartner, S.M. Clift, J. Schwartz, *J. Am. Chem. Soc.*, **1983**, *105*, 640.

38. a) G.C. Fu, R.H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 5426; b) R.H. Grubbs, G.C. Fu, X. Fujimara, *J. Org. Chem.*, **1994**, *59*, 4029; c) S.F. Martin, Y. Liao, H.-J. Chen, M. Pätzel, M.N. Ramser, *Tetrahedron Lett.*, **1994**, *35*, 6005; d) G.C. Fu, R.H. Grubbs, *J. Am. Chem. Soc.*, **1992**, *114*, 7324.

39. a) R.R Schrock, R. DePue, J. Feldman, C.J. Schaverien, J.C. Dewan, A.H. Liu, *J. Am. Chem. Soc.*, **1988**, *110*, 1423; b) R.R Schrock, R. DePue, J. Feldman, K.B Yap, W.M. Davis, L.Y Park, M. DiMare, M. Schofield, J. Anhaus, E. Walborsky, E. Evitt, C. Kruger, P. Betz, *Organometallics*, **1990**, *9*, 2262.

40. S.F. Martin, Y. Liao, T. Rien, *Tetrahedron Lett.*, **1994**, *35*, 691.

41. *Prog. in Inorg. Chem.*, ed. S.J. Lippard, Wiley, New York, 1991; J. Feldman, R.R. Schrock, ch. 1, p. 1.

42. A. Aguero, J. Kress, J.A. Osborn, *J. Chem. Soc. Chem. Commun.*, **1986**, 531.

43. A. Aguero, J. Kress, J.A. Osborn, *J. Chem. Soc. Chem. Commun.*, **1985**, 793.

44. R.R. Schrock, *J. Organomet. Chem.*, **1986**, *300*, 249 and references cited therein.

45. F.N. Tebbe, G.W. Parshall, G.S. Reddy, *J. Am. Chem. Soc.*, **1978**, *100*, 3611.

46. a) L.W. Messerle, P. Jennische, R.R. Schrock, G. Stucky, *J. Am. Chem. Soc.*, **1980**, *102*, 6744; b) S.J. McLain, J. Sancho, R.R. Schrock, *J. Am. Chem. Soc.*, **1980**, *102*, 5610; c) J.D. Fellman, R.R. Schrock, G.A. Rupprecht, *J. Am. Chem. Soc.*, **1981**, *101*, 5752.

47. a) R.R. Schrock, J.S. Murdzek, G.C. Bazan, J. Robbins, M. DiMare, M. O'Regan, *J. Am. Chem. Soc.*, **1990**, *112*, 3875; b) H.H. Fox, R.R. Schrock, R. O'Dell, *Organometallics*, **1994**, *13*, 635; c) *Advances in Metal Carbene Chemistry*, ed. U. Schubert, Kluwer, Boston, 1989; J. Feldman, R.T. DePue, C.J. Schaverien, W.M. Davis, R.R. Schrock, p.323.

48. a) R.H. Grubbs, L.R. Gillon, *J. Am. Chem. Soc.*, **1986**, *108*, 733; b) R.R. Schrock, J. Feldman, R.H. Grubbs, L. Canizzo, *Macromolecules*, **1987**, *20*, 1169.

49. For general reviews using group 9-11 metal catalysts see a) M.P. Doyle, *Chem. Rev.*, **1986**, *86*, 919; b) M.P. Doyle, *Acc. Chem. Res.*, **1986**, *19*, 348; c) A. Padwa, K.E. Krumpe, *Tetrahedron*, **1992**, *48*, 5385.

50. a) J.K. Gallos, T.V. Koftis, A.E. Kombis, *J. Chem. Soc. Perkin Trans. 1*, **1994**, 611; b) R.M. Moriarty, J. Kim, L.A. Guo, *Tetrahedron Lett.*, **1993**, *34*, 4129; c) D.J. Fairfax, D.J. Austin, S.L. Xu, A. Padwa, *J. Chem. Soc. Perkin Trans. 1*, **1992**, 2837; d) M. Ochiai, M. Kunishima, S. Tani, Y. Nagao, *J. Am. Chem. Soc.*, **1991**, *113*, 3135.

51. Intramolecular insertions into X-H bonds show preferences for formation of more strained ring sizes in the presence of other C-H bonds. For leading references see a) G.G. Cox, D. Haigh, R.M. Hindley, D.J. Miller, C.J. Moody, *Tetrahedron Lett.*, **1994**, *35*, 3139; b) G.G. Cox, C.J. Moody, D.J. Austin, A. Padwa, *Tetrahedron*, **1993**, *49*, 5109; c) A. Padwa, D.J. Austin, A.T. Price, M.A Simones, M.P. Doyle, M.N. Protopopova, W.R. Winchester, A. Tran, *J. Am. Chem. Soc.*, **1993**, *115*, 8669.

52. a) *Comprehensive Organic Synthesis*, eds. B.M. Trost, I. Fleming, Pergamon press, Oxford, 1991; D.F Taber, vol. 3, ch. 4.2, p. 1045; b) D.F. Taber, M.J. Hennessy,

J.P. Louey, *J. Org. Chem.*, **1992**, *57*, 436; c) N. Ikota, S.D. Young, B. Ganem, *Tetrahedron Lett.*, **1981**, *22*, 4163.

53.   A. Nickon, F. Huang, R. Weglein, K. Matsuo, H. Yagi, *J. Am. Chem. Soc.*, **1974**, *96*, 5264.

54.   a) M.P. Doyle, W.H. Tamblyn, V. Bagheri, *J. Org. Chem.*, **1981**, *46*, 5094; b) M.P. Doyle, J.H. Griffin, D. van Leusen, *J. Org. Chem.*, **1984**, *49*, 1917.

55.   R.G. Salomon, M.F. Salomon, T.R Heyne, *J. Org. Chem.*, **1975**, *40*, 756.

56.   M.P. Doyle, J.H. Griffin, V. Bagheri, R.L. Dorrow, *Organometallics*, **1984**, *3*, 53.

57.   E.J. Roskamp, C.R. Holmquist, *J. Org. Chem.*, **1989**, *54*, 3258.

58.   a) K. Hori, H. Kazuno, K. Nomura, E. Yoshii, *Tetrahedron Lett.*, **1993**, *34*, 2183; b) for related behaviour of diazoacetamides see T. Iida, K. Hori, K. Nomura, *Heterocycles*, **1994**, *38*, 1839.

59.   a) E. Clemmensen, *Chem. Ber.*, **1913**, *46*, 1837; b) E. Clemmensen, *Chem. Ber.*, **1914**, *47*, 681; c) E.L. Martin, *Org. React.*, Wiley, New York, **1942**, *1*, 155; d) E. Vedejs, *Org. React.*, Wiley, New York, **1975**, *22*, 401.

60.   a) H.E. Simmons, R.D. Smith, *J. Am. Chem. Soc.*, **1958**, *80*, 5323; b) H.E. Simmons, R.D. Smith, *J. Am. Chem. Soc.*, **1959**, *81*, 4256; c) for a more detailed review of the developments in organozinc carbenoid chemistry, see W.B. Motherwell, C.J. Nutley, *Contemporary Organic Synthesis*, **1994**, *1*, 219.

61.   This reagent was first prepared by Emschwiller: G.C. Emschwiller, R. Emschwiller, *Seances Acad. Sci.*, **1929**, 155.

62.   a) G. Wittig, A. Schwarzenbach, *Angew. Chem.*, **1959**, *71*, 652; b) G. Wittig, A. Schwarzenbach, *Ann.*, **1961**, *650*, 1; c) G. Wittig, F. Wingler, *Ann.*, **1962**, *656*, 18; d) G. Wittig, F. Wingler, *Chem. Ber.*, **1964**, *97*, 2146; e) G. Wittig, M. Jautelet, *Ann.*, **1967**, *702*, 24.

63.   a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.*, **1966**, 3353; b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron*, **1968**, *24*, 53; c) J. Nishimura, J. Furukawa, N. Kawabata, M. Kitayama, *Tetrahedron*, **1971**, *27*, 1799.

64. a) R.S. Schank, H. Schechter, *J. Org. Chem.*, **1959**, *24*, 1825; b) E. Le Goff, *J. Org. Chem.*, **1964**, *29*, 2048; c) R.J. Rawson, I.T. Harrison, *J. Org. Chem.*, **1970**, *35*, 2057.

65. J.-M. Denis, C. Girard, J.-M. Conia, *Synthesis*, **1972**, 549.

66. E.C. Friedrich, S.E. Lunetta, E.J. Lewis, *J. Org. Chem.*, **1989**, *54*, 2388.

67. E.C. Friedrich, S.E. Lunetta, E.J. Lewis, *J. Org. Chem.*, **1990**, *55*, 2491.

68. K. Takai, T. Kakiuchi, K. Utimoto, *J. Org. Chem.*, **1994**, *59*, 2671.

69. E.C. Friedrich, J.M. Domek, R.Y. Pong, *J. Org. Chem.*, **1985**, *50*, 4640.

70. S. Durandetti, S. Sibille, J. Périchon, *J. Org. Chem.*, **1991**, *56*, 3255.

71. a) S.H. Goh, L.E. Closs, G.L. Closs, *J. Org. Chem.*, **1969**, *34*, 25; b) S.H. Goh, K.C. Chan, H.L. Chong, Aust. J. Chem., **1976**, *29*, 1699.

72. a) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.*, **1968**, 3495; b) J. Nishimura, N. Kawabata, J. Furukawa, *Tetrahedron*, **1969**, *25*, 2647; c) J. Nishimura, J. Furukawa, N. Kawabata, *Bull. Chem. Soc. Jpn.*, **1970**, *43*, 2195; d) J. Nishimura, J. Furukawa, N. Kawabata, H. Koyama, *Bull. Chem. Soc. Jpn.*, **1971**, *44*, 1127.

73. S. Miyano, H. Hashimoto, *Bull. Chem. Soc. Jpn.*, **1973**, *46*, 892.

74. S.E. Denmark, J.P Edwards, *J. Org. Chem.*, **1991**, *56*, 6974.

75. a) S.E. Denmark, J.P. Edwards, S.R. Wilson, *J. Am. Chem. Soc.*, **1991**, *113*, 723; b) S.E. Denmark, J.P. Edwards, S.R. Wilson, *J. Am. Chem. Soc.*, **1992**, *114*, 2592.

76. R.C. Neuman, Jr., *Tetrahedron Lett.*, **1964**, 2541.

77. a) T.H. Hudlicky, B.C. Ranu, S.M. Naqvi, A. Srnak, *J. Org. Chem.*, **1985**, *50*, 1231; b) K.H. Buchel, F.Z. Forte, *Z. Naturforsch.*, **1962**, *17B*, 349; c) H.E. Simmons, T.L. Cairns, S.A. Vladuchick, C.M. Hoiness, *Org. React.*, Wiley, New York, **1973**, *20*, 1.

78. a) Z. Kosarych, T. Cohen, *Tetrahedron Lett.*, **1982**, *23*, 3019; b) A. Thomas, G. Singh, H. Ila, H. Junjappa, *Tetrahedron Lett.*, **1989**, *30*, 3093; c) L.H. Bhat, A. Thomas, H. Ila, H. Junjappa *Tetrahedron*, **1992**, *48*, 10377.

79. W.G. Dauben, G.H. Berezin, *J. Am. Chem. Soc.*, **1963**, *85*, 468.

80. S. Winstein, J. Sonnenberg, *J. Am. Chem. Soc.*, **1961**, *83*, 3235.

81. E.J. Corey, S.G. Reid, A.G. Myers, K.H. Halil, *J. Am. Chem. Soc.*, **1987**, *109*, 918.

82. I. Arai, A. Mori, H. Yamamoto, *J. Am. Chem. Soc.*, **1985**, *107*, 8254.

83. H. Takahashi, M. Yoshikoshi, M. Ohno, S. Kobayashi, *Tetrahedron Lett.*, **1992**, *33*, 2575.

84. W. Steinkopf, A. Wolfram, *Ann.*, **1923**, *430*, 113.

85. T. Nakabayashi, *J. Am. Chem. Soc.*, **1960**, *82*, 3900, 3906 and 3909.

86. J.H. Brewster, *J. Am. Chem. Soc.*, **1954**, *76*, 6361 and 6364.

87. G.A. Risinger, E.W. Mach, K.W. Barnett, *Chem. Ind.*, **1965**, 679.

88. E. Müller, G. Fiedler, H. Huber, B. Narr, H. Suhr, K. Witte, *Z. Naturforsch.*, **1963**, *18B*, 5.

89. J. Burdon, R.C. Price, *J. Chem. Soc. Chem. Commun.*, **1986**, 893.

90. a) I. Elphimoff-Felkin, P. Sarda, *J. Chem. Soc. Chem. Commun.*, **1969**, 1065; b) I. Elphimoff-Felkin, P. Sarda, *Tetrahedron*, **1975**, *31*, 2785.

91. J.C. Bryan, J.M. Mayer, *J. Am. Chem. Soc.*, **1987**, *99*, 7213.

92. R. Imwinkelried, L.S. Hegedus, *Organometallics*, **1988**, *7*, 702.

93. a) R.M. Vargas, R.D. Theys, M.M. Hossain, *J. Am. Chem. Soc.*, **1992**, *114*, 777; b) R.M. Vargas, R.D. Theys, M.M. Hossain, *Inorg. Chim. Acta*, **1994**, *223*, 159.

94. J. Furukawa, N. Kawabata, *Advan. Organomet. Chem.*, **1974**, *12*, 83.

95. S.-C. Chang, R.H. Hauge, Z.H. Kafafi, J.L. Margrave, W.E. Billups, *J. Chem. Soc. Chem. Commun.*, **1987**, 1682.

96. T.P. Hamilton, H.F. Schaefer III, *J. Chem. Soc. Chem. Commun.*, **1991**, 621.

97. W.B. Motherwell, *J. Chem. Soc. Chem. Commun.*, **1973**, 935.

98. E.J. Corey, S.G. Pyne, *Tetrahedron Lett.*, **1983**, *24*, 2821.

99. J.-H. So, M.-K. Park, P. Boudjouk, *J. Org. Chem.*, **1988**, *53*, 5871.

100. A.K. Banerjee, M.C. Sulbaran de Carrasco, C.S.V. Frydrych-Houge, W.B. Motherwell, *J. Chem. Soc. Chem. Commun.*, **1986**, 1803.

101. a) J.E. McMurray, *Acc. Chem. Res.*, **1983**, *16*, 405; b) J.E. McMurray, *Chem. Rev.*, **1989**, *89*, 1513.

102. C.A.M. Afonso, W.B. Motherwell, D.M. O'Shea, L.R. Roberts, *Tetrahedron Lett.*, **1992**, *33*, 3899.

103. J. Adams, D.M. Spero, *Tetrahedron*, **1991**, *47*, 1765.

104. A. Padwa, R.L. Chinn, S.F. Hornbuckle, L. Zhi, *Tetrahedron Lett.*, **1989**, 301.

105. A. Padwa, L. Zhi, *J. Am. Chem. Soc.*, **1990**, *112*, 2037.

106. W.B. Motherwell, L.R. Roberts, *J. Chem. Soc. Chem. Commun.*, **1992**, 1582.

107. L.R. Roberts, PhD Thesis, University of London, 1992.

108. K.A.M. Kremer, P. Helquist, *J. Organomet. Chem.*, **1985**, *285*, 231.

109. Z. Hou, S. Takamine, O. Aoki, H. Shirahashi, J. Fujiwara, H. Taniguchi, *J. Org. Chem.*, **1988**, *53*, 6077.

110. P.K. Freeman, K.E. Swenson, *J. Org. Chem.*, **1982**, *47*, 2033.

111. a) Y. Yamamoto, S.-I. Murahashi, I. Moritani, *Tetrahedron*, **1975**, *31*, 2663; b) L.S. Press, H. Schechter, *J. Am. Chem. Soc.*, **1979**, *101*, 509; c) A. Nickon, J.K. Bronfenbrenner, *J. Am. Chem. Soc.*, **1982**, *104*, 2022.

112. C.P. Casey, L.D. Albin, T.J. Burkhardt, *J. Am. Chem. Soc.*, **1977**, *99*, 436.

113. C.P. Casey, W.H. Miles, H. Tukada, *J. Am. Chem. Soc.*, **1985**, *107*, 2924.

114. H.E. Simmons, E.P. Blanchard, R.D. Smith, *J. Am. Chem. Soc.*, **1964**, *86*, 1347.

115. a) L. Friedman, H. Schechter, *J. Am. Chem. Soc.*, **1959**, *81*, 5512; b) R.H. Shapiro, *Org. React.*, **1976**, *23*, 405.

116. a) P. Hodge, M.N. Khan, *J. Chem. Soc. Perkin Trans 1*, **1975**, 809; b) W.S. Zhou, H.Q. Zhou, G. Roussi, Z.Q. Wang, *Synthesis*, **1990**, 1073; c) W.S. Zhou, H.Q. Zhou, G. Roussi, Z.Q. Wang, *J. Chem. Soc. Perkin Trans 1*, **1990**, 2281; d) W.S. Zhou, B. Jiang, X.F. Pan, *Tetrahedron*, **1990**, *46*, 3173; e) Z.W. Shan, B. Jiang, X.F. Pan, *J. Chem. Soc. Chem. Commun.*, **1989**, 612.

117. *The Chemistry of Functional Groups*, Supplement D, pt. 2, eds. S. Patai, Z. Rappoport, Wiley, New York, **1983**; G. Baciochi, p. 1173; For a Ni^0 mediated elimination see a) S. Jeropoulos, E.H. Smith, *J. Chem. Soc. Chem. Commun.*, **1986**, 1621; b) M.C. Hennington, S. Jeropoulos, E.H. Smith, *J. Org. Chem.*, **1989**, *54*, 3015.

118. B. Singaram, M.V. Rangaishevni, H.C. Brown, C.T. Goralski, D.L. Hasha, *J. Org. Chem.*, **1991**, *56*, 1543.

119. R.M. Adlington, A.G.M. Barrett, *Acc. Chem. Res.*, **1983**, *16*, 53.

120. *The Chemistry of the Organic Silicon Compounds*, pt. 2, eds. S. Patai, Z. Rappoport, Wiley, Chichester, 1989; G. Raabe, J. Michl, ch. 17, p. 1015.

121. C.L. Smith, J. Arnett, J. Ezike, *J. Chem. Soc. Chem. Commun.*, **1980**, 653.

122. D.P.N. Satchell, J.L. Wardell, *J. Chem. Soc.*, **1964**, 4296; this order of Lewis acid strength is reversed in acetone: $ZnBr_2 > ZnI_2 > ZnCl_2$; see D.P.N. Satchell, R.S. Satchell, *Trans. Faraday Soc.*, **1965**, *61*, 1118.

123. B. Müller, M. Ruf, H. Vahrenkampf, *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 2089.

124. C.A.M. Afonso, W.B. Motherwell, L.R. Roberts, *Tetrahedron Lett.*, **1992**, *33*, 3367.

125. B.H. Lipschutz, R.S. Wilhelm, D.M. Floyd, *J. Am. Chem. Soc.*, **1981**, *103*, 7672.

126. For the reduction of sulfoxides to thioethers with zinc/chlorotrimethylsilane in THF see A.H. Schmidt, M. Russ, *Chem. Ber.*, **1981**, *114*, 822.

127. G.A. Olah, A. Husain, B.P. Singh, A.K. Mehrotra, *J. Org. Chem.*, **1983**, *48*, 3667.

128. J. March, *Advanced Organic Chemistry*, Wiley, New York, 1985, 3rd edn., ch. 10, p. 251.

129. a) S.W. Smith, M.S. Newman, *J. Am. Chem. Soc.*, **1968**, *90*, 1249; b) R.M. Hahn, C.S. Hudson, *J. Am. Chem. Soc.*, **1944**, *66*, 1909; c) S.A. Barker, E.D. Bourne, *Advan. Carbohydrate Chem.*, **1952**, *7*, 137.

130. a) D.F. DeTar, *J. Am. Chem. Soc.*, **1980**, *102*, 4505; b) A.J. Kirby, *Advan. Phys. Org. Chem.*, **1980**, *17*, 208; c) E.L. Eliel, *Stereochemistry of Carbon Compounds*, Mc Graw-Hill, 1962, p. 197-202.

131. M.S. Newman, R.S. Harper Jr., *J. Am. Chem. Soc.*, **1958**, *80*, 6350.

132. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983, ch. 2, p. 4.

133. T.H. Fife, L.K. Jao, *J. Org. Chem.*, **1965**, *30*, 1492.

134. Y. Guidon, R. Fortin, C. Yoakim, J.W. Gillard, *Tetrahedron Lett.*, **1984**, *25*, 4717.

135. W.A. Nugent, J.M. Mayer, *Metal-Ligand Multiple Bonds*, Wiley, New York, 1988, ch. 1, p. 1, and references cited therein.

136. M. Brookhart, S.E. Kegley, G.R. Husk, *Organometallics*, **1984**, *3*, 650.

137. E. Wenkert, M.E. Alonso, B.L. Buckwalter, J.K. Chou, *J. Am. Chem. Soc.*, **1977**, *99*, 4778.

138. I. Rhu, T. Aya, S. Otani, S. Murai, N. Soneda, *J. Organomet. Chem.*, **1987**, *321*, 279.

139. G.M. Rubottom, M. Lopez, *J. Org. Chem.*, **1973**, *38*, 2097.

140. P. Knochel and R.D. Singer, *Chem. Rev.*, **1993**, *93*, 2217.

141. a) P. Knochel, M.J. Rozema, M.C.P. Yeh, *J. Am. Chem. Soc.*, **1989**, *111*, 6474; b) P. Knochel, T.-S. Chou, H.G. Chen, M.C.P. Yeh, M.J. Rozema, *J. Org. Chem.*, **1989**, *54*, 5202.

142. K. Takai, T. Kakiuchi, Y. Kataoaka, K. Utimoto, *J. Org. Chem.*, **1994**, *59*, 2668.

143. *Dictionary of Steroids*, eds. R.A. Hill, D.N. Kirk, H.J. Malkin, G.M. Murphy, Chapman and Hall, 1991, p.145.

144. L. Caglioti, *Tetrahedron*, **1963**, *19*, 1127.

145. a) *Dictionary of Steroids*, eds. R.A. Hill, D.N. Kirk, H.J. Malkin, G.M. Murphy, Chapman and Hall, 1991, p.149; b) D.N. Jones, A.C.F Edwards, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 459.

146. *Dictionary of Steroids*, Chapman and Hall, 1991, eds. R.A. Hill, D.N. Kirk, H.J. Malkin, G.M. Murphy, p.150.

147. R. Damann, M. Brown, D. Seebach, *Helv. Chim. Acta*, **1976**, *59*, 2821.

148. T. Sakai, K. Miyata, M. Utaka, A. Takeda, *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 1063.

149. C.G. Overberger, C. Yaroslavsky, *Tetrahedron Lett.*, **1965**, 4395.

150. *Dictionary of Organic Compounds*, 5th edn., ed. J. Buckingham, Chapman and Hall, New York, 1982, vol. 3, 2895.

151. *Dictionary of Organic Compounds*, 5th edn., ed. J. Buckingham, Chapman and Hall, New York, 1982, vol. 3, p. 2898.

152. G.L. Larson, I. Montes de Lopez-Cepero, L. Rodriguez Mieles, *Org. Synth.*, **1989**, *67*, 125.

153. W.E. Parham, M.E. Kalinis, D.R. Theissen, *J. Org. Chem.*, **1962**, *27*, 721.

154. G. Mann, M. Muhlstadt, J. Braband, E. Döring, *Tetrahedron*, **1967**, *23*, 3393

155. *Dictionary of Organic Compounds*, 5th edn., ed. J. Buckingham, Chapman and Hall, New York, 1982, vol. 4, p.2552.

156. S.K. Henderson, A. Witchwoot, W.W. Nawar, *J. Am. Oil Chem. Soc.*, **1980**, *57*, 409.

157. P. Gaubert, R.P. Linstead, H.N. Rydon, *J. Chem. Soc.*, **1937**, 1971.

158. *Dictionary of Organic Compounds*, 4th edn., eds. J.R.A Pollock, R. Stevens, Chapman and Hall, New York, 1965, vol. 4, p. 2525

159. S. Tsuboi, X.H. Wu, S. Maeda, S. Ono, A. Kuroda, K. Kuroda, A. Takeda, *Bull. Chem. Soc. Jpn.*, **1987**, *69*, 1103.

160. *Dictionary of Organic Compounds*, 4th edn., eds. J.R.A Pollock, R. Stevens, Chapman and Hall, New York, 1965, Vol. 4, p. 2525

161. T. Izawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 555.

162. K. Heidig, L. Lex, *J. Chem. Soc. Perkin Trans 1*, **1986**, 1431.

163. E.J. Corey, M. Jautelat, *Tetrahedron Lett.*, **1968**, 5787

164. *Dictionary of Organic Compounds*, 4th edn., eds. J.R.A Pollock, R. Stevens, Chapman and Hall, New York, 1965, Vol. 3, p1591.

165. K.C. Nicolau, S.P. Seitz, M.R. Pavia, N.A. Petasis, *J. Org. Chem.*, **1979**, *44*, 4011.

166. C.R Noller, R. Adams, *J. Am. Chem. Soc.*, **1926**, *48*, 1074.

167. R.R. Mod, F.C. Magne, E.L. Skau, *J. Am. Oil Chem. Soc.*, **1967**, *44*, 235.

168. T. Sato, T. Kumagawa, A. Sugimoto, K. Yamakawa, *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 301.

169. A. Bury, H.A. Earl, C.J.M. Stirling, *J. Chem. Soc. Perkin Trans. 2*, **1987**, *9*, 1281.

170. W.J. Baumann, E.W. Schupp, J.T. Lin, *Biochemistry*, **1975**, *14*, 841.1

171. G. Bellucci, G. Berti, F. Maroni, A. Marsili, *Tetrahedron*, **1970**, *26*, 4627.

172. E.L. Eliel, R.G. Haber, *J. Org. Chem.*, **1959**, *24*, 143.

173. R. Caputo, C. Ferreri, G. Palumbo, *Synthesis*, **1987**, 386.

174. K. Furata, T. Nagata, H. Yamamoto, *Tetrahedron Lett.*, **1988**, *29*, 2215.

175. a) *Chem. Abs.*, **1967**, *66*, 3609, 37850r; b) K. Kulka, *Perfum. Essent. Oil Reac.* **1966**, *57*, 427.

176. A.P. Johnson, A. Pelter, *J. Chem. Soc.*, **1964**, 520.

177. A.C. Cope, J.K Hecht, *J. Am. Chem. Soc.*, **1962**, *84*, 4872.

178. *Dictionary of Organic Compounds*, 5th edn., ed. J. Buckingham, Chapman and Hall, New York, 1982, vol. 4 , p. 4381.

179. G.K. Cooper, L.J. Dolby, *Tetrahedron Lett.*, **1976**, 4675.

180. C. Xu, Z. Chen, *Tetrahedron Lett.*, **1991**, *32*, 2933

181. J. Muzart, P. Pale, J.P. Pete, A. Riahi, *Bull. Chim. Soc. Fr.*, **1988**, 731

182. P. Cazeau, F. Moulines, O Laporte, F. Duboudin, *J. Organomet. Chem.*, **1980**, *201*, C9.

183. J. Dugonges, A. Ekouya, R. Calas, N. Duffaut, *J. Organomet. Chem.*, **1975**, *87*, 151.

184. *Dictionary of Organic Compounds*, 4th edn., eds. J.R.A Pollock, R. Stevens, Chapman and Hall, New York, 1965, vol. 1, p. 247

185. D.E. Appelquist, R.D. Gdanski, *J. Org. Chem.*, **1981**, *46*, 2502.

Corrigenda

p. 8   line 13   "Caproate" should read "Caprolactamate"

p. 11   line 2   "us" should read "is"

p. 26   Scheme 1.14.b   should be drawn as
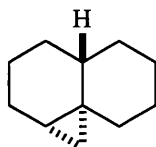
p. 34   line 10   "acetates" should read "acetate"

p. 45   line 13   "surface by" should read "surface followed by"

p. 49   line 11   "Chlorotrimethylsilane" should read "chlorotrimethylsilane"

p. 50   scheme 1.46   should be drawn as
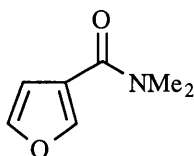
p. 72   Scheme 2.20   compounds (58) and (61) should be drawn respectively as
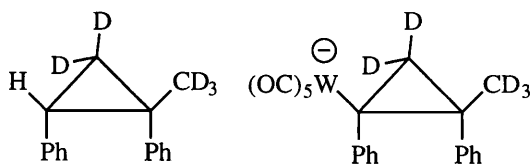
p. 85   line 6   "trimeric could" should read "trimeric iodide could"

p. 137   line 2   "*trans cis*" should read "*cis*"

p. 137   line 18   "pent-2-ene" should read "pent-1-ene"

p. 154   line 17   "(NaCl/KBr disc, thin film/neat)" should read "(NaCl, thin film), 3076, 2979, 2928, 2857, 1735, 1641, 1465, 1419, 1374, 1302, 1252, 1180, 1115, 1034, 995, 910, 860"

p. 161   line 3   "amalgam (490 mg, 6.9 mmol, 10 eq.)," should read "amalgam (490 mg, 6.9 mmol, 10 eq.) and zinc chloride (203 mg, 1.50 mmol, 6 eq.),"

p. 166, 167   compound (145) should be named **2-(2-Phenylethyl)-pent-3-enenitrile**

p. 167   line 3   "575 ml, 6.65. mol" should read "575 µl, 6.65 mmol"

p. 168, 169   compound (95) should be named **2-(2-Phenylethyl)-but-3-enenitrile**

p. 193   line 15   "610 ml" should read "610 µl"

p. 202   compound (116) should be named **3-(4-Methylbenzenesulfonyl)-prop-1-ene**

p. 113   line 18   "choride" should read "chloride"

239