

CYCLOPENTANE ANNULATION STUDIES
AND THEIR APPLICATION IN THE POLYQUINANE AREA

a thesis presented by

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ABSTRACT

This thesis is divided into two parts. In the initial review section, the preparation and selected reactions of alkylidene- and vinylidene- cyclopropanes are surveyed.

The second section describes endeavours directed towards the development of new approaches to the construction of five membered carbocycles, with a view to their application to polyquinane sesquiterpenoid synthesis. The first approaches explored utilised addition of an unsaturated three carbon atom unit to an olefin, followed by elaboration to a penultimate 1-vinyl-1-cyclopropanol precursor for thermal rearrangement. As anticipated, α -alkoxy allylic carbenes were insufficiently reactive to provide convenient access to the required cyclopropanols. Methods for oxidative allylic transposition of readily available alkylidenecyclopropanes were studied. Thus, three component condensation of cyclohexene with 2-phenylseleno-cyclohexanone and diethyl diazomethyl phosphonate under basic conditions furnished a suitable precursor for [2,3] sigmatropic rearrangement of the derived selenoxide. The scope and generality of this strategy was investigated with a range of substrates, and found to suffer from disadvantages of competing ketone enolisation, facile allylic phenylselenide rearrangement, and over-oxidation to afford oxaspiropentanes. Alternative

strategies employing singlet oxygen gave products of radical cleavage.

In an alternative approach cyclopropyl phosphonates, prepared by efficient copper(I) catalysed decomposition of diethyl diazomethyl phosphonate in the presence of electron rich olefins, were used in a Wadsworth-Emmons reaction to give (diphenylmethylene)cyclopropanes of diverse substitution pattern. Further elaboration provided precursors for the first intramolecular variant of a palladium(0) catalysed $[2\pi + 2\sigma]$ cyclisation to afford substituted bicyclo[3.3.0]octanes in high yield. Nickel(0) catalysed reaction gave different products including a low yield of a novel intramolecular Diels-Alder adduct.

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I also applaud the contributions, of incalculable value, made by my proof readers Willie, Dennis, Jerry, Tony, Matt and John, and praise their patience, stamina and thoroughness, and by Miss D S Dobson whose sterling efforts transformed my hieroglyphics into type.

I am particularly indebted to colleagues past and present in the Barton, Whiffen, Harwood and Perkin Laboratories for their friendship, wit and erudition which have made these years all the more enjoyable.

TO MY PARENTS

ABBREVIATIONS

AN	-	Acrylonitrile
<i>n</i> -BuLi	-	<i>n</i> -Butyllithium
Bu	-	<i>n</i> -butyl
<i>t</i> -BuLi	-	<i>t</i> -Butyllithium
Bz	-	Benzyl
COD	-	Cyclooctadienyl-
DBA	-	Dibenzylideneacetone
DBU	-	Diazobicyclo[5.4.0]undec-7-ene
DCM	-	Dichloromethane
DHP	-	3,4-Dihydro-2H-pyran
DAMP	-	Diethyl Diazomethyl Phosphonate
DMAP	-	<i>N,N</i> -Dimethyl-4-aminopyridine
DME	-	1,2-Dimethoxyethane
DMF	-	<i>N,N</i> -Dimethylformamide
DMSO	-	Dimethylsulphoxide
Et	-	Ethyl
EtO	-	Ethoxy
eq	-	Equivalents
H.P.L.C	-	High performance liquid chromatography

KOBu ^t	-	Potassium <u>t</u> -Butoxide
LDA	-	Lithium diisopropylamide
mCPBA	-	<i>m</i> -Chloroperbenzoic acid
Me	-	Methyl
MeO	-	Methoxy
Ms	-	Methanesulphonyl (mesyl)
n.m.r	-	Nuclear magnetic resonance
n.O.e	-	Nuclear Overhauser effect
Ph	-	Phenyl
PLC	-	Preparative layer chromatography
PPTS	-	Pyridinium <i>p</i> -toluenesulphonate
<u>i</u> Pr	-	isopropyl
r.t	-	room temperature
TBAF	-	Tetra- <i>n</i> -butylammonium fluoride
TMEDA	-	<i>N,N,N',N'</i> -Tetramethylethylenediamine
Tf	-	Trifluoromethanesulphonate (triflate)
THF	-	Tetrahydrofuran
t.l.c	-	Thin layer chromatography
TMS	-	Trimethylsilyl
Trisyl	-	2,4,6-Triisopropylbenzenesulphonyl
Ts	-	<i>p</i> -Toluenesulphonyl- (tosyl)

CONTENTS

ABSTRACT	2
ACKNOWLEDGEMENTS	4
ABBREVIATIONS	6
A REVIEW OF THE PREPARATION AND REACTIONS OF ALKYLIDENE CYCLOPROPANES	10
REVIEW REFERENCES	110
RESULTS AND DISCUSSION	123
INTRODUCTION	124
1.0 1-VINYL-1-CYCLOPROPANOLS AS IMPORTANT PRECURSORS TO CYCLOPENTANOIDS; A DIRECT APPROACH	126
2.0 REARRANGEMENT OF ALLYL SELENOXIDES	137
2.1 Preparation of Diethyl diazomethyl phosphonate	139
2.2 Preparation and reaction of (Phenylselenoalkylidene)cyclopropanes	141
3.0 SINGLET OXYGEN ENE REACTIONS	157
Radical allylic oxidation	162
4.0 THE SYNTHESIS OF POLYQUINANE SKELETONS BY APPLICATION OF $[2\sigma + 2\pi]$ TRANSITION METAL CATALYSED CYCLOCODIMERISATION OF ALKYLIDENECYCLOPROPANES WITH OLEFINS AND ACETYLENES	165
4.1 A Wadsworth-Emmons approach to (Diphenylmethylene)cyclopropanes	167
4.2 A model approach to linear triquinanes	174

4.2.1	Synthesis of the (Diphenylmethylene)cyclopropane precursor (82)	174
4.2.2	The palladium(0) promoted cyclisation reaction	185
4.2.3	The nickel(0) promoted reaction	200
4.3.	An approach to angular triquinanes	203
4.3.1	Synthesis of the (Diphenylmethylene)cyclopropane precursor (92)	206
4.3.2	Synthesis of methylenecyclopropane precursor (93)	212
	PERSPECTIVES AND CONCLUSION	215
	APPENDIX X- ray data and selected n.m.r spectra	218
	EXPERIMENTAL	223
	REFERENCES	309

PREPARATION AND REACTIONS
OF ALKYLIDENE CYCLOPROPANES

REVIEW CONTENTS

	INTRODUCTION	14
1.0	<u>PART 1 : METHODS OF PREPARATION</u>	15
1.1	Wittig reaction	15
1.2	Wadsworth-Emmons reaction	17
1.3	Petersen olefination	18
1.4	From α -halo- α -lithiocyclopropanes	19
1.5	From α -lithio- α -phenylthiocyclopropanes	20
1.6	From α -lithio- α -selenocyclopropanes	21
1.7	1-Seleno-1-vinyl-cyclopropanes	22
1.8	Singlet oxygen ene reaction	24
1.9	β -Elimination strategies	25
1.10	1,4-Elimination strategies	30
1.11	Rearrangement of cyclopropenes	31
1.12	Ring closure as the final step	35
1.13	Enamines and enol ethers	39
1.14	Cyclobutylidene rearrangement	41
1.15	Carbene addition to allenes	41
1.15.1	Simmons Smith reagents	41
1.15.2	Diazoalkanes	45
1.15.3	Dihalocarbenes	46
1.16	Decomposition of alkylidene pyrazolines	47
1.17	Alkylidene carbene insertions	49
1.17.1	N-Nitroso-oxazolidones	51
1.17.2	Vinylamines	51
1.17.3	Diazoethenes (Diazomethyl phosphonates)	51

1.17.4	Tosylazo alkenes	52
1.17.5	α -Bromo-vinylmercury bromides	52
1.17.6	α -Halo-vinylsilanes	53
1.17.7	Vinyl-trifluoromethane sulphonates	55
1.17.8	Halides	56
1.17.8a	Acetylenic	56
1.17.8b	Primary vinyl halides	57
1.18	Alkylidene cyclopropane rearrangement	58
2.0	<u>PART 2 : REACTIONS</u>	59
2.1	Palladium(0) & Nickel(0) catalysed [2 π + 2 π] & [2 π + 2 σ] reactions	59
2.1.1	Nickel catalysed [2 π + 2 σ] reactions	59
2.1.2	Palladium catalysed [2 π + 2 σ] reactions	67
2.1.3	[2 π + 2 π] reactions & cyclodimerisation	70
2.2	Chloropalladation of methylenecyclopropanes	73
2.3	Some other transition metal chemistry	79
2.4	Electrocyclic reactions	84
2.4.1	[4 π + 2 π] reactions	84
2.4.1a	as dienes	84
2.4.1b	as dienophiles	86
2.4.2	[2 π + 2 π] reactions	87
2.4.2a	Dimerisation	87
2.4.2b	Cross dimerisation	89
2.4.3	[3 + 2] cycloadditions	90
2.4.4	Cope rearrangements	92
2.5	Intramolecular nucleophilic attack	93
2.5.1	Alkylidenecyclopropanes	93

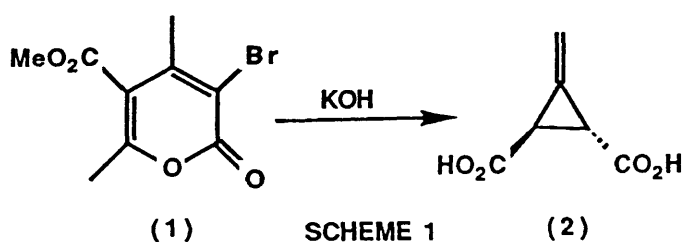
2.5.2	Alkenylidenecyclopropanes	95
2.6	Electrophilic additions	98
2.6.1	Epoxidation	98
2.6.2	Carbene insertion	99
2.7	Singlet oxygen ene reactions	100
2.8	Nucleophilic attack on the olefin	102
2.9	Reducing agents	103
2.9.1	Alkene reduction	103
2.9.1a	catalytic hydrogenation	103
2.9.1b	metal hydrides	104
2.9.1c	boranes	105
2.9.1d	dissolving metal systems	106
2.9.2	Hydrodehalogenation	106
2.10	Metallation	107
2.11	Rearrangements	108
	CONCLUSION	109

PREPARATION AND REACTIONS OF ALKYLIDENE

CYCLOPROPANES

INTRODUCTION

Since 1893 when Feist's Acid (2), arising from the alkaline hydrolysis of pyrone (1) was first isolated,¹ there has been active interest in the preparation and reactions of alkylidene cyclopropanes.



The novel rearrangements which occur in such systems have stimulated considerable research efforts amongst physical organic chemists.² The presence of the structure in a variety of compounds possessing important biological activity³⁻⁵ has spurred development of new synthetic strategies to this structural unit. The utility of these versatile synthetic intermediates has recently been explored.^{6a,7-16,17d}

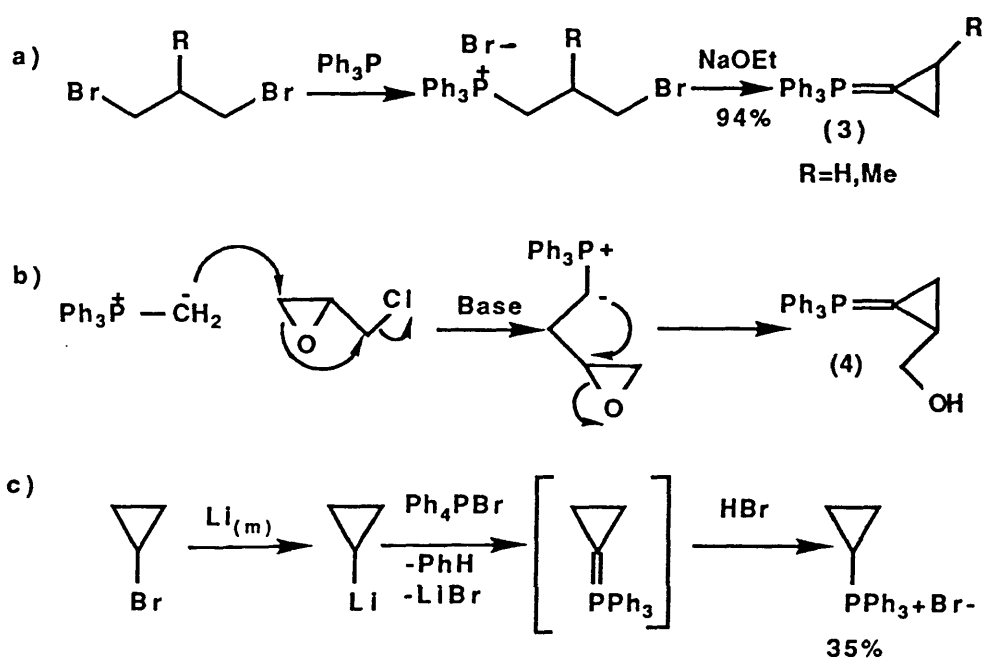
This review covers the synthetic approaches to these systems, and some of their more synthetically useful transformations. Detailed consideration of theoretical aspects associated with the reactions is necessarily beyond its scope; many of the mechanistic aspects are not as yet fully understood.

1.0 PART 1 : METHODS OF PREPARATION

1.1) Wittig Reaction

Wittig methodology has been extensively employed, due to the ready availability of cyclopropyltriphenylphosphorane¹⁸ (3),

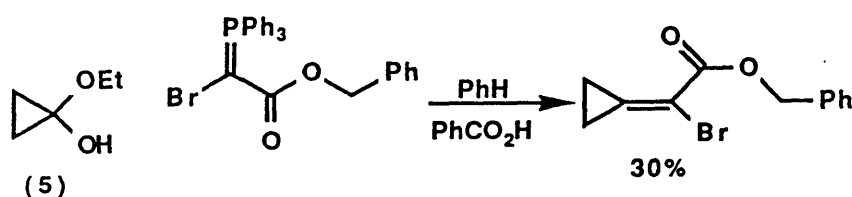
(Scheme 2a).



SCHEME 2

These ylids react with a diversity of aldehydes and ketones,^{6,18} although yields are sometimes less than spectacular. Cyclopropyl phosphonates bearing ring substituents are not generally readily available. 2-Hydroxymethylcyclopropyltriphenylphosphorane (4) (Scheme 2b) was prepared by the action of methylenetriphenyl phosphorane on epichlorohydrin.¹⁹ The Arbuzov approach from cyclopropyl bromide was demonstrably unsuccessful.²⁰ Longone and Doyle, however, circumvented the problem by application of methodology developed by Seyferth^{18e} (Scheme 2c). The ready

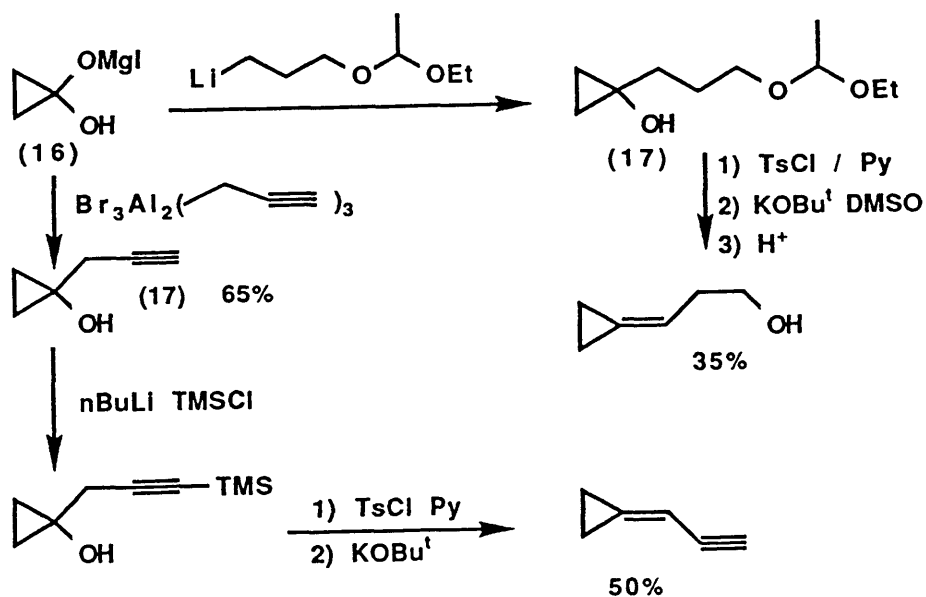
availability of monobromocyclopropanes by dehalogenation of the corresponding gem-dibromocyclopropanes, in turn accessible from olefins, should allow preparation of substituted phosphoranes. This possibility does not seem to have been exploited. Cyclopropanones are unstable entities, and are therefore unsuitable for the alternative Wittig disconnection. Cyclopropanone hemiacetals, however, are known to act as cyclopropanone equivalents.²¹ In the presence of catalytic benzoic acid, a phosphorane has been induced to react with cyclopropanone hemiacetal (5), albeit in modest yield,³ (Scheme 3).



SCHEME 3

Benzyl-bromoacetate formation was a competing side reaction which could be partially suppressed by azeotropic removal of the ethanol generated. Other examples of this reaction have since been reported to proceed in better yield (40-87%).²² The magnesium salt of cyclopropanone hemiacetal, prepared by reaction of the parent with an equivalent of Grignard reagent, also reacts with phosphoranes^{21,23} bearing aromatic substituents. However, the scope is somewhat limited by the mediocrity of the yields (34-51%), and the fact that the range of the compatible phosphoranes is narrow. Electron withdrawing aromatic substituents are not tolerated, whilst cyclohexyltriphenylphosphorane was reported to undergo betaine formation, but

surprisingly did not proceed to the olefin.²³ The rationalisation for these observations is unclear. Hemiacetals are available by reaction of ketenes with carbenes in the presence of an alcohol to trap the cyclopropanone in situ. Ring substituents are therefore more easily introduced than is the case with cyclopropyl phosphoranes. In a related sequence, magnesium salts of cyclopropanone hemiacetals (16) reacted with organo-lithium and organo-alane reagents to give 1-alkyl-1-cyclopropanols (17). The corresponding tosylates β -eliminated with potassium *t*-butoxide to give alkylidene cyclopropanes^{23a} (Scheme 4).



SCHEME 4

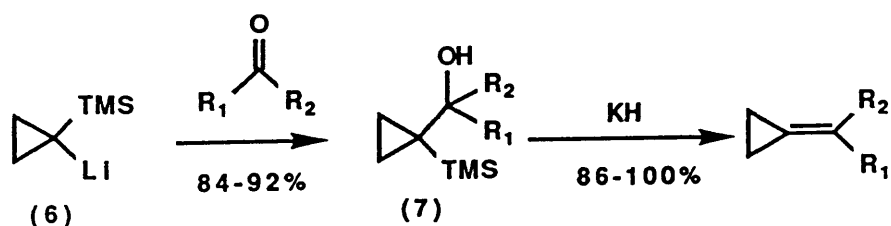
1.2) Wadsworth-Emmons Reaction

Application of the Wadsworth-Emmons reaction to vinylidene

cyclopropanes has received much less attention. The magnesium salt of cyclopropanone hemiacetal reacted with sodium triethylphosphonoacetate to give the Wadsworth-Emmons adduct in 10% yield, together with ethyl propanoate derived from ring cleavage.²³ Surprisingly, although cyclopropyl phosphonates have been known since 1971²⁴, only recently has their reactivity under Wadsworth-Emmons conditions been investigated.²⁵ Reactions with aldehydes gave high yields of β -hydroxy phosphonates in many cases.^{25a} Oxaphosphetane formation and decomposition was observed to be slow in the case of the lithium salt of the betaine, but was achieved by formation of the sodium salt with sodium hydride-18-crown-6 in THF^{25a} or, better, with sodium hydride in DMF at 80°C.^{25b} Whilst aldehydes^{25a} and benzophenone^{25b} give good results, acetone^{25a} apparently does not react. The requisite cyclopropyl phosphonates are available from olefins either by dibromocarbene insertion followed by Arbuzov reaction and debromination,^{25a,c} or more directly and in superior yield by a modification^{25b} of the copper catalysed insertion of dialkyldiazomethyl phosphonates pioneered by Seyferth.²⁴ Diverse ring substitution patterns are therefore readily available. Cyclopropyl phosphonates have also been prepared by reaction of phosphinyl-substituted sulphonium ylids with α,β -unsaturated esters.

1.3) Petersen Olefination

Cyclopropyl Petersen reagents have also been recently explored.^{26,27} α -Lithio- α -trimethylsilylcyclopropanes (6) (Scheme 5) gave β -hydroxysilanes (7) with aldehydes or ketones in good yield.



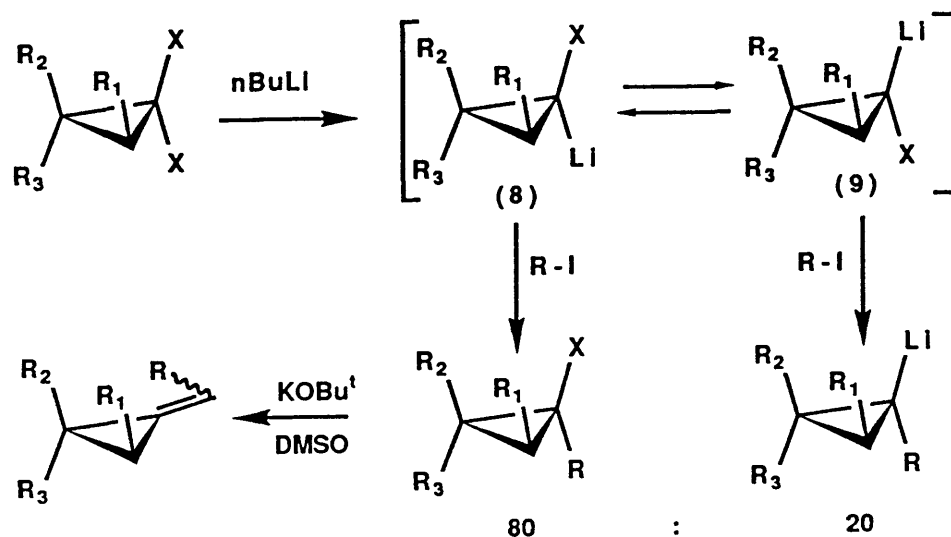
SCHEME 5

The adducts (7) are derived from the more thermodynamically stable cyclopropyl anion. In common with cyclopropyl phosphonates, the anions are not configurationally stable at -95°C . Treatment with potassium hydride in THF smoothly effected β -elimination. In a number of cases, the β -elimination unaccountably failed. The problem was circumvented by preparation of the corresponding β -chloride with thionyl chloride, followed by fluoride induced β -elimination. Olefin stereochemistry was governed by the usual rules .

1.4) α -Halo- α -Lithio Cyclopropanes

Gem-dihalocyclopropanes are readily lithiated^{28,29} at the less hindered halide (8). Although initial lithiation is stereoselective, isomerisation to the more thermodynamically stable isomer (9), occurs rapidly with bromides, but is slower with the corresponding chlorides. Stereoselective monoalkylation occurs upon treatment with alkyl iodides in 74-90% yield. Dehydrohalogenation, effected by potassium *t*-butoxide in DMSO, proceeds in 48-87% yield (Scheme 6). Where the alkylating agent possesses a β -hydrogen, dehydroiodination is a competing reaction, which is suppressed by the addition of copper (I) salts.

The active species under these conditions is presumably a cuprate.

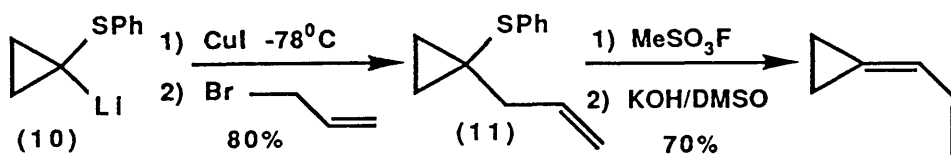


SCHEME 6

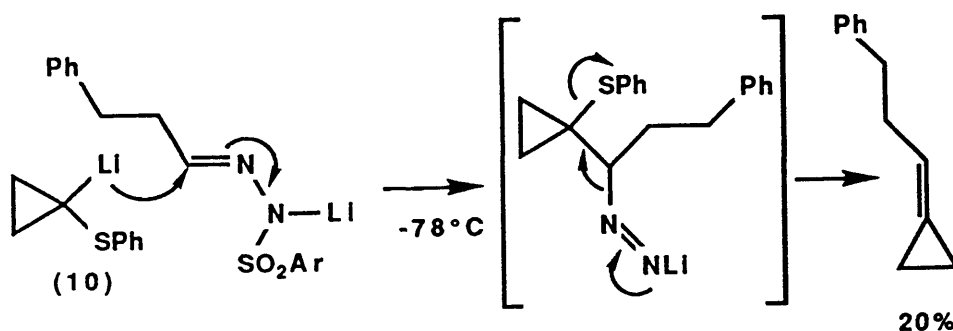
1.5) α -Lithio- α -Phenylthio-Cyclopropanes

Reaction of 1-lithio-1-phenylthio cyclopropane (10), with N-lithiated tosyl hydrazones of aldehydes and non-enolisable ketones³⁰ occurs at -78°C . Extrusion of nitrogen and lithium thiophenoxide gives alkylidene cyclopropanes in low yield (Scheme 7).

Of greater utility is Krief's approach,³¹ in which (10) is treated with cuprous iodide, followed by alkyl bromides, to give 1-alkyl-1-phenylthiocyclopropane (11) in 80% yield (Scheme 8). After alkylation on sulphur, base induced β -elimination proceeds smoothly.



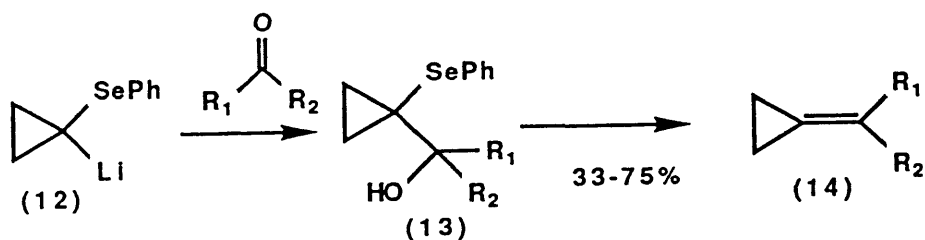
SCHEME 8



SCHEME 7

1.6) α -Lithio- α -Seleno Cyclopropanes

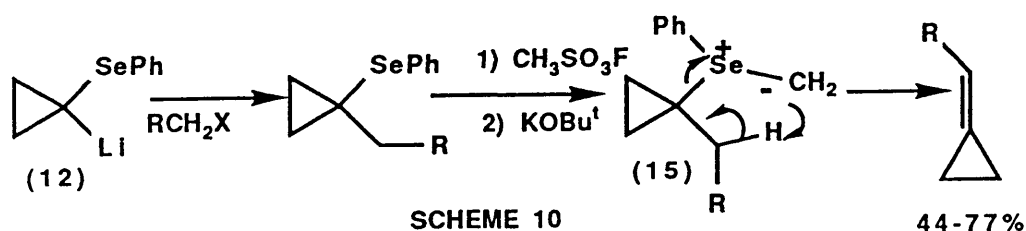
1-Lithio-1-phenylseleno cyclopropane (12) reacts with a variety of aldehydes and ketones to give β -hydroxycyclopropyl-phenylselenides (13) in 54-75% yield.³² With *p*-toluenesulphonic acid at reflux in wet benzene, (13) underwent ring expansion to cyclobutanones. Treatment of (13) with carbonyldiimidazole, (aldehyde adducts), at 110°C, or with phosphorus triiodide-triethylamine at 20°C (ketone adducts), gave alkylidene cyclopropanes (14) in 33-75% yield. (Scheme 9).



SCHEME 9

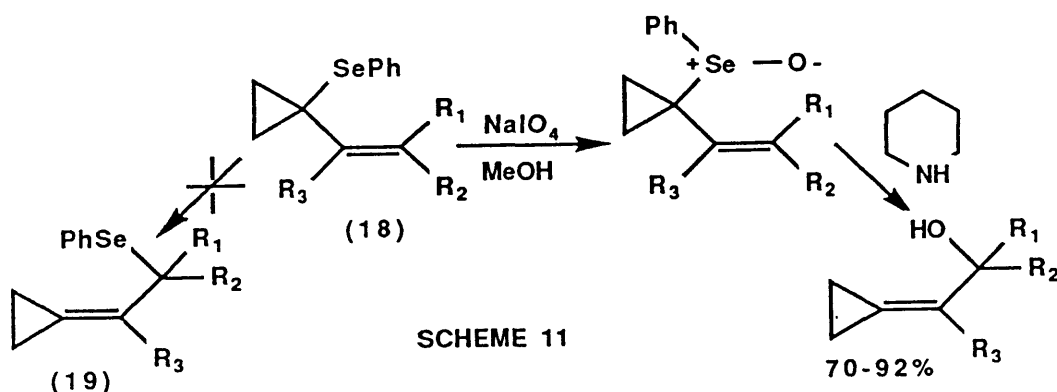
Alkyl halides reacted analogously with 1-lithio-1-phenylselenocyclopropanes (12).³³ Selenoxide elimination could not be induced to give useful yields of alkylidene cyclopropanes. However, alkylation at selenium followed by base treatment generated methylene selenurane ylids (15), which β -

eliminated smoothly in 42-77% yield. (Scheme 10). The isolation of traces of cyclopropenes suggested that initial proton abstraction from the ring might occur, followed by migration of the cyclopropene bond to the more stable exo-position (see below).

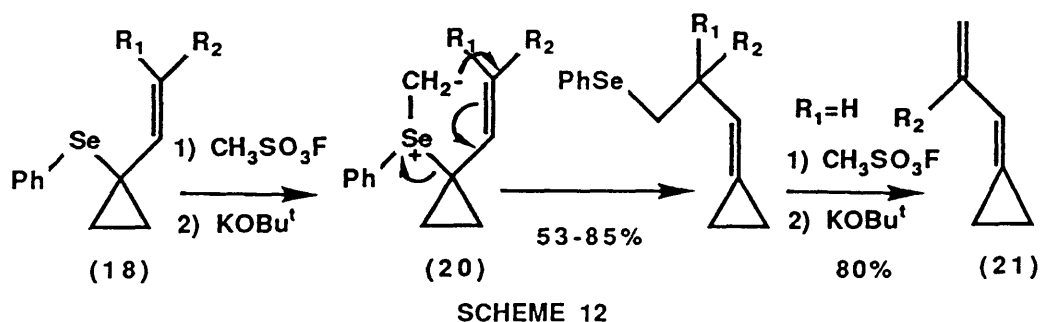


1.7) 1-Seleno-1-vinylcyclopropanes

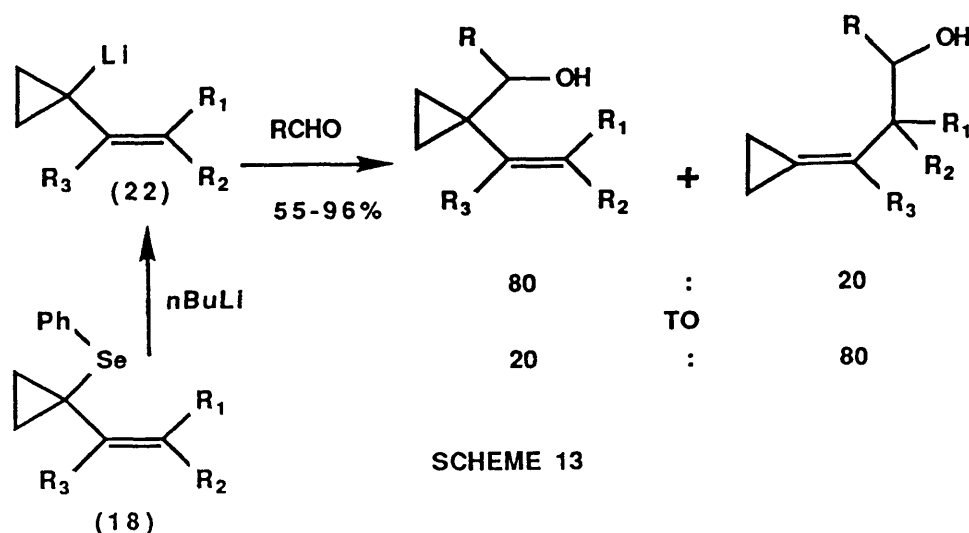
Halazy and Krief³⁴ have investigated application of the [2,3] sigmatropic rearrangement of vinyl selenoxides and vinyl selenuranes to alkylidene cyclopropane synthesis. Oxidation of 1-phenylseleno-1-vinylcyclopropane (18) with hydrogen peroxide gave a disappointing 33% yield of desired product. Other oxidation procedures were less successful. However, in the presence of an added selenophile, such as piperidine, rearrangement proceeded cleanly in 70-92% yield. (Scheme 11).



The difficulties encountered in the selenoxide rearrangement, and the failure to observe alkyl selenide rearrangements to (19) were explained in terms of the increase in strain energy on forming the methylene cyclopropane. The related rearrangement of vinylselenurane ylids (20) proceeded without difficulty in 53-85% yield (Scheme 12). Since the selenium is retained, further application of β -elimination methodology (see above) gave dienes (21) in good yield.



Vinyl selenides (18) are transmetalated with *n*-butyllithium ^{34b} to give 1-lithio-1-vinylcyclopropanes (22), which could be alkylated with a variety of electrophiles. Aldehydes, however, behaved anomalously, giving mixtures of allylically transposed products suggestive of a delocalised allyl anion intermediate. The proportion of alkylidene cyclopropane is substituent dependent (Scheme 13).



1.8) Singlet Oxygen-ene Reaction With Vinyl Cyclopropanes

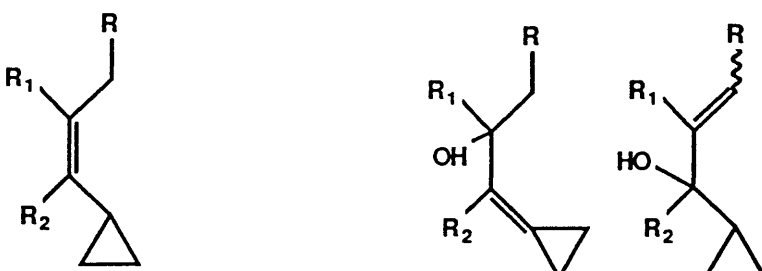
Mechanistically the singlet photo-oxygenation of alkenes is regarded as occurring predominantly via an intermediate per-epoxide, or by a concerted ene-reaction. The mode and rate of attack of singlet oxygen on the olefin is sensitive both to the nucleophilicity of the double bond, and to the conformation of the starting material. Additionally, the C-H bond of the abstracted allylic proton is aligned parallel to the p-orbitals constituting the olefin's π -system.³⁵ Given the distorted geometry of the cyclopropane system, free rotation about the cyclopropane-olefin bond axis is necessary to meet these requirements.³⁶ Success is strongly influenced by the substitution pattern, and where a choice of allylic protons exists, preferential abstraction of the non-cyclopropyl proton is

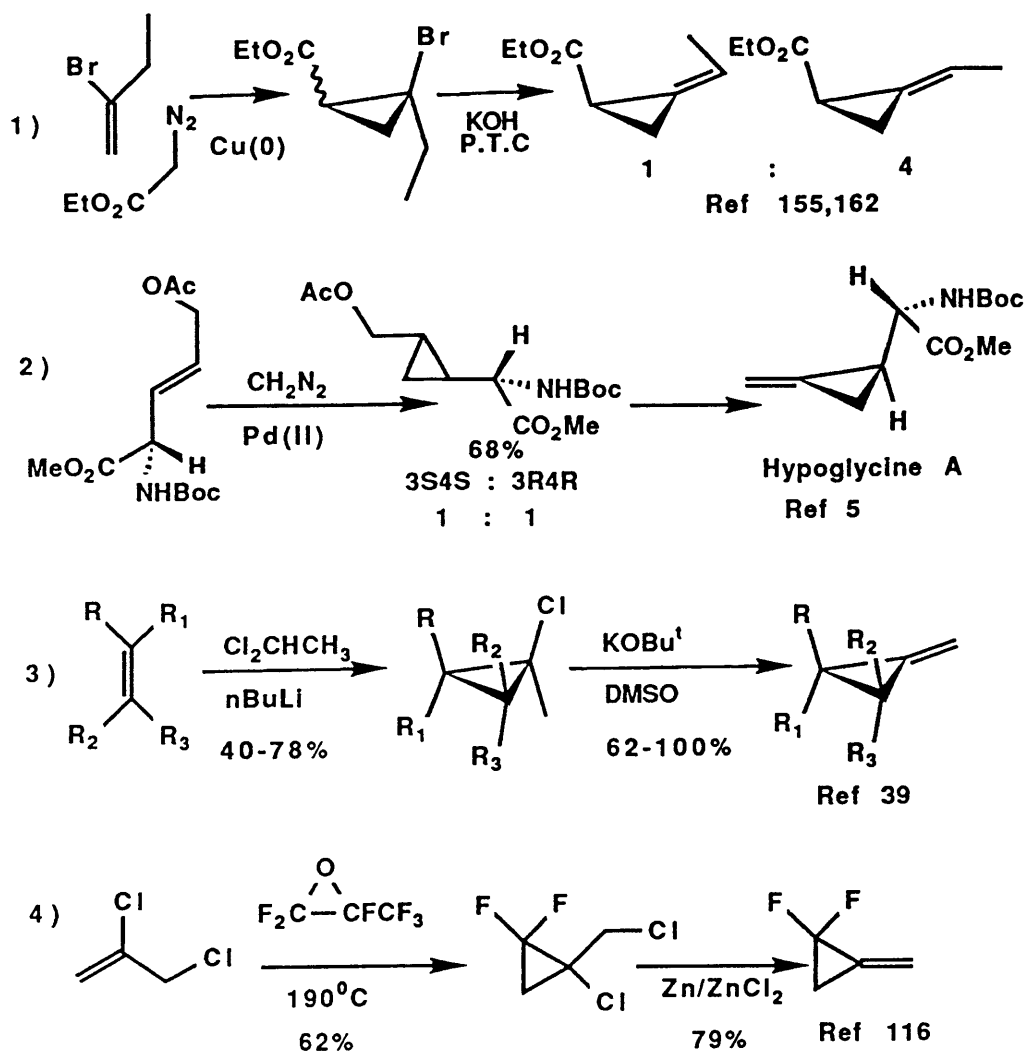
observed. Even in these cases alkylidene cyclopropane formation competes in spite of an 11.4Kcal increase in strain energy on formation.^{37,38} Because of uncertainty with regard to the mechanism, the logic behind these observations remains unclear. Nevertheless, the reaction has synthetic utility, as shown. (Scheme 14).

1.9) β -Elimination in Functionalised Cyclopropanes

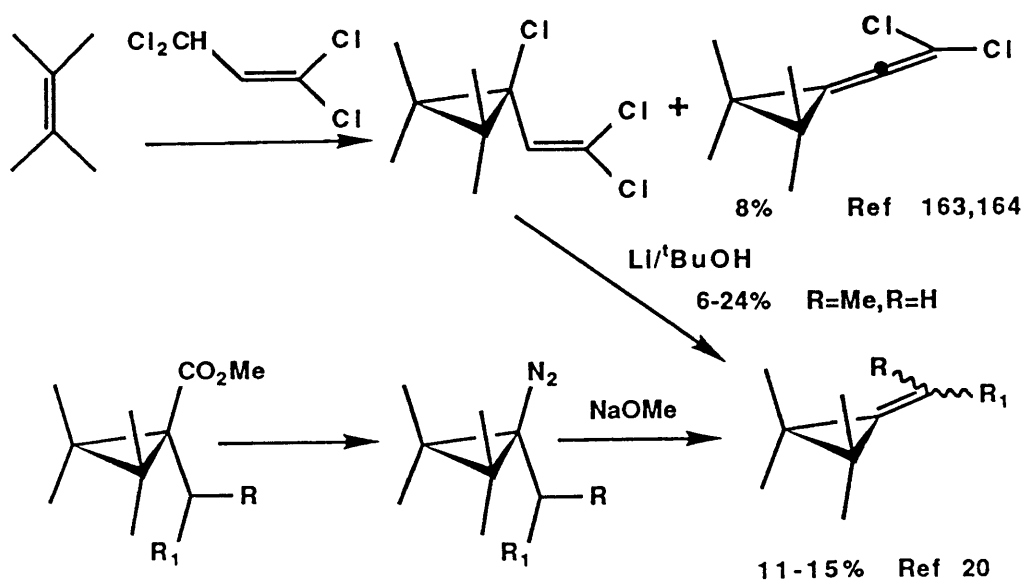
Functionalised carbene insertions into olefins allow access to alkylidene cyclopropane precursors of diverse substitution pattern. Examples of these are summarised in Scheme 15. Binger's methodology³⁹ (Example 3) is particularly useful for preparation of methylene cyclopropanes, with sodium hexamethyldisilazide giving superior yields to *n*-butyllithium. Scheme 16 contains some further examples in which alkylidene cyclopropanes have been observed as byproducts of other reactions. In each case, it should be possible, by alteration of the reaction conditions, to avoid the competing solvolysis reactions.

SCHEME 14

						
R	R1	R2	A	:	B	Ref
H	Me	CP	60		40	35,37,38
H	Me	CP	35		65	"
-CH ₂ CH ₂ -		CP	100		0	"
-(CH ₂) ₃ -		CP	27		73	"
-(CH ₂) ₄ -		CP	75		25	"
-(CH ₂) ₂ -		Ph	86%			"
RCH ₂	R1	R2				
MeO	H	Ph				
"	"	Me(CIS)				
"	"	H				
H	MeO	Me(TRANS)				
H	"	H(TRANS)				

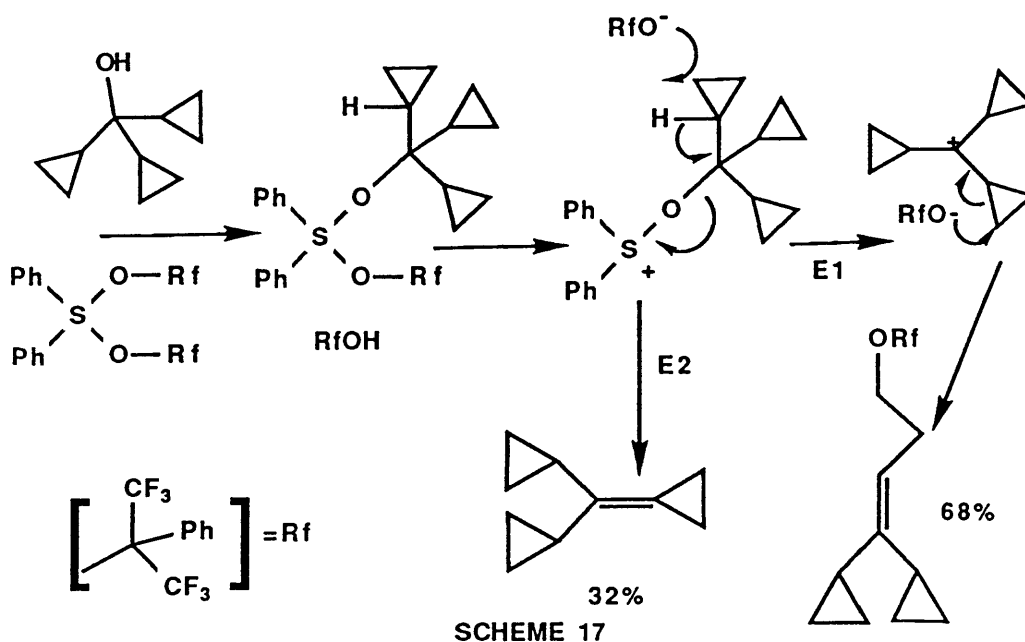


SCHEME 15



SCHEME 16

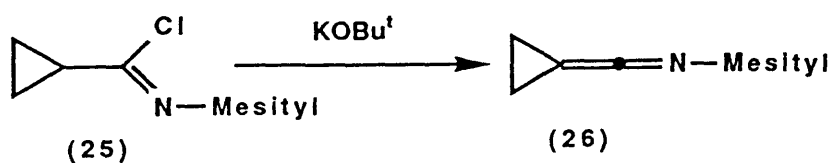
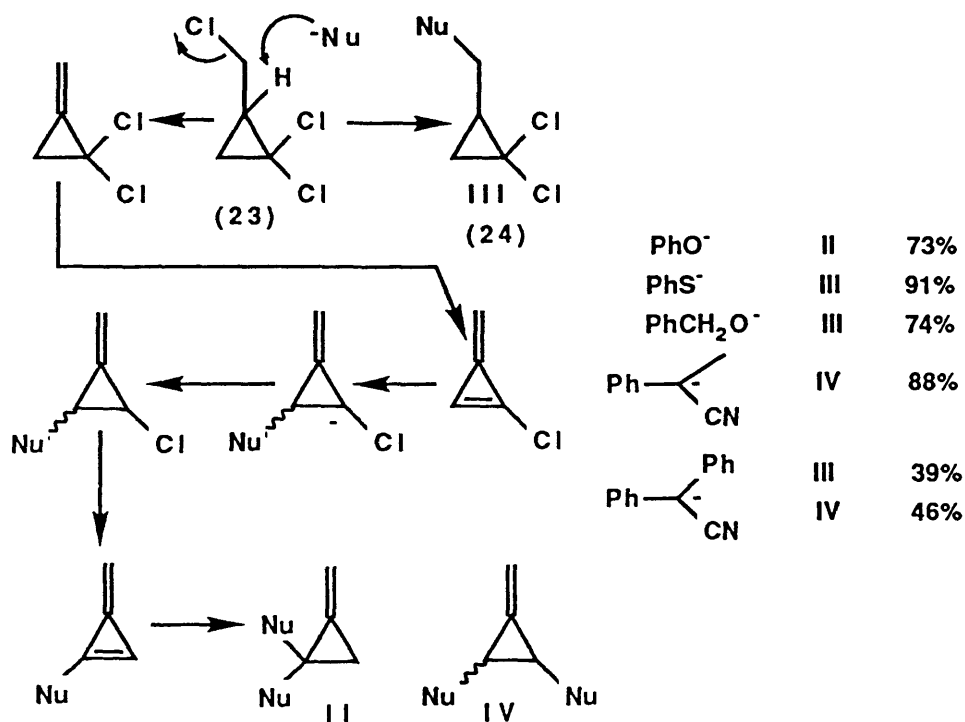
A notable β -elimination strategy which deserves special attention is that due to Martin.⁴⁰ Sulfurane mediated elimination gives superior results to acidic methods (Scheme 17).



An investigation of the reaction of nucleophiles with 1,1-dichloro-2-chloromethyl-cyclopropane (23) gave methylene cyclopropanes or (24) depending on nucleophile basicity.⁴¹ (Scheme 18). The substituted acetonitriles gave no gem-disubstitution due to steric factors.

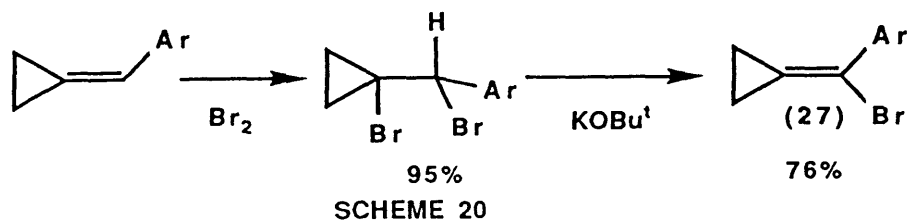
N-mesitylcyclopropylformimidoyl chloride (25) was dehydrochlorinated with KO^tBu to yield N-mesitylcyclopropylidene azomethine (26), an unstable compound which readily underwent cycloaddition with electron deficient double bonds⁴² (Scheme 19).

SCHEME 18



SCHEME 19

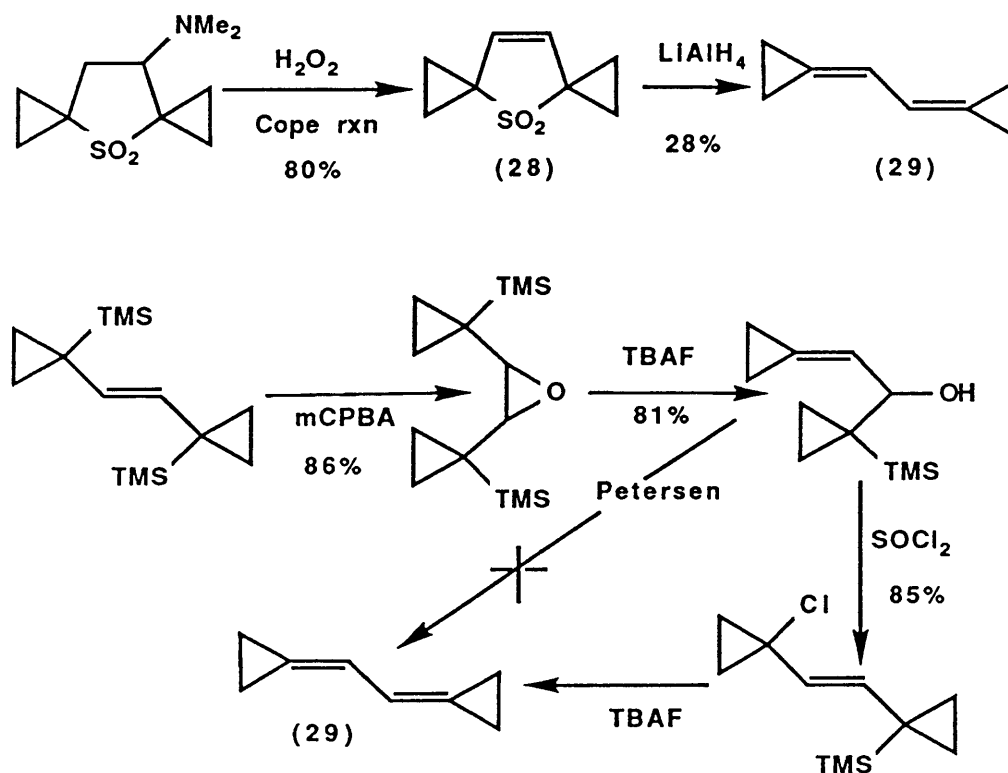
Halogen addition to the double bond of alkylidene cyclopropanes followed by dehydrohalogenation has been used to prepare halomethylenecyclopropanes (27),⁴³ (Scheme 20).



1.10) 1,4-Elimination

Two 1,4-elimination strategies^{44,45} have been applied to dicyclopropylidene ethane (29). The syntheses are outlined in Scheme 21.

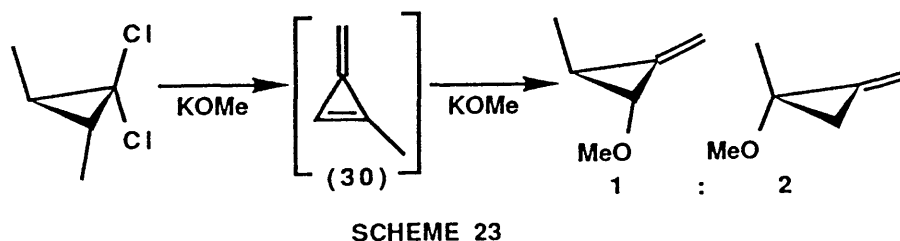
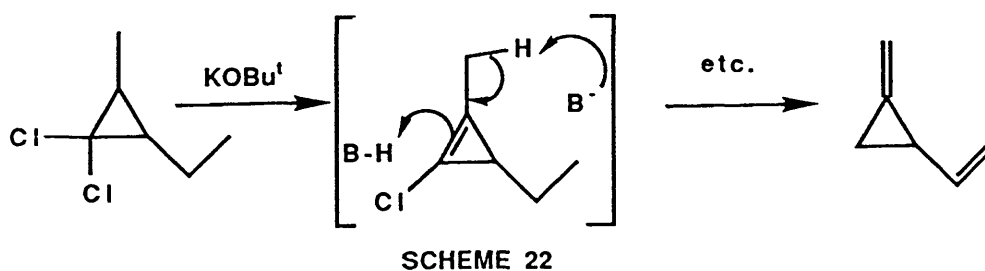
Tusuji's approach,^{44a} reaction (a), employs the Cope reaction to introduce the double bond into (28). The thermal retro-sulfolene reaction failed to liberate the diene, although (28) was fairly stable to thermolysis. Catalytic chelotropic elimination of sulphur dioxide was achieved by treatment with excess lithium aluminium hydride in THF at reflux. The exact mechanism of this curious reaction is not known.^{44b} The Paquette approach⁴⁵ is notable for its solution to a tricky Petersen reaction.



SCHEME 21

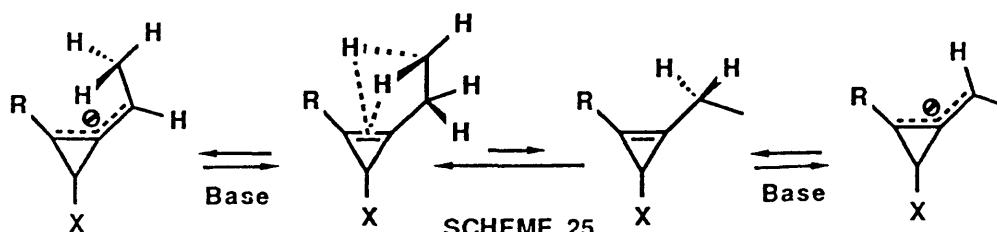
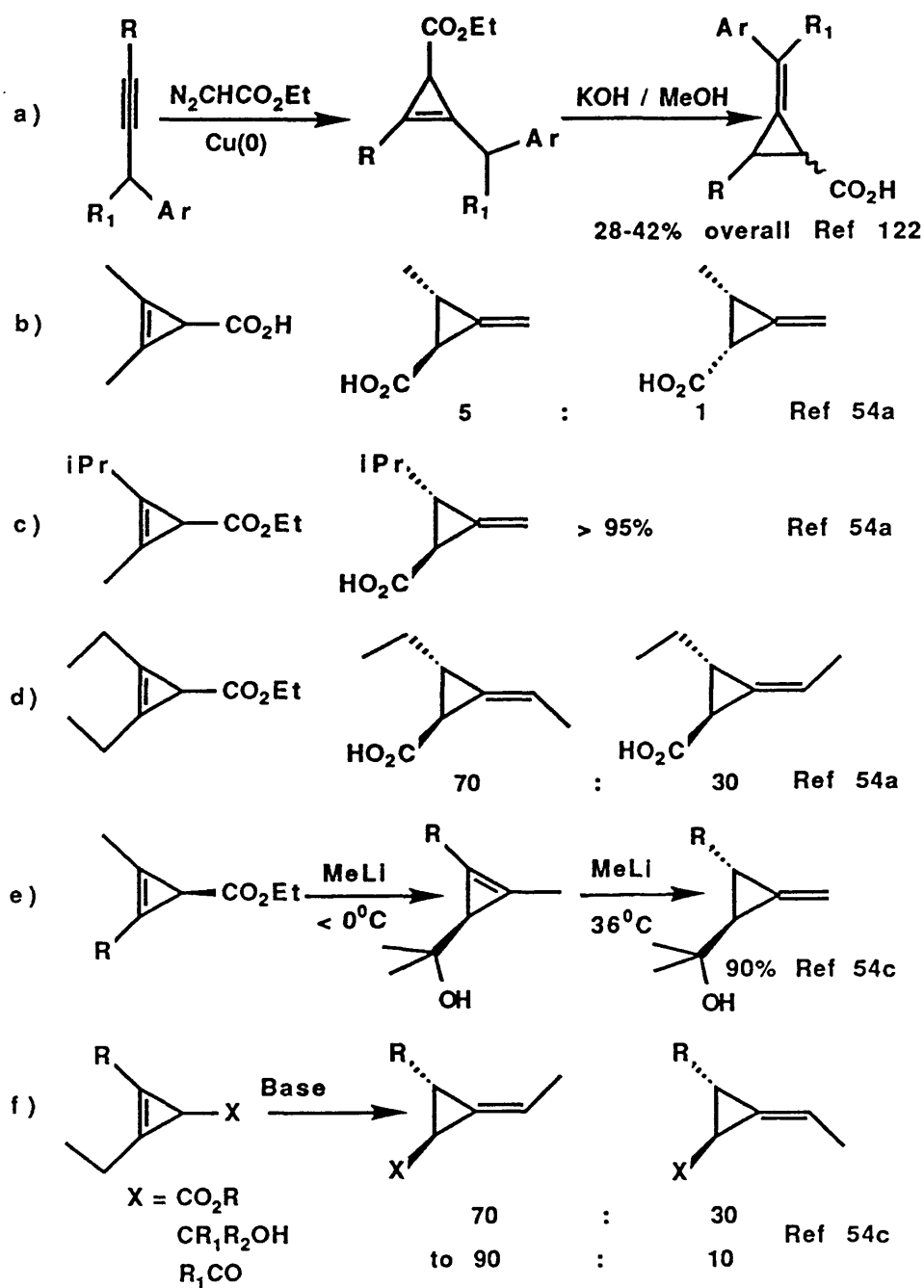
1.11) Rearrangement of Cyclopropenes

Molecular orbital calculations,⁴⁶ heats of combustion,⁴⁷ and hydrogenation⁴⁸ of alkyl cyclopropenes and their isomeric alkylidene cyclopropanes indicate the latter to be thermodynamically more stable than the former by 6-10 Kcal mol⁻¹, due to a decrease in ring strain. It is this which drives the base-induced migration of the double bond to the exocyclic position. Substituted gem-dihalocyclopropanes are of course readily available from olefins. A single equivalent of base effects dehydrohalogenation to the cyclopropene, although excess base is usually employed without isolation of the intermediate cyclopropene. Potassium t-butoxide in DMSO is usually used to trigger the exocyclic migration, which occurs by allylic deprotonation, Scheme 22.⁴⁹ Yields are often high (43-95%).^{43a,49-53}



The pioneering work of Shields *et al.*⁵³ showed that nucleophiles could be added to cyclopropenes (30) (Scheme 23) under the rearrangement conditions. The reaction is not confined to halocyclopropanes, further activation of the allylic proton being unnecessary. This was exploited in the elegant studies of Vidal, Vincens *et al.*⁵⁴ (Scheme 24), where rearrangement of cyclopropene carboxylic acid esters was triggered on saponification with potassium hydroxide. Furthermore, double bond migration was only observed at elevated temperatures, which allowed preparation of ketones or tertiary alcohols by treatment of the cyclopropene esters with alkyl lithium reagents below 0 °C (entry e, Scheme 24). Exocyclic double bond migration could be stimulated by a further equivalent of methyl lithium in diethyl ether at reflux. In addition, the reaction was observed to be both regiospecific and stereospecific in that only the trans-products were observed, and bond migration occurred selectively towards the least substituted substituent. In cases where migration into a secondary or tertiary substituent occurs, more forcing conditions are necessary, and mixtures of Z- and E-exocyclic olefins result, but the Z isomer predominates. Perhaps surprisingly, considering the reactivity of cyclopropenes^{53,54b}, nucleophilic attack at the cyclopropene double bond did not compete with its migration. Anchimeric participation by the carboxylate or alcohol substituent was invoked to explain the observed stereospecificity, although minimisation of steric

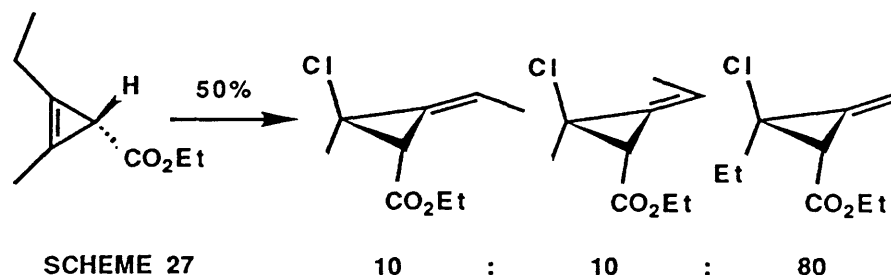
SCHEME 24



interactions between ring substituents is probably largely responsible for the trans- geometry. The observed selectivity in olefin formation was rationalised in terms of interaction between the β -protons and the π -system of ring favouring geometry which leads to the E- isomer (Scheme 25).

Consistent with the results reported above, 3-(hydroxymethyl)-1,2-dialkyl-cyclopropanes were reported⁵⁵ not to give addition products with n-butyllithium. In contrast, however, double bond migration was reported to occur at -78°C in the presence of n-BuLi albeit in poor yield, apparently contradicting the previous observation⁵⁴ that elevated temperatures are necessary.

A radical induced double bond migration occurs during allylic chlorination of cyclopropenes with t-butylhypochlorite⁵⁶ (Scheme 27). High regio- and stereospecificity were observed in the same sense as for the anion approach,⁵⁴ and are rationalised in terms of a transient allyl radical.



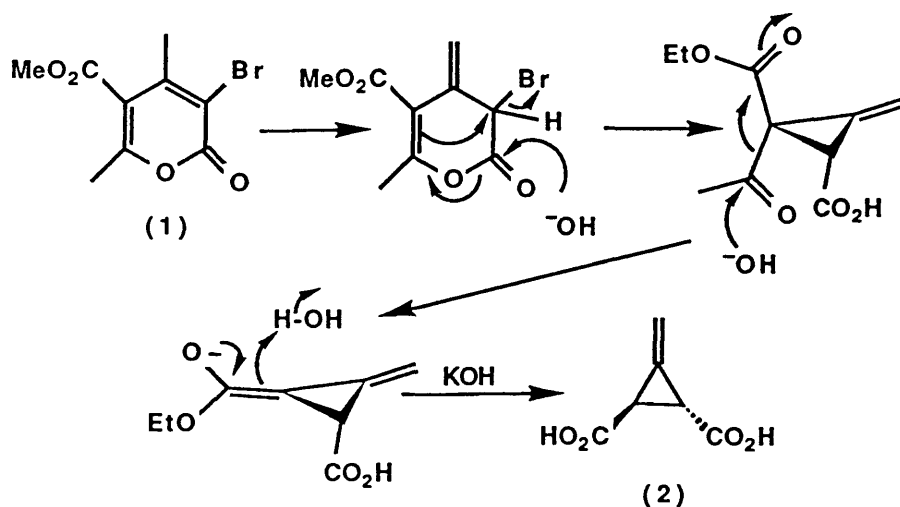
Thus trans-disposition of ring substituents, and a preference for the least substituted exocyclic double bond were observed. The stereo- and regiochemistry of the chlorination arise from attack

of the t-butoxy radical from the least hindered face, and at the site which gives the most stable radical.

In the reactions above it is not clear why there is a preference for the least substituted exocyclic double bond, unless the interactions between eclipsed carbon-carbon bonds of a tri- or tetra-substituted double bond are sufficiently large to dominate the reaction.

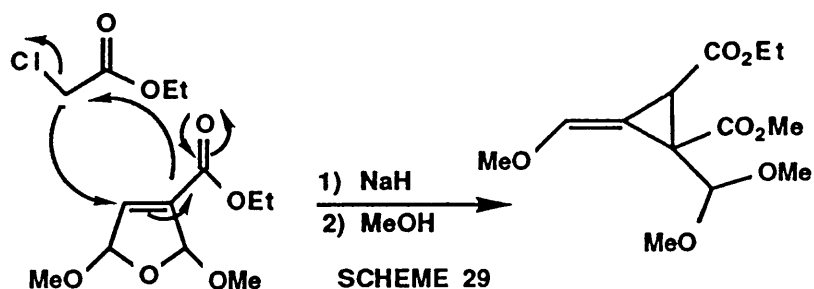
1.12) Ring Closures

A variety of approaches to alkylidene cyclopropanes have involved ring closure as the final step. Historically, the first example was the synthesis of Feist's acid^{1,57} by the action of hot aqueous alkali on pyrone (1), (Scheme 28), for which a mechanism was proposed by Ullmann.⁵⁸

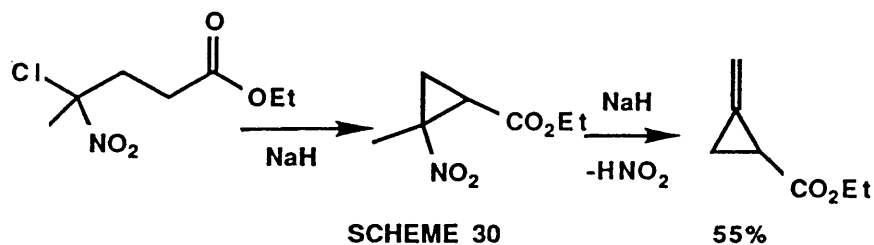


SCHEME 28

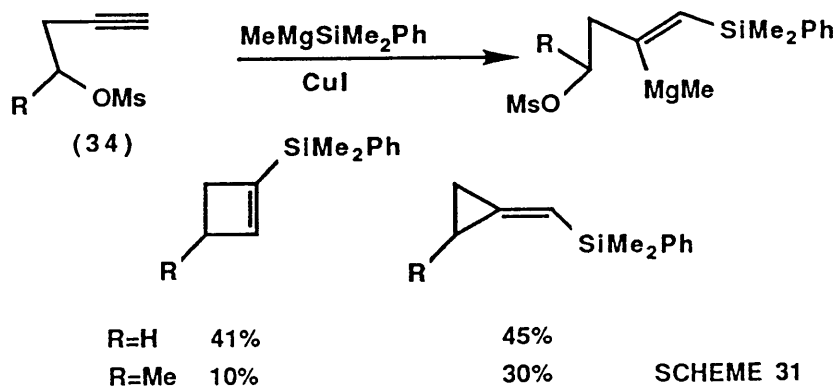
Czech workers⁵⁹ reported a double Michael reaction between ethyl chloroacetate and dihydrofuran (32), (Scheme 29), in the presence of sodium hydride, though stereochemistry was not determined.



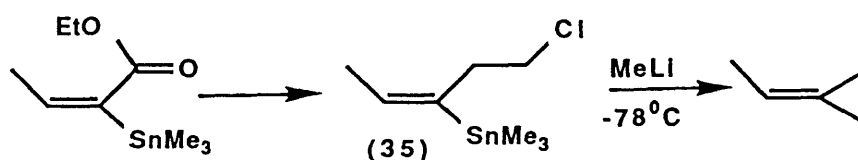
Russell *et al.*⁶⁰ similarly cyclised an ester enolate onto a γ -halide (33), to give, after accompanying elimination of HNO₂, the methylene cyclopropane in 55% yield (Scheme 30).



Sequences employing closure of a vinyl anion onto a homo-allylic halide have been reported. Nozaki *et al.*⁶¹ found that cuprous iodide catalysed addition of methylmagnesium dimethylphenylsilane to a terminal acetylene possessing a β -leaving group (34) gave poor yields of silyl-substituted methylenecyclopropanes (Scheme 31).

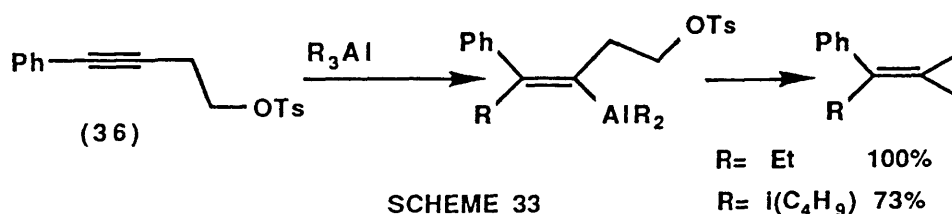


The occurrence of cyclobutenes by 4-endo dig closure of a homopropargylic radical suggested a competing single electron transfer mechanism for the reagent. Similarly Piers *et al.*⁶² obtained methylenecyclopropane on treatment of 1-homoallyl-chlorovinyl stannanes (35) with methyl lithium in unspecified yield (Scheme 32).



SCHEME 32

The most successful application of the strategy, made by Tolstikov and Dzhemilev,⁶³ involved carbo-alumination of homopropargylic tosylates (36) when cyclisation occurred in excellent yield (Scheme 33).

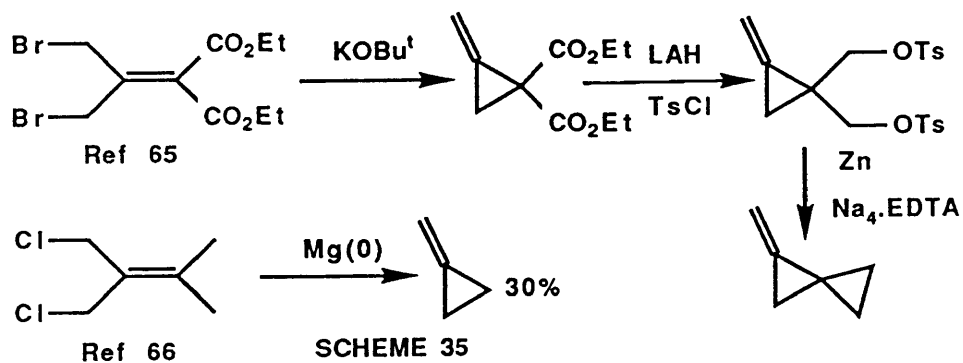
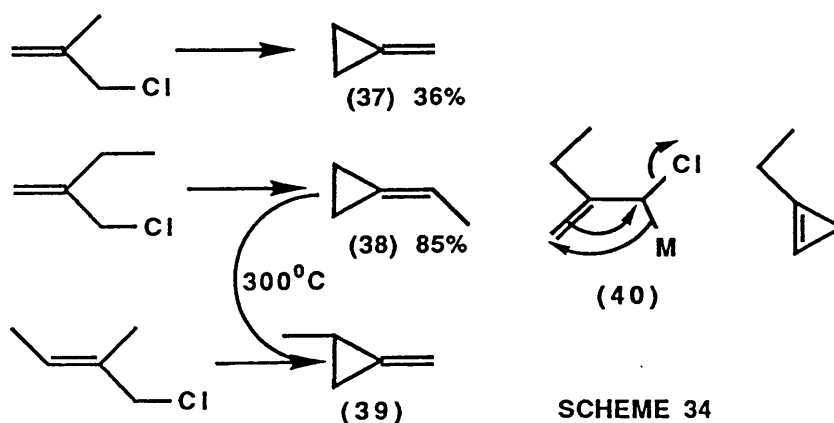


SCHEME 33

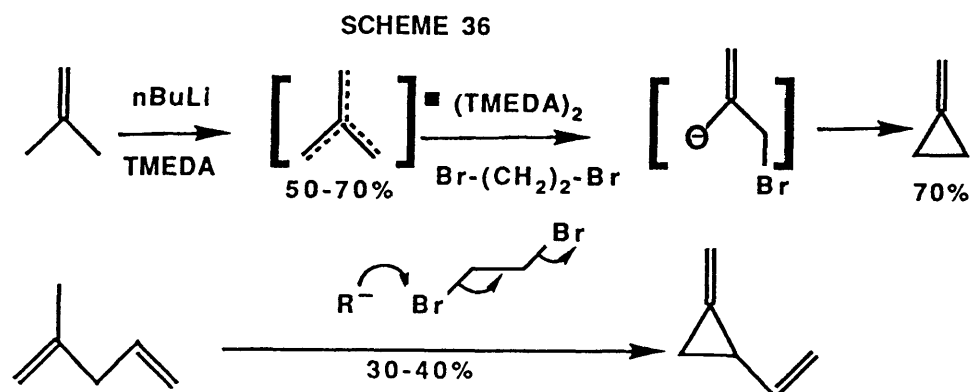
Binger⁶⁴ developed a route amenable to the large scale synthesis of the parent methylene cyclopropane (37) in 36% yield, by treatment of commercially available methallyl chloride with potassium amide in THF at reflux. Other alkali metal amides gave mixtures predominating in cyclopropenes; these are considered to

be likely intermediates via allyl anions (40). Ethylidene cyclopropane (38) and 2-methylmethylenecyclopropane (39) were likewise prepared⁶⁴ (Scheme 34).

Strategies similar to that adopted by Binger have been employed previously.^{65,66} (Scheme 35).



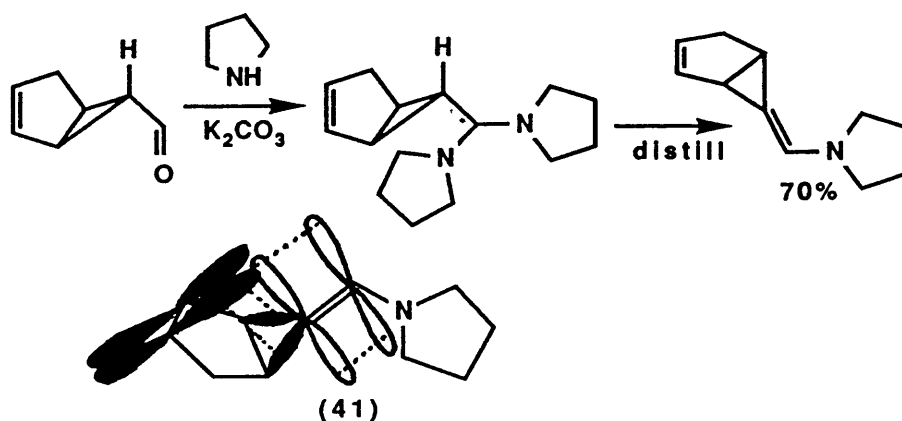
A closely related method involves similar intermediates generated from substituted allyl dianions by bromination with dibromoethane (Scheme 36)⁶⁷ Complexes of the intermediate dianions were isolated.



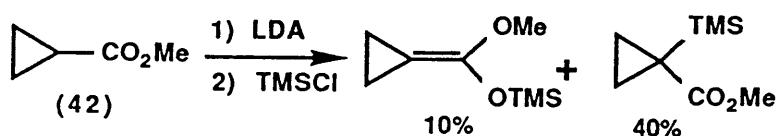
1.13) Enamines and Enol Ethers

Members of this special class of methylene cyclopropanes are relatively rare. Cyclopropylenamines are formed on heating cyclopropylcarbinyl aminals containing a further suitably placed double bond with which the π -system of the enamine can interact. The extra stabilisation available by homoconjugative overlap apparently outways the increased ring strain involved. Pseudo-conjugation between the double bond and the σ -bonds of the ring is also available since the axis of the π -bonds is held parallel with the plane of the ring in a rigid bicyclic fused system (41). Cyclopropylcarbinyl aminals lacking the conformationally locked olefinic system did not form enamines on heating, illustrating the importance of the extra structural unit⁶⁸ (Scheme 37).

Enolethers have also been prepared in poor yield by treatment of methyl cyclopropylcarboxylate (42) with LDA followed by TMSCl . (Scheme 38).

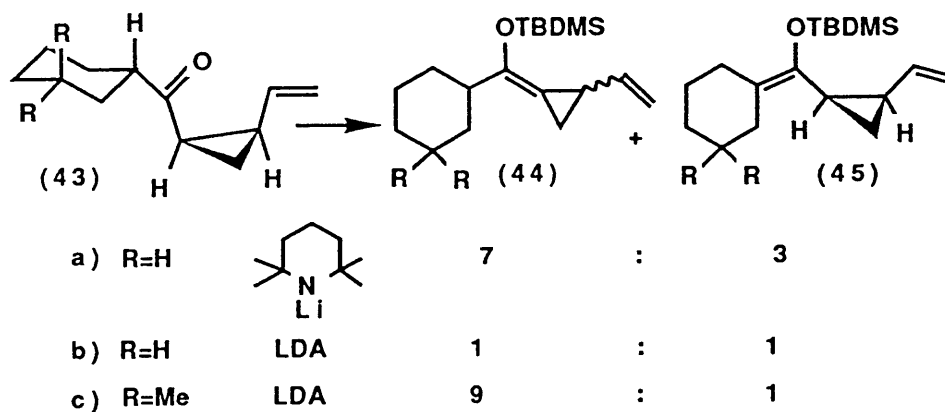


SCHEME 37



SCHEME 38

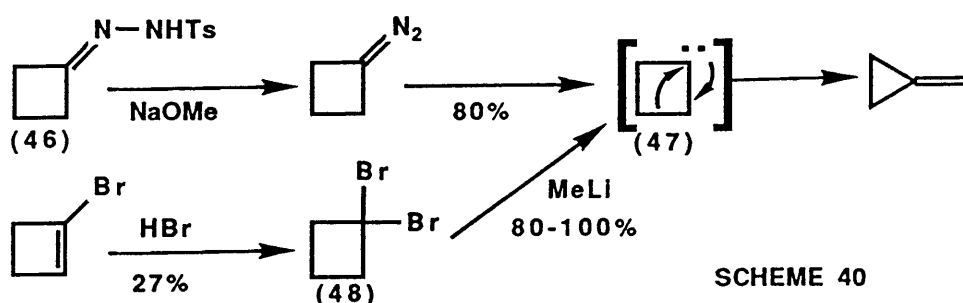
Cyclopropyl ketone (43c) (Scheme 39) is enolized towards the cyclopropane when treated with a strong hindered base, because the alternative proton was too sterically hindered (44). The acidity of the cyclopropyl proton was enhanced by an electronic effect involving conjugation between the cis vinyl group and the ketone. The corresponding trans isomer enolised exclusively towards the cyclohexane (45) (Scheme 39).⁶⁹ Other cyclopropyl ketones have also been enolised.⁷⁰



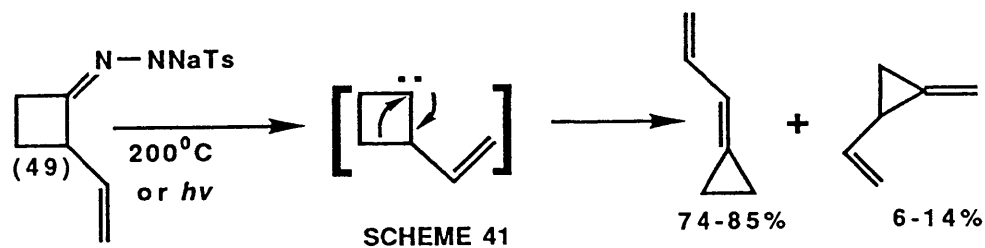
SCHEME 39

1.14) By Cyclobutylidene Rearrangement

Cyclobutylidene (47) has been prepared from cyclobutanone-tosylhydrazone (46) by the Bamford-Stevens reaction ^{71a-d}, and by treatment of gem-dibromo cyclobutane (48) with methyllithium ^{71e} (Scheme 40).



The reactions are high yielding in the case of methylenecyclopropane, although material generated from (48) is contaminated by small quantities of cyclobutene, and the precursors are tedious to prepare ^{71a}. Attempted preparation of substituted methylenecyclopropanes was reported to be messy ^{71b}, although recent work on vinyl substituted cyclobutanes (49) gave good results ^{71c,d} (Scheme 41).



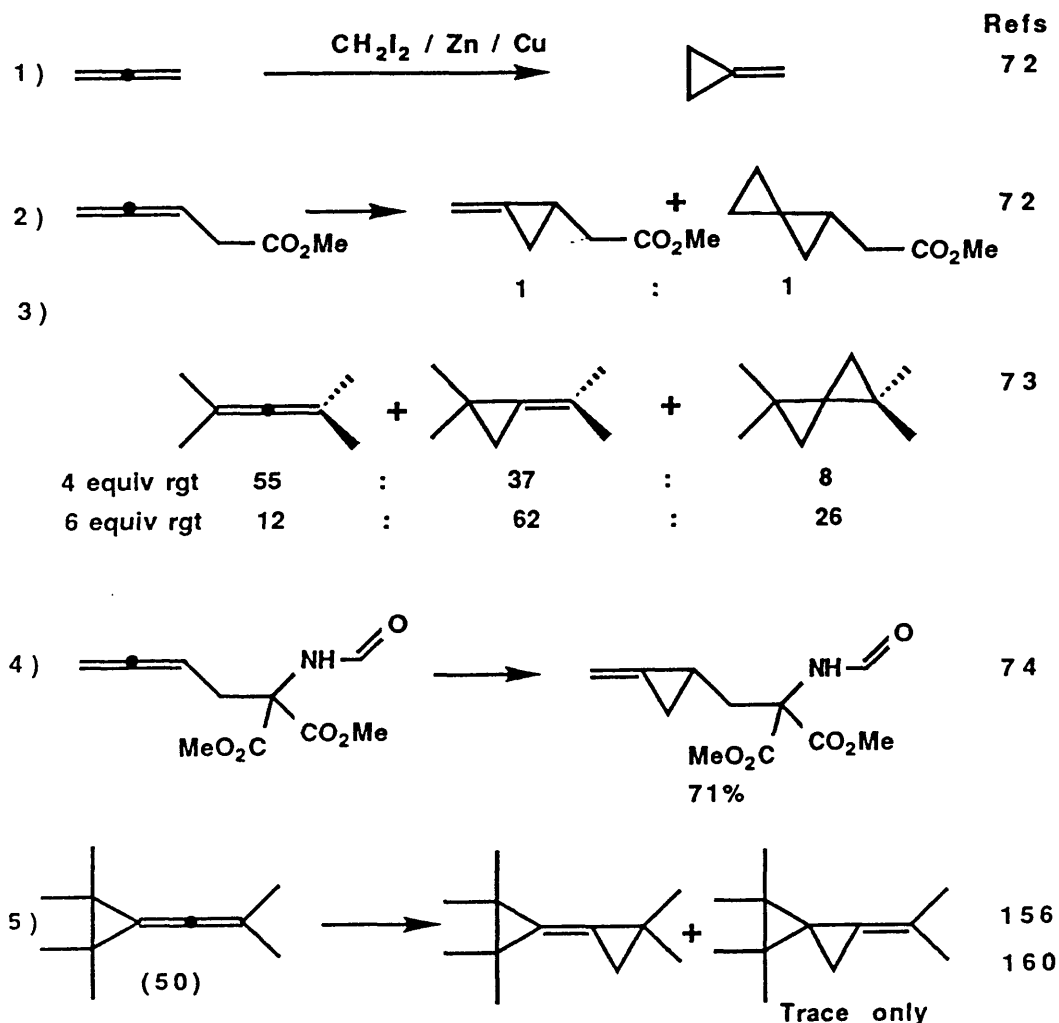
1.15) Carbene Addition to Allenes

1.15.1) Simmons-Smith reagents

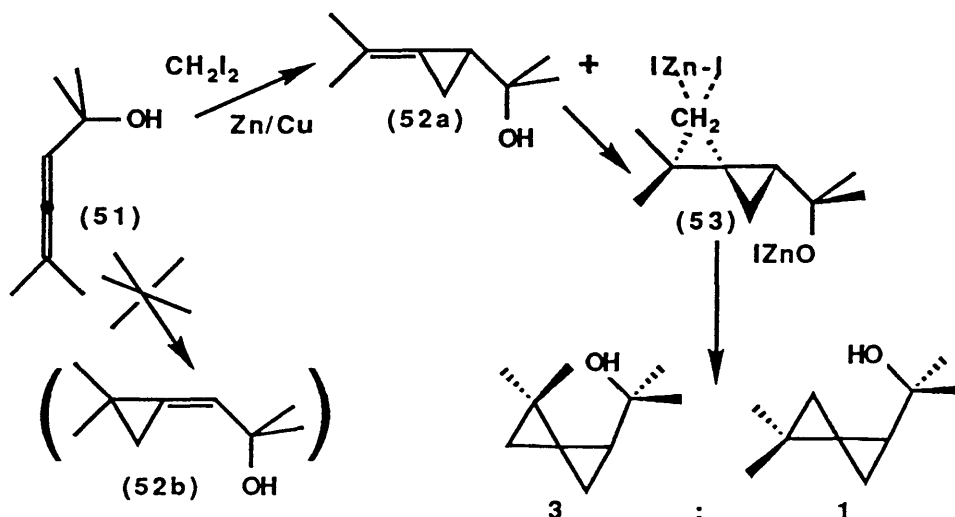
The advent of the Simmons-Smith reaction in 1958 was followed by a number of studies of its utility for preparing methylene cyclopropanes from allenes. For a brief review of the early work in this area the reader is referred to Ref. 72. The parent compound, methylenecyclopropane was the first example to which the method was applied. It soon became apparent that the reactivity of the carbenoid intermediate was such that reaction did not stop at the methylene cyclopropane. Spiropentanes form competitively in the presence of the excess reagent normally employed to effect reasonable conversion ⁷³ (entry 3, Scheme 42). This did not appear to be a problem with Black's synthesis of (+)-hypoglycin A ⁷⁴ (entry 4, Scheme 42) where the desired methylene cyclopropane was obtained in 71% yield. The reaction was, however, described as "temperamental", anhydrous conditions and good quality zinc couple being essential. The initial attack on the allene is highly regio-selective in favour of the more highly substituted and therefore nucleophilic double bond. The high selectivity observed for the cyclopropanation of the terminal double bond of tetramethyl-(dimethylvinylidene)cyclopropane (50) (entry 5, Scheme 42), is ascribed to its greater nucleophilicity, and also due to minimisation of steric interactions with the cyclopropane ring substituents. Spiropentane formation in this system occurred in trace amounts only in the presence of a large excess of reagent. The known ability of a suitably appended hydroxy function to direct cyclopropanation has been exploited. Thus Bertrand and Maurin ⁷⁵ observed methylenecyclopropane formation from α -allenic alcohols (51) to occur exclusively by addition of Simmons-Smith reagent to the

less nucleophilic α,β -double bond (52a) (Scheme 43).

SCHEME 42



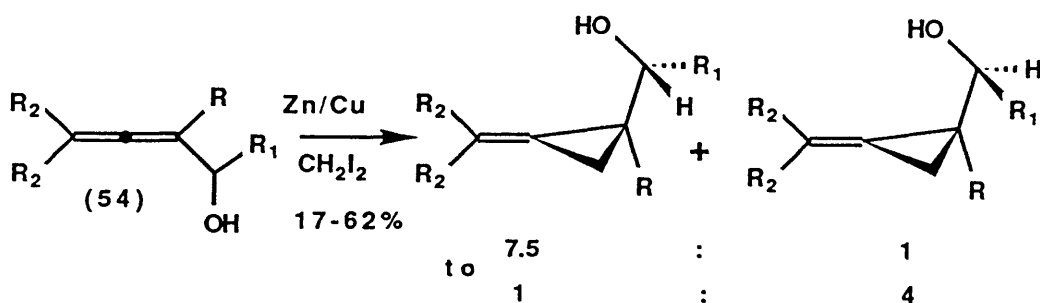
That methylene cyclopropane (52b) is not formed competitively, and undergoes further cyclopropanation more rapidly may be ruled out by the observation that spirocyclopentane formation occurred preferentially by approach of the reagent from the less encumbered face of (52a). The alcohol forms a bulky zinc complex which effectively shields the other face (53).



SCHEME 43

A further study by the same workers ⁷⁶ showed that secondary α -allenic alcohols (54) were cyclopropanated diastereoselectively, the nature and extent of the diastereoselection being dictated by the adjacent substituents R and R_1 (Scheme 44).

Aside from the Simmons-Smith procedure, carbenes generated from haloforms, and diazoalkanes have also been inserted into allenes.

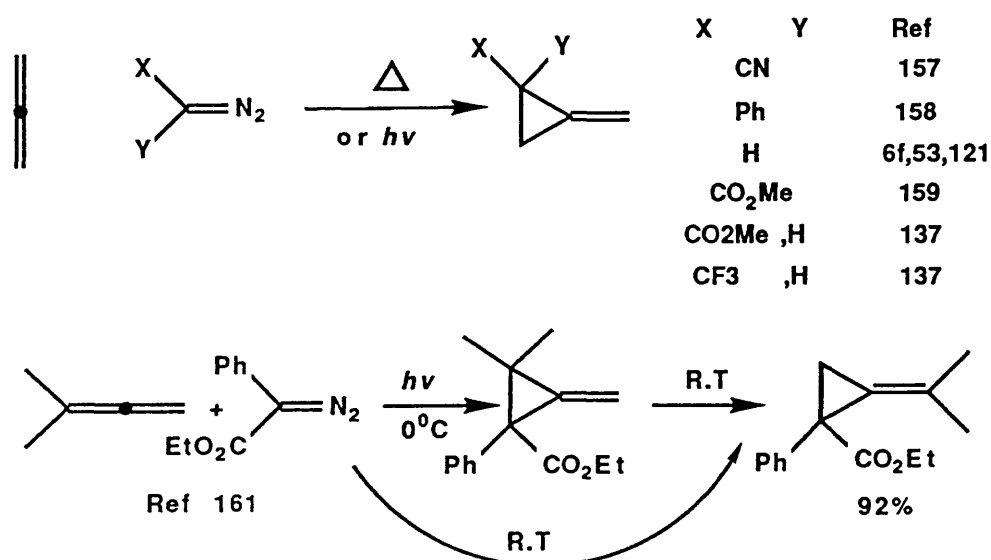


SCHEME 44

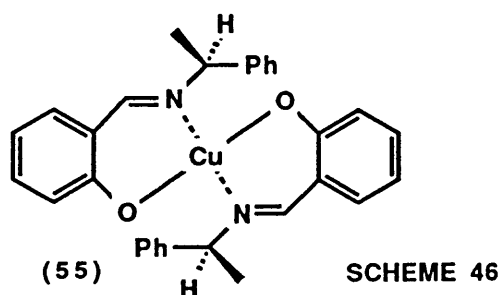
1.15.2) Diazoalkanes

A wide range of substituted diazomethanes have been employed. This approach is particularly useful for introducing functional groups into the cyclopropane ring. Some examples are given in Scheme 45. The carbene is most frequently generated by

SCHEME 45

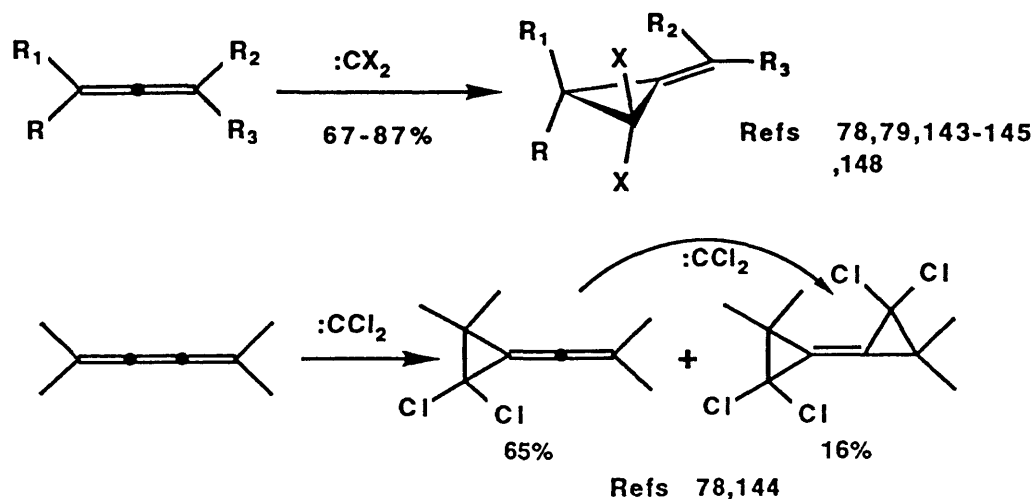


photolysis, when the reaction is relatively clean. Application of a chiral copper catalyst (55) (Scheme 46) to the addition of diazomethane to allenes gave optically active methylene cyclopropanes, but lack of a suitable handle to permit resolution prevented determination of optical yield and absolute configuration. Yields of methylene cyclopropane were poor due to competing spirocyclopentane formation.⁷⁷ The initial promise shown in chiral induction does not appear to have been followed up.



1.15.3) Dihalocarbenes

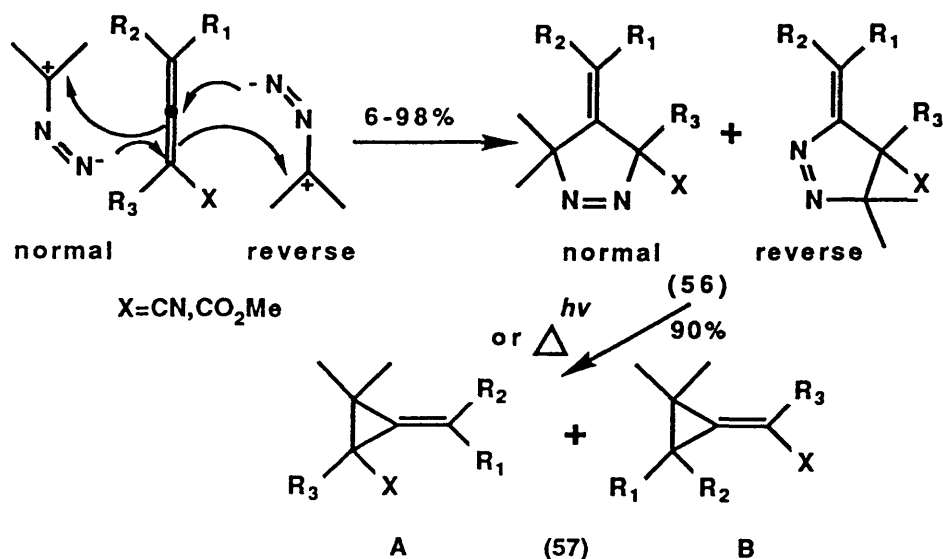
Dihalocarbenes, as expected, also add to the most nucleophilic double bond of the allene system, to give, generally, high yields of methylene cyclopropane, and less spiro-pentane formation than is the case with the Simmons-Smith procedure. The work of Skattebol ⁷⁸ suggests that dichlorocarbene is slightly superior to dibromocarbene in this respect. Representative examples are shown in Scheme 47. Dihalocarbenes are, of course, available from numerous sources (for a brief survey, see Ref. 79). Many require basic conditions. A notable exception is the mild decomposition of phenyl-(trihalomethyl)mercury compounds at 80°C in benzene, methodology developed by Seyferth. ⁷⁹



SCHEME 47

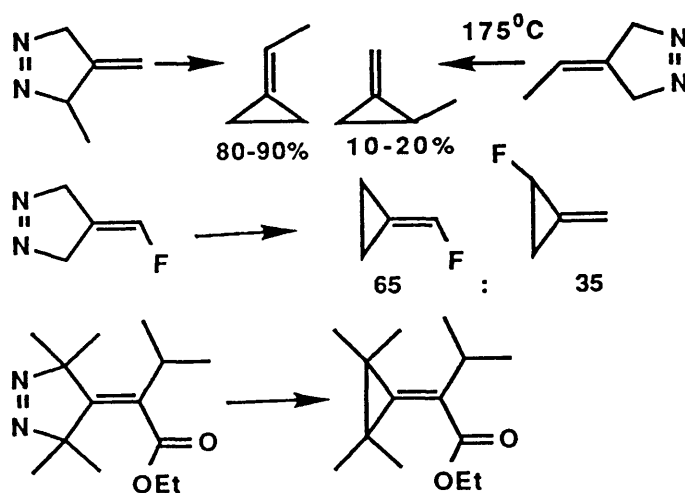
1.16) Photolysis/Pyrolysis of 4-Alkylidene-1-Pyrazolines (56)

4-Alkylidene pyrazolines (56) relate to the foregoing discussion in that they are synthesised from allenes by 1,3-dipolar addition of diazomethanes⁸⁰ (Scheme 48). The importance of these compounds lies more in the mechanistic and theoretical aspects of their decomposition to vinylidene cyclopropanes than in the synthetic utility of the reaction. Although the exact details concerning loss of nitrogen from the molecule are subject to some debate, it is likely that a trimethylenemethane biradical is involved at the point of ring closure; hence the mechanistic importance of these compounds.⁸¹ From a synthetic standpoint, the reaction is limited by the thermal or photolytic decomposition step, which tends to result in mixtures of methylene cyclopropanes by virtue of methylene cyclopropane rearrangements occurring under the reaction conditions.



SCHEME 48

It was reported⁸⁰ that photolysis via a singlet state gave (57) A:B in 77:23 ratio, whilst benzophenone sensitised photolysis via a triplet pyrazoline gave (57) A:B in 25:75 ratio. Pyrolysis, however, gave predominantly rearrangement product (57B), although (57A) was shown to predominate during the early stages. This review is not intended to cover the theoretical and



SCHEME 49

mechanistic aspects of trimethylene methane, which would warrant

a review of its own. The interested reader is referred to the excellent paper of Bushby *et al.*⁸² for a concise account of current knowledge in this area, or ref. 81 for greater depth. Some of the more preparatively useful examples are shown in Scheme 49.

1.17) Alkylidene Carbenes

This important route to a wide variety of alkylidene and vinylidene cyclopropanes has been extensively reviewed elsewhere⁸³. The reader is particularly referred to ref.84, both for an extensive review of α -elimination strategies, and also for a detailed discourse on the structure and the reactivity of the intermediate carbenes or carbenoids involved. Only a brief account is given here of the more popular methods, with greater emphasis being given to more recent developments.

A number of generalisations may be made. Yields of adducts are rather variable, depending on method of carbene generation, solvent, and nucleophilicity of olefin. Steric effects with substituents on the alkylidene carbene are especially important with sterically demanding olefins; these problems do not occur with vinylidene carbenes⁸⁶, where the carbene substituents are too far away, and occupy a plane orthogonal to that containing the olefinic substituents. The majority of alkylidene carbenes are generated in the singlet ground state, i.e. one orbital contains the unshared spin-paired electrons, the remaining orbital being vacant. Consequently, olefin insertion is stereospecific⁸⁷ by virtue of the interaction of the empty carbenic p-orbital with the olefinic carbon bearing the largest

π -orbital coefficient. Thus greatest stereoselectivity is observed with highly polarised alkenes. The polarisation of the π^* -orbital, which interacts with the carbenic lone pair is also important. High stereoselectivity is expected only for those olefins where the π - and π^* - orbitals are strongly polarised in the same direction. Where the polarisation is low, the transition state energies for the various modes of attack are similar, resulting in competition, and loss of selectivity. Stereoselectivity is also observed to arise from steric interactions between the two approaching components, and therefore increases with the steric bulk of the substituents. Alkylidene carbenes bearing β -protons or aromatic substituents undergo Wolff rearrangement,⁸⁸ also known as the Fritsch-Buttenberg-Wiechell rearrangement⁸⁴ to the corresponding acetylene. β -Substituents possessing a suitable γ C-H bond may undergo [1,5] intramolecular C-H insertion to give cyclopentenenes, etc. Intermolecular olefin insertion is unable to compete with these intramolecular rearrangements, which limits the scope of this strategic disconnection to gem-dialkyl substituted methylene cyclopropanes. Intramolecular rearrangements are not a problem with vinylidene carbenes. Finally, reactions going via the "same" intermediate unsaturated carbene may have drastically different success under different methods of generation, or even a change of solvent composition. Such effects are indicative of carbenoid rather than free carbene intermediates, and co-ordination of ether solvents often results in greater stability. Dimethoxyethane is a particularly good choice in this respect.

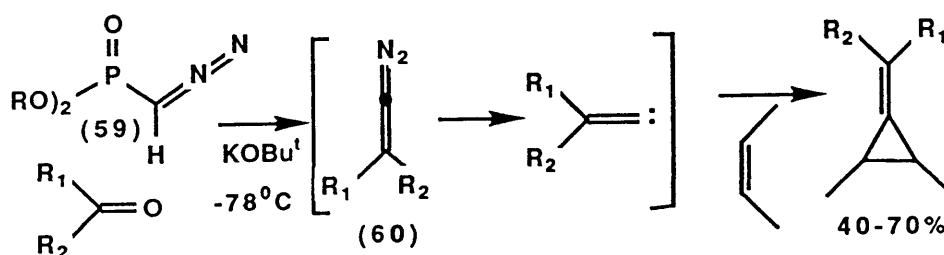
1.17.1) N-Nitroso-oxazolidones⁸⁹

The base initiated decomposition of nitro-oxazolidones developed by Newman⁹⁰ has not been used extensively owing to inaccessibility of the precursors, and the variable (14-86%) yields of products. This method has since been superseded.

1.17.2) Vinylamines⁹¹

9-(aminomethylene)-fluorene was treated with isoamyl nitrite in the presence of olefin at 80°C. Tetramethylethylene gave only 9% of alkylidene cyclopropane due to steric hindrance.⁹¹ Again the method has not been widely applied. Because the aromatic rings of the fluorene nucleus are tethered, Wolff rearrangement does not occur. Aliphatic vinyl amines are not readily accessible.⁹²

1.17.3) Diazoethenes by Horner-Wadsworth Emmons Reaction of Diazomethyl Phosphonates (59)



The reaction, developed by Gilbert et al.,⁹² gives good results with a wide variety of ketones and olefins, providing a mild, direct, and highly convergent approach to methylene cyclopropanes from readily available starting materials. The intermediate

diazoethene (60) is not isolable, but decomposes in situ at -78°C .

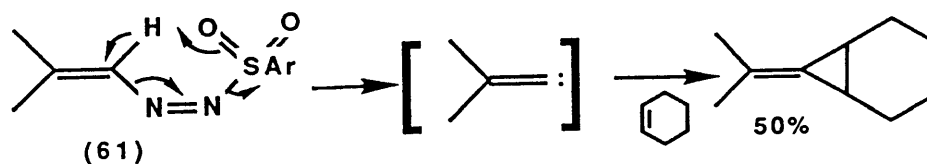
We have observed that DME gives superior results to THF.

This may be rationalised in terms either of crown-like nature solvating the potassium t-butoxide more efficiently, or,

alternatively, co-ordination with the carbene may be important⁹³⁻⁹⁵ - see below. Aldehydes and aromatic ketones give acetylenes. Ketones which undergo facile enolisation give poor results.

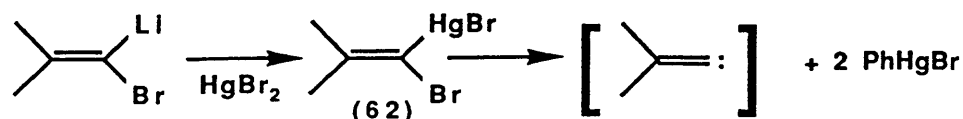
1.17.4) Tosylazo Alkenes⁹³

The crystalline precursors (61) are stable indefinitely at -20°C , but decompose at room temperature in the presence of excess olefin in chloroform with sodium carbonate to remove the toxic acid as it is formed. However, the yields were not as good as those obtainable by other methods. The mechanism is open to speculation.



1.17.5) α -Bromo Vinylmercury Bromides

α -Bromo vinylmercury bromides (62) were developed by Seyferth and Dagani⁹⁶ in 1976 as a means of generating vinylidene carbenes by non-basic means. The organomercury precursor decomposed at 150°C in the presence of diphenylmercury and excess olefin to give 24-87% yield of alkylidene cyclopropanes. Having tested their



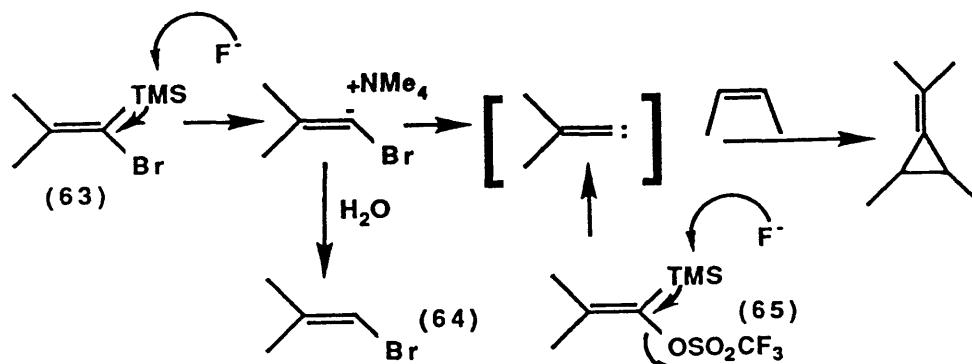
methodology on a wide variety of olefins, they were justified in claiming yields that were better than any other method available at that time. Other approaches developed since give higher yields in certain cases, but this method remains of great importance since it is still the only truly non-basic route to vinylidene carbenes. (The fluoride induced α -eliminations to be discussed shortly are certainly mild, but fluoride anion still possesses quite strongly basic properties).

1.17.6) α -Halo Vinyl Silanes. (63)

α -Silylvinyltrifluoromethane-sulphonates (65)

Shortly after Seyferth reported his organomercury methodology, the work of Cunio and Han⁹⁴ on the fluoride mediated α -elimination of Trimethylsilyl halides was reported. They obtained good yields of alkylidene cyclopropanes under rigorously anhydrous conditions. This was necessary because protodesilylation competed. Further studies showed the α -elimination sequence to be a stepwise process, with initial loss of trialkylsilyl fluoride to give a vinyl anion, which could pick up a proton instead of α -eliminating the halide, to give (64). Though the conditions are relatively mild, anhydrous

fluoride is a basic entity. In addition, anhydrous fluorides are

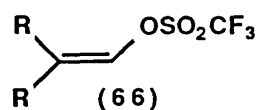


difficult to obtain and handle, and the α -bromovinylsilane precursors (63) are tedious to prepare. A logical development of this idea was made by Stang and Fox⁹³, who substituted the halide with a triflate, which has superior leaving group properties. Proto-desilylation was found no longer to be a problem, presumably since α -elimination of trimethylsilyltrifluoromethane sulphonate is virtually a concerted process and long-lived vinyl anions are not therefore generated under the reaction conditions. As a result, alkylidenecyclopropanes were prepared in 80-90% yield in the presence of excess olefin in DME at $0^\circ C$. Whilst potassium fluoride gave best results, phase transfer catalysis with potassium fluoride-aliquot 336 gave quite acceptable results. Employment of DME as co-solvent was important to obtain high yields. It is postulated that DME co-ordinates to the carbene thus stabilising it. Similar effects were observed with THF. Although the reaction conditions are much less demanding on the experimentalist, the α -silylvinyltriflates are more difficult to

prepare, being obtained from acylsilanes in moderate yield.

Unless the substrate olefin is particularly sensitive to basic, or thermal conditions, some of the more traditional methods of vinylidene carbene generation offer greater practicality despite lower yields.

1.17.7) Vinyl Trifluoromethane Sulphonates ⁹⁵



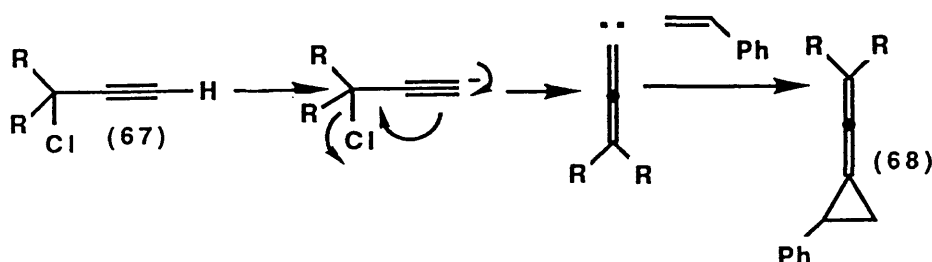
Primary vinyl triflates (66) on treatment with potassium t-butoxide at -23°C in a 3:1 mixture of excess alkene and DME gave alkylidene cyclopropanes via a singlet carbene. This method, also developed by Stang and Fox, was the forerunner of the α -silylvinyl triflate methodology. Though not particularly mild, nor as high yielding the principle advantage over the later developments is the greater accessibility of the carbene precursor. Enol triflates are not trivial to prepare, (they are best made by reaction of silylenol ethers with triflic anhydride), but a wide variety of suitable aldehydes are readily available. The reaction conditions are milder than for the vinyl halides formerly employed (see below).

1.17.8) Halides:

1.17.8a) Acetylenic

Vinylidene carbenes of extended unsaturation have been available for some time, yet few methods have been devised for

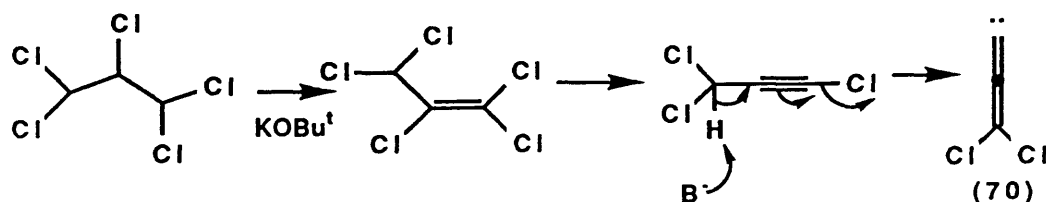
making them. One of the oldest of the available methods, which is still widely used, involves rearrangement of acetylide anions containing a suitably positioned leaving group. Thus substituted vinylidene carbenes have been widely prepared by the method of Hartzler.^{17a} The carbene precursor (67) is readily available by



reaction of a ketone with lithium acetylide, followed by treatment with thionyl chloride. Base treatment in the presence of excess olefin gave vinylidene cyclopropanes (68) in 7-64% yield¹⁷. Best results were obtained under phase transfer conditions with aqueous potassium hydroxide 18-crown-6, or quaternary ammonium salts.^{17f} Potassium *t*-butoxide^{17d} was also effective. Though yields are unspectacular in many cases, the simplicity and directness of the approach still recommends it. Esters have been used in place of chloride as leaving group^{17g,h} although this does not appear significantly to affect yields. Carbenes of greatly extended conjugation have also been prepared by this route.^{17g} Dichloroethenylidene carbene (70) was prepared by a related reaction.⁹⁷

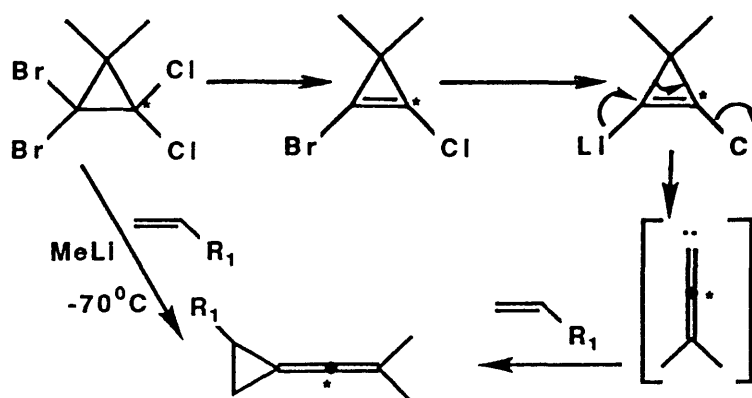
1.17.8b) Primary Vinyl Halides

Amongst the earliest approaches to alkylidene carbenes, superseded by primary vinyl triflates, was α-elimination from primary vinyl halides. In common with the lithium-halogen



exchange- α -elimination reaction of gem-dibromoalkenes, the relatively forcing conditions (potassium t-butoxide in THF at reflux), and low yields of carbene adducts (typically 8-20%),⁹⁸ have favoured the alternative approaches. It is still employed for generation of vinylidene carbenes, where it has been reported to give significantly higher yields than the acetylene route described above.^{17b} Patrick⁹⁹ has studied various modes of carbene generation, and found yields of insertion products to be highest under phase transfer conditions (sodium hydroxide/aliquot 336 - a quaternary ammonium salt). Indeed yields under these conditions were found to be of the order of 20% greater than achieved in the corresponding potassium t-butoxide induced reaction. Competition studies with olefin mixtures suggested an intermediate other than the unassociated vinylidene carbene assumed to be generated with potassium t-butoxide.

Baird has recently reported¹⁰⁰ that vinylidene carbenes may be generated by cleavage of halogenated cyclopropanes, as illustrated in Scheme 50.



SCHEME 50

1.18) Alkylidene Cyclopropane Rearrangements

The methylene cyclopropane rearrangement has been extensively studied by physical organic chemists. The current consensus of opinion concerning the mechanism is that it proceeds via a non-planar trimethylenemethane biradical. Further discussion is beyond the scope of this review, but the interested reader is referred to a number of recent papers.² The rearrangement has been employed to prepare methylene cyclopropanes of substitution patterns inaccessible by other means, via more readily available isomers.¹⁰¹

2.0) PART 2 : REACTIONS

Apart from those reactions normally expected of cyclopropanes, such as hydrogenolytic ring cleavage as a route to the gem-dimethyl moiety, or vinyl cyclopropane ring expansions, the chemistry of alkylidene and vinylidene cyclopropanes is dominated by the exocyclic double bond. sp^3 hybridisation at C-1 of the double bond releases of the order of 11 Kcal mol⁻¹ of strain energy,¹⁰² which provides an excellent driving force for many reactions. Additionally, the cyclopropane bonds are activated by the proximity of a double bond, as of course are the allylic hydrogens. This reactivity, associated with the ready availability of the methylenecyclopropane moiety suggests that they are ideally suited as synthetic intermediates. Discussed below are some of the more synthetically useful transformations of alkylidene- (and vinylidene-) cyclopropanes. In many cases the chemistry exhibited by these systems is unique .

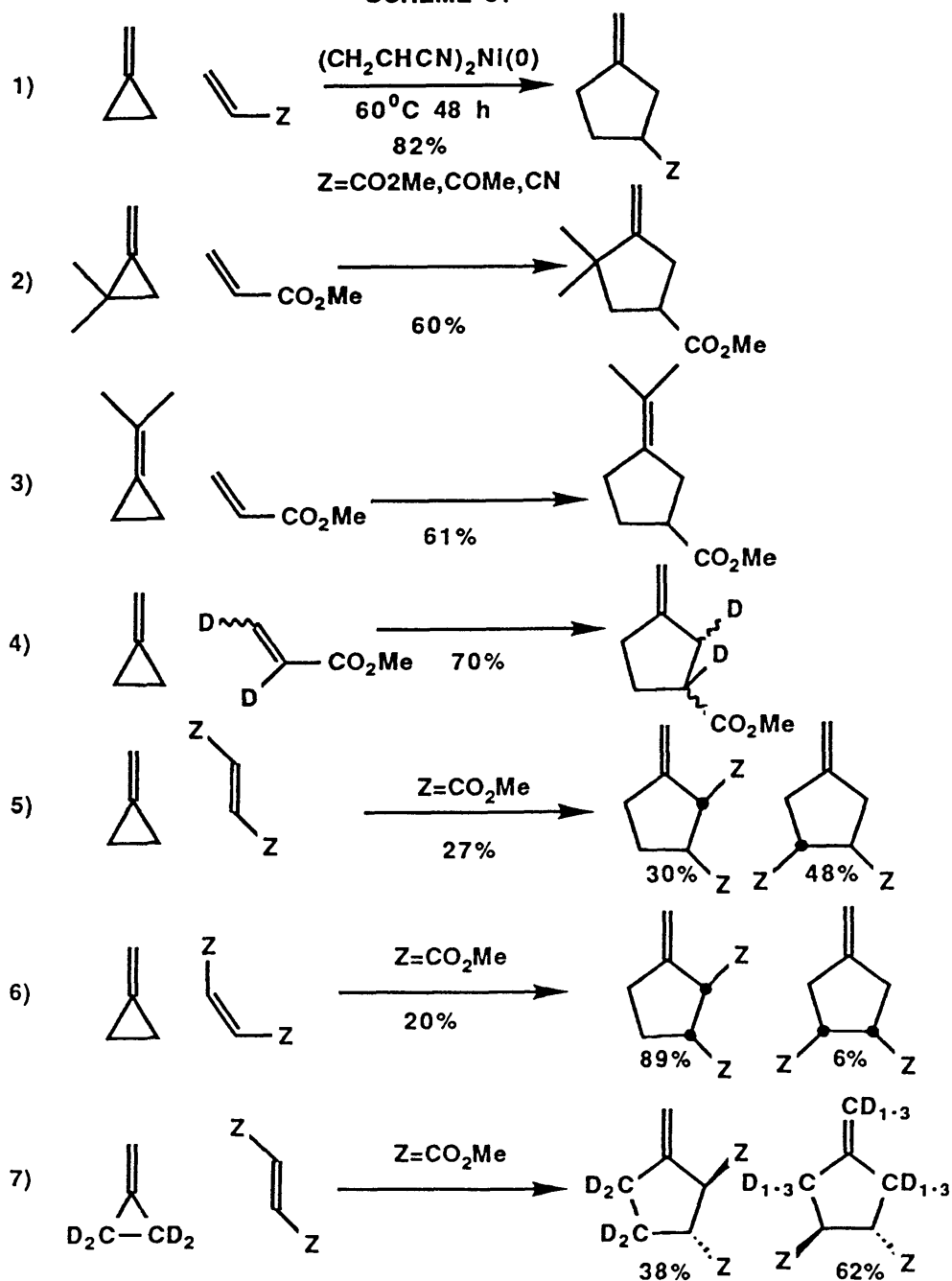
2.1) Palladium(0) and Nickel(0) Catalysed [2 π + 2 π] and [2 π + 2 σ] Reactions

2.1.1) Nickel catalysed [2 π + 2 σ] reactions

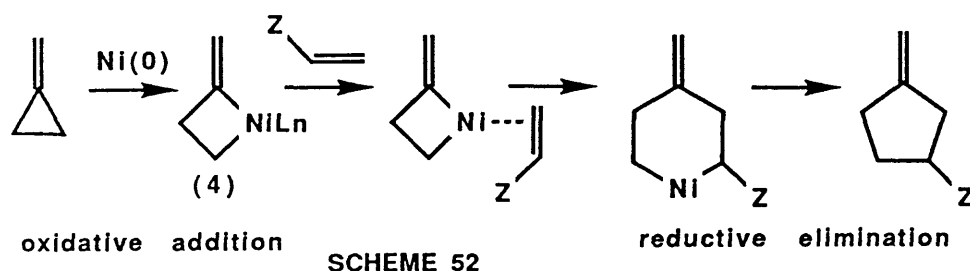
Noyori's discovery⁷ in 1970 that methylenecyclopropane underwent formal [2 π + 2 σ] cycloaddition with polarised electron deficient double bonds, in the presence of a Nickel (0) catalyst, opened an important field of research (Scheme 51). The intervening years have seen extensive studies on this type of [3+2] cyclisation reaction of alkylidenecyclopropanes particularly by the groups of Noyori and of Binger. Although the

subtleties of the mechanisms operating are not fully understood, sufficient is currently known for the methodology to be of synthetic utility, offering an alternative (with subtle variations) to the trimethylenemethane methodology of Trost.⁸

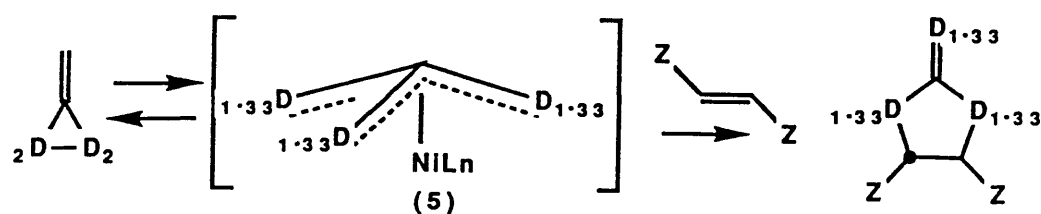
SCHEME 51



Noyori showed that nickel(0) catalysed reaction of methylene-(1) and isopropylidene-(2) cyclopropanes (Scheme 51, entries 1-4) with polarised electron deficient alkenes proceeded by exclusive cleavage of the C_1-C_2 (proximal) cyclopropane bond. An intermediate trimethylenemethane-metal complex was ruled out on the basis that isopropylidenecyclopropane (2) (Entry 3) and 2,2-dimethylmethylenecyclopropane (3) (Entry 2) would pass through a common intermediate, but were observed to give different products. Consequently, formation of a metallo-cyclobutane (4) (Scheme 52) by oxidative addition of a strained carbon-carbon σ -bond to the d^{10} nickel(0) species was proposed.⁷

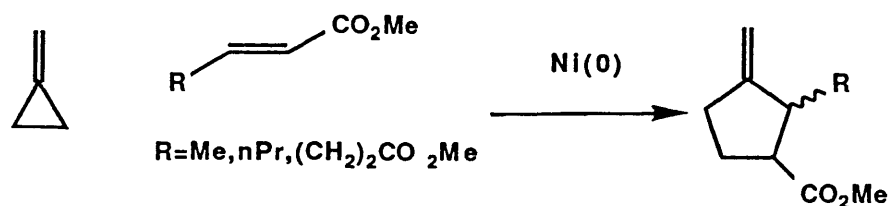


In contrast, the reactions with fumarates and maleates under comparable conditions led to mixtures of C_1-C_2 and C_2-C_3 insertion products in poor yield, with predominant retention of olefin geometry. Elegant deuteration studies (Entry 7 Scheme 51) showed that the expected C_1-C_2 insertion adduct was formed by the previously proposed metallocycle (Scheme 52), whilst statistical scrambling of the deuterium label in the formal C_2-C_3 insertion product suggested intermediacy of a trimethylenemethane complex (5) (Scheme 53).⁹ The pathway which predominates seems to be determined by the structure of the olefin in these cases, however, it is unclear why the E-olefin should favour the latter



SCHEME 53

mechanism, while the Z-isomer proceeds predominantly via the former. Further investigation by Binger^{10,11} with β -substituted acrylates showed that C_1 - C_2 -insertion dominated, as expected, but that some scrambling of olefin stereochemistry occurred, (typically 3:1 in favour of trans) (Scheme 54).

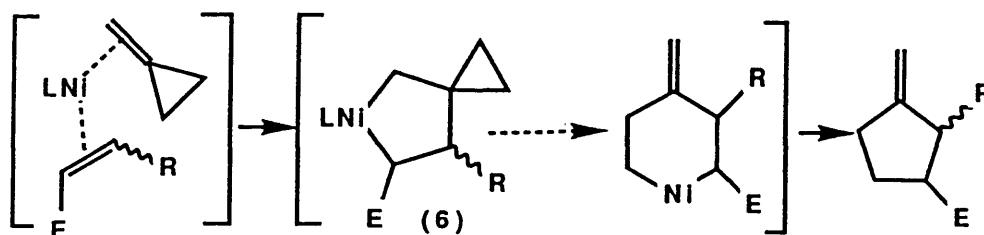


SCHEME 54

25 cis : 75 trans

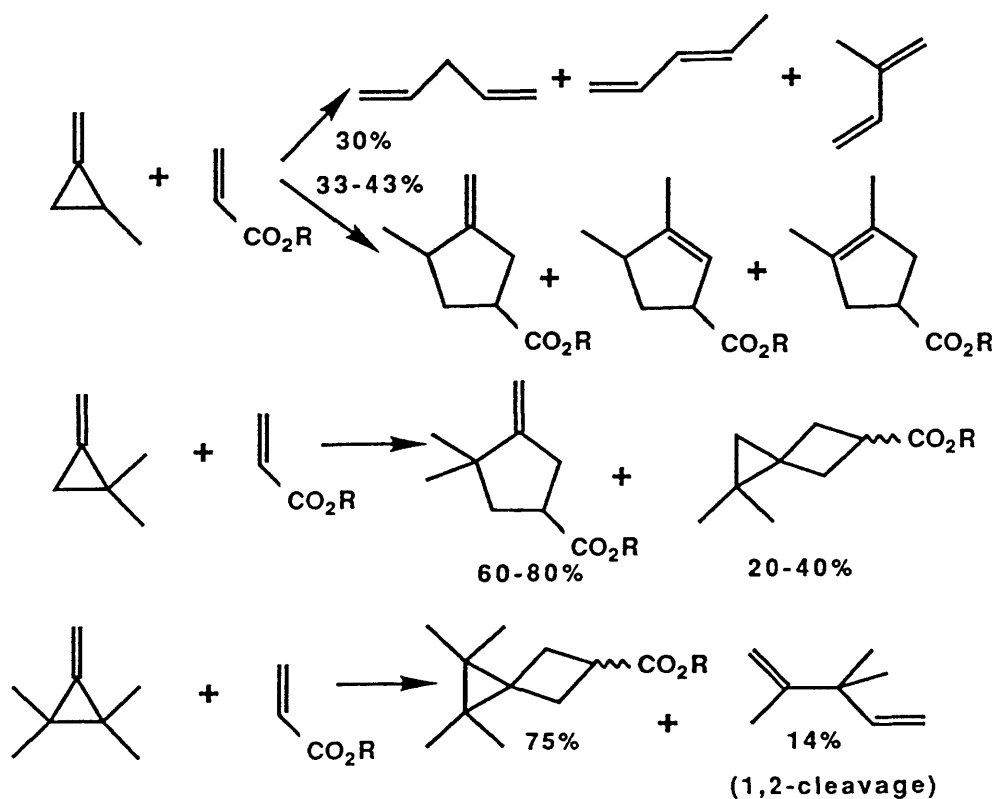
However, reaction with fumarates and maleates at 80 to 100^oC with nickel(COD)₂/triphenylphosphite catalyst gave different results from those observed by Noyori. Only methylene-cyclopentanes resulting from cyclopropane C_2 - C_3 cleavage were observed; trans stereochemistry predominated irrespective of the olefin employed.¹⁰ Since the reaction conditions were very similar, this dichotomy of regio- and stereochemical outcome may be ascribed to the difference in catalyst employed, (Noyori^{7b} used bis(acrylonitrile)nickel(0)). This may be attributed to the Binger catalyst forming a trimethylenemethane complex more easily than the metallocyclobutane proposed by Noyori to account for his observations. Binger has also proposed an alternative mechanism for the 1,2-insertion reaction (Scheme 55), via a

metallocyclopentane (6) for which some precedent exists.¹²



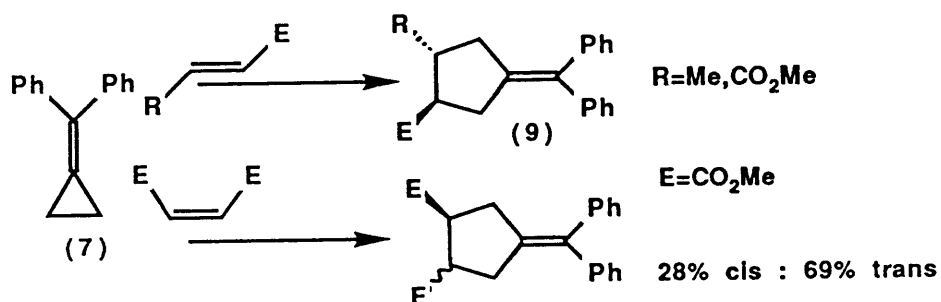
SCHEME 55

Further investigation into the effect of substitution at the exo-methylene,¹³ or on the cyclopropane ring¹¹ complicated the picture still further. Ring substitution was found to lower the reactivity of the cyclopropane, with the result that competing ring cleavage to olefins, and $[2\pi+2\pi]$ reactions with the exo-cyclic methylene became more important (Scheme 56) especially with sterically demanding ester groups.



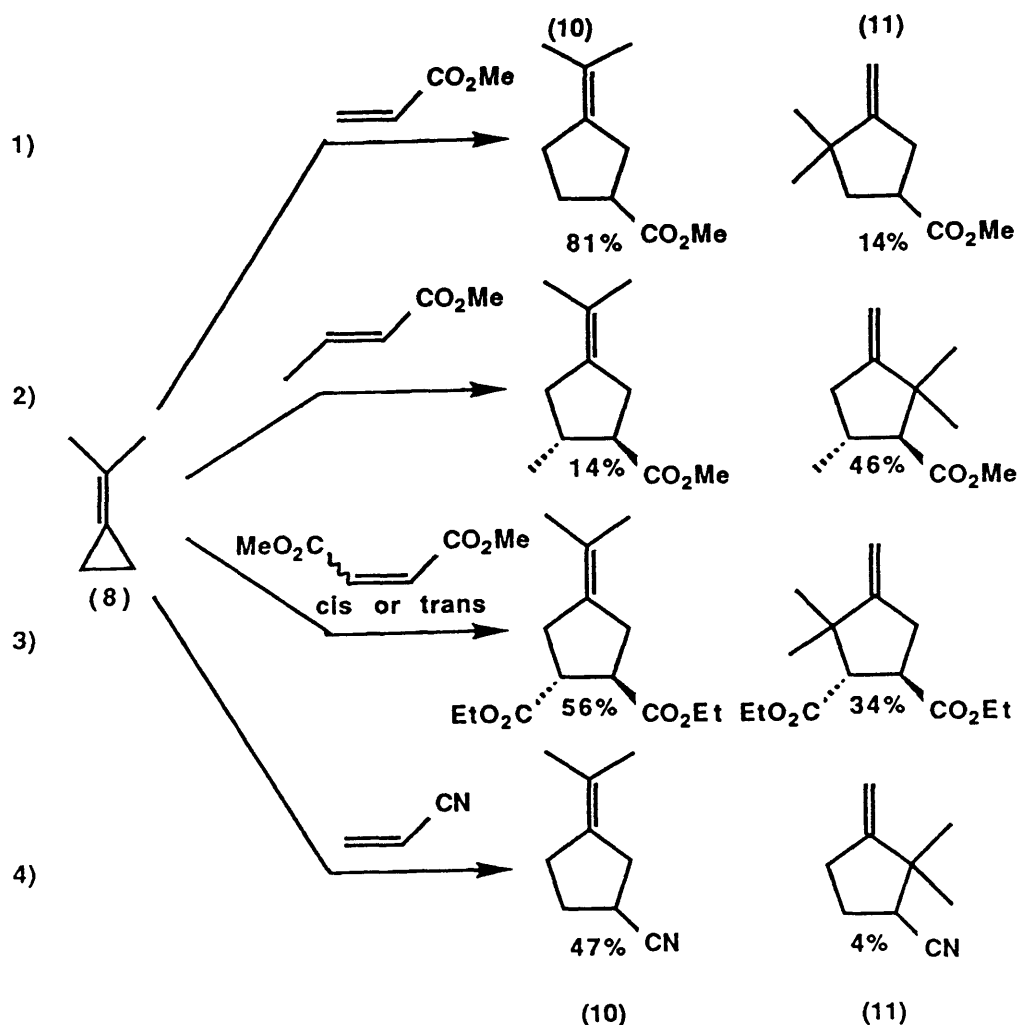
SCHEME 56

It is not clear whether these cyclisation reactions occur by C_1-C_3 or C_2-C_3 bond cleavage, but trimethylenemethane intermediates may be ruled out on the basis that no isopropylidenecyclopentanes were observed. Reactions of diphenylmethylene- (7) and isopropylidene- (8) cyclopropanes gave more synthetically useful results. With diphenylmethylenecyclopropane (7) exclusive insertion into the C_2-C_3 cyclopropane bond is observed (Scheme 57) to give 3,4-disubstituted diphenylmethylenecyclopentanes (9).¹³ Cis olefins again give predominantly trans adducts.



SCHEME 57

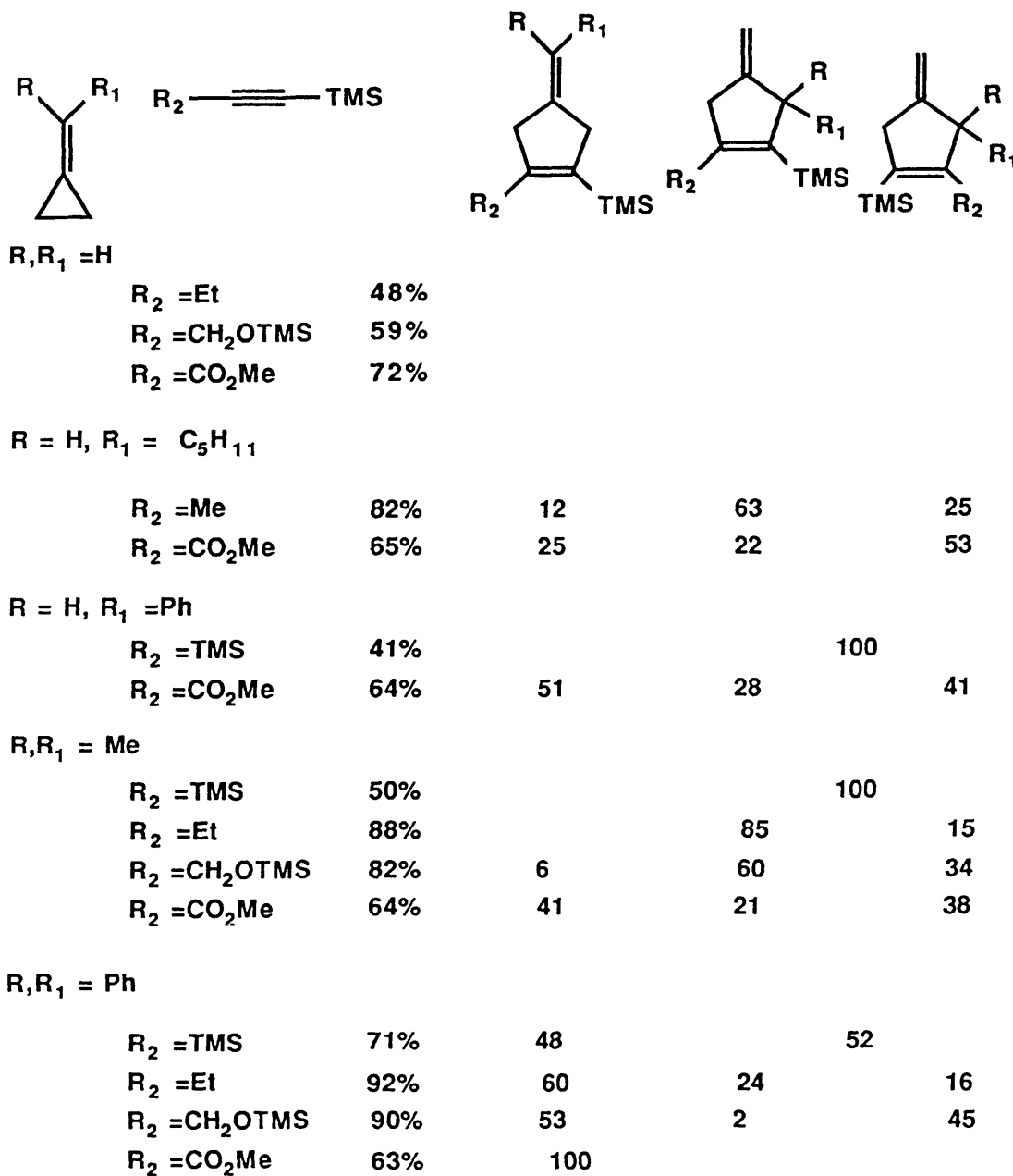
Isopropylidenecyclopropane (8) is observed to give mixtures of isopropylidene- (10) and 2,2 dimethyl-1-(methylene)- (11) cyclopentanes, the former being the major product in most cases (Scheme 58). The adducts (11) resulting from 'migration' of the gem-dimethyl moiety into the ring are formed regiospecifically, with none of the alternative isomer being reported. The regiospecificity observed varies with the olefin, (contrast entry 1 with entry 4), for reasons which remain obscure. A trimethylenemethane complex is, in all probability participating at some point!



SCHEME 58

$\alpha\beta$ -unsaturated ketones were reported to oligomerise too rapidly for cycloaddition to be observed. Similar problems were experienced with propiolate esters, terminal acetylenes and dialkyl acetylenes.¹⁴ A variety of other acetylenes do undergo reaction in 40-92% yield (Scheme 59). Ratios of the possible cycloaddition products are found to be dependent on both methylene substituents and acetylene substituents. In cases where the original methylene substituents migrate into the ring, mixtures of regioisomers result. Except with

diphenylmethylenecyclopropane where products retaining the exo diphenylmethylene moiety prevail, very few generalisations may be



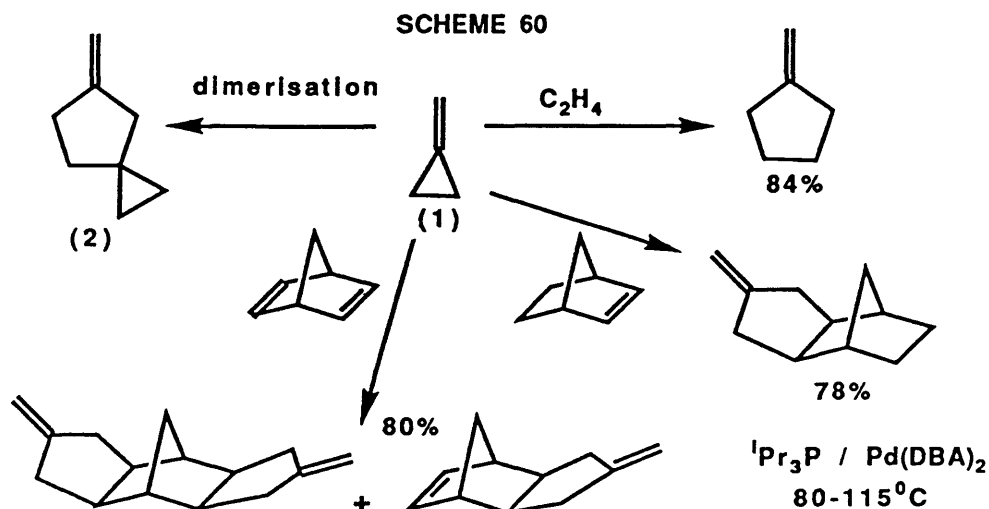
SCHEME 59

made. It does appear, however, that all cycloaddition reactions with acetylenes proceed by cleavage of the distal (C_2-C_3) cyclopropane bond. The claim that all alkenes also give distal cleavage with substituted methylenecyclopropanes¹⁴ is at odds with Noyori's original suggestion and is unsubstantiated. There exists at present no incontrovertible proof of this although, it may be taken as a useful rule of thumb since exceptions are likely to give the same final product by whichever bond cleavage.

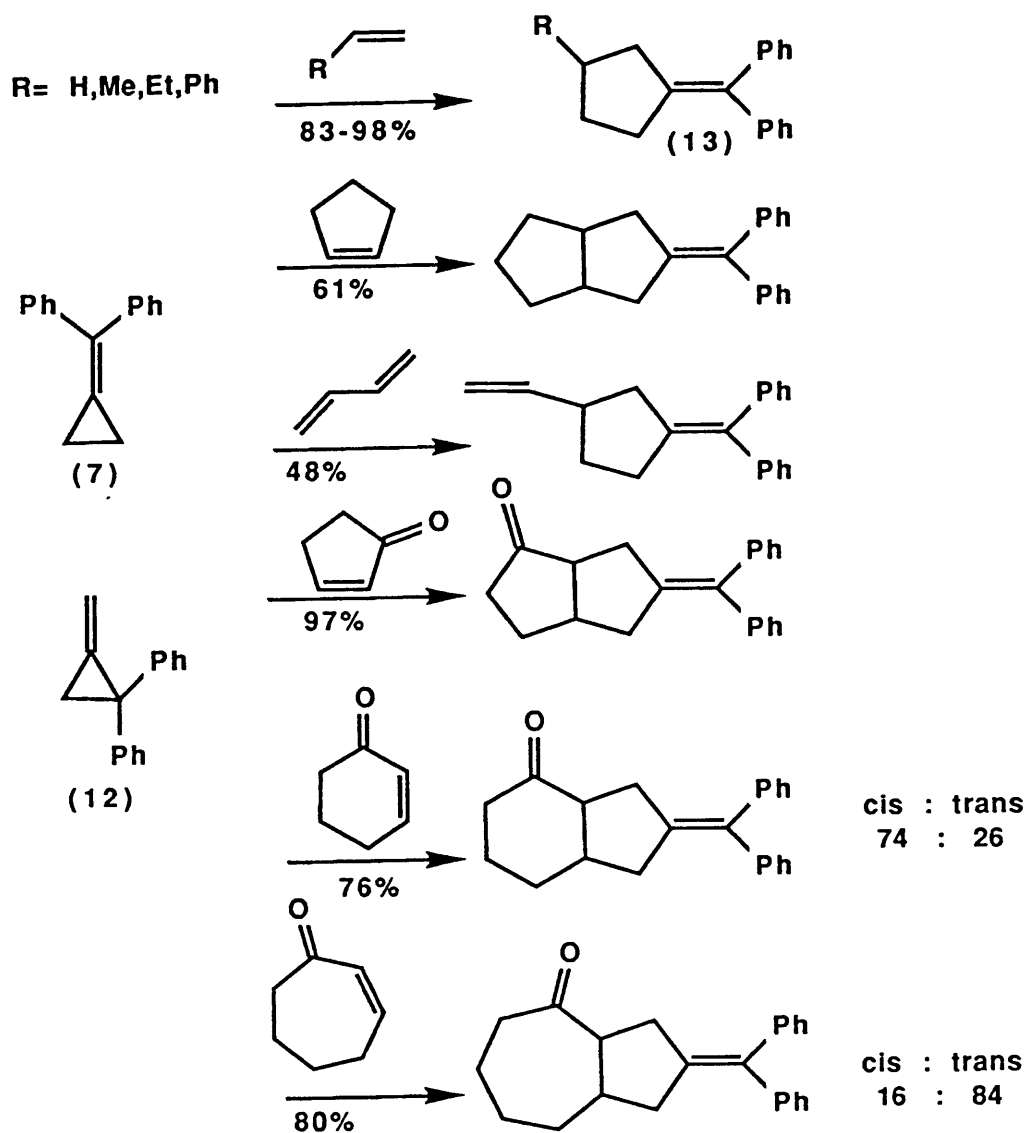
An investigation into choice of triaryl- and trialkyl-phosphines and phosphites with regard to catalyst activity in the nickel promoted reactions revealed that triarylphosphites give best results, whilst trialkyl and triarylphosphines retard or inhibit the reaction. The rate of reaction appears to be inversely related to the donor properties of the phosphine. This is to be expected since these ligands must be displaced by weakly co-ordinating olefin ligands before reaction can proceed.¹³

2.1.2) Palladium catalysed [2π + 2σ] reactions

Binger has investigated the corresponding palladium catalysed reaction to the point where it is now of synthetic utility. With methylenecyclopropane it is applicable to certain electron-rich double bonds (Scheme 60).^{15,16} Unactivated (i.e. unstrained) olefins did not react. The high reactivity of the methylenecyclopropane double bond allowed competing cyclodimerisation. This may be suppressed by use of excess olefin. With electron-deficient olefins results are similar to the nickel catalysed reactions, with the exception that



palladium always cleaves the C_2-C_3 cyclopropane bond,^{16,103} and there is a greater tendency for migration of the double bond into the ring. Higher reaction temperatures and shorter reaction times give better yields and less oligomerisation. It is also interesting to note that trialkylphosphines are the best ligands, in contrast to the situation which prevails with nickel. As with palladium, more than one equivalent of phosphine, with respect to the metal, inhibits the reaction. Palladium catalysed reaction of 1-(diphenylmethylene)cyclopropane (7) or the 2,2-diphenylmethylenecyclopropane isomer (12) (Scheme 61) gave identical results.¹⁰⁴ Reactions are much cleaner than the corresponding nickel catalysed examples. The gem-diphenyl-substitution appears to activate the ring towards a much wider range of electron-rich or electron-deficient olefins than could previously be employed. Only the diphenyl-substituted methylenecyclopentane (13) is observed, in good yield. The phenyl groups also deactivate the double bond to the extent that

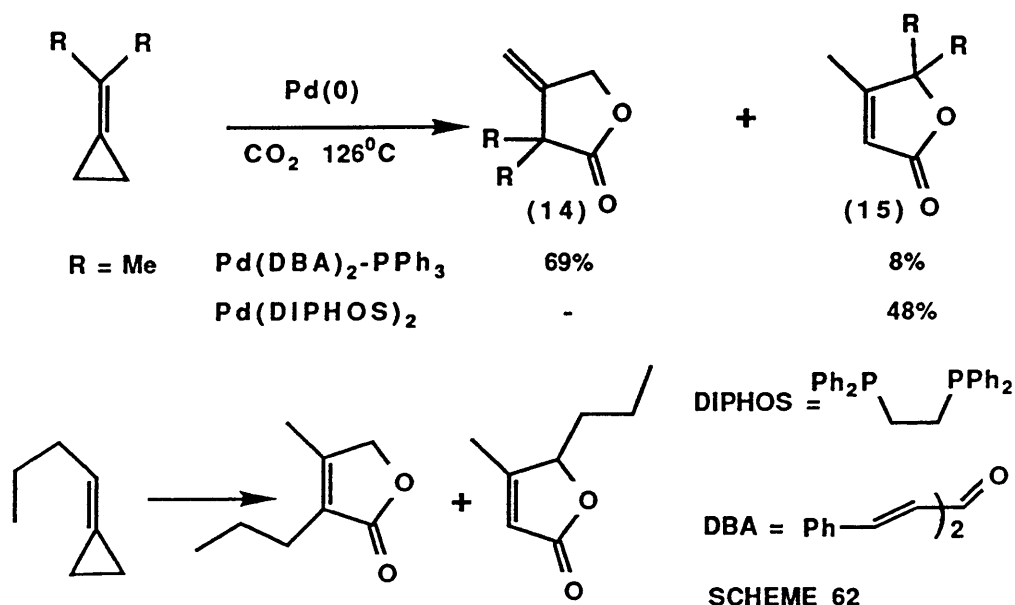


SCHEME 61

cyclodimerisation or diene formation no longer compete. Scheme 61 shows some examples.¹⁰⁴ Since both (7) and (12) gave identical products, a trimethylene-methane complex is a likely intermediate.

Alkyldienecyclopropanes also undergo palladium catalysed cycloaddition with carbon dioxide to give lactones¹⁰⁵. Mixtures of regio-isomers were formed, but the exact distribution appears to be catalyst dependent (Scheme 62).

Methylenecyclopropanes bearing ring substituents did not react.

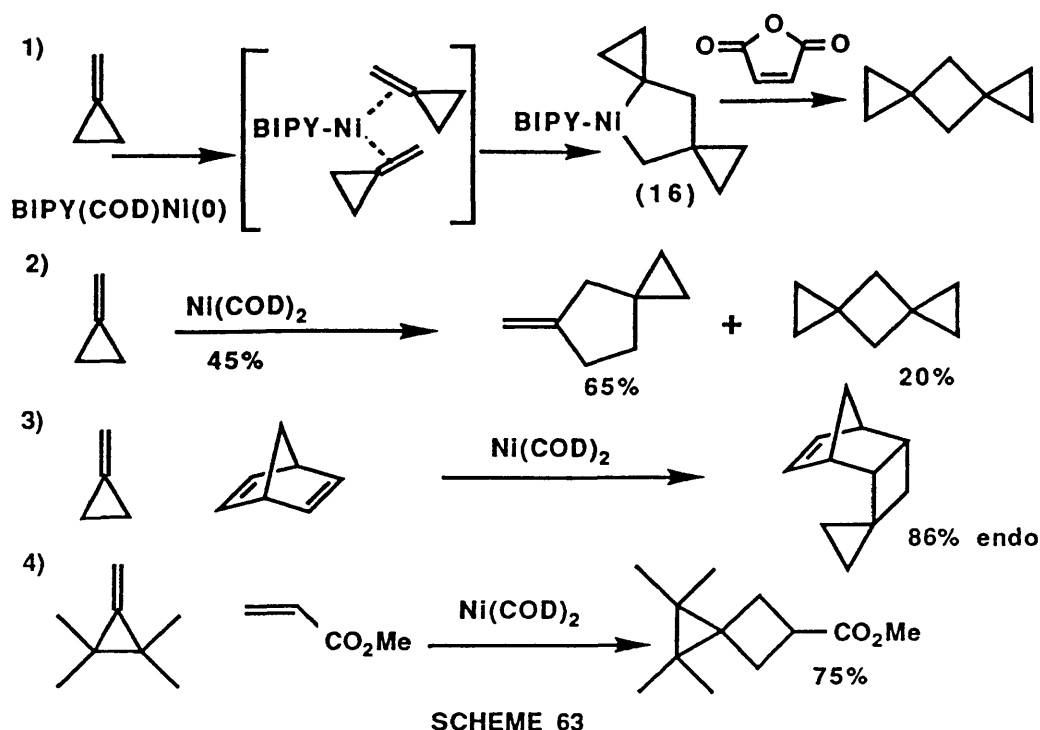


A dependence on the phosphine ligands was observed which may account for this: less basic phosphines such as triphenylphosphine or triethylphosphine favour formation of lactone (14), while more basic phosphines (such as diphos) give lactone (15), and tend to isomerise the double bond into conjugation with the ester.

Binger also investigated cycloadditions with allenes¹⁰⁶ but reactions were messy and low yielding, with allene oligomerisation being the favoured competing reaction.

2.1.3) $[2\pi + 2\pi]$ Reactions and Cycloolimerisation

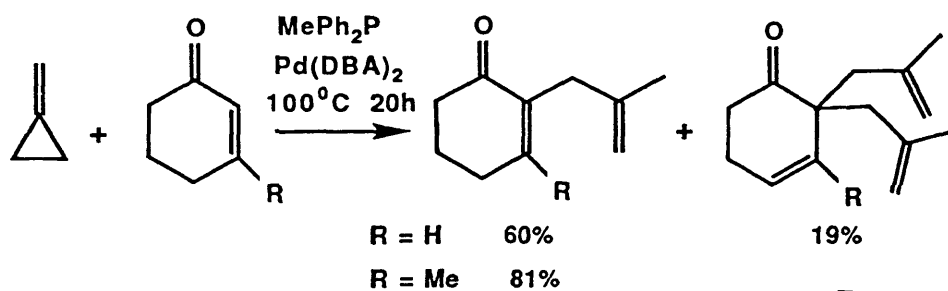
Cyclodimerisation of methylenecyclopropanes has been more commonly observed under palladium catalysis, but also occurs with nickel. The corresponding $[2\pi + 2\pi]$ cycloaddition has only been observed under nickel catalysis^{11,12,107,108} (Scheme 63).



The nature of the nickel-bipyridyl metallocycle (16), (scheme 63 entry 1)¹² was rigorously established by x-ray crystallography. Treatment with reactive olefins displaced the metallocycle as the formal $[2\pi + 2\pi]$ adduct of methylene cyclopropane. Noyori¹⁰⁷ (equation 3) obtained exclusively the endo- $[2\pi + 2\pi]$ adduct with norbornadiene. The yield and stereospecificity dropped when catalyst/phosphine ratio varied significantly from the optimum 1:1 ratio. The corresponding asymmetric cycloaddition using a chiral nickel(0) catalyst, derived from a chiral phosphine ligand, furnished the corresponding optically active $[2\pi + 2\pi]$ adduct in 48% yield, although absolute configuration and optical yields were not determined. Binger observed competing cyclobutane formation in the reaction of methylenecyclopropanes with acrylate esters¹¹ (See Scheme 56). It was suggested that these predominated when steric hindrance caused by ring substituents inhibited the

[3+2] reaction, despite the expected tendency for cleavage to become more facile to relieve steric interactions. Cyclobutane formation could also be enhanced by employing the more sterically demanding *t*-butyl esters.

Finally, in this section, a single report¹⁰⁹ of a rather intriguing α -alkylation of α,β -unsaturated ketones with methylenecyclopropane deserves special mention (Scheme 64). In



SCHEME 64

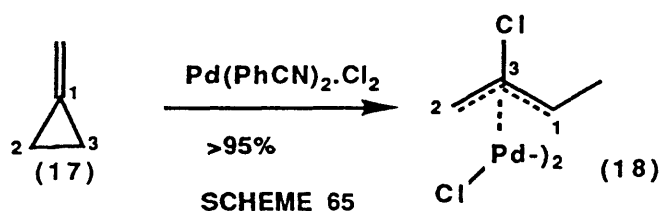
the absence of phosphine, or when greater than two equivalents were employed, no reaction was observed. The selectivity for monomethylation when *R* = methyl is ascribed to formation of a tetra-substituted double bond, which is too sterically congested to co-ordinate the palladium effectively. Where the substituent is not present, the ratio of mono- to dialkylation can be substantially increased by employing excess ketone. No reports of similar reactions were made in any of the other studies referenced either before or since this discovery, nor has any mechanism been proffered.

Whilst the palladium and nickel induced cyclisation reactions of methylenecyclopropanes have been clearly demonstrated to possess important potential for organic synthesis, a considerable number of ambiguities and unanswered

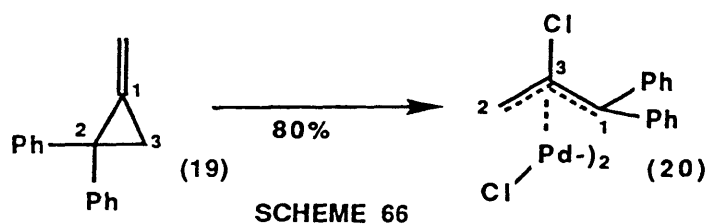
questions remain. This area of organometallic chemistry can only benefit from the detailed and careful mechanistic studies which have been applied to other transition metal-methylenecyclopropane complexes in recent years (see below).

2.2) Chloropalladation of Methylenecyclopropanes

Like much of the transition metal chemistry of methylenecyclopropanes, it was a discovery made by Noyori¹¹⁰ which initiated research in this area. Methylenecyclopropane (17) was observed to form a crystalline π -allyl complex (18) on treatment with dichloro-bis(benzonitrile)palladium at room temperature, by exclusive cleavage of the C₁-C₂ (proximal) cyclopropane σ -bond (Scheme 65).



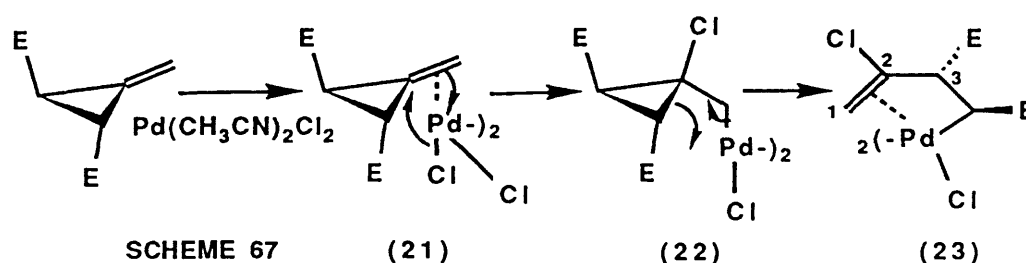
Similar reaction of 2,2-diphenyl-methylenecyclopropane (19) gave an 80% yield of π -allyl complex (20) by exclusive cleavage of the cyclopropane C₂-C₃ (distal) bond (Scheme 66). It was the



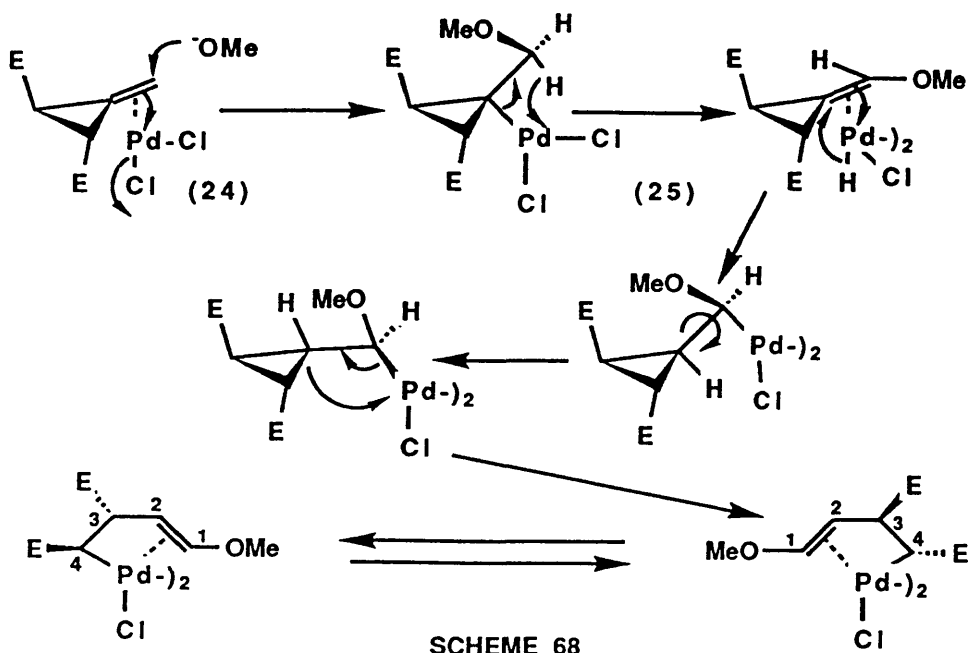
dichotomy of regioselectivity in ring cleavage, apparently

substituent dependent, which stimulated the further work.

Green and Hughes¹¹¹ showed that cis- or trans- methyl esters of Feist's acid gave exclusive cleavage of the cyclopropane C₁-C₂ σ -bond in analogy with methylenecyclopropane. The observed stereochemistry of the π -allyl complexes allowed a mechanism for 1,2-insertion to be suggested. Initial formation of a η^2 -methylenecyclopropane complex (21) is followed by intramolecular nucleophilic attack by chloride on the internal olefinic carbon (22). Electrophilic attack by palladium on the 1,2-bond of the ring then leads to stereospecific ring opening to give (23) (Scheme 67) with retention of configuration at the erstwhile ester substituted cyclopropane carbon.



Furthermore, in the presence of an external source of nucleophile (methoxide), no chlorinated material was observed. Enol ethers were the only products observed. In this case, η^2 -complex formation is followed by nucleophilic attack exclusively at the exocyclic carbon, (24). Hydride transfer via the metal (25) then precedes electrophilic ring opening as before (Scheme 68). With sterically undemanding nucleophiles, (methanol, ethanol), only the trans-enol ether is formed. Bulky nucleophiles, however, (t-butanol), gave exclusively the cis-enol ether.



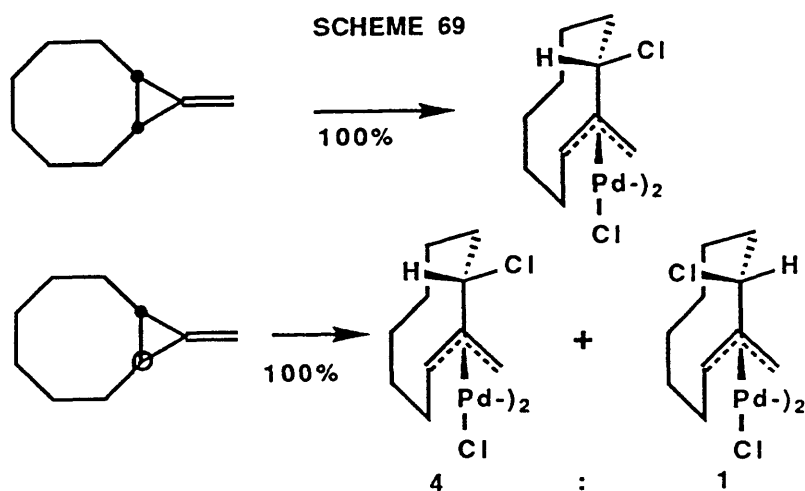
Isopropanol, being of intermediate steric requirements, gave a cis- and trans- mixture. In addition, the enol ether exists in solution as an equilibrating mixture of both ring conformers. This is not the case for the vinyl chloride products, an observation as an equilibrating mixture of both ring conformers. This is not the case for the vinyl chloride products, an observation attributed to conformational locking by minimisation of steric interactions between the chloride substituent at the 2 position with the ester appended at position 3 (Scheme 67). With the enol ethers this situation does not apply, and conformers may interconvert by dissociation of the olefin, rotation about the C_2-C_3 bond, and reformation of the olefin-metal bond.

A similar study of the cis- ester of Feist's acid showed a much faster rate for chloropalladation in non-nucleophilic solvents, which is consistent with intramolecular delivery of the chloride. In nucleophilic solvents, such as alcohols, only alkyl enolethers are observed, as before. However, in all cases,

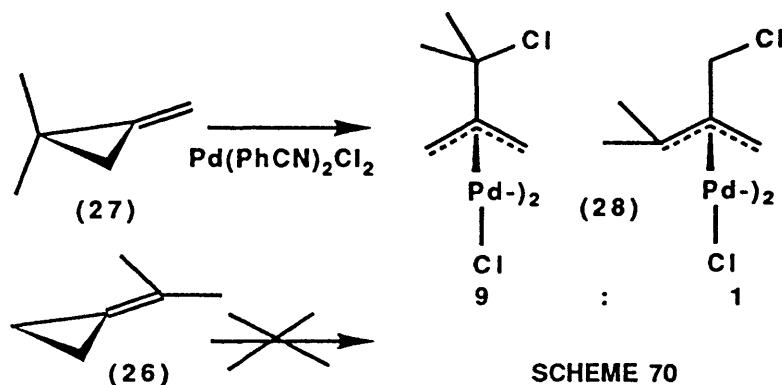
regardless of steric bulk, the trans- enol ether was formed exclusively.

While steric factors are obviously at play in the chloropalladation reactions, the mechanism is not clear. Consequently the difference in regioselectivity of nucleophilic attack between the intramolecular and intermolecular reactions remains unexplained.

Further work by Albright *et al*¹¹² on cis- and trans- fused bicyclic methylenecyclopropanes showed that the elements of palladium and chlorine were added in 1,3-fashion to the methylenecyclopropane moiety in a suprafacial sense, with disrotatory ring cleavage at the C₂-C₃ σ-bond (Scheme 69), in analogy with 2,2-diphenyl-methylenecyclopropane. Furthermore, isopropylidenecyclopropane (26) was found to be completely inert towards chloropalladation, an observation for which no rationale

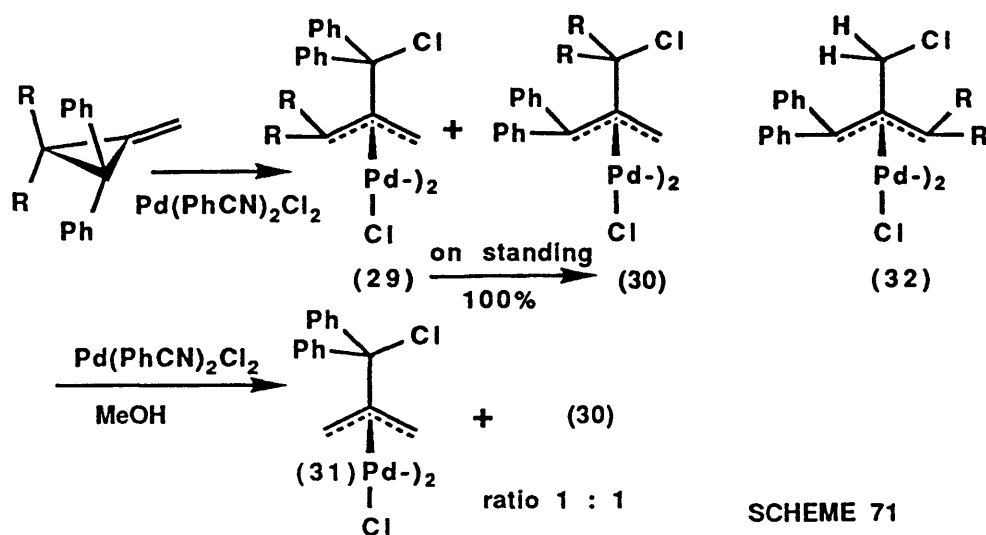


has been proposed. 2,2-Dimethyl-methylenecyclopropane (27) gave predominantly the C₂-chlorinated π-allyl palladium complex (28) (Scheme 70).



The minor isomer derived from chlorination at C_3 was not interconvertible with the major product. Cis- and trans-2,3-dimethyl-methylenecyclopropane each separately gave an identical product distribution of two diastereoisomeric-enantiomeric pairs. Clearly a different mechanism operates in these cases since not only does chloropalladation proceed with C_2 - C_3 cyclopropane bond cleavage and chloride migration to a saturated ring carbon atom, but reaction in nucleophilic solvents such as methanol gives only chloropalladation. No methoxide incorporation is observed.

In view of the reported transformation of (27) to (28), Hughes et al.¹¹³ reinvestigated the original reaction of 2,2-diphenyl-methylenecyclopropane¹¹⁰ (19). Chloropalladation gave initially π -allyl complexes derived from chlorination at C_2 (29) or C_3 (30) of the cyclopropane in equal proportions. On standing, quantitative conversion to (30) occurred (Scheme 71). With added methanol a 1:1 mixture of (30) and (31) was obtained, which did not isomerise further. Deuteration at C_3 of (19) proved that chlorination was initiated only at C_2 or C_3 . Isomerisation then gave (30) and (32) in 3:1 ratio. No (32) was formed initially. In conjunction with results obtained on chloropalladation of 2-phenyl-methylenecyclopropane, it was shown

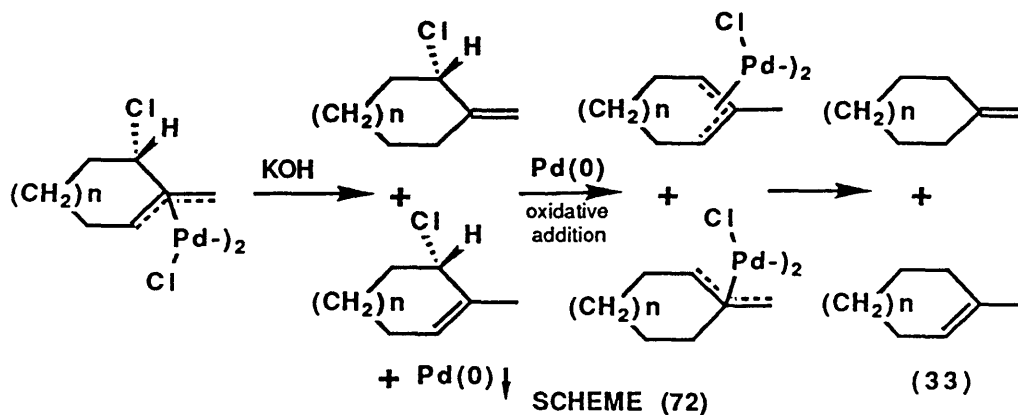


that (31) arose by attack of methanol on the (29) formed initially. Thus it transpires that chloropalladation of phenyl-substituted methylenecyclopropanes occurs with no initial selectivity between chlorination at C_2 or C_3 . 2,2-Dimethyl methylenecyclopropane (27), however, shows a strong kinetic preference for chlorination at the more highly substituted centre of C_2 .

One clear fact emerges from the detail of the foregoing discussion; the mechanism of the chloropalladation reaction is highly dependent on the substitution pattern of the methylenecyclopropane substrate. The yields of π -allyl complexes obtained are very high in all cases studied, with the exception of isopropylidenecyclopropane (26) which is totally inert. High regio- and diastereoselectivity are often observed.

Finally, Donaldson and Taylor¹¹⁴ have shown that treatment of the palladium-allyl complexes with 1 molar potassium hydroxide at room temperature simultaneously cleaves the palladium and

reduces the C-Cl bond as well. This reduction is considered to arise from reformation of a π -allyl complex from the allylic chloride initially released (Scheme 72).

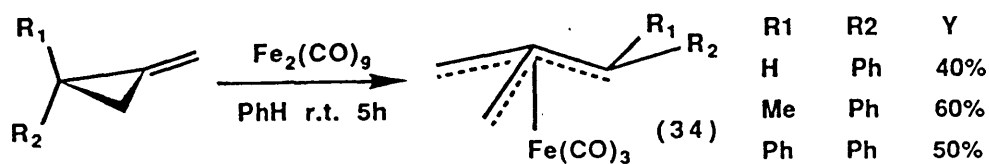


The endocyclic olefin (33) predominates. Minor traces of allyl ethers are also formed by solvolysis of the allyl chloride intermediate.

Although further development is required before the full synthetic potential of the chloropalladation reaction can be realised, these initial results hold much promise for the future.

2.3) Some Other Transition Metal Chemistry of Alkylidene Cyclopropanes

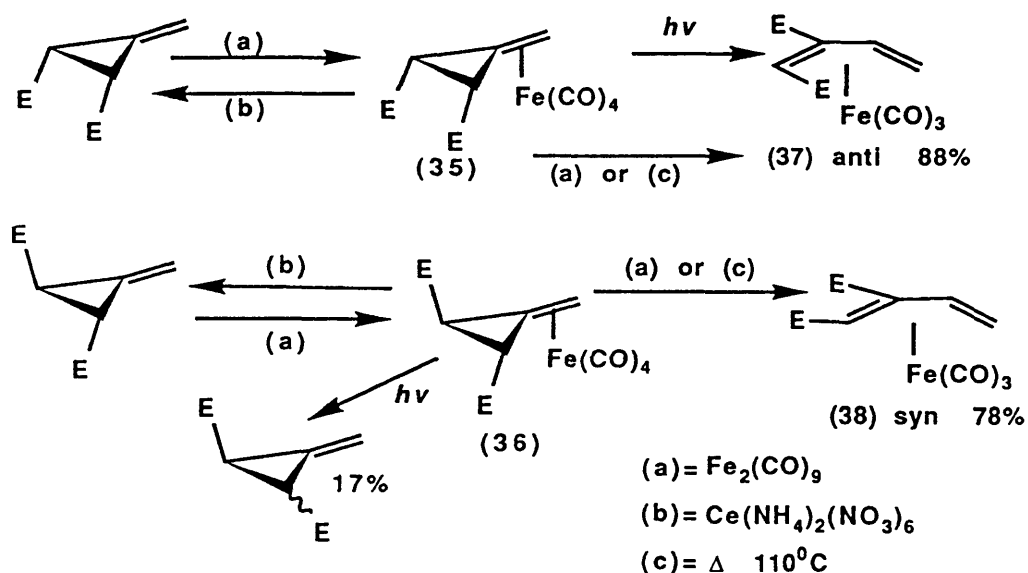
Again, Noyori's contribution ¹¹⁵ was at the pioneering stage when he reported in 1969 the preparation of a number of tricarbonyl-(phenyltrimethylenemethane)-iron complexes (34) by reaction of substituted methylenecyclopropanes with di-iron nonacarbonyl at room temperature (Scheme 73).



SCHEME 73

Methylenecyclopropane itself was reported not to give a trimethylenemethane complex.

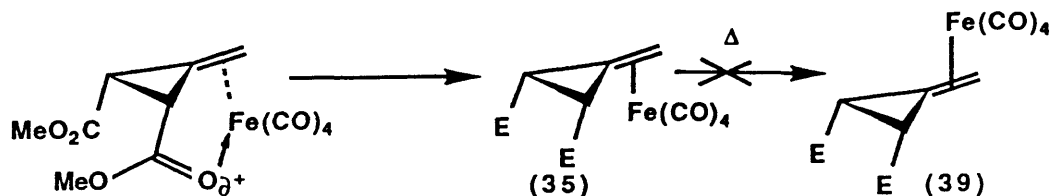
An early report by Whitesides⁴, in a series of thorough and elegant studies in this field, indicated that similar reaction with cis- or trans- methyl esters of Feist's acid gave the corresponding η^2 -iron tetracarbonyl complexes (35) and (36) in 65% and 88% yields respectively. On treatment with ceric ammonium nitrate, complex (36) released the intact Feist ester in high yield without isomerisation. Thermolysis in toluene, or treatment of the η^2 -complex with excess di-iron nonacarbonyl at room temperature gave good yields of diene complexes (37) and (38) by a stereospecific route (Scheme 74).



SCHEME 74

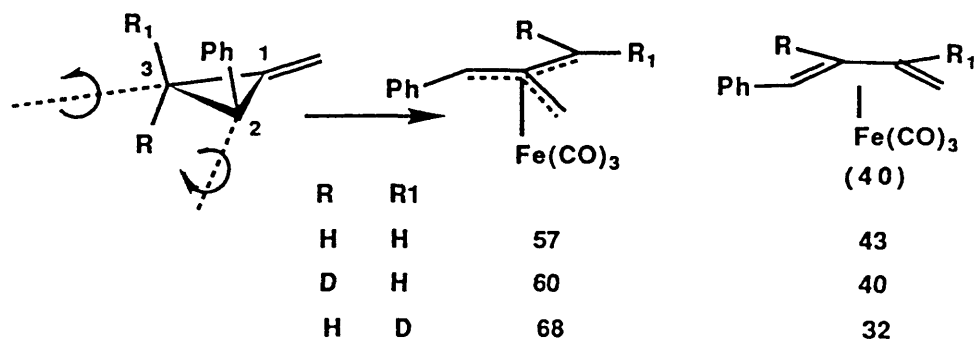
That the complex (35) formed from the cis-methyl ester of Feist's acid has the cis-cis stereochemistry, with the metal atom occupying the same face of the ring as the ester substituents, was determined by x-ray diffraction studies¹¹⁶. Anchimeric assistance from the ester carbonyl was invoked to explain its formation (Scheme 75). Cis-cis isomer (35) appears relatively

thermally stable, showing no tendency to rearrange to the less sterically encumbered trans-isomer (39).



SCHEME 75

Kagan et al.¹¹⁷ reported a similar study in which a chiral Feist ester was shown to remain optically pure throughout the complexation-decomplexation procedure. The cis- η^2 -complex (35) was epimerised to the trans- isomer (36) by treatment with sodium ethoxide. Carpenter then reported¹¹⁸ his detailed studies on the original observations of Noyori, which also served to explain the stereospecific formation of the iron-diene complexes (40). Various stereospecifically deuterated phenylmethylenecyclopropanes were prepared, and the reaction with di-ironnonacarbonyl studied (Scheme 76).

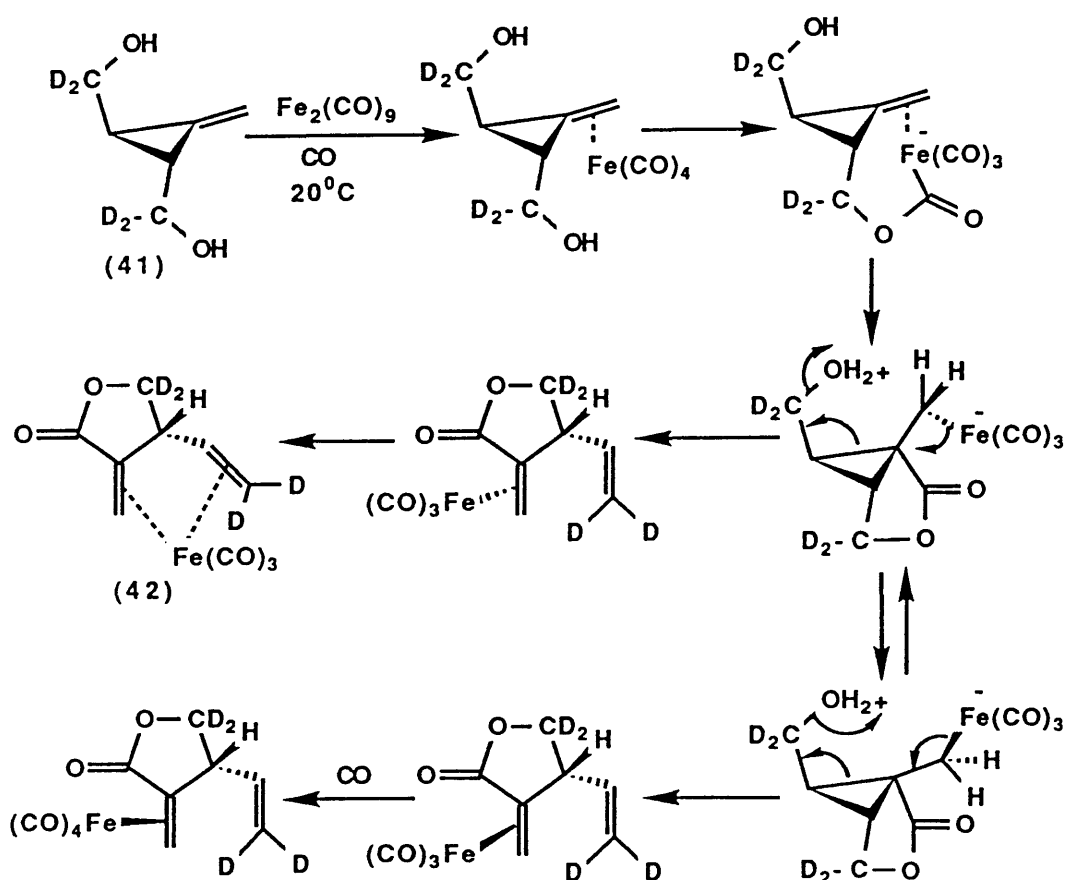


SCHEME 76

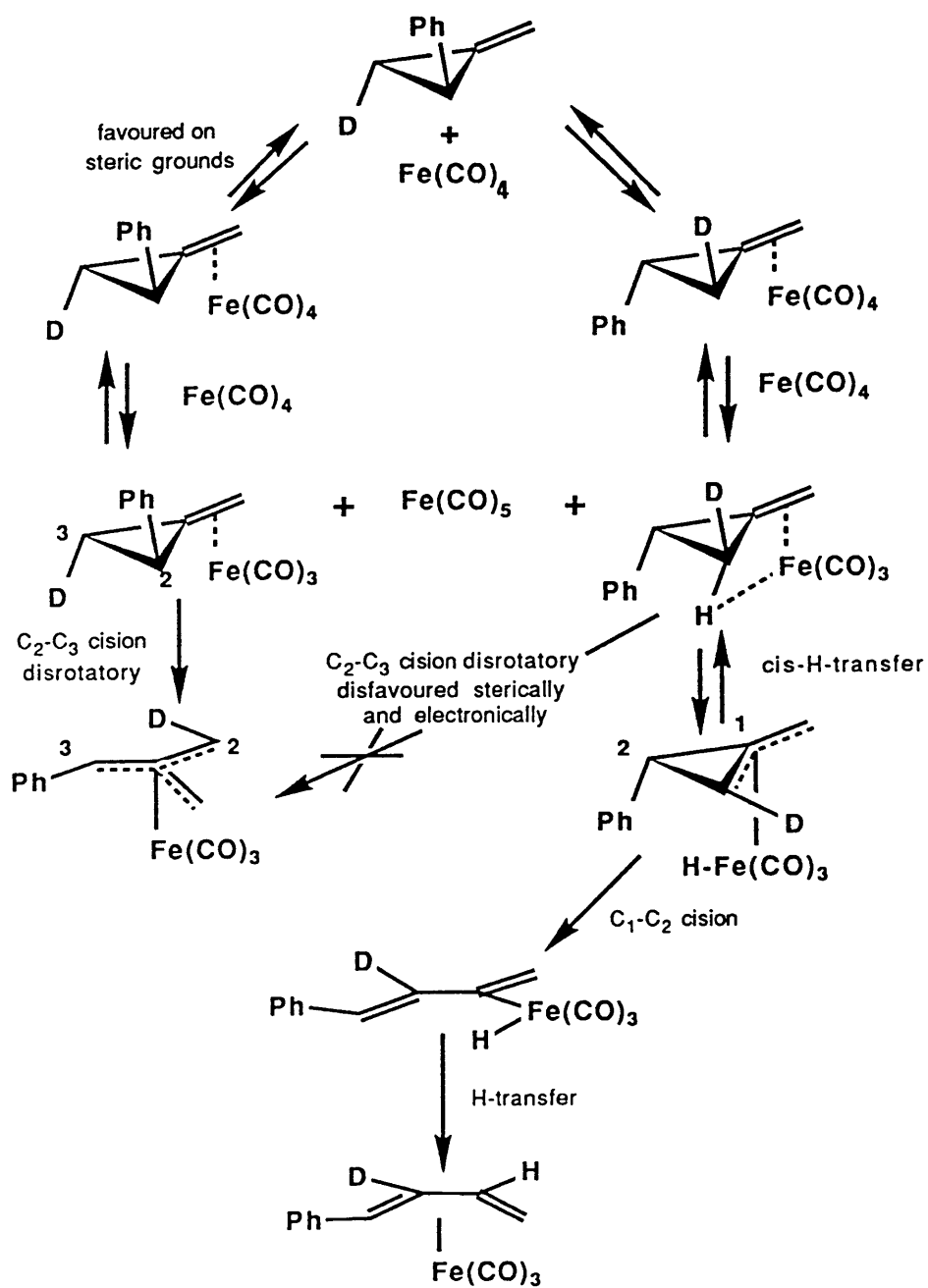
These results brought to light a number of interesting points.

- (a) Ring opening to the trimethylenemethane complex proceeds by a stereospecific disrotatory cleavage of the $\text{C}_2\text{-C}_3$ σ -bond.

(b) Diene complexes, not observed by Noyori, formed on prolonging the reaction time. Formation of these requires C_1-C_2 bond cleavage and proton migration from C_3 to C_1 . This migration is also stereospecific; only the proton (deuteron) cis to the phenyl substituent migrates. From these and other¹¹⁹ results, a mechanism was proposed which explained all the observations (Scheme 77). Welch et al¹⁷⁰ observed carbon monoxide insertion to form γ -lactones (42) when trans-2,3-bis(hydroxymethyl)methylene-cyclopropane (41) was treated with di-iron nonacarbonyl under an atmosphere of carbon monoxide. Again on the basis of deuteration studies a mechanism was proposed (Scheme 78).

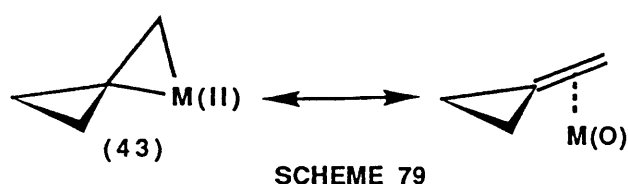


SCHEME 78



SCHEME 77

The propensity for methylenecyclopropanes to form η^2 -complexes is well known for a range of transition metals. This susceptibility is ascribed¹¹⁶ to the importance of resonance form (43) (Scheme 79) when acting as a π -acceptor; reducing the strain energy of the system by partial destruction of the double-bond character of the exomethylene moiety. η^2 -bonded complexes of rhodium(I), iridium(I), platinum(0) and platinum(II) are



known for a variety of substituted methylene cyclopropanes.¹⁷¹ These complexes are both thermally and photochemically stable. Very interestingly molybdenum, however, shows a tendency to give trimethylenemethane complexes even with methylenecyclopropane itself.¹⁷² In common with iron, the ring opening has been shown to proceed stereospecifically in a disrotatory sense.

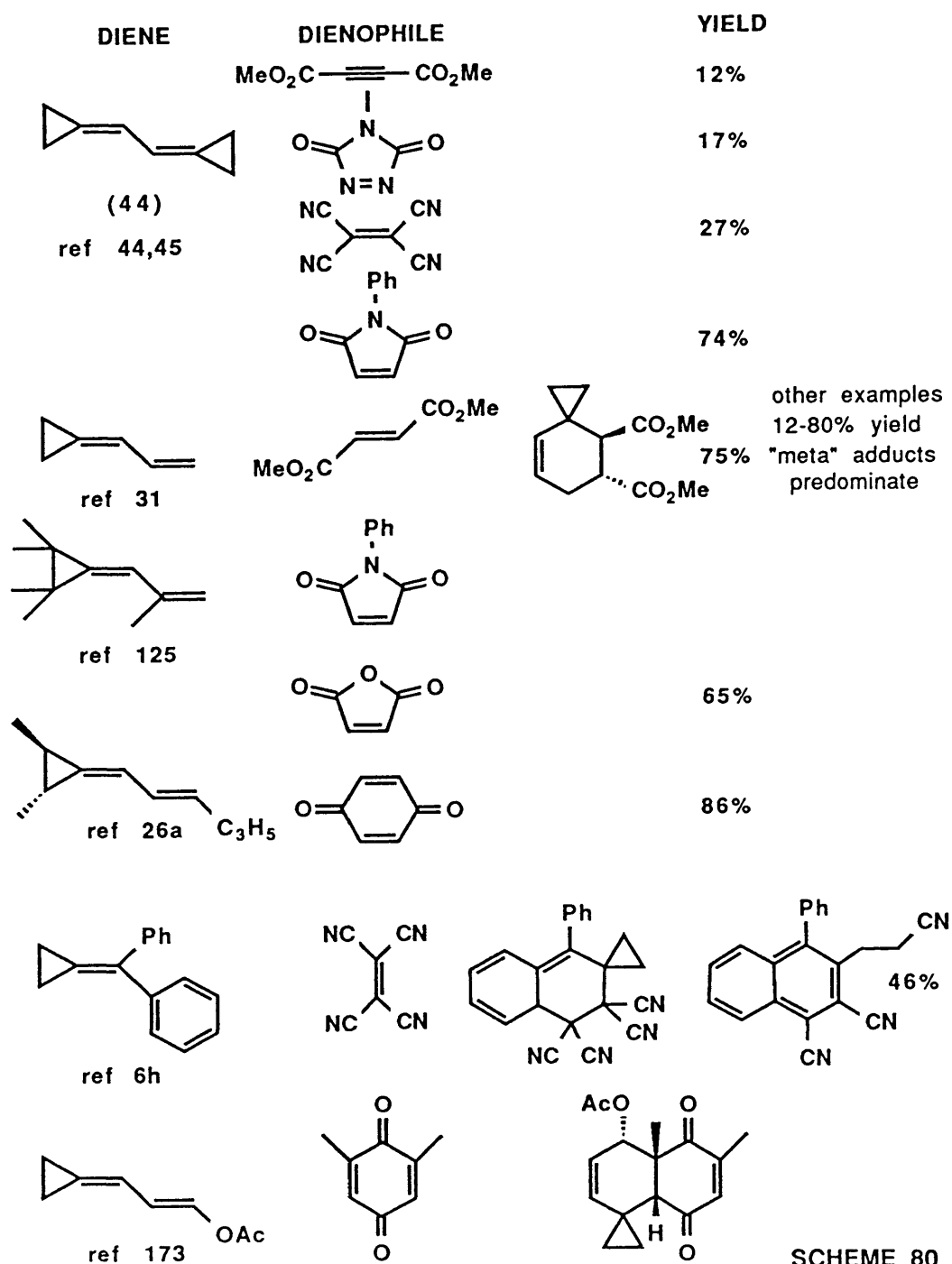
2.4) Electrocyclic Reactions

2.4.1) [4 π + 2 π]

2.4.1a) As Dienes

The importance of alkylidenecyclopropanes as part of a diene system lies in their much greater reactivity than the corresponding dienes with gem-dimethyl groups at the terminus. Paquette for example⁴⁵ showed dicyclopropylideneethane (44) (Scheme 80) to be a much more reactive diene than 1,1,4,4-tetramethylbutadiene. This is due in part to the less sterically demanding nature of the cyclopropane ring, and also to the

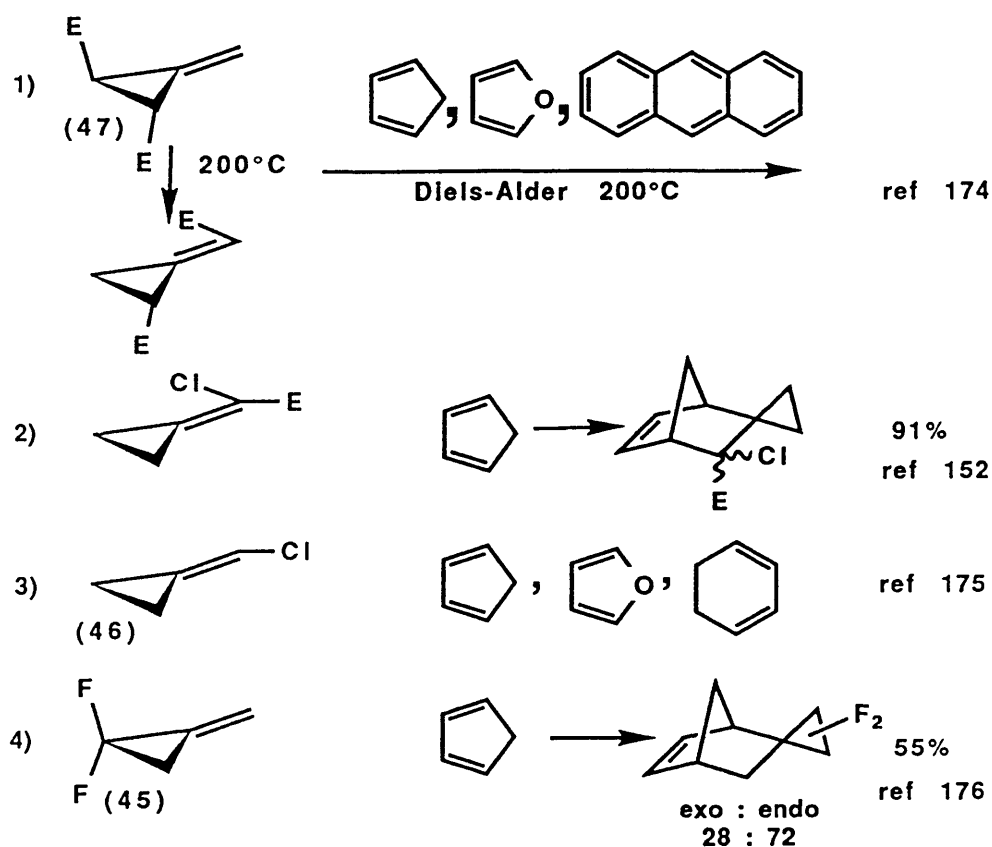
considerable release of strain energy (22kcal) when two methylenecyclopropane moieties are destroyed on cyclisation. The cyclopropane moieties thus incorporated in the Diels-Alder adduct are equivalent to masked gem-dimethyl substituents, released by hydrogenolysis. Such a diene was employed in a Diels-Alder approach to the AB ring system of Forskolin¹⁷³.



SCHEME 80

2.4.1b) As Dienophiles

As reactive double bonds, alkylidenecyclopropanes undergo Diels-Alder reactions with a variety of active dienes. Examples are given in Scheme 81. Trans-Feist ester (entry 1) underwent thermal rearrangement under the reaction conditions, to give two

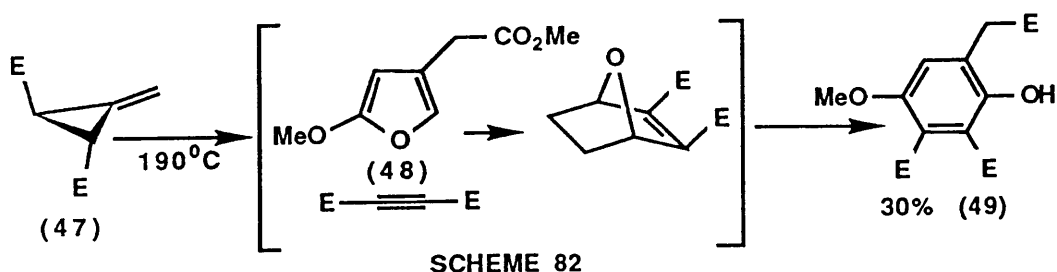


SCHEME 81

sets of Diels-Alder adducts. 2,2-Difluoromethylenecyclopropane (45, entry 4) gave predominantly endo-Diels-Alder adducts. The isomeric difluoromethylenecyclopropane did not undergo Diels-Alder cyclisation in keeping with the generally poor dienophilic properties of fluorinated alkenes. The allylic gem-difluoride substituents of (45) activate the double bond towards dieneophiles by lowering the energy of the LUMO, presumably by inductive electron withdrawal from the π -system. Chloromethylene-

cyclopropane (46, entry 3) also gave predominantly kinetic endo-adducts with a variety of dienophiles. However, further heating of the reaction mixture resulted in isomerisation to the thermodynamic exo-adduct by a cycloreversion-recyclisation mechanism.

A reported¹⁷⁴ rearrangement of trans-Feist ester (47) at 190°C gave furan (48) which was trapped with methyl acetylene dicarboxylate to give the highly functionalised aromatic (49) in 30% yield (Scheme 82).



2.4.2) [2 π +2 π] Adducts and Dimers

The reactions described herein are thought to be radical in nature, the electrocyclic thermal [$\pi_s^2 + \pi_s^2$] cycloaddition being disallowed by Woodward-Hoffman rules. The disqualification on these grounds is somewhat contentious!.

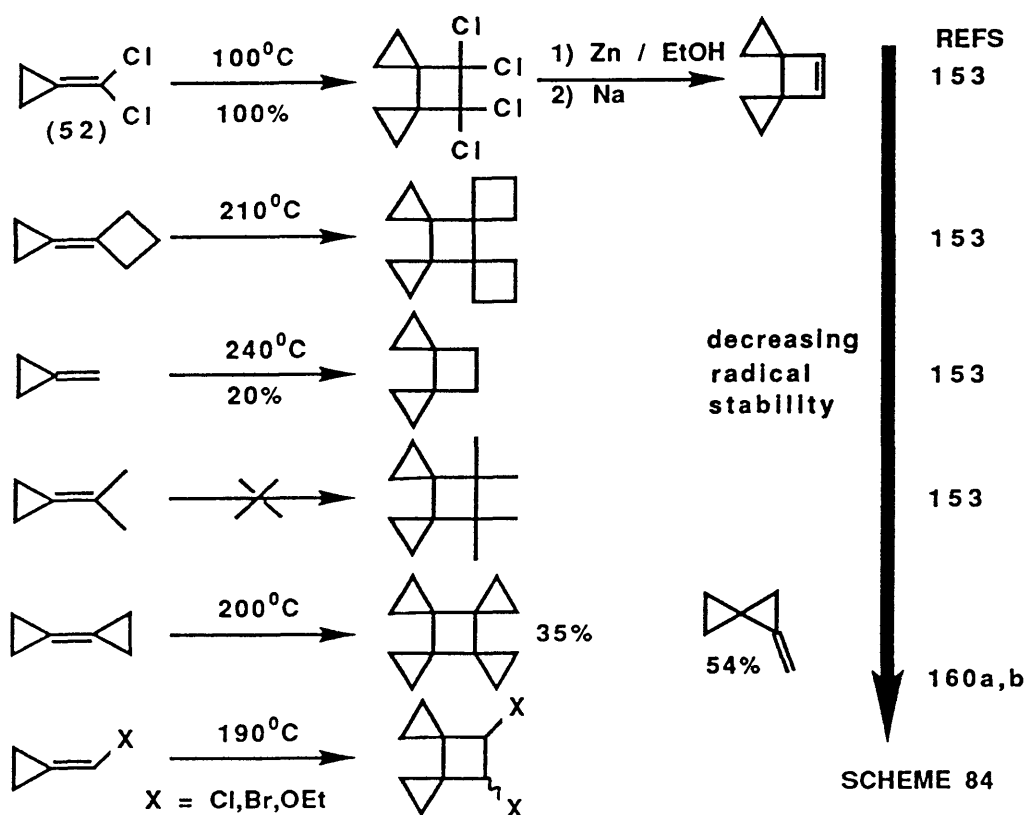
2.4.2a) Dimerisation

The dimerisation of methylenecyclopropanes invariably gives the head-to-head adduct. This is a consequence of the mechanism of dimerisation, in which the cyclopropyl-cyclopropyl bond forms first, as shown in Scheme 83. Formation of the more unstable cyclopropyl radical is thus avoided. The driving force for the dimerisation was provided by the release of $\sim 11 \text{ Kcal mol}^{-1}$ of

strain energy upon destruction of the double bond in each of the two components, in addition to the formation of two σ -bonds. The facility of cyclobutane formation depends upon the antagonistic combination of radical stability and steric interactions in the acyclic biradical intermediate. Where steric considerations predominate, polymerisation occurs. A number of examples are cited in Scheme 84.

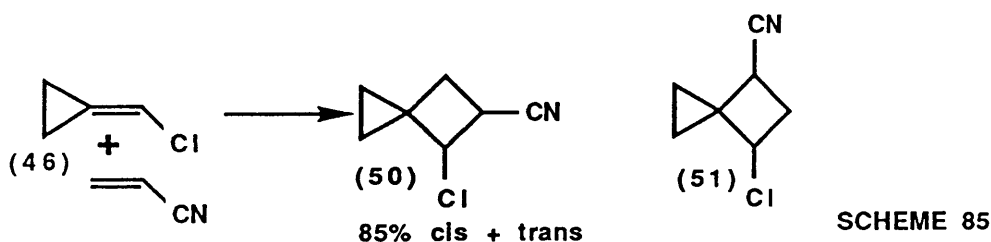


SCHEME 83

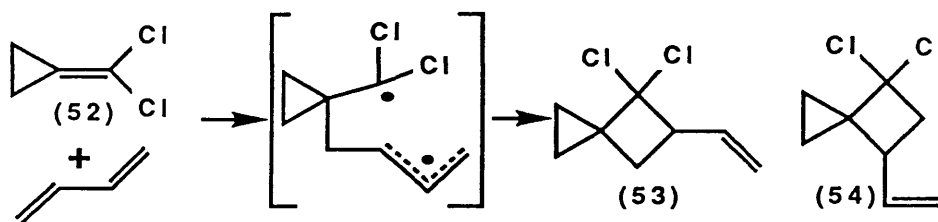


2.4.2b) Cross-Dimerisation

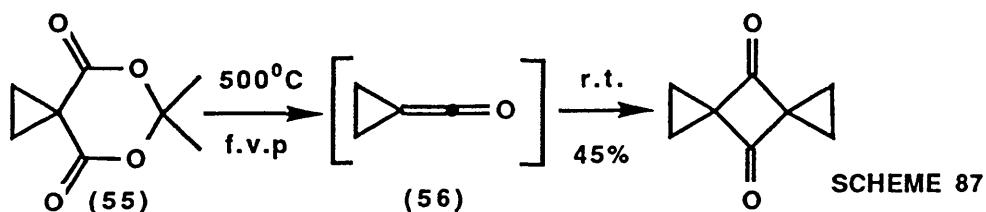
When diluted with excess of suitable olefin, cross dimerisation of methylenecyclopropanes may be achieved. The same considerations of radical stability and steric congestion apply. Thus chloromethylenecyclopropane (46) gave cyclobutanes on reaction with acrylonitrile, but failed with styrene and stilbene, presumably on steric grounds (Scheme 85).¹⁷⁵ In this



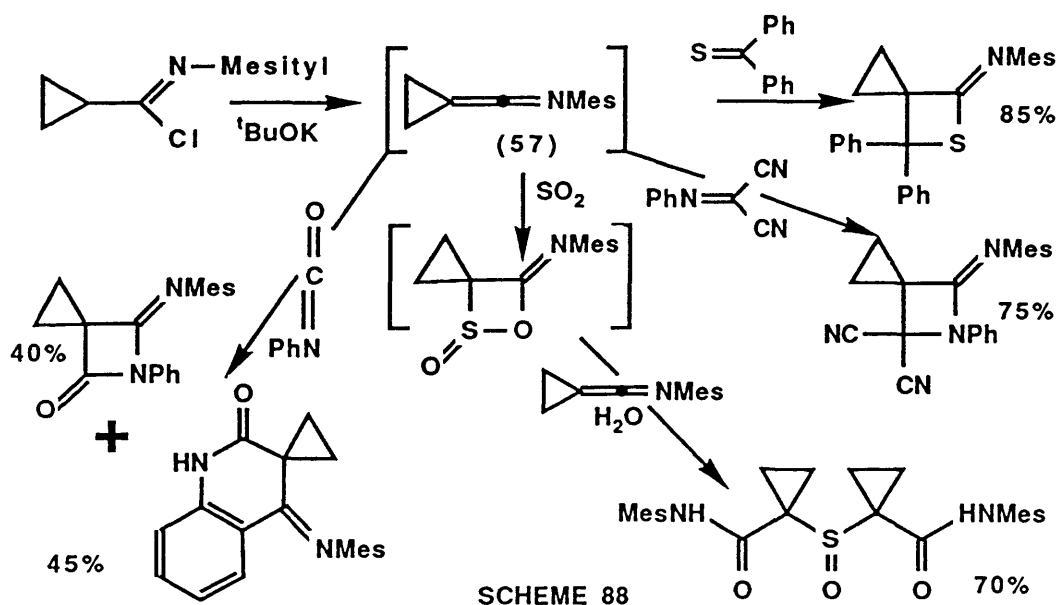
case, it is interesting to note that none of the regioisomer (51) was detected. Similarly, dichloromethylenecyclopropane (52) reacted with butadiene to give (53) but not (54) (Scheme 86).¹⁷⁶



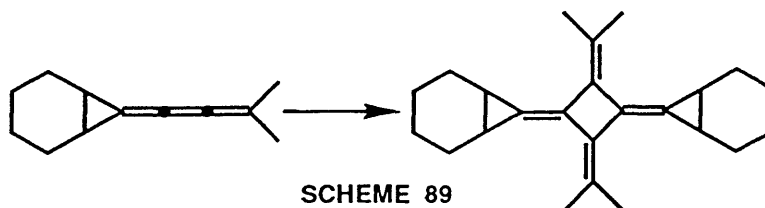
Difluoromethylenecyclopropane, unreactive in the Diels-Alder sense, gave the corresponding fluorinated version of (53) in 42% yield on reaction with butadiene.¹⁷⁶ Methylenecyclopropane is much less reactive.⁶⁶ Dimethyleneketene (56) has been generated by flash vacuum pyrolysis of Meldrum's acid derivative (55) at 500°C. Ketene (56) dimerises at room temperature (Scheme 87).



N-Mesityl-cyclopropylidene azomethine (57) was trapped with a variety of activated π -systems (Scheme 88).⁴²



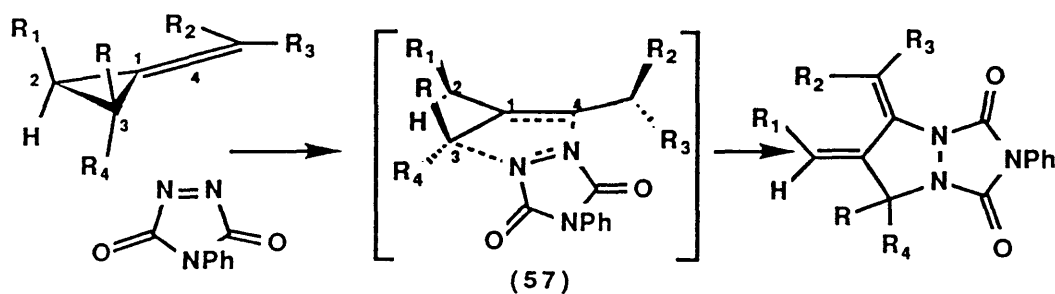
Allenylidenecyclopropanes of extended unsaturation do not dimerise at the exo-methylene double bond in spite of the energetic advantage to be gained from relief of strain. Steric effects must be more influential in these cases (Scheme 89).^{17g}



2.4.3) [3+2] Cycloadditions

Pasto and Borchardt¹⁷⁷ have studied [3+2] reactions of

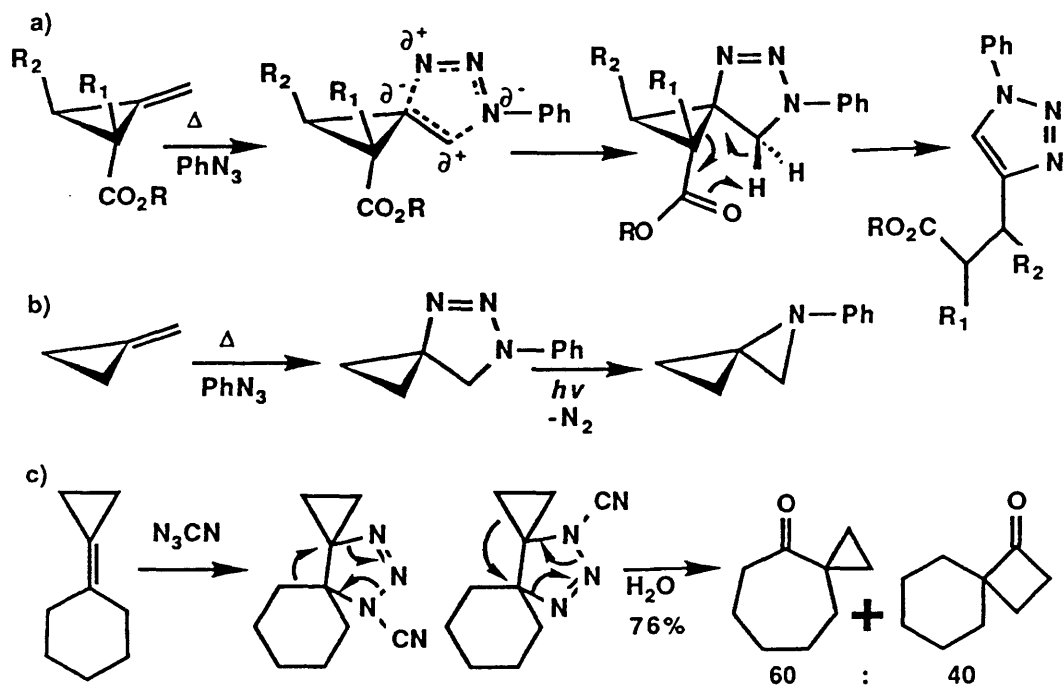
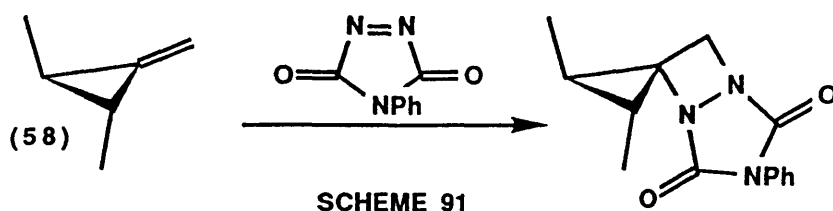
alkenylidene cyclopropanes. The cycloaddition is considered to be a concerted process via an orbitally controlled transition state, and is formulated as being a $[(\pi_{1-4}^2 + \pi_{4-5}^2 + \pi_{2-3}^2) + 2\pi]$ 8 electron electrocyclic process via a Mobius transition state. Optical activity in the starting material is retained with inversion in the product at reaction temperatures below 0°C. Above 60°C reaction was not stereospecific and racemisation occurred. This was explained by considering that the rate of cyclisation exceeds rotation about the C₁-C₄ bond at low temperature (57). Ring substituents influence the course of reaction. As expected, electron releasing substituents enhance the reaction rate whilst unsaturated or other inductive electron withdrawing groups decrease it. Electrophilic attack occurs on the least hindered face of the ring and at the more alkylated ring carbon, (a consequence of its larger orbital coefficient) with inversion at this centre (Scheme 90).



SCHEME 90

Methylene-cyclopropane (58), on the other hand gave formal $[2\pi + 2\pi]$ adducts under these circumstances (Scheme 91).¹⁷⁸

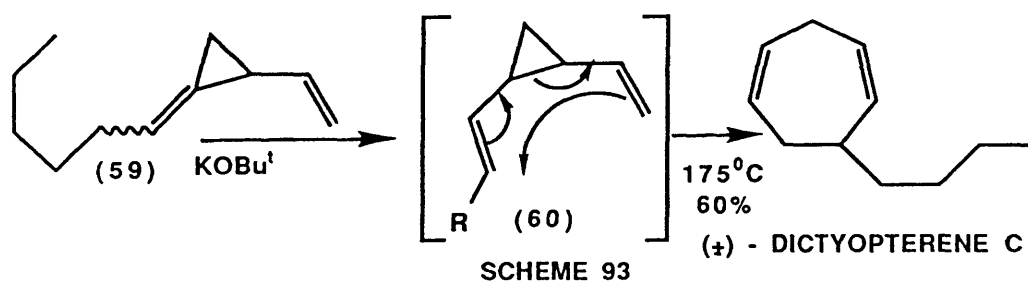
The π -system of methylenecyclopropane does participate in 1,3-dipolar addition with phenyl azide (Scheme 92a).¹⁷⁹ When the cyclopropane bears an ester substituent, cyclopropane cleavage to



SCHEME 92

form a triazole occurs. Photolytic extrusion of dinitrogen forms an azaspiropentane (Scheme 92b). The cyanogen azide ring expansion protocol of McMurry¹²⁰ provides a further example (Scheme 92c).

2.4.4) Cope Rearrangements

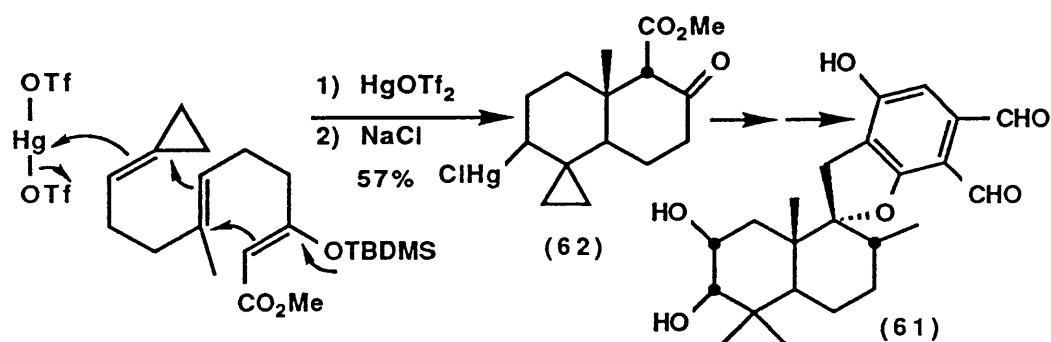


($\pm$)-Dictyopterene C, a C_{11} hydrocarbon is a major component isolated from the essential oil of algae of genus Dictyopteris was prepared by base induced isomerism of methylenecyclopropane (59) to 1,2-divinyl cyclopropane (60), which underwent facile Cope rearrangement.⁵⁰ (Scheme 93). Examples of direct participation of a methylenecyclopropane in Cope rearrangements are also known.^{49a,121}

2.5 Intramolecular Nucleophilic Attack

2.5.1 Alkylidenecyclopropanes

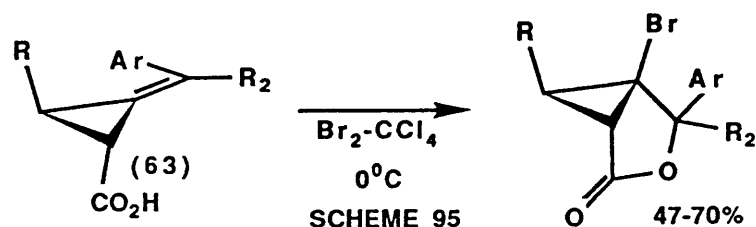
There exist a number of useful examples of intramolecular nucleophilic attack on alkylidenecyclopropanes in the presence of suitable electrophilic activation. Perhaps most notable amongst these is the electrophile induced poly-ene cyclisation strategy of McMurry in his approach to the synthesis of compliment inhibitor K-76 (61), a fungal metabolite, (Scheme 94).^{6a}



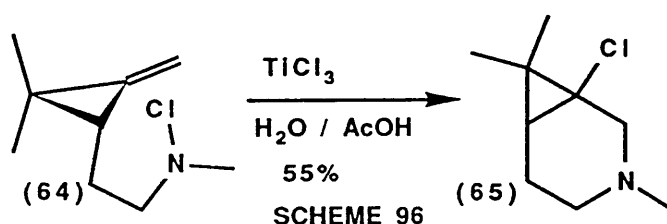
The presence of a cyclopropane rather than a gem-dimethyl moiety in (62) resulted in a change in conformation of the ring, since 1,3-diaxial interactions with the methyl at the ring junction were removed. This allowed cis-hydroxylation at a later stage to

proceed with the desired stereoselectivity.

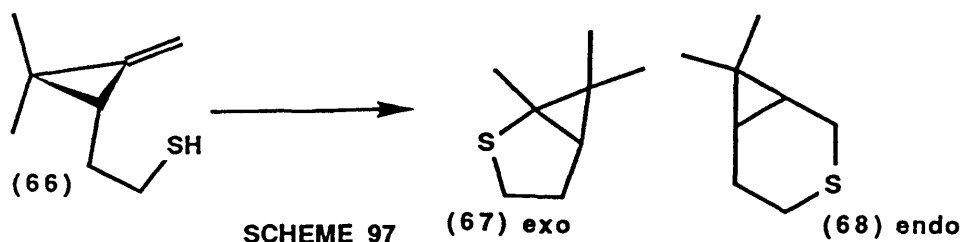
2-Arylmethylenecyclopropane carboxylic acid (63) underwent facile bromo-lactonisation at 0°C in 47-70% yield¹²² (Scheme 95).



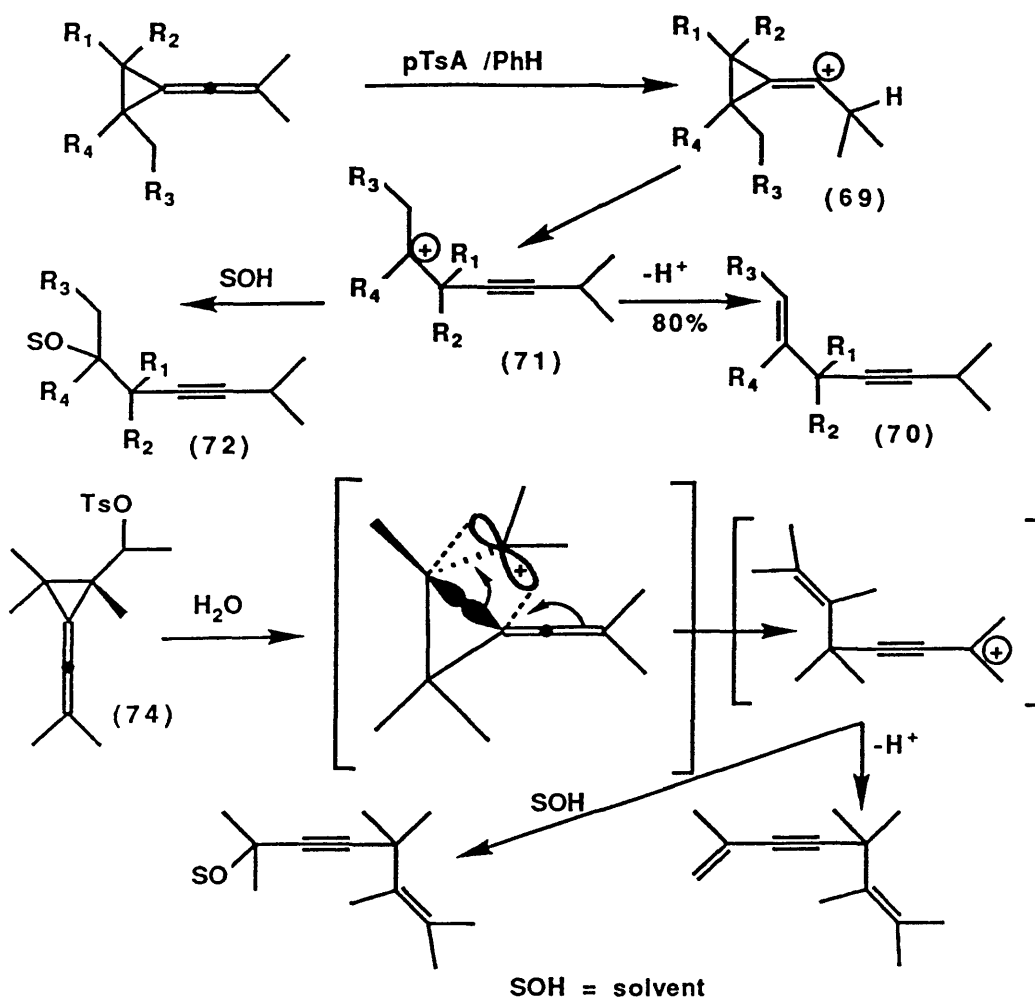
Examples of radical cyclisations are also known. The N-chloro-β-methylenecyclopropylamine (64) gave 55% yield of azabicycloheptane (65) by intramolecular addition of a claimed aminyl radical generated in the presence of aqueous titanium trichloride (Scheme 96).



Photolysis of (64) gave only 18% yield of (65). The absence of the corresponding pyrrolidine system was ascribed to unfavourable strain in the transition state.¹²³ Photochemically induced cyclisation of the corresponding thiols (66) was also studied (Scheme 97). In these cases, tetrahydrothiophene (67) formation predominated at -70°C (65% yield). At high temperatures more thiopyran (68) formation was observed. Both cyclic thioethers were thermally unstable giving products of cyclopropane ring cleavage and polymerisation.¹²⁴



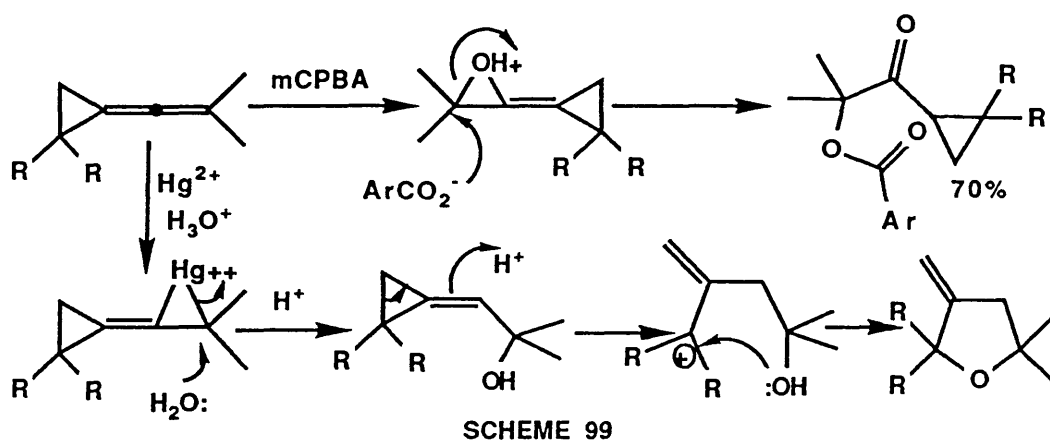
2.5.2 Alkenylidene Cyclopropanes



SCHEME 98

In contrast to allenes, where electrophilic attack occurs at the central carbon, products arising from terminal electrophilic attack on C₅ of alkenylidenecyclopropanes are observed.¹²⁵⁻¹²⁸ The difference is ascribed to stabilisation of carbocation (69) by the neighbouring cyclopropane ring. In the absence of

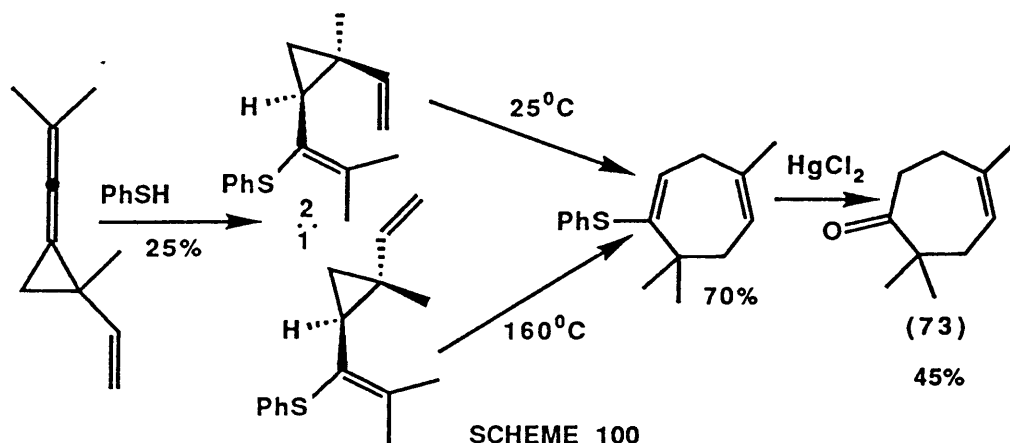
nucleophiles enynes (70) form in high yield. Otherwise cation (71) is intercepted to give (72) (Scheme 98). Epoxidation and mercuration give the expected regioselectivity of attack at the central carbon (C_4) due to preferred nucleophilic attack at the sp^3 -centre of the cyclic intermediates (Scheme 99).



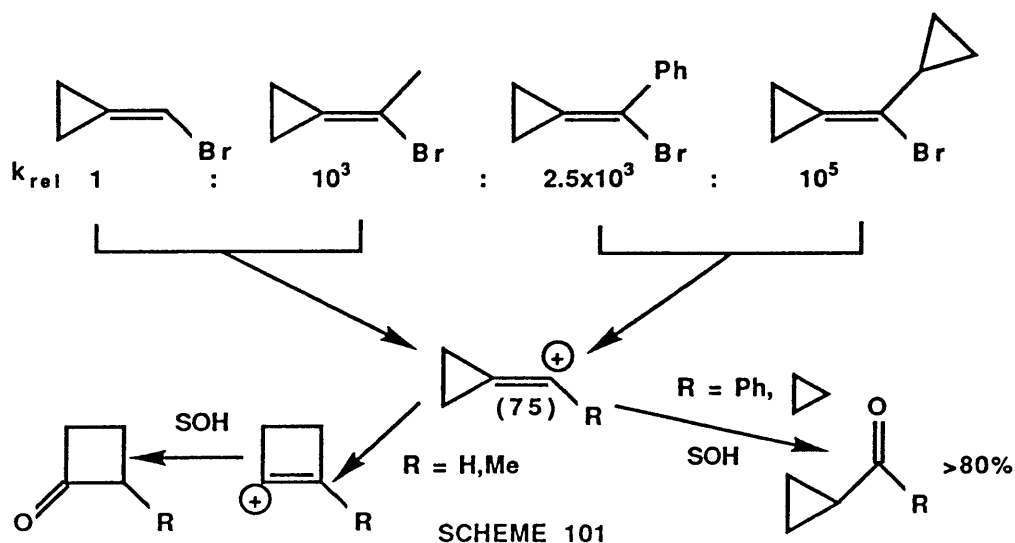
When electron withdrawing cyclopropane ring substituents are present, cation (69) is destabilised relative to the cyclopropyl carbonium ion, and electrophilic attack on the C_1 - C_4 double bond is observed.¹²⁶ Isobutenyldenecyclopropanes with a pendant unsaturated moiety on the ring have been used to prepare monoterpene skeletons by acid induced ring cleavage.¹²⁸ The corresponding cyclopropyl carbinyl tosylates (74) (Scheme 98) behave similarly on hydrolysis^{17e}, the intermediate α -cyclopropyl cation being stabilised by overlap of the empty p-orbital with the adjacent cyclopropane σ -bond.

In contrast, nucleophilic attack occurs across the C_1 - C_4 bond.^{97,129} This strategy was applied to the synthesis of Karahanaenone (73), an odiferous component of Japanese hop and cypress oil (Scheme 100).⁶⁶

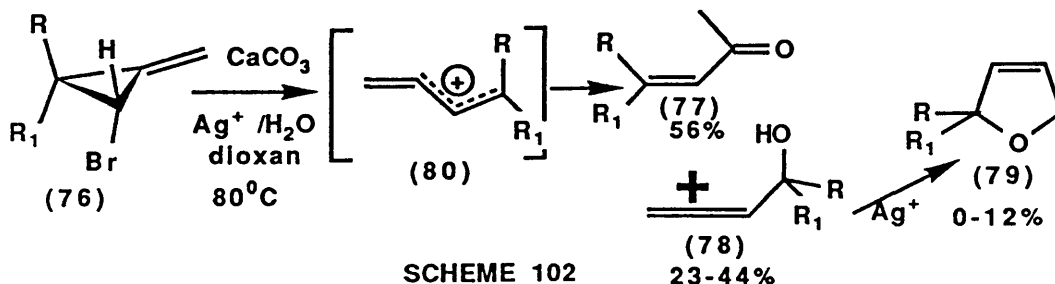
For a more detailed account of solvolysis mechanisms, the reader is referred to refs. 6c,g, 43a, 120 in addition to those cited above. The solvolysis reactions tend to be messy and are not therefore considered to be preparatively useful. The rates of solvolysis and of products derived from bromomethylene-



cyclopropanes were determined¹³⁰, and found to be dependent on the substituent (Scheme 101). It transpires that the products depend on the stability of the intermediate carbonium ion (75). Only when R is capable of stabilising the adjacent carbonium ion do non-rearranged products predominate. The remarkable



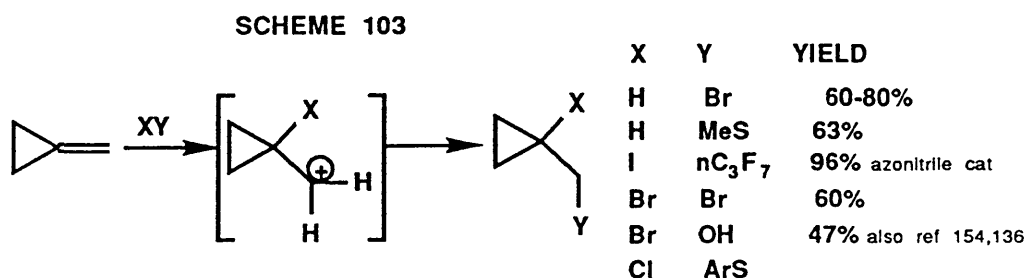
stabilising influence of an α -cyclopropyl substituent is reflected in the solvolysis rate. The solvolysis of 2-bromo-momethylene cyclopropanes (76) has also been studied (Scheme 102). The methylene-allyl cation (80) forms by disrotatory ring opening.



Solvolysis at C_2 gives rise to enones (77), while C_4 attack gives allenes (78). In the absence of silver ions, these predominate (61-69%).¹³¹

2.6 Electrophilic Additions to Methylene Cyclopropanes

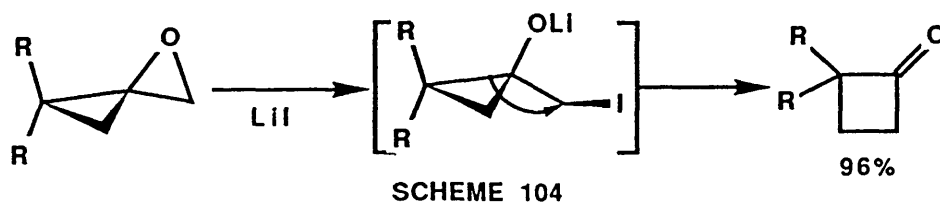
Anderson has studied a wide range of electrophilic additions to the exo-cyclic double bond (Scheme 103).⁶⁶



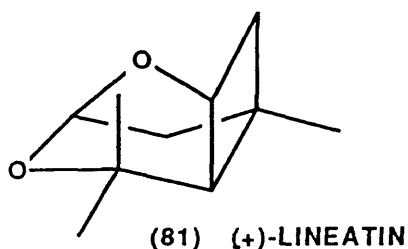
2.6.1 Epoxidation

Epoxidation of methylenecyclopropanes with buffered peracids has been widely used¹³² for the preparation of oxaspiropentanes. The facile acid catalysed rearrangement to cyclobutanones is a practical problem, although employment of *p*-nitroperbenzoic acid in dichloromethane usually allows isolation of the epoxide, since

the acid generated precipitates out. Rearrangement to cyclobutanones^{132d,e}, catalysed by lithium iodide, proceeds in excellent yield and regioselectively by migration of the more highly substituted cyclopropane bond (Scheme 104).

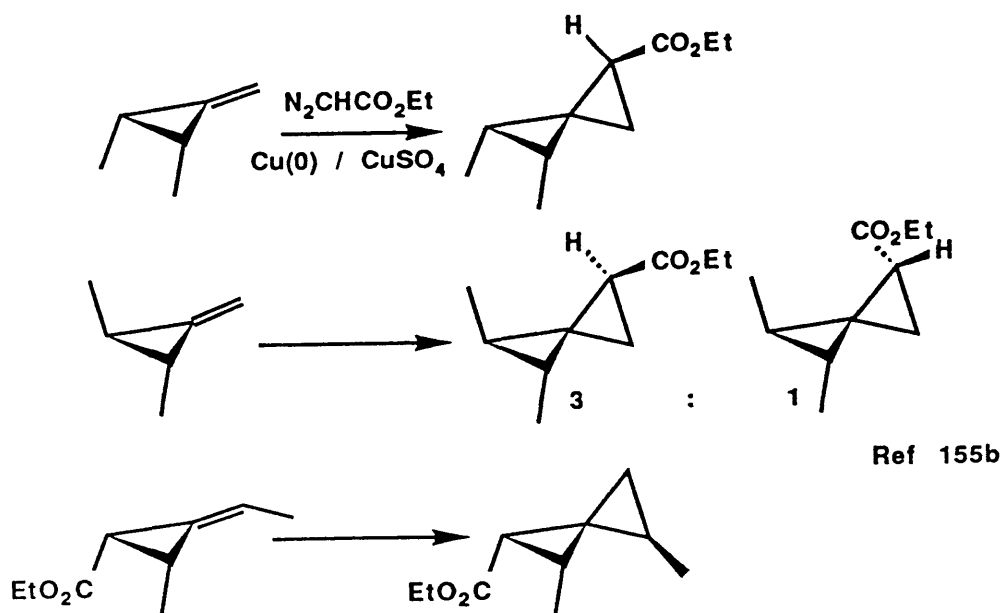


Epoxidation and ring expansion to a cyclobutanone was elegantly employed in the synthesis of R(+)-Lineatin (81), the aggregation pheromone of the timber beetle *Trypodendron lineatum*.^{132h}



2.6.2 Carbene Insertion

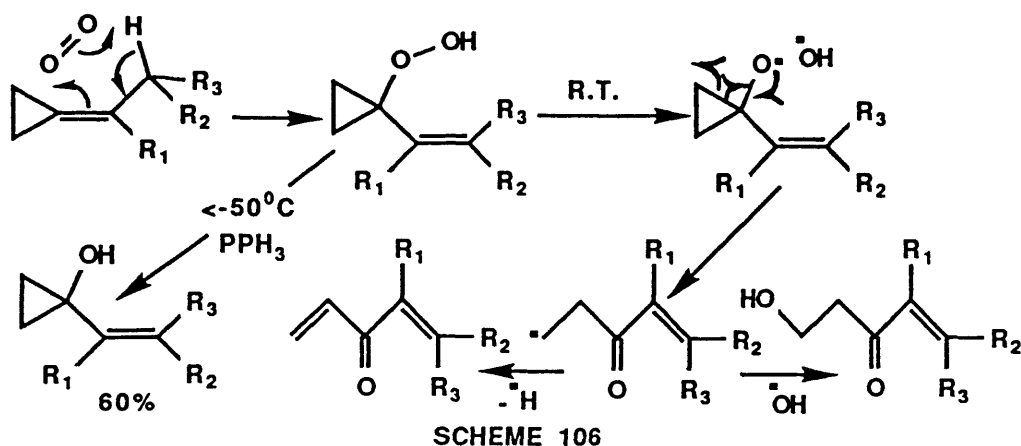
In the preparation of methylene cyclopropanes from allenes by carbene addition, the double bond of the product was also prone to cyclopropanation. Spiropentanes are thus readily obtainable in high yield. Regio and stereoselectivity are usually good. Some illustrative examples are shown in Scheme 105. Others were discussed in Part (a) (see Schemes 42 and 43).



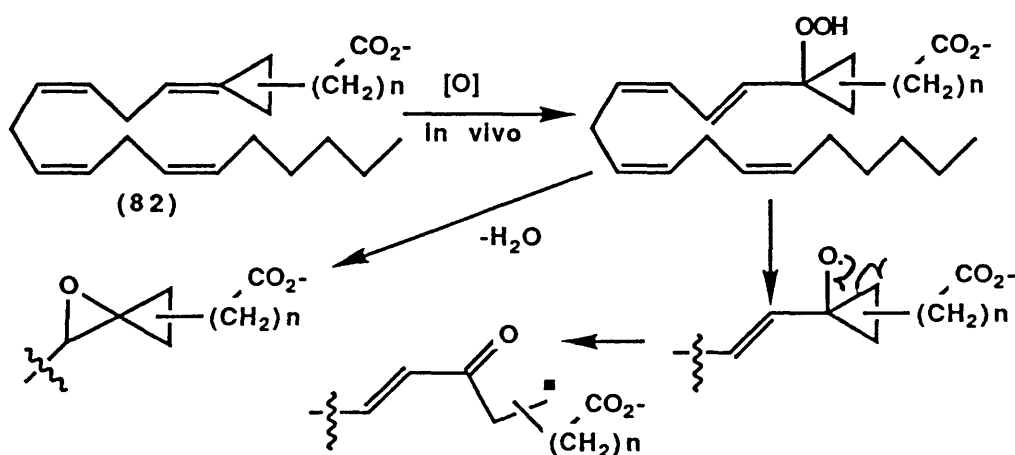
SCHEME 105

2.7 Singlet Oxygen Ene Reactions

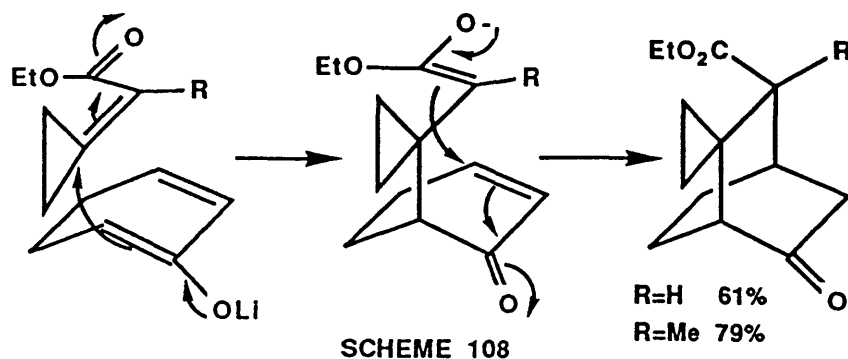
Though several reports exist for the preparation of methylenecyclopropanes from vinylcyclopropanes^{35-38,89}, (See Part 1), the singlet oxygenation reaction of methylene cyclopropanes has not been extensively studied. Rousseau *et al*¹³³ established that the complicated product distribution observed^{133,134} when the ene reaction is conducted at ambient temperature resulted from instability of the intermediate hydroperoxides. The products arose by radical rearrangements as shown in Scheme 106. At -50°C , however, the hydroperoxides are stable, and may be reduced in situ with triphenyl phosphine. Vinyl cyclopropanols were obtained in reasonable yields. The rate of photo-oxygenation was observed to be slow relative to normal olefins. This implies that the transition state does not benefit from the release of strain energy, in turn suggesting a reactant like transition state.¹³⁴ Systems possessing no allylic



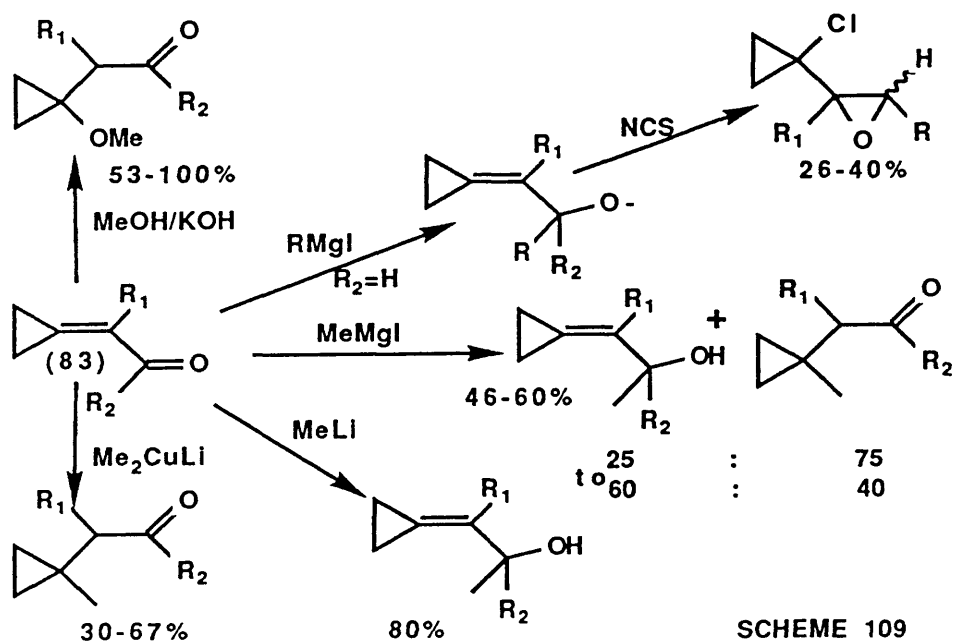
protons apart from the cyclopropyl protons, were found to be completely inert to singlet oxygen. Presumably the allylic ring protons are geometrically inaccessible for a six membered ring ene-transition state.^{134,135} An attempt was made to put the known instability of vinyl cyclopropane hydroperoxide to use. Methylene cyclopropane analogues of arachidonic acid (82) were prepared in the hope that *in vivo* oxidation would cause irreversible binding to block active sites.^{27b} The success of the concept has not yet been reported (Scheme 107).



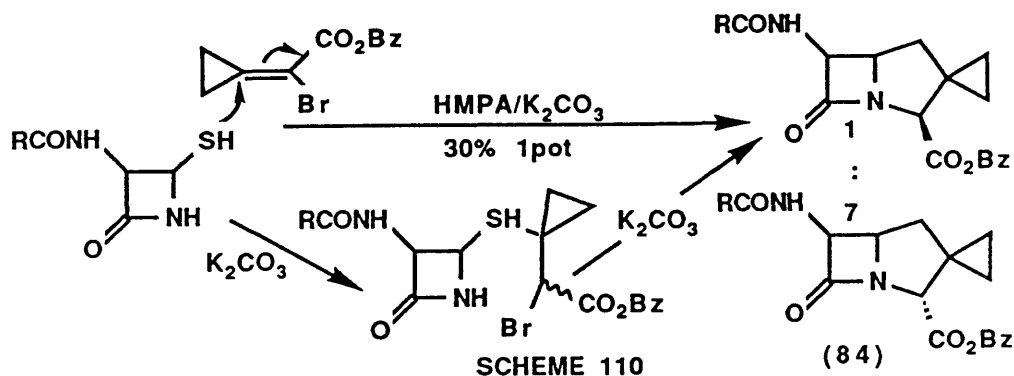
2.8 Nucleophilic Attack on the Olefin



Cyclopropylidene carboxylic esters proved to be good acceptors for the double Michael reaction with dienolate anions. (Scheme 108).²² Conia et al¹³⁶ investigated the attack of a range of nucleophilic reagents on α -cyclopropylidene aldehydes and ketones (83) (Scheme 109). With these systems, 1,4-addition of nucleophiles predominates, except with Grignard reagents which were observed to give more 1,4-addition products than with α -isopropylidene ketones, perhaps because there is less steric



hindrance to attack at the 4-position, or more probably, due to benefits gained from release of strain energy. The propensity for cyclopropylidene carboxylates to undergo 1,4-addition of nucleophiles was utilised in the synthesis of spirocyclopropane-bis-norpenuillanic acid derivatives (84) (Scheme 110)³.

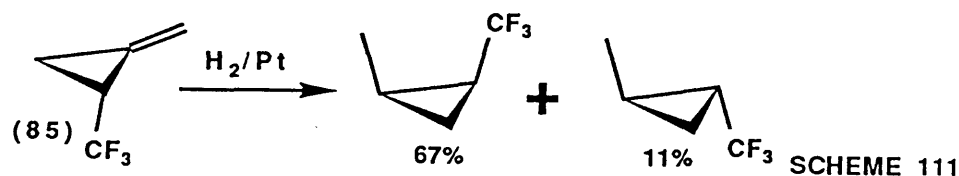


2.9 Reducing Agents

2.9.1) Double Bond reduction

2.9.1a) Catalytic Hydrogenation

The hydrogenation of 2-trifluoromethyl-methylenecyclopropane (85) at a platinum catalyst gave in addition to the expected cis-cyclopropane, 11% of the trans-isomer (Scheme 111)¹³⁷. Though no explanation was proffered at the time, in view of the platinum-methylenecyclopropane complexes prepared since, (see above), it is possible that traces of platinum salts cause homogeneous catalysis.

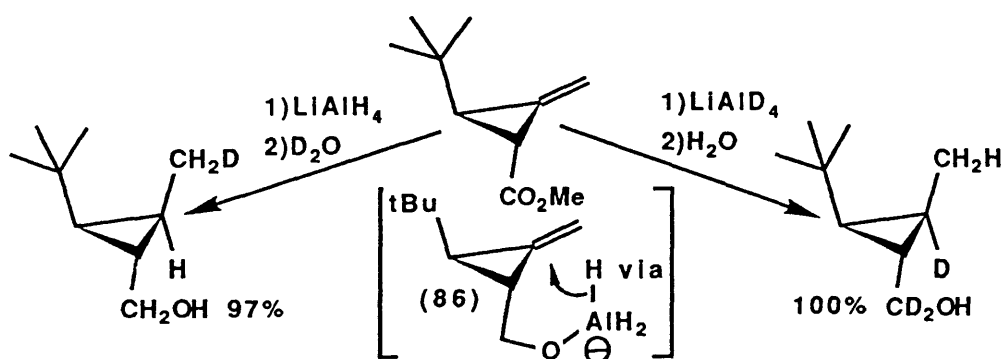


Raney nickel has also been used effectively^{136a}. Exhaustive hydrogenation at palladium gives ring cleavage.⁴²

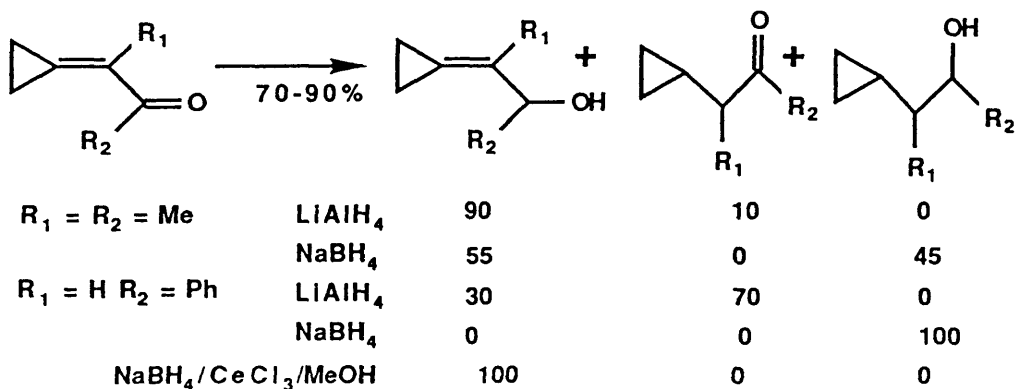
2.9.1b) Metal Hydrides

2-Methylene-cyclopropyl carboxylate esters were shown to undergo directed regiospecific and stereospecific reduction (Scheme 112)¹³⁸. Whilst below 35°C only the ester was reduced, at 120°C complete and stereospecific reduction occurred by intramolecular delivery of hydride from a co-ordinated alkoxy aluminium hydride species (86).

Hydride reductions of α -cyclopropylidene aldehydes and ketones (87) have also been studied.¹³⁶ A greater tendency towards reduction of the double bond was observed than in the corresponding isopropylidene ketones, attributable to favourable release of the strain energy. The selectivities are substituent dependent (Scheme 113). Aldehydes gave lower yields and less favourable ratios.

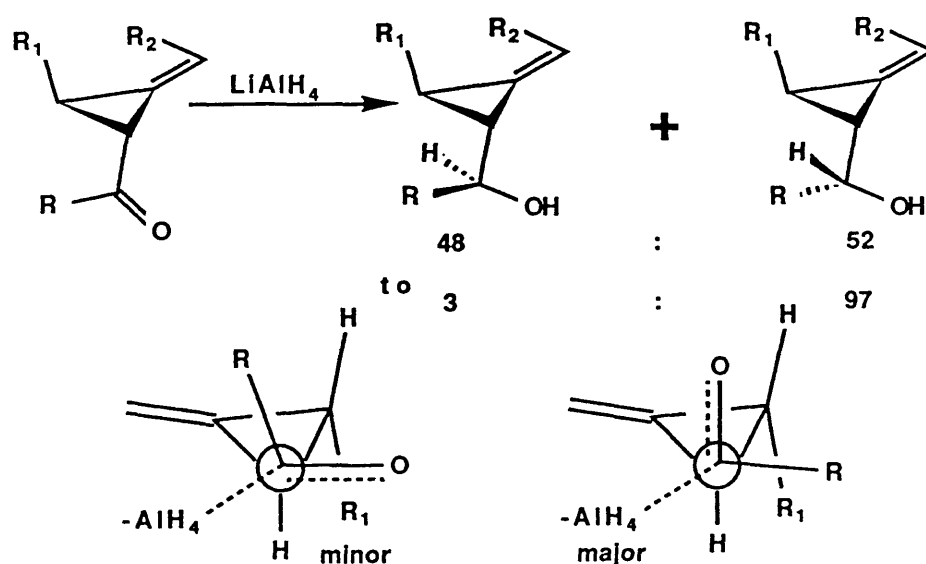


SCHEME 112



SCHEME 113

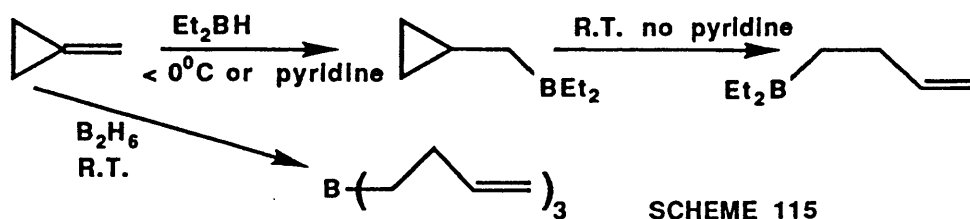
In common with the observation for esters (see above), ketone substituents appended to the cyclopropane ring may be selectively reduced in high yield without affecting the alkyldiene moiety.^{76,139} A degree of diastereoselection is obtainable, by virtue of a Felkin type transition state, the magnitude of which depends upon the steric bulk of the substituents (Scheme 114).¹⁴⁰



SCHEME 114

2.9.1c) Boranes

It was discovered that whilst borane reduction of methylene cyclopropane at room temperature proceeded with ring cleavage, at 0°C, or in the presence of pyridine, cyclopropyl methyl boranes could be isolated (Scheme 115).^{64a}

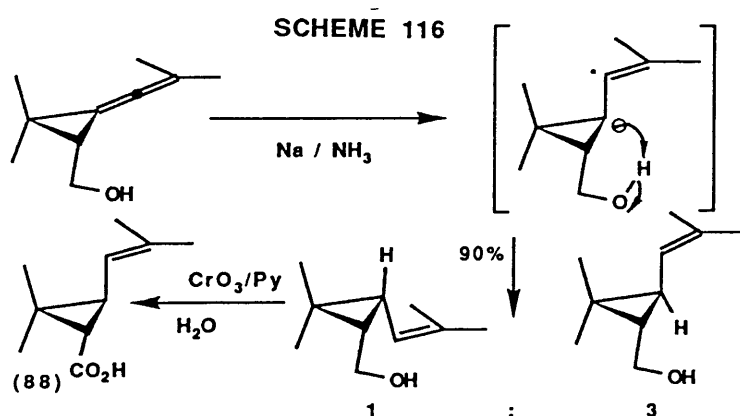


SCHEME 115

Diimide reduction occurs by attack from the least hindered side of the double bond to give the cis-isomer^{141,142} in a manner similar to that observed for di-isopinocampheyl borane, which was employed for the kinetic resolution of Z- and E-vinylidenecyclopropanes¹⁴².

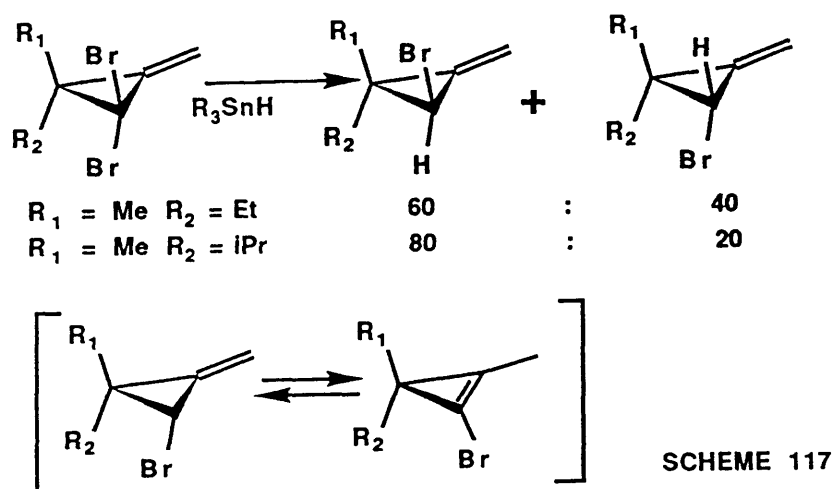
2.9.1d) Dissolving Metal Systems

Hydride reductions were found to be unsuitable for the stereospecific reduction of isobutenylidenecyclopropanes. Stereoselective reduction was, however, achieved by treatment with sodium in liquid ammonia. In this case the stereoselectivity arose from intramolecular delivery of a proton by the pendant alcohol moiety to the intermediate radical anion. No stereoselectivity was observed with protected alcohols (see also ref. 132c). The selectivity thus obtainable was exploited in a concise synthesis of the insecticide trans-Chrysanthemic acid (88) (Scheme 116)^{17d}.



2.9.2) Reduction of Halogen Substituents

This has been achieved with lithium/t-butanol or sodium/methanol reductions, but the reactions are seldom clean.^{143,144} These methods have been superseded by tributyltin hydride hydrodehalogenation. With gem-dihalides, it is possible to stop at the mono-halide.¹⁴⁵ The reduction is stereoselective with abstraction of the least hindered halogen being favoured. The intermediate radical then allows equilibration to the more thermodynamically stable form which is trapped. Best results are obtained when one face of the molecule is sterically congested. Yields are usually good (Scheme 117)^{139,146}.



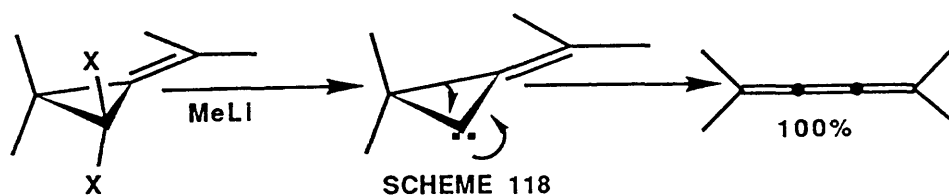
2.10 Metallation

Methylene cyclopropane is lithiated at the allylic position by *n*-butyllithium at -10°C ; the anion was quenched with aldehydes, ketones and lactones in 47-85% yield.¹⁴⁷ 2-Bromo-methylenecyclopropanes readily undergo lithium / halogen exchange with retention of configuration; the anions react with epoxides as well as carbonyl electrophiles^{139,146,148}. The anions are reportedly stable at room temperature,¹⁴⁸ which is in accord with

Seyferth's original studies on cyclopropyllithium¹⁴⁹. A variety of ring-substituted alcohols are thus readily available. Although acidic oxidising agents are not compatible with the methylenecyclopropane moiety, chromium trioxide/pyridine reagents have been applied successfully on a number of occasions¹⁵⁰. The corresponding aldehydes, ketones and acids are therefore also readily available by this strategy.

Bromomethylenecyclopropane has been successfully lithiated with *t*-butyllithium^{120d} at -80°C . The vinyl lithium obtained reacted in 60% yield with ethylene or propylene oxides.

2,2-Dihalo-(alkylidene)cyclopropanes on metallation undergo α -elimination with rearrangement to give excellent yields of cumulenes (Scheme 118).⁷⁸



2.11 Rearrangements

2-Vinyl-methylene cyclopropanes undergo ring expansion¹⁵¹ in a manner analogous to the vinyl cyclopropane rearrangement. Unlike the latter, however, the possibilities in organic synthesis have not yet been explored.

CONCLUSION

It has been demonstrated that vinylidene and alkylidene cyclopropanes are readily available from a diversity of precursors. The strain energy locked into the methylene cyclopropane moiety provides a superb driving force for the variety of reactions in which they participate. The value of building strain into synthetic intermediates has only recently begun to be appreciated, and it remains to be seen whether progress in harnessing such driving forces creatively will lead to an awakening of interest in these fascinating structural units amongst synthetic organic chemists, and in particular to the development of regio- and stereospecific processes.

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+ refs cited

RESULTS AND DISCUSSION

*If a man will begin with certainties, he shall end in doubts;
but if he will be content to begin with doubts, he shall end in certainties.*

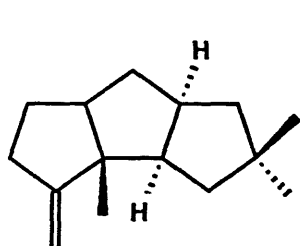
Francis Bacon.

RESULTS AND DISCUSSION

INTRODUCTION

"By the mid 1970's it had become clear that the area of polyquinane chemistry was on the verge of an explosive growth period. There were several underlying reasons for this surge of interest in molecules whose frameworks featured mutually fused cyclopentane rings. Perhaps the most evident was the realisation that little attention had previously been paid to methodology for annulating one five-membered ring to another." ... L Paquette.¹

SOME IMPORTANT NATURALLY OCCURRING POLYQUINANES

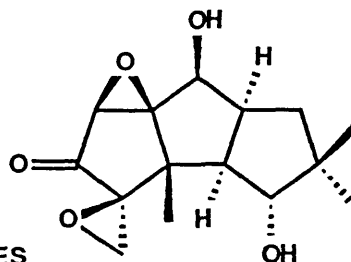


HIRSUTENE

Tatsuta (1979)³

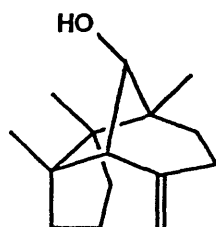
LINEAR TRIQUINANES

Antitumor, Antibiotic



CORIOLIN

Danishefsky (1980)⁴

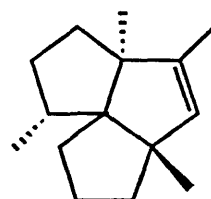


GYMNOMITROL

Coates (1979)⁶

DIQUINANE

ANGULAR TRIQUINANE

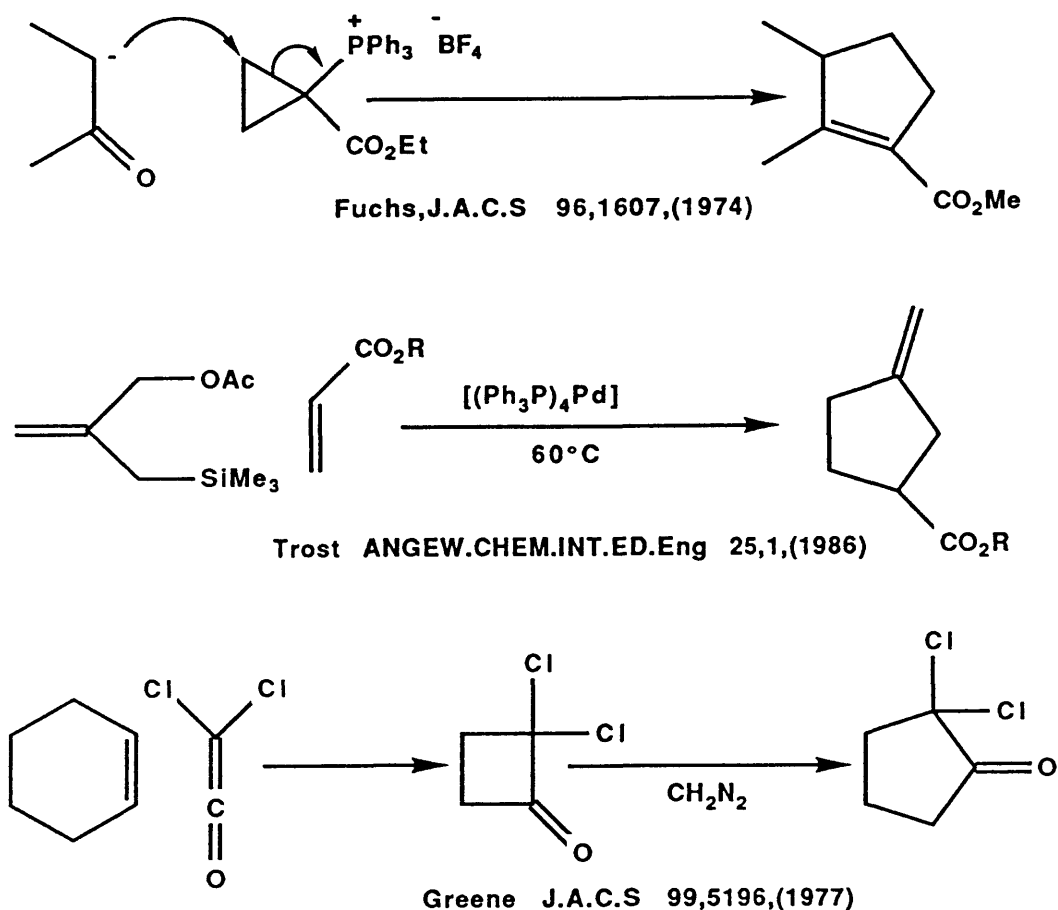


ISOCOMENE

Oppolzer (1979)⁵

SCHEME 1

The quest for new cyclopentaannulation strategies has continued unabated, spurred on by the plethora of reports concerning isolation of natural products containing the cyclopentanoid moiety, which present a stimulus and a challenge to existing synthetic methodology. Additionally, many of these natural products possess important biological activity. Scheme 1 shows examples of some compounds which have attracted recent attention. The number of excellent reviews on cyclopentaannulation strategies bear testament to the continued active interest in this field.¹⁻⁶

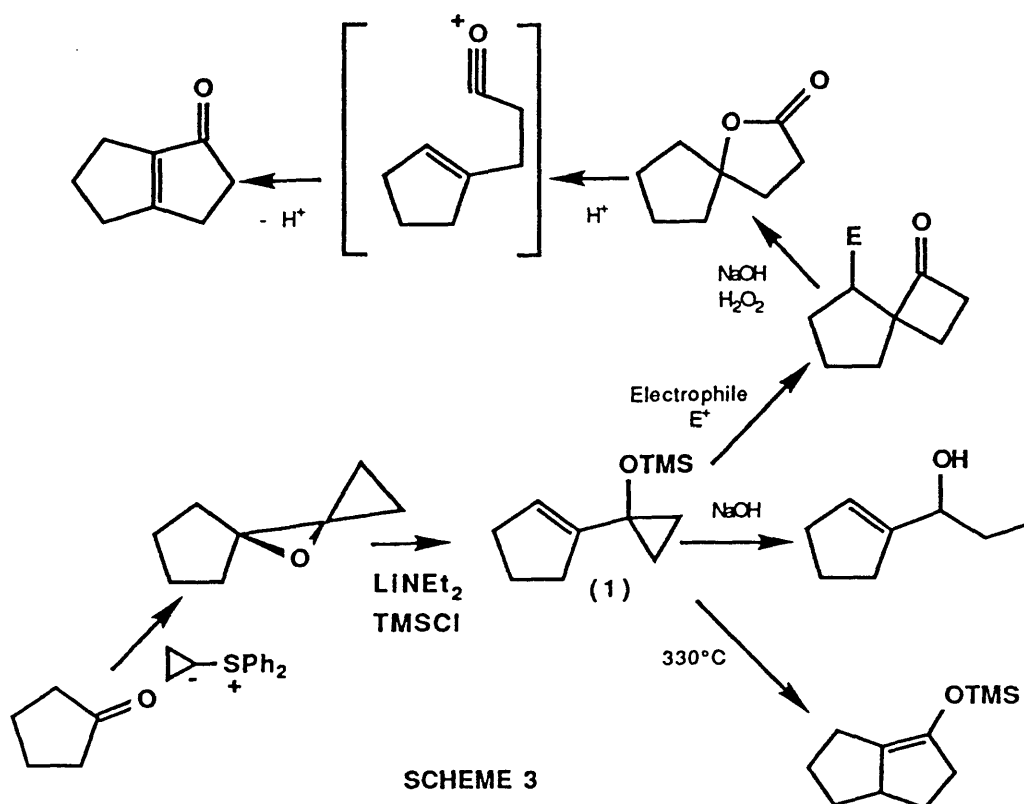


Review Ramalah SYNTHESIS (1984),529

SCHEME 2

Despite the advances made in recent years, there still exists considerable scope for the development of novel methods of cyclopentaannulation. Thus it was that we initiated exploration of the avenues of research reported herein. In particular we were interested in methods employing electron rich olefins, since very few methods of cyclopentane construction currently utilise such substrates, electron deficient olefins and ketones being much more popular¹⁻⁶, (Scheme 2).

1.0) 1-VINYL-1-CYCLOPROPANOLS AS IMPORTANT PRECURSORS TO
CYCLOPENTANOIDS



SCHEME 3

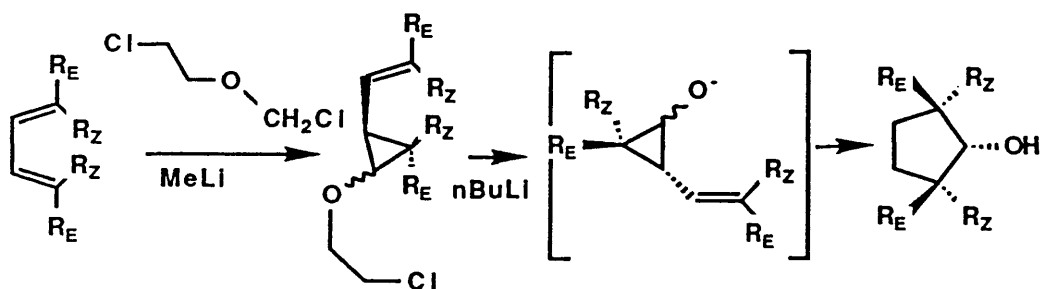
The silyl ethers of 1-vinyl-cyclopropanols (1) have been extensively employed as precursors to functionalised

cyclopentanes via the vinyl cyclopropane rearrangement at 330°C ¹¹. Trost, in an elegant and comprehensive study has also illustrated how these versatile intermediates may also be used to prepare cyclobutanones, γ -lactones, and other important moieties (Scheme 3)¹¹.

The major disadvantages of the thermal vinylcyclopropane rearrangement of silyl ethers (1) are the relatively high temperatures necessary, which preclude application to large molecules, or those containing sensitive functionality, and the difficulties encountered in preparing poly-substituted cyclopropanes by this route.

Subsequent to the work of Trost, Danheiser¹² reported that the lithium alkoxides of 2-vinyl cyclopropanols (2), prepared by insertion of 2-(chloroethoxy)-carbene into 1,3-dienes (Scheme 4), underwent the vinylcyclopropane rearrangement at room temperature.

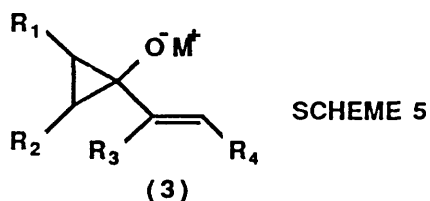
SCHEME 4



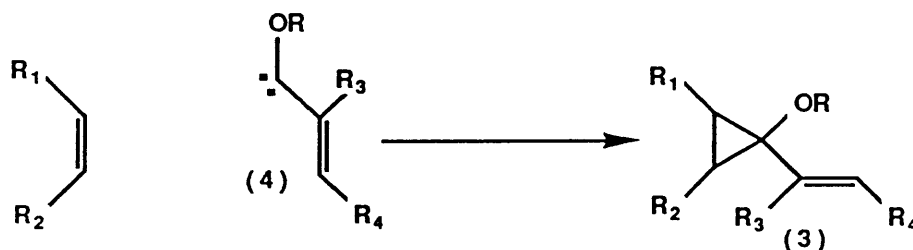
The observation by Evans¹³ that Cope rearrangements were accelerated by an alkoxy anion appended adjacent to the bond undergoing cleavage, led to the proposal that bond homolysis was being promoted by radical stabilisation as a result of interaction between the oxygen and radical orbitals. This

"delocalisation" via a 2-centre 3-electron bond is considerably more favourable in the case of the alkoxide than for the parent alcohol, thus lowering the activation energy of homolytic cleavage typically by some $13\text{--}17\text{ kcal mol}^{-1}$. This so-called "Evans-effect" may be responsible for the dramatic acceleration of the vinylcyclopropane rearrangement observed by Danheiser.

These considerations prompted us to speculate upon the facility of rearrangement of 1-vinyl-cyclopropanol alkoxides of general type (3) (Scheme 5).

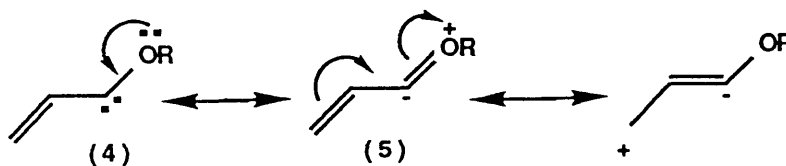


Calculations¹⁴ performed in our group suggested that although maximum benefit from the "Evans effect" is obtained when the vinyl group is appended at the 2-position (cf Danheiser), 1-vinyl cyclopropanol alkoxides should also be expected to profit from oxy-anion assisted ring cleavage. Indeed Carpenter¹⁵ had also speculated on this possibility. Thus was born a program of research directed towards the construction of functionalised cyclopropanes from electron rich olefins, via 1-vinyl-cyclopropanes.



Conceptually, a direct and highly convergent route to the desired 1-vinyl-cyclopropanols (3) appeared to be via insertion of an allyloxy carbene equivalent (4) into an electron rich olefin (Scheme 6). Danheiser¹² had previously employed a similar though less convergent strategy, (Scheme 4) to afford unspectacular yields of 2-vinylcyclopropanols. The simplicity and highly convergent nature of the proposed approach, if successful, would recommend it for the synthesis of a wide range of highly substituted 1-vinylcyclopropanols such as would be required for compounds exhibiting the molecular complexity typified by the polyquinanes.

Much is known¹⁶⁻²² about the reactivity of alkoxy-carbenes towards olefins (Scheme 8). These observations have been



SCHEME 7



SCHEME 8

R	METHOD CARBENE GENERATION	REACTION WITH OLEFINS		REFS
		e ⁻ rich	e ⁻ poor	
Ph	Thermal	x	✓	17,19
Me	Hydrazone/heat	x	✓	18
Ph	Photolysis	✓	X	19
Cl		✓	✓	20
H	RLi/-HCl geminal	✓	X	21
R	Thermal/photolytic	X	✓	22

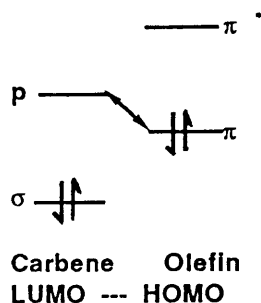
rationalised by invoking oxygen lone pair overlap with the empty

p-orbital of the adjacent singlet carbene. This imparts significant double bond character to the C=O linkage in the singlet ground state where the vacant p-orbital is available to accept electron donation from an oxygen lone pair. The observed nucleophilicity of certain oxy-carbenes is ascribed to a significant contribution from the double bond resonance structure (5) (Scheme 7). The other substituent at the carbenic centre also influences its electrophilicity (Scheme 8).

The reversal of selectivity observed when carbenes are generated photolytically is ascribed to promotion to the triplet state, in which the oxygen lone pair donation is precluded, since the adjacent carbon p-orbital is no longer vacant. A molecular orbital theoretical approach has also been applied, by Moss²³ to the same effect, (Scheme 9).

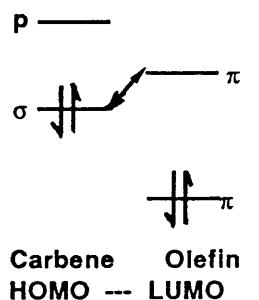
ELECTROPHILIC C:

Net transference of electron density FROM alkene- π TO carbene-p orbital in T.S. Hence electron donors on alkene aid reaction.



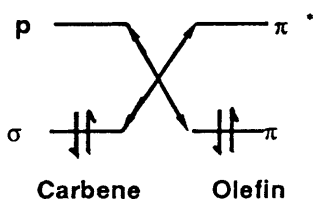
NUCLEOPHILIC C:

Net transfer of electron density FROM carbene- σ TO alkene- π^* orbital in T.S. Electron acceptors on alkene assist.



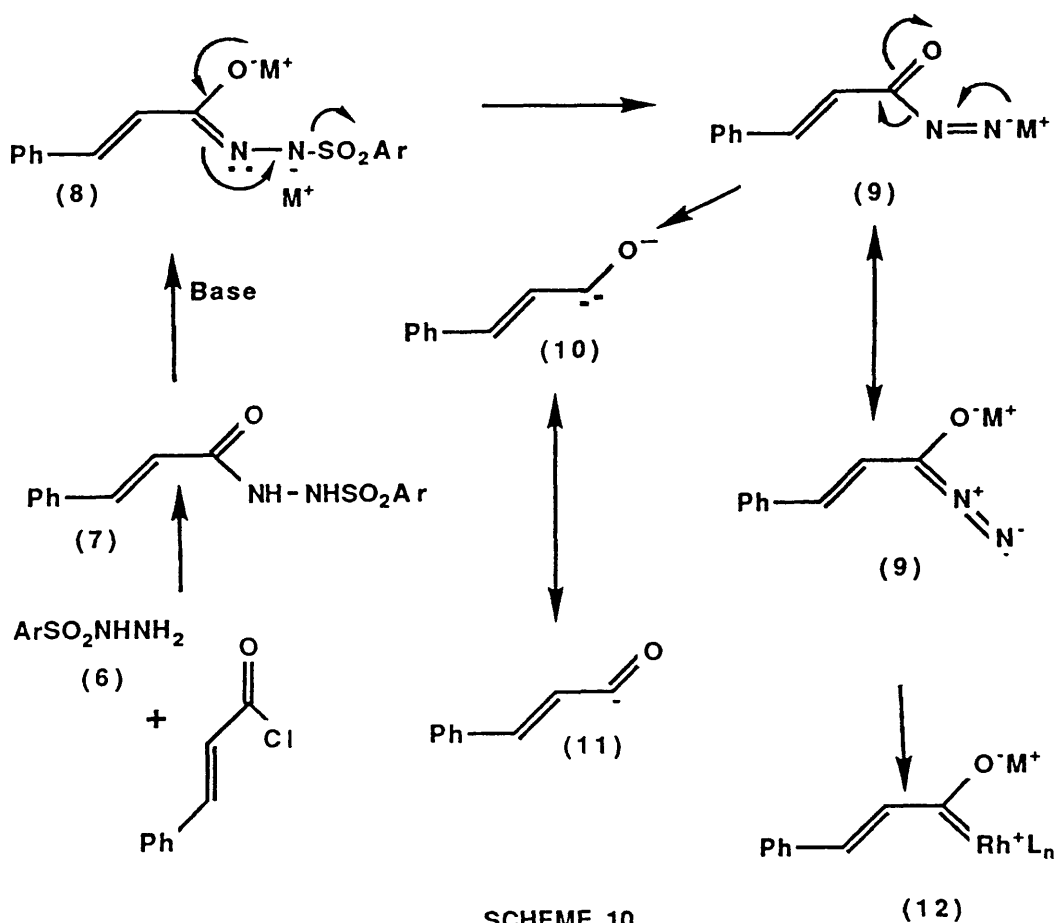
AMBIPHILIC C:

A comparable energy difference exists between both sets of available orbitals.



SCHEME 9

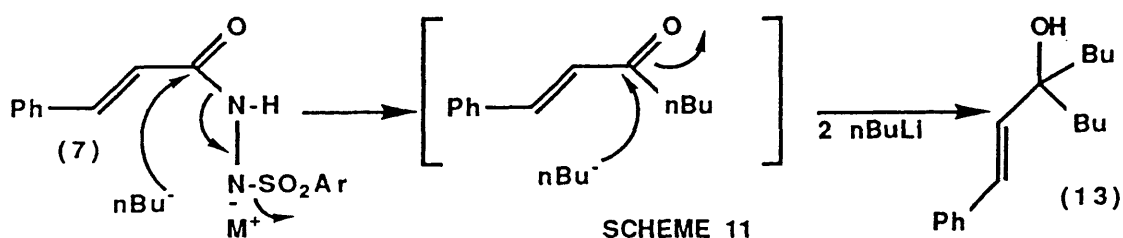
Interaction between the oxygen lone pair and an adjacent carbenic p-orbital hinders p- π interaction with an electron rich olefin, but aids $\sigma-\pi^*$ donation as a result of increased electron density at the carbenic centre. Hence such species are more reactive towards electron deficient olefins.



With these precedents in mind the electrophilicity of singlet α -alkoxy-carbenes bearing an additional allylic substituent was explored. Examination of the possible resonance structures (Scheme 7), suggested that the allyl moiety might contribute towards the undesirable nucleophilic properties. However, it was speculated that a suitable transition metal

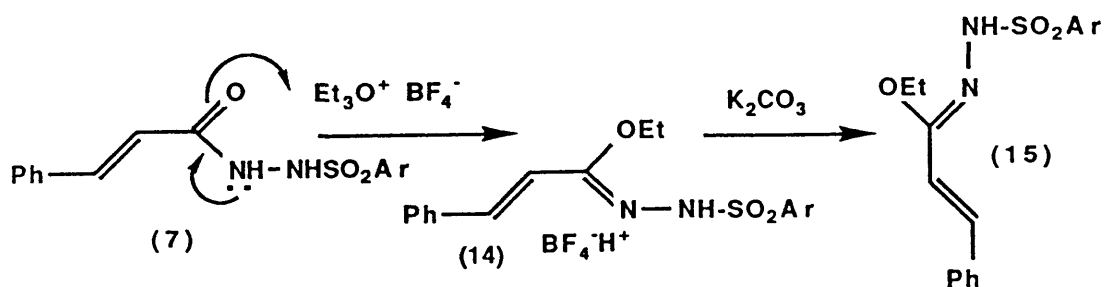
catalyst might temper these tendencies by formation of a carbenoid intermediate such as (12) (Scheme 10).

Initially a rather speculative Bamford-Stevens type approach to carbenes (10) was considered, even though these intermediates are simply a resonance form of the acyl anion (11) which would be expected to be high in energy!. A suitably functionalised triisopropylbenzenesulphonyl ester hydrazone was the required precursor. Thus N'-2,4,6-triisopropylbenzenesulphonyl cinnamohydrazide (7), was readily prepared in 93% yield by reaction of cinnamoyl chloride with triisopropylbenzenesulphonyl hydrazine (6). Attempted generation of the corresponding dianion (8) by treatment with 2.2 equivalents of *n*-butyllithium in the presence of cyclohexene and catalytic dirhodium tetraacetate, at low temperature, resulted in extensive transmigration ; 1,1-di(*n*-butyl)cinnamyl alcohol (13) (Scheme 11), isolated in low yield, was the only characterised product. The alcohol probably arises by direct attack of *n*-butyllithium on the anion of hydrazide (7) (Scheme 11).



Similarly, whilst treatment of hydrazide (7) with 1.1 equivalents of L.D.A. afforded a yellow solution of the mono-anion which appeared stable at ambient temperature, (showing only starting material by T.L.C. analysis), 2.5 equivalents of base generated a dark red solution at low temperature which was

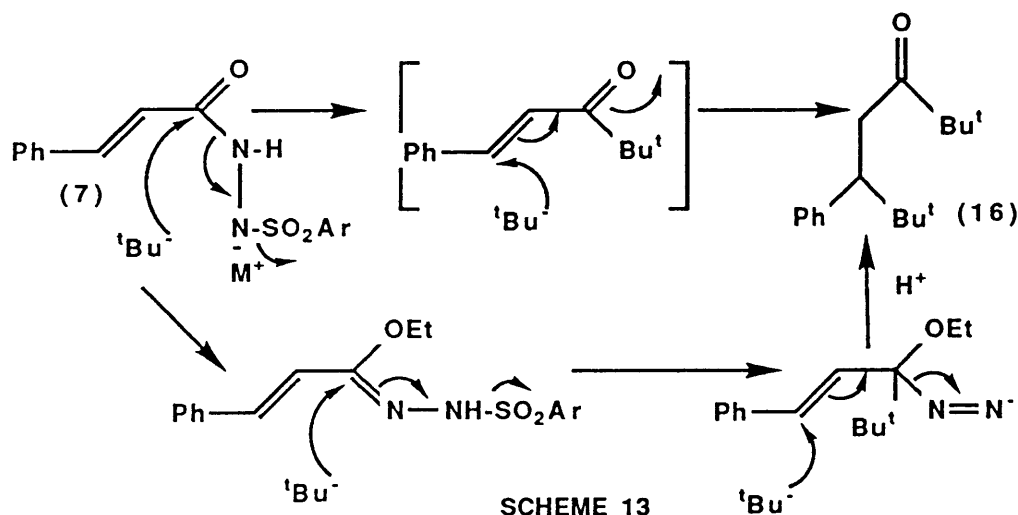
discharged on addition of methyl iodide. However, the resulting mixture of products proved too complex to merit further study. In view of the instability of the "dianionic species" and the failure to observe carbene derived products, a less speculative approach was considered, employing a trisyl ester hydrazone as the Bamford-Stevens substrate.^{17,18,24} Attempted silylation of hydrazide (7) by treatment with trimethylsilyltrifluoromethane sulphonate-triethylamine in DCM afforded silylated material which proved to be too unstable to handle; readily undergoing hydrolysis to afford the hydrazide. In consequence the ethylimino ether (15) was formed by treatment of hydrazide (7) with triethyloxonium tetrafluoroborate according to the method of Paquette²⁵ (Scheme 12). This compound also proved to be sensitive to hydrolysis which was initially considered surprising in view of the reported stability of related compounds.^{17,18,24} Fortunately the alkylation appears to be clean, indicating only O-alkylation as judged by proton nmr spectroscopy of the crude material, and proceeds in high yield. The tendency of the intermediate fluoroborate salt (14) to hydrolyse on neutralisation is quite pronounced, and considerable care is necessary. The apparent instability of iminoether (15) is



SCHEME 12

ascribed to practical difficulties associated with freeing the material from the intermediate fluoroborate salt (14). Other routes to ester hydrazones^{17,18,24} employ less acidic conditions and isolation of the iminoether is therefore less problematical.

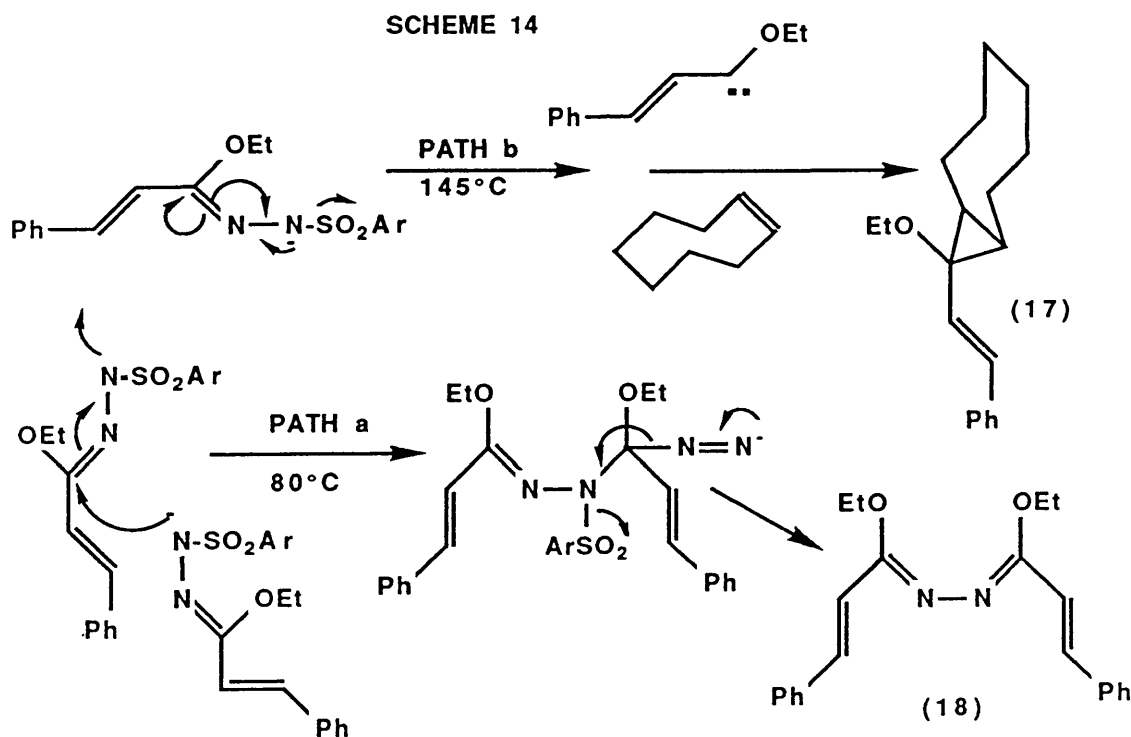
Treatment of a solution of ethyl cinnamate-2,4,6-triisopropylbenzenesulphonyl hydrazone (15) in cyclooctene with 1.3 equivalents of *t*-butyllithium afforded after heating at reflux (145°C) in the presence of catalytic dirhodium tetrapivalate for 48 h, a complicated mixture of products! From this mixture was isolated ketone (16) (Scheme 13). This unexpected product is postulated to have arisen by a mechanism similar to that illustrated in Scheme 11 for generation of di-*n*-butylcinnamyl alcohol (13). The ketone is considered to have arisen from hydrolysed material since it is difficult to conceive a plausible mechanism from the ester hydrazone.



Steric hindrance is invoked to explain 1,4- rather than 1,2-addition of the second *t*-butyl group.

To circumvent problems of nucleophilic attack, hydrazone

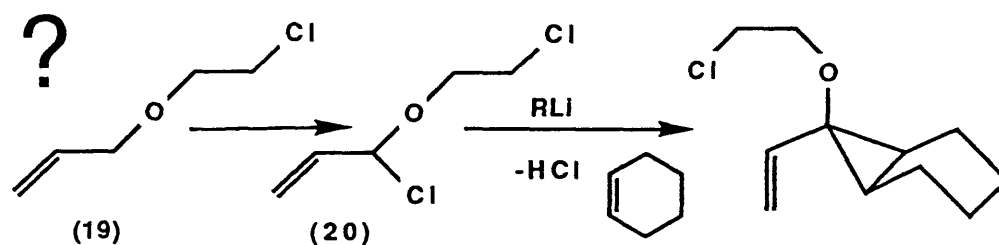
(15) was deprotonated by treatment with potassium-hydride-18-crown-6 in cyclooctene. After heating to 145°C in the presence of catalytic dirhodium tetrapivalate (the pivalate is more soluble than the acetate in hydrocarbon solvents), 9-ethoxy-9-(1-phenyl ethen-2-yl)-bicyclo[6.1.0]nonane (17) was isolated in 47% yield (path b Scheme 14). Similar reaction at room temperature or in cyclohexene at reflux (80°C) afforded different product distributions in which no cyclopropane adducts were detected. In these cases low yields of ethyl cinnamate azine (18) (path a Scheme 16) were isolated. Similar results were obtained employing LDA as base. These results suggest that the



ionic mechanism which leads to azine (18) is favoured at lower temperatures. This in turn implies that employment of the trisyl as opposed to the more usual tosyl leaving group has little effect on the activation energy for its expulsion. The

bulky trisyl group had been chosen for its superior leaving properties which arise from relief of steric hindrance. Additionally the rhodium catalysts did not appear to be favouring carbenoid formation to any significant extent since the yield of cyclopropane obtained was no better than previously reported from uncatalysed reactions of similar substrates^{17,18,24}. It is doubtful whether the catalysts are capable of surviving the vigorous reaction conditions employed.

An approach similar to that adopted by Danheiser¹² was also considered (Scheme 15).



SCHEME 15

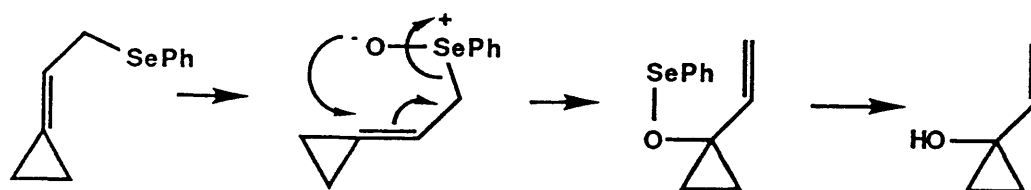
This strategy required access to α -chloro-allyl ethers of type (20). The proposed route to these species consisted of radical halogenation at the highly reactive allylic position of readily available 3-(2-chloroethoxy)-1-propene (19). This known compound was readily prepared in 89% yield by condensation of allyl alcohol and 2-chloroethanol under copper(I)/ acid catalysis according to the procedure of Stephenson.²⁶ On treatment with *t*-butylhypochlorite according to the method of Walling *et al.*,²⁷ however, selective monochlorination could not be achieved. Inseparable mixtures of trichlorinated species as evidenced by mass spectroscopic and proton nmr studies were formed. The observation of over-reaction was not surprising in

view of the high reactivity of allyl radicals, particularly when appended by alkoxy and chloro radical stabilising groups. Consequently further investigations were not pursued, and alternative approaches to vinylcyclopropanols (3) were considered.

2.0 REARRANGEMENT OF ALLYLSELENOXIDES

INTRODUCTION

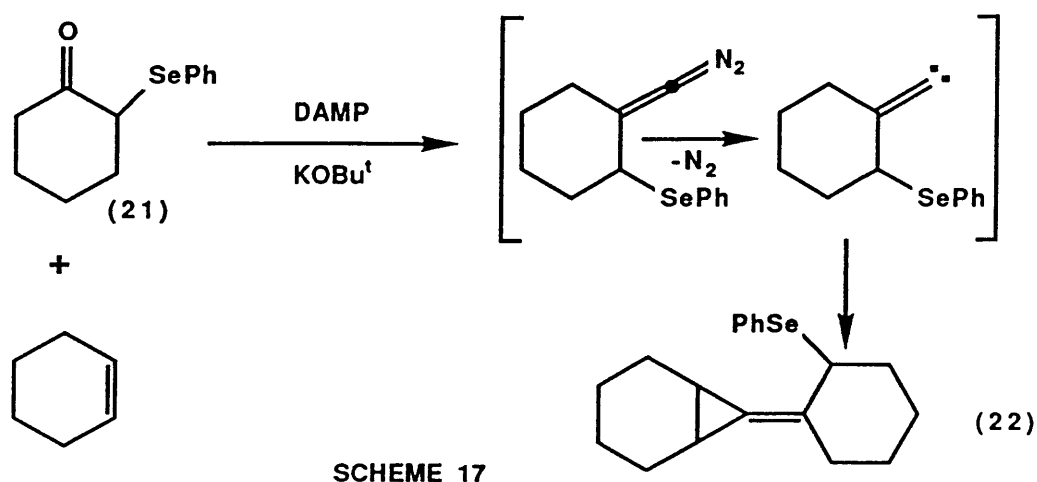
Following the failure of allyloxycarbene approaches to vinylcyclopropanols an alternative and more novel approach was considered, involving functionalisation with allylic transposition of suitably substituted alkylidene cyclopropanes. A logical choice for effecting such a transformation is utilisation of the mild and facile [2,3] sigmatropic rearrangement of allyl selenoxides²⁸ (Scheme 16).



SCHEME 16

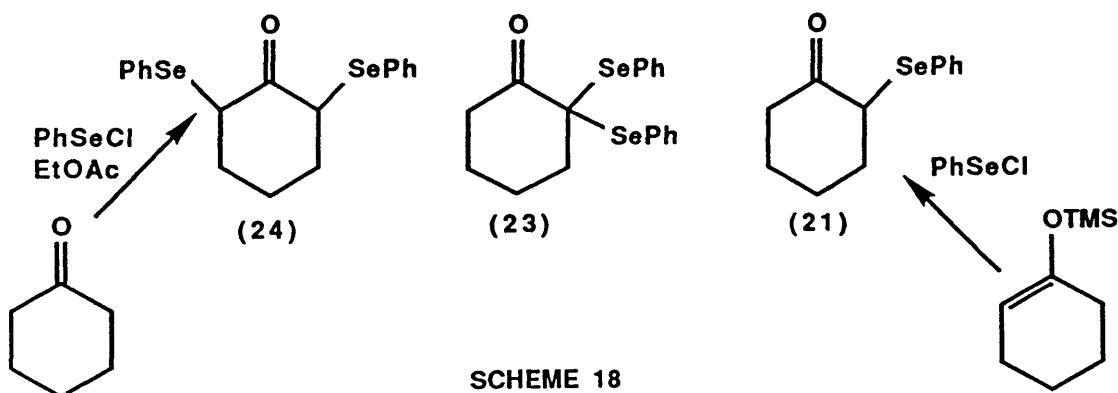
The corresponding sulphoxide methodology, was dismissed on the grounds of the much more forcing conditions required to effect the transformation²⁹. Thus the problem could be reduced to developing a method for the construction of selenium substituted alkylidene cyclopropanes. The conception of the whole route lay in adaption of the work of Gilbert and Weerasooriya³⁰, who initiated development of a method for construction of alkylidene cyclopropanes of diverse substitution pattern from ketones and

olefins. This highly convergent and efficient three component one-pot condensation method for construction of four carbon-carbon bonds has been described in the review (section 1.17.3) . It was envisaged that employment of 2-phenylselenoketones,⁴³ (readily available by reaction of ketone enolates,³¹ enols,³² or enol ethers⁴³ with phenylselenenyl chloride) under these reaction conditions should allow direct and efficient access to the required selenium substituted alkylidene cyclopropanes e.g. (22) (Scheme 17).



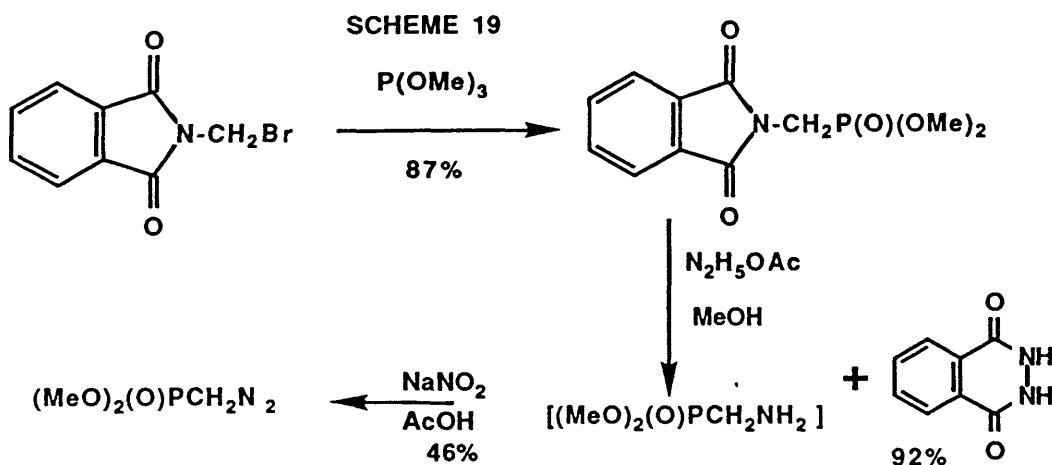
SCHEME 17

Accordingly, 2-phenylselenocyclohexanone (21) was prepared by acid catalysed reaction of phenylselenenyl chloride with cyclohexanone in ethyl acetate³². Contrary to the literature report, it was discovered that mixing the two reagents in a 1:1 ratio afforded a mixture of the required 2-phenylseleno-cyclohexanone, together with significant quantities of 2,2-diphenylseleno- (23) and 2,2'-diphenylselenocyclohexanone (24). These problems were surmounted either by using the ketone as solvent, or by reaction of phenylselenenylchloride with the readily prepared trimethylsilyl enol ether⁴³ at low temperature.



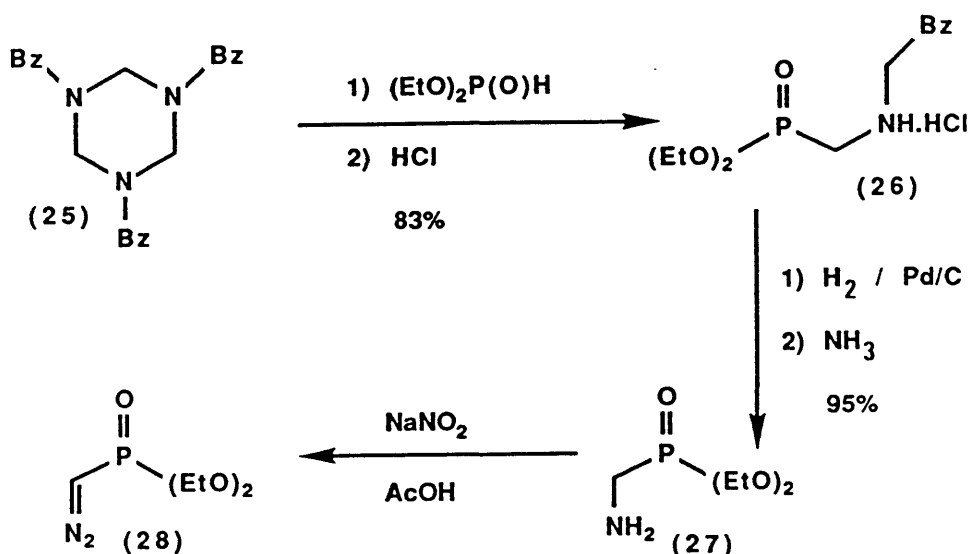
2.1 PREPARATION OF DIETHYL DIAZOMETHYL PHOSPHONATE (28)

Access to substantial quantities of diethyl diazomethyl phosphonate (DAMP) (28) was required, and spurred development of an alternative approach to the inefficient and rather expensive method utilised by Seyferth³³ (Scheme 19). The Ratcliffe-Christensen preparation of aminomethyl diethyl phosphonate (27) was considered more attractive³⁵ (Scheme 20).



Starting from the readily available tri-*n*-benzylhexahydro-*s*-triazine³⁴ (25), prepared by reaction of benzylamine with formalin in 86% yield, Michaelis-Becker reaction with diethyl phosphite afforded the *N*-benzylaminomethyl phosphonate, isolable as the

hydrochloride salt (26) (83%). Hydrogenolytic de-N-benzylation and diazotisation of the known amine (27) thus obtained³⁵, afforded the diazomethyl phosphonate in 73% yield. This material appears to be stable almost indefinitely at 4°C shielded from light. The notable stability of α-diazophosphorus compounds is thought to be due to P-Cπ bonding interactions³³. Apart from the long shelf life of the reagent, the material is also safely distillable provided that all traces of acids are first removed. This route, proved amenable to the large scale preparation of DAMP.



SCHEME 20

Most workers who have prepared DAMP have opted for the original Seyferth route. This may, or may not be attributable to the rather scanty experimental "details" published by Ratcliffe and Christensen. The hydrogenolytic step was initially found to be rather capricious. This difficulty is considered to arise from the presence of catalytic poisons, not entirely suprising in view of the ligating properties of amines and phosphites! The purity of the hydrochloride salt (26) is crucial in determining the success of the debenzylation step. This in turn is related to the

purity of the s-triazine. Reduced pressure distillation of the s-triazine is not recommended since it is prone to decomposition. Crystallisation from aqueous ethanol is a more practical proposition. Reagent purity at each stage was assessed by ³¹Pnmr. Because of the central importance of DAMP to the material presented in this thesis, a complete description of its preparation has been included in the experimental section.

2.2 PREPARATION AND REACTION OF (PHENYLSELENOALKYLIDENE)CYCLOPROPANES

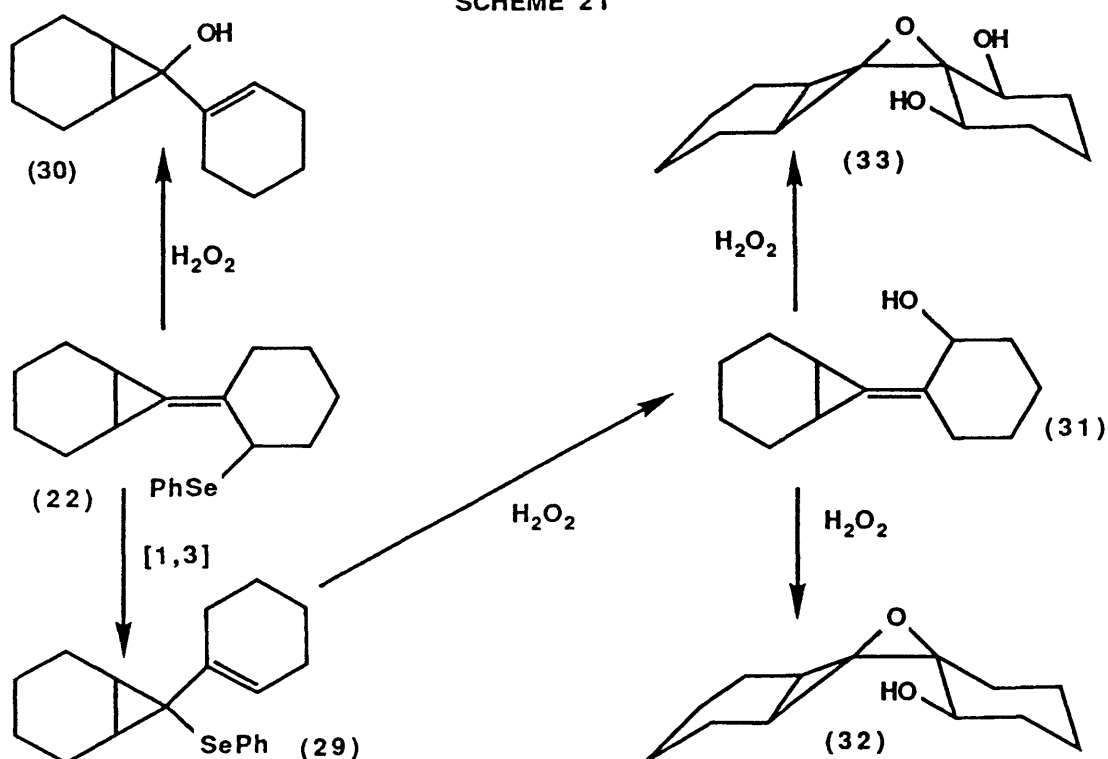
Reaction of 2-phenylselenocyclohexanone with DAMP in the presence of freshly sublimed potassium-*t*-butoxide, THF, and cyclohexene at -78°C according to the method of Gilbert *et al.*,³⁰ afforded the allyl selenide (22) (Scheme 17) in 50-60% yield. Employing DME as co-solvent in place of THF, due to its superior power in solvating potassium salts and ability to stabilise carbenoid intermediates³⁶ resulted in an 82% yield of allyl selenide (22) under analogous conditions.

Oxidation of the selenide proceeds in most cases with concomitant [2,3] sigmatropic rearrangement of the intermediate allylic selenoxide to give on workup the transposed allylic alcohol (Scheme 16). This reaction is favoured over selenoxide *syn*-elimination to give dienes which requires higher temperatures²⁸. A number of oxidative methods have been employed,^{28b} but those employing aqueous hydrogen peroxide under basic conditions appear to be most popular^{28,31,32,38}.

Application of hydrogen peroxide oxidation procedures in pyridine³⁸, pyridine-DCM^{28a,b,31}, or pyridine-THF^{28a,c} to allylselenide (22) gave equally complex results, affording a

mixture of allylic alcohols and also epoxides, arising from over-oxidation (Scheme 21). The reason behind the complicated product distribution was traced to a particularly facile [1,3]- allyl selenide rearrangement^{28b}. That rearrangement occurs so easily is rationalised in terms of release of 11Kcal mol^{-1} of strain energy on rehybridisation at C_7 of the norcarane. The reverse process is likewise precluded³⁷. Furthermore, it appears that rearrangement is accelerated under the conditions of the reaction by which the selenide is made. Significant rearrangement was found to occur if the reaction mixtures were allowed to reach room temperature prior to aqueous workup. However, by quenching the reaction at low temperature, regiochemically pure 7-(2-phenylselenosylohexylidene)-norcarane (22) could be isolated.

SCHEME 21

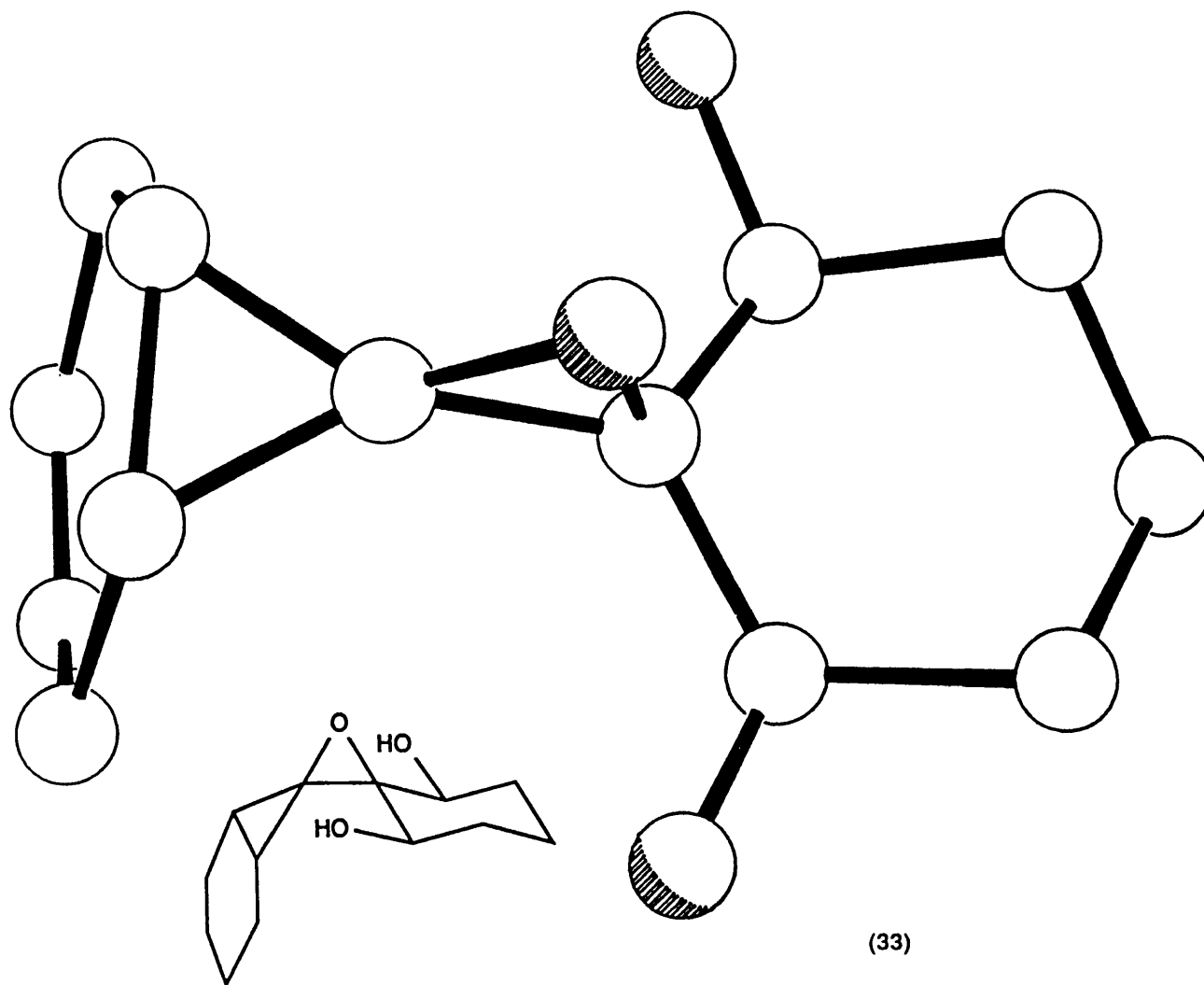


Rearrangement to 7-cyclohexenyl-7-phenylseleno-norcarane (29) proceeded cleanly to completion simply on standing at 4°C; occurring to the extent of 70% within 5 days but requiring approximately 60 days to complete. The mechanism of the reaction is unknown^{28b}, but in view of the ease with which Se-C bonds are homolysed⁴⁹, a radical mechanism appears plausible. Formation of the transposed allylic alcohol (31) from (29) is more surprising in view of the 11Kcal mol⁻¹ barrier to re-institution of the alkylidene cyclopropane double bond, the reason proposed by Halazay and Krief³⁷ for the failure of the reaction in their hands. Subjection of isomerically pure vinyl-cyclopropyl selenide (29) to hydrogen peroxide oxidation at room temperature in pyridine afforded the transposed allylic alcohol (31) in 53% yield, apparently questioning the previous observations. However, like other reactions of these systems, success or failure may rest for reasons of conformational requirements in the transition state, on the substitution pattern of the cyclopropane.⁵⁸

Epoxide (32) is considered to arise from phenylseleninic acid catalysed hydrogen peroxide oxidation of the reactive cyclohexylidene cyclopropane system. Indeed this process, may offer a solution to the problems inherent with preparing the synthetically important oxaspiropentanes³⁹ from alkylidene cyclopropanes. Peracid epoxidation methods currently employed⁴⁰ present practical difficulties in isolating the epoxide due to facile acid catalysed rearrangement to cyclobutanones. The possibility of this type of mild acid catalysed hydrogen peroxide epoxidation does not appear to have been explored hitherto.

Trace quantities of the unusual epoxy-diol (33) were also isolated and its remarkable structure was determined by x-ray diffraction. It is suggested that traces of diphenyldiselenide present in the starting material prior to oxidation, and liberated during the oxidation by disproportionation of the first-formed phenylselenenic acid, generates a peroxy-selenium species formulated as $\text{PhSeO}_2\text{H} \cdot \text{H}_2\text{O}_2$ ⁴¹ by reaction with hydrogen peroxide. This potentially powerful oxidising species, (apparently explosive above 53⁰C!), may be responsible for allylic oxidation of alcohol (31) prior to epoxidation of the activated double bond, as before. Considering the expected reactivity of the double bond towards oxidation, the formation of (33) is still more remarkable. The x-ray structure (Scheme 22) clearly shows that all three oxygen atoms occupy the same face of the molecule. This may be attributed to approach of the oxidising species from the more accessible convex face of the substrate and/or hydroxy-directed epoxidation.

An attempt to prevent over-oxidation by low temperature oxidation of the selenide with ozone in DCM at -78⁰C followed by warming to room temperature^{28b} to effect allylic transposition of the selenoxide proved to be less satisfactory. Hydrogen peroxide oxidation of regiochemically pure allyl selenides employing short reaction times gave relatively clean reaction to afford the desired vinylcyclopropanol in modest yield. Problems with the oxidative rearrangement were not considered to be insurmountable; sodium periodate would have been a better choice of oxidant in this respect.^{28b} However, at this stage it was deemed more important

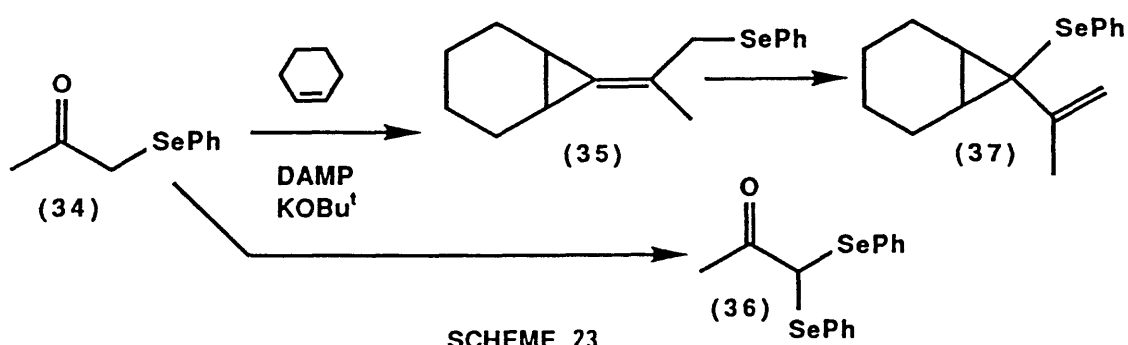


(33)

SCHEME 22

to define the general applicability of the methodology.

Consequently 2-phenylselenoacetone (34) was prepared by addition of an ethyl acetate solution of phenylselenenylchloride dropwise with stirring to excess acetone. Reaction with DAMP, cyclohexene and potassium *t*-butoxide in THF under the Gilbert conditions³⁰, afforded a 71% yield of isomeric allyl selenides (35) and (37) (Scheme 23). Since acetone is clearly much less amenable than



cyclohexanone to Wittig reactions⁴², an extensive investigation of the Wadsworth-Emmons reaction of 2-phenylselenoacetone with DAMP was undertaken. The large proportion of unreacted ketone isolated was indicative of enolisation occurring under the reaction conditions thus preventing nucleophilic attack. Further evidence in support of this comes from the isolation of α,α -diphenylselenoacetone (36), which Liotta postulates⁴³ to arise by a series of intermolecular phenylseleno-proton exchange reactions to afford the most stable enolate.

This observation is not surprising in view of the greater acidity of α -phenylseleno ketones (by ca. 3 pKa) compared with their unselenated parents.⁴⁴ Stabilisation of the enolate arises by conjugative charge delocalisation through interaction of the selenium orbitals with the carbanionic p-orbital. Acetone is

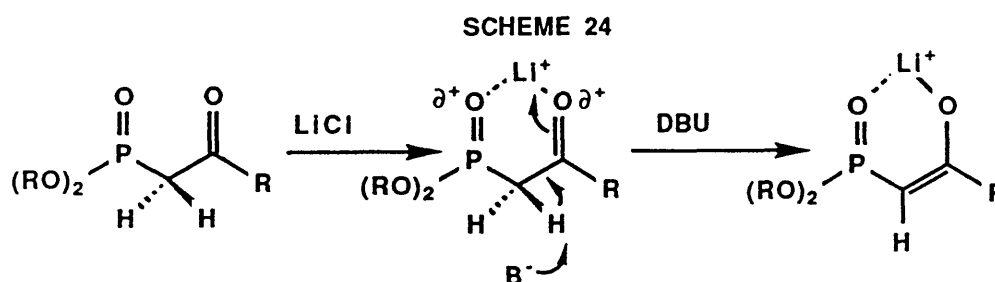
reported to have a pKa of 20, *t*-butanol pKa 19⁴⁵, and phenylselenoacetone a projected pKa of 17-18. Hence a problem is always likely to exist. The pKa value for DAMP is not known, but it is likely to be intermediate between the acidity of *t*-butanol and that of the selenoketone since the DAMP anion is assumed to be responsible for ketone enolisation under the reaction conditions. (The 58% yield reported for the analogous reaction with acetone does not suggest competing enolisation to be a problem in this case³⁰). For success to be achieved it is necessary to displace the equilibria which exist between all these species in the desired direction!

A number of approaches to modification of the DAMP anion basicity were explored. Of paramount importance in this regard is the metal counter-ion employed, which determines the degree of covalent or ionic contribution to the organometallic intermediate, hence controlling its nucleophilicity/basicity. Potassium and sodium salts were generated from potassium or sodium *t*-butoxide; lithium and magnesium salts from organometallic reagents; zinc⁴⁶, copper⁴⁷, and cerium⁴⁸ salts by treatment of the corresponding lithium salt with the appropriate transition metal halides. In view of the recognised instability of the DAMP anion, particularly the lithium salt, reaction with transition metal halides was conducted at -78°C, and the reaction mixture then allowed to reach the appropriate temperature.

Zinc, copper and cerium organometallics are recognised for their superior nucleophilicity and inferior basicity. The effect of such "esoteric" counter-ions on the rate of betaine

decomposition to oxaphosphetane is not known. In the present case, these species are not expected to be stable, so whilst attack at the carbonyl moiety is favoured by the greater covalent properties of the organometallic reagent, the olefin formation is not. The results obtained reflect this hypothesis, negligible yields being obtained with counter cations other than sodium or potassium.

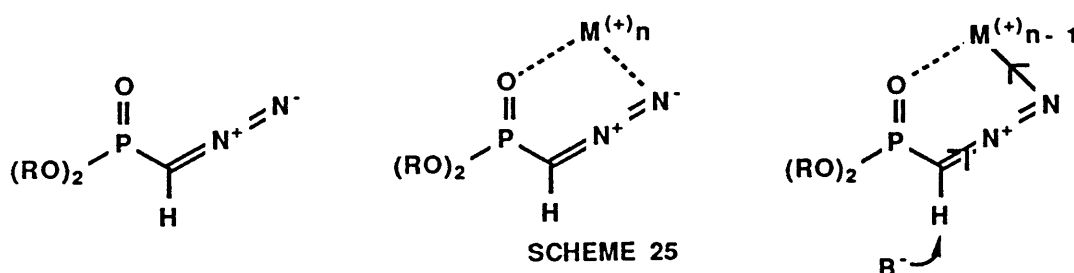
Attempt was also made to enhance the acidity of the diazomethyl phosphonate with respect to the selenoketone so that the possibility of enolisation was suppressed. The elegant trick exploited by Masamune⁵⁰ to increase the acidity of β -keto phosphonates, achieved by addition of lithium chloride was applied. Co-ordination of lithium between the two carbonyl oxygens (Scheme 24) enhances the acidity of the α -proton by favouring the enol resonance form. DBU was then sufficiently basic to remove an α -proton.



Clearly such an approach is not directly applicable in the case of a diazomethyl phosphonate. However, co-ordination of a metal ion might help by inductive electron withdrawal, thus enhancing the acidity of the α -proton (Scheme 25) and reducing the basicity of the resulting anion.

Zn^{2+} and Ce^{3+} were chosen on the grounds of oxaphilicity and

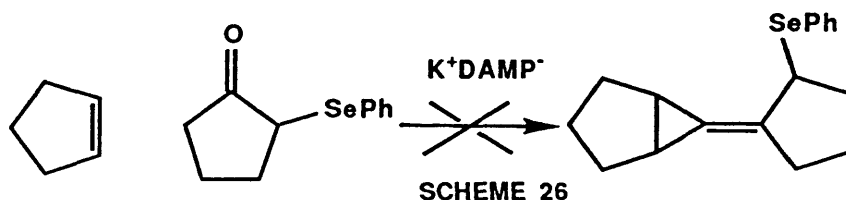
electron withdrawing power of the cations. Treatment of DAMP with zinc chloride in the presence of potassium *t*-butoxide prior to addition of the ketone did not improve the yields obtained. However, a similar reaction employing, potassium hydride-cerium chloride afforded a 36% yield of the allyl selenides. Although a step in the right direction, the effect was not as dramatic as had been hoped.



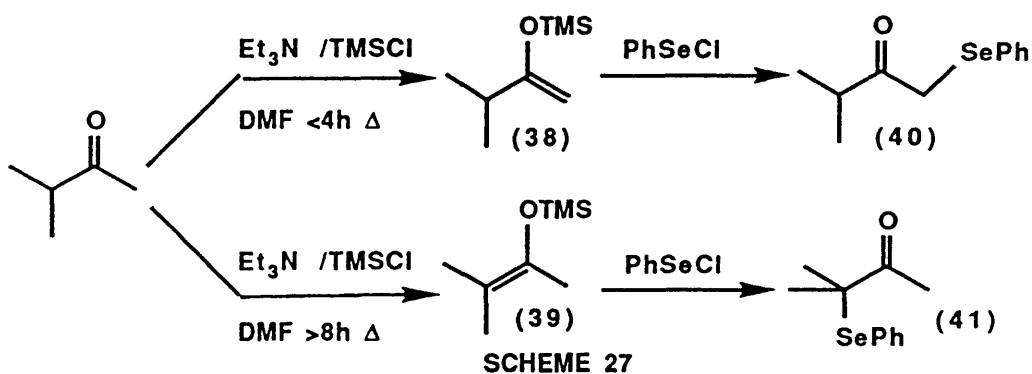
Attempts to enhance the electrophilicity of the carbonyl group of the ketone by addition of Lewis acids (BF_3 etherate) by analogy with the acid catalysis of Wittig reactions,⁴² served only to enhance ketone enolisation, and also caused decomposition of the diazomethyl phosphonate! It was during these investigations that the superior solvating-stabilising properties of DME first manifested itself. The optimal reaction conditions for 2-phenylselenoacetone eventually proved to be substantially similar to those originally employed by Gilbert³⁰, but employing DME as co-solvent in place of THF. A 43% yield of allyl selenides was thus achieved.

The behaviour of a number of other seleno-ketones was investigated. 2-Phenylselenocyclopentanone, a potentially important substrate for polyquinane synthesis (Scheme 26), failed to give more than traces of allyl selenides with a number

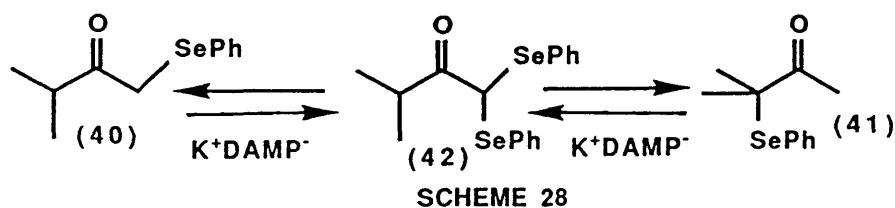
of olefins. These disappointing results are attributable to the still greater kinetic acidity of the cyclopentanone (0.5-1 pKa less than acetone⁴⁵) and serve to illustrate how finely balanced is the success of the desired reaction on the substitution pattern of the α -phenylselenoketone.



Isopropyl methyl ketone was chosen as an example of an unsymmetrical ketone. Regiospecific phenylselenation was achieved by reaction of phenylselenenyl chloride with the corresponding regiospecific silyl enol ethers⁵¹ (Scheme 27).



Reaction of either isomer under the standard conditions in the presence of cyclohexene gave, in addition to very low yields of the desired adducts, a mixture of recovered diselenated (42) and regioisomeric mono-selenated ketones (40) and (41) in which scrambling of the selenium between the two possible positions had occurred by intermolecular rearrangement (Scheme 28)⁴³,



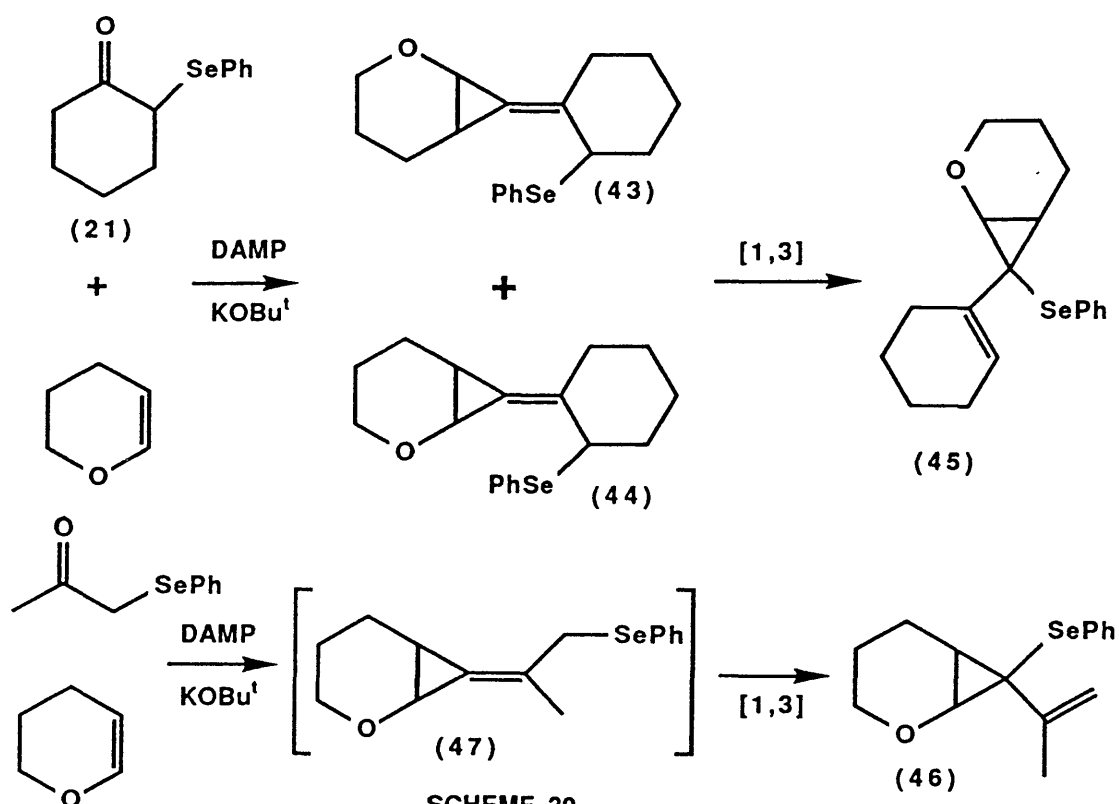
providing additional and conclusive evidence for enolisation of the ketones under the reaction conditions. This result was also important in that the regiochemical outcome of the selenoxide rearrangement performed on an adduct derived from an unsymmetrical ketone could not be guaranteed. That scrambling of the phenylselenenyl group of (1-methyl-1-phenylseleno-ethyl) methyl ketone (41) was also observed is surprising since there are no acidic α -protons in this case. Relief of steric congestion is also known to be important in the rearrangement reaction⁴³, and may account for this observation. The mechanism of the rearrangement has not been studied in detail, but generation of sodium (and presumably potassium) enolates, which are less regiochemically stable than their lithium congeners, enhances the reaction. It appears that the conditions employed to effect the desired 3-component condensation reaction are also ideally suited to scrambling of the regiochemistry of the α -phenylselenoketone. For this reason, phenylthiomethyl isopropyl ketone was prepared by reaction of the kinetic lithium enolate of methyl isopropyl ketone with diphenyldisulphide⁵². These species merited investigation in that radical induced allylic rearrangement of allyl phenylthioethers appeared to be much less favourable⁵³.

α -Phenylthioketones are known to be more acidic than the selenium analogues since conjugative charge delocalisation is more efficient because of better orbital overlap of the less diffuse sulphur orbitals with the carbanionic p-orbital¹⁷. Consequently recovery of the ketone intact and regiochemically pure from reaction with DAMP and potassium *t*-butoxide at -78°C although not entirely unexpected was none-the-less galling!

Having amply demonstrated that the reaction was balanced too finely on the basicity-nucleophilicity knife-edge, currently a major unsolved challenge to organic chemists, to be of any general synthetic use as regards choice of ketone, the generality with regard to tolerance of alkene substitution pattern was probed.

Dihydropyran reacts well with α -phenylselenocyclohexanone in an astounding 99% yield to afford the desired 7-(2-phenylselenocyclohexylidene)-2-oxanorcarane as a mixture of *cis* and *trans* isomers (43) and (44) (Scheme 29).

SCHEME 29

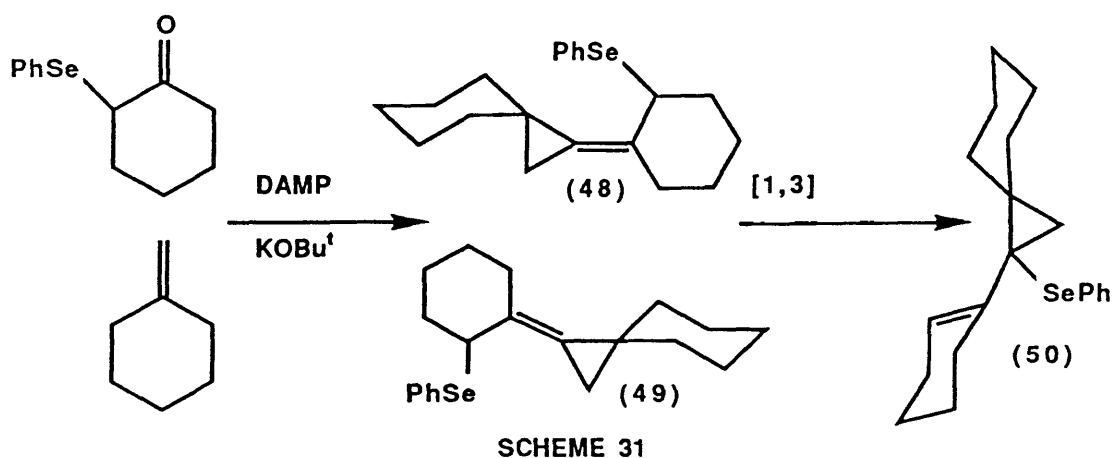


SCHEME 30

These compounds, as expected, undergo facile allyl selenide rearrangement to afford vinyl-cyclopropyl-phenylselenide (45). Reaction of 2-phenylselenoacetone with dihydropyran afforded in

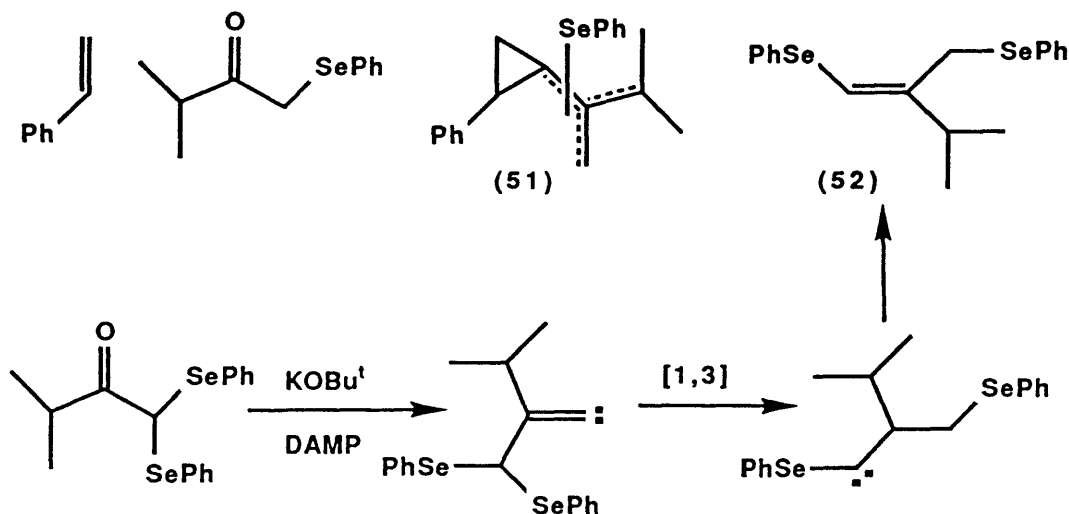
28% yield exclusively the rearranged 7-phenylseleno-7-(2-propenyl)-2-oxanorcarane (46) (Scheme 30). This is in keeping with the observed greater tendency of the 1-phenylselenomethyl-ethylidene cyclopropanes (e.g. (35)) to undergo the allyl selenide rearrangement (to (37)) when compared with their (2'-phenylselenocyclohexylidene)cyclopropane (e.g. (22)) counterparts. This difference presumably reflects the energy difference between migration of the double bond into the 6-membered ring introducing ring strain, versus formation of an acyclic olefin.

Methylenecyclohexane also reacted with phenylselenocyclohexanone to afford a mixture of allylic selenides in 65% yield. Characterisation of the adducts was complicated by the increased number of possible isomers due to lack of symmetry (Scheme 31).



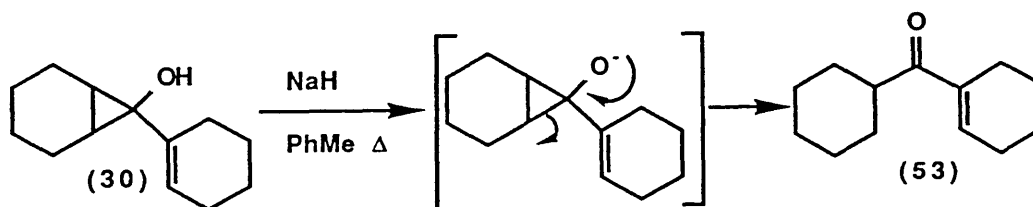
Finally, reaction of styrene with phenylselenomethyl isopropyl ketone (40) was observed to give in addition to traces of the expected isomeric allyl selenides (51) the curious vinyl selenide (52) as the major product. A possible mechanism of formation is proffered in Scheme 32. Phenylselenoacetone behaved

analogously in the presence of styrene. Similar reactions were not observed in any other cases, and the reason for this unusual result is unknown.



SCHEME 32

Although the idea as originally conceived had failed to provide a general route to 1-vinylcyclopropanols, access had finally been gained to a 1-vinylcyclopropanol suitable for investigating the proposed "oxy-anion" assisted vinylcyclopropane rearrangement. Accordingly, treatment of the alcohol (30) with sodium hydride in toluene at reflux afforded a single product in 72% yield, identified as the $\alpha\beta$ -unsaturated ketone (53).



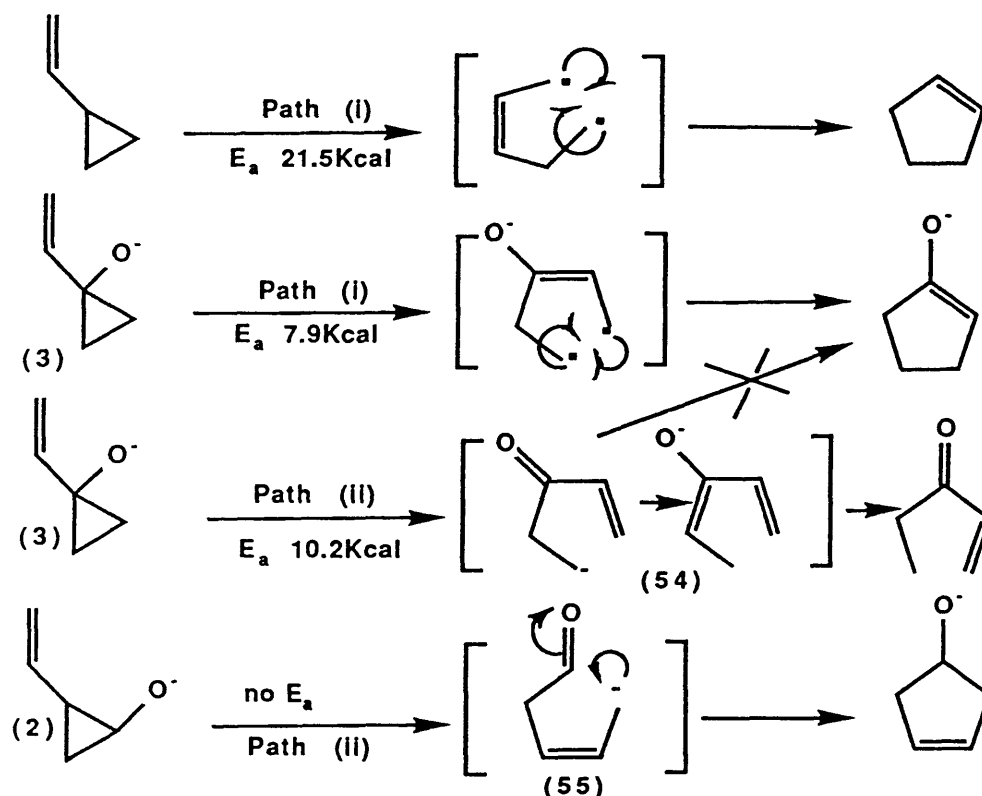
SCHEME 33

This compound is postulated to have arisen by the mechanism shown in Scheme 33.

MNDO calculations on the ring cleavage step performed by

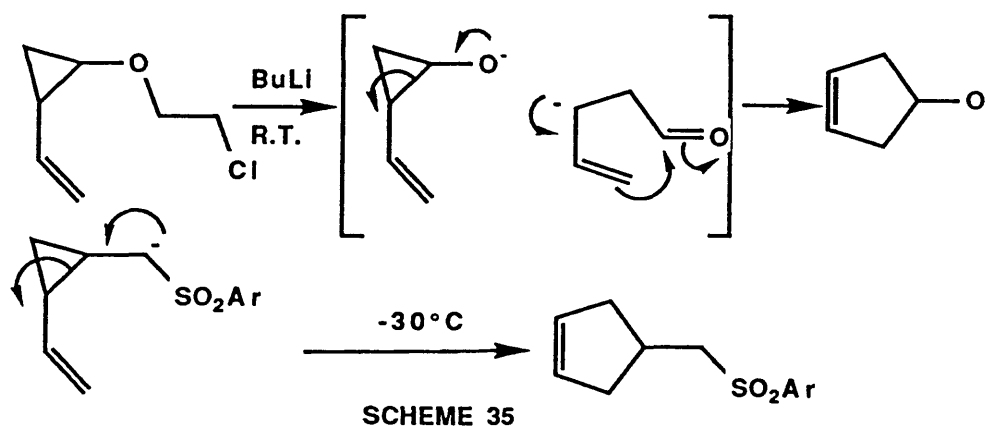
Karim¹⁴ suggested the activation energy for ring cleavage of a 1-vinyl-1-cyclopropoxide (3) by a stepwise free radical mechanism (path i) to be 7.9Kcal mol^{-1} and 10.2Kcal mol^{-1} for the stepwise ionic mechanism (path ii), whilst for the 2-vinyl-1-cyclopropoxides (2) employed by Danheiser, no transition state was observed, ring cleavage being spontaneous (Scheme 34).

SCHEME 34



These results showed that whilst less facile than cleavage of 2-vinyl cyclopropoxides, cleavage of 1-vinylcyclopropoxides, particularly by the radical mechanism was considerably more energetically favourable than for the parent vinylcyclopropane (c) ($21.52\text{Kcal mol}^{-1}$). The facility with which ring cleavage occurs bears out these calculations, but does not account for the failure of ring closure. Though of lower activation energy, the stepwise radical mechanism, which would be predicted to lead to the cyclopentane

is clearly not operating. Considering the alternative mechanism for the observed transformation suggests this to be more energetically favourable due to formation of the more stable intermediate enolate. The observation provides further evidence of a non-concerted ionic mechanism for the oxy- and carbanion assisted vinyl cyclopropane rearrangements investigated by Danheiser (Scheme 35).



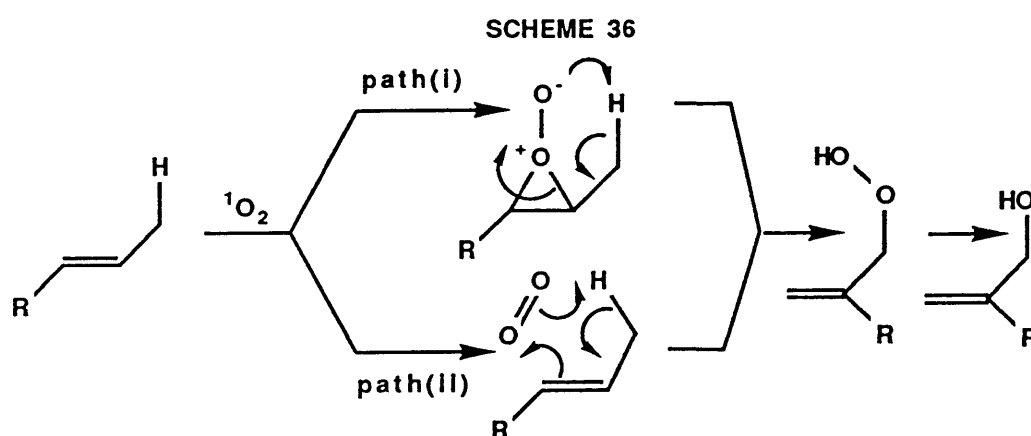
The intermediate anion (54) postulated as arising from base induced cleavage of cyclopropanol (55) would have to cyclise in 1,4- fashion by the stereoelectronically disfavoured 5-endo-trig mode,⁵⁴ whereas the Danheiser intermediates cyclise by a favourable 5-exo-trig-mode.

Danheiser also reports the carbanion mediated rearrangement to proceed with much greater facility (at -30°C) than the corresponding alkoxide (which rearranges at room temperature). This illustrates that the contribution made by the "Evans effect" is much less important than originally anticipated. The subsequent discovery of a "report" by Salaun⁵⁶ in a footnote of his review, that unpublished investigations along these lines had failed to provide cyclopentanes (although no mention of the actual outcome of the reaction was reported) confirms these

observations. The reaction has also been observed by Trost, albeit under aqueous conditions, with sodium hydroxide as base (see Scheme 3)⁵⁷.

Despite this setback, 1-vinyl-1-cyclopropanols are recognised as important synthetic intermediates⁵⁷ since they allow access to cyclobutanones via electrophilic attack on the double bond (Scheme 3) or to cyclopentanones by flash vacuum pyrolysis of the silyl ethers. Clearly the difficulties experienced with the selenium approach to these compounds arose from the acidity conferred on the protons α - to the selenium and ketone moieties, and also from the facility of the allyl selenide rearrangement. Other approaches to vinylcyclopropanols by functionalisation with allylic transportation were therefore considered.

3.0 SINGLET OXYGEN ENE REACTIONS

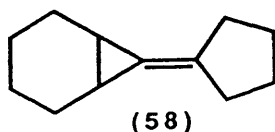


A mild single step reaction which seemed ideally suited to this application was the singlet oxygen-ene reaction. There is some debate in the literature as to whether the mechanism of the

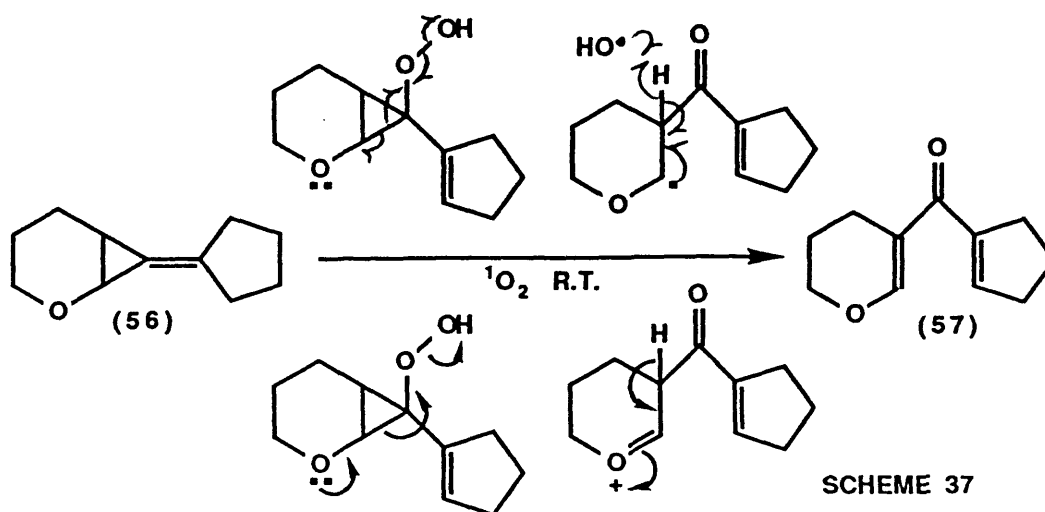
reaction is a true electrocyclic-ene-type pathway (Scheme 36 path ii) or proceeds stepwise via a perepoxide intermediate (path i Scheme 36). In either case, allylic transposition accompanies oxidation, as required. Also favouring the desired reaction is the release of 11Kcal mol^{-1} of strain energy when the "sp²" centre of the alkylidene cyclopropane rehybridises. The proposed reaction has some literature precedent⁵⁸ (review section 2.2). Many examples are also known of singlet oxygenation of tetrasubstituted double bonds.⁵⁹

The required unfunctionalised alkylidenecyclopropanes were readily prepared by reaction of ketones with the potassium anion of DAMP in a mixture of DME and olefin at -78°C , analogous with the approach adopted to the selenium substituted congeners. Thus was prepared 7-cyclopentylidene-2-oxanorcarane (56) from dihydropyran and cyclopentanone. Singlet oxygenation by the method of Ando et al⁶⁰ conducted at ambient temperature (ca. 30°C), resulted in isolation of a single major product in 42% yield. This material proved to be the dienone (57) and may be considered to have arisen either by an ionic or a radical pathway as shown (Scheme 37).

In view of the cleanliness of the reaction when compared with the available literature precedents, the influence of the pyranyl oxygen atom on the outcome of the process was investigated. 7-cyclopentylidene-norcarane (58) was readily prepared in 89% yield from cyclopentanone and cyclohexene.



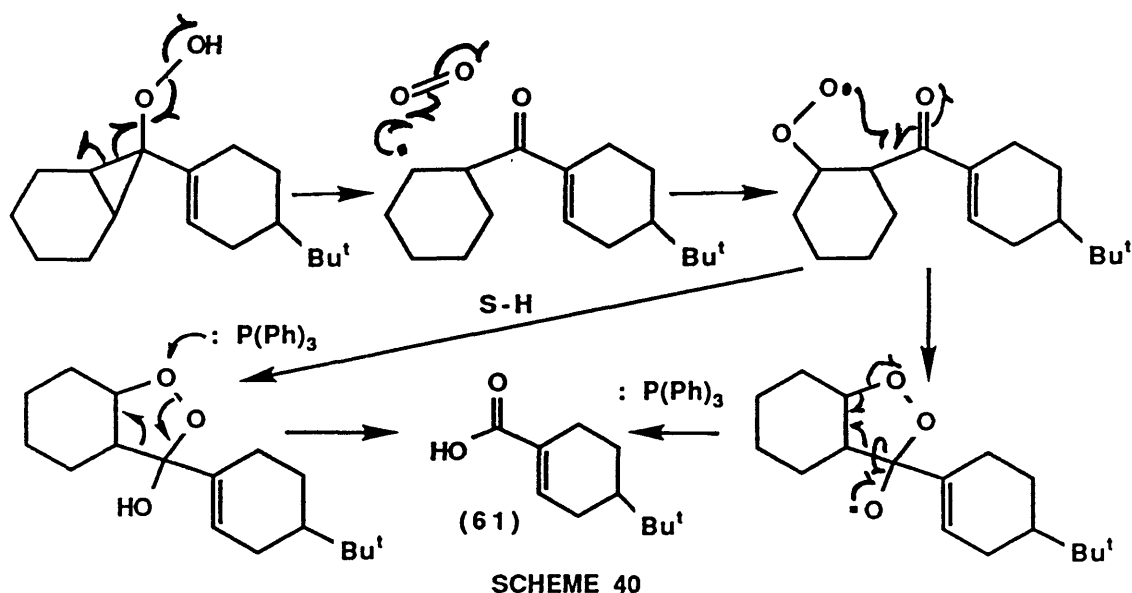
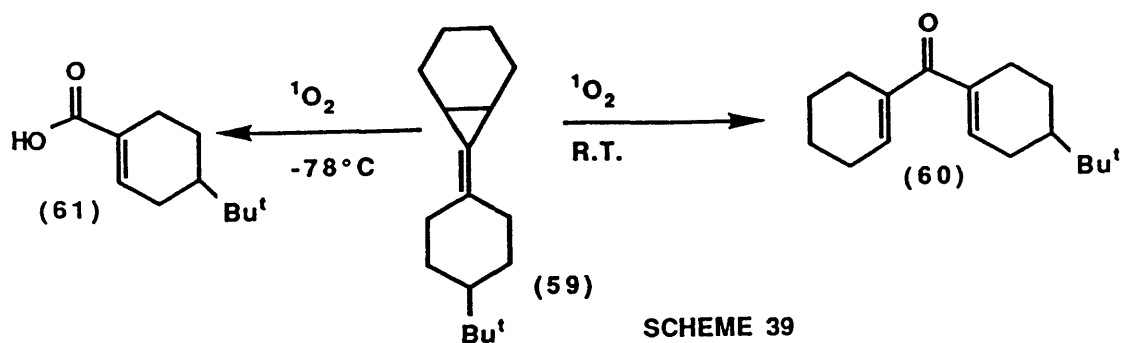
SCHEME 38



Singlet oxygenation of this material under identical conditions resulted in destruction of the starting material. After the usual triphenylphosphine workup, only 20% of the original mass of material was recovered as a multicomponent mixture, none of which appeared to be the expected ketone as determined by mass spectroscopic evidence. Employment of methanol as solvent with methylene blue as sensitizer⁵⁹ did not improve the mass balance. The observation leads to the conclusion that the pyranyl oxygen has a strong influence upon the rearrangement of the expected intermediate hydroperoxide. However, concerned by the poor mass balance, and literature precedent⁵⁹ for such hydroperoxides to be cleaved to ketones under acidic conditions, 7-(4-t-butyl cyclohexylidene)-norcarane (59) was synthesised from 4-t-butyl cyclohexanone and cyclohexene in 67% yield. If cleavage to a volatile ketone had previously been responsible for the poor mass balance, any generation of 4-t-butyl-cyclohexanone should be observable. Singlet oxygenation of this material, executed as previously, afforded on workup a 45% mass balance, with no 4-t-

butylcyclohexanone having been detected by TLC during the reaction. Of this material, the main constituent (20% yield) was the expected dienone (60)(Scheme 39). Isolation of this material, in conjunction with previous proposals as to the instability of the intermediate hydroperoxides to homolytic cleavage⁵⁸ (review section 2.7) tends to favour the radical mechanism proposed (Scheme 37).

The extra stability conferred on a radical α to oxygen explains the higher yield of the dienone obtained from the pyran derivative. The poor mass balance is ascribed to the expected instability on silica of some of the alternative decomposition products⁵⁸. Previous workers in this field had overcome the instability of the hydroperoxides at ambient temperature by conducting the singlet oxygenation reaction and subsequent triphenylphosphine workup below -50°C .⁵⁸ A similar approach was adopted, irradiating through the side of a non silvered dewar containing the reaction vessel immersed in dry ice/acetone. Due to the long reaction time, a heat filter (consisting of two parallel glass sheets between which cool air passed) was necessary to conserve the cooling mixture employed. Upon workup, by addition of a chilled solution of triphenylphosphine in toluene, the only isolable product, 4-t-butyl-cyclohexene carboxylic acid (61) was obtained in 65% yield. The totally unprecedented rearrangement, involving apparent extrusion of cyclohexene is postulated to arise as shown in Scheme 40.



The proposed cyclohexene by-product was neither sought nor observed due to the unexpected nature of the reaction. A colourless solid was observed to precipitate during the singlet oxygenation in toluene at low temperature. This may be the postulated peroxy-acetal intermediate. The proposed intermediate may decompose by a radical mechanism affording cyclohexene and the peracid as the initial products. Triphenylphosphine workup would then be expected to yield the observed carboxylic acid. Alternatively the intermediate peroxy-acetal may give rise to the final product by direct attack at the peroxy moiety as shown. Why initial radical cleavage of the hydroperoxide occurs at low

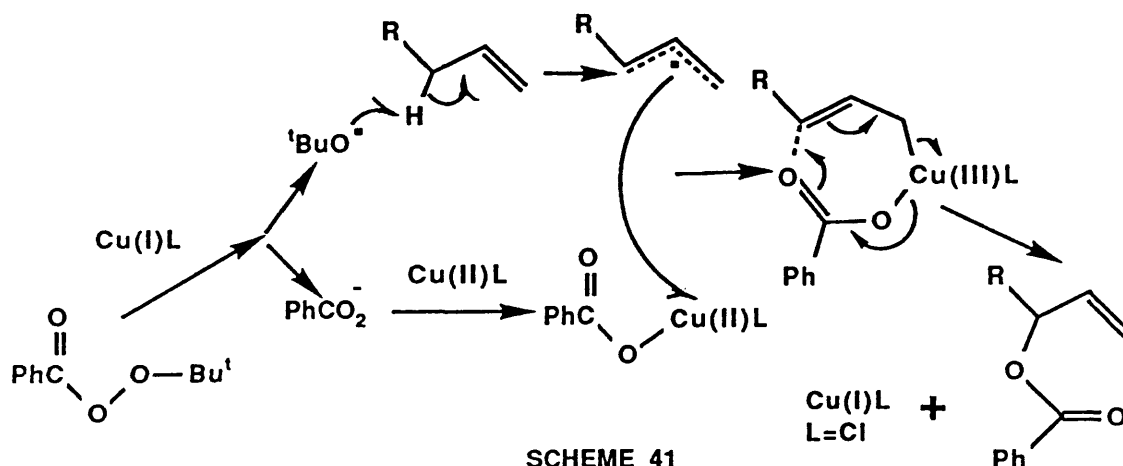
temperature where the species is supposed to be stable⁵⁸ is unclear. The extra substituents borne by our substrates when compared with the literature examples may be stabilising the required intermediate radicals to the extent that this pathway becomes competitive. The temperature dependence of the reaction pathway was not studied. The low temperature reaction is obviously cleaner. It cannot be certain that the acid was not also formed in reactions conducted at ambient temperature due to the difficulty in visualising the compound on t.l.c by standard techniques. Further clarification of this point was not sought.

In the light of these experiences, alternative avenues of approach to 1-vinyl-cyclopropanols from alkylidene cyclopropanes were considered.

Various other means of achieving the desired allylic functionalisation with double bond transposition were considered, in particular the possibilities offered by transition metal carboxylates. However, the necessity of employing a large excess of olefin in these reactions in order to avoid multiple functionalisation precluded their application to the proposed methodology. A recent thorough study on the mechanism of copper catalysed allylic oxidation by peroxy esters conducted by Beckwith⁶¹ prompted further consideration.

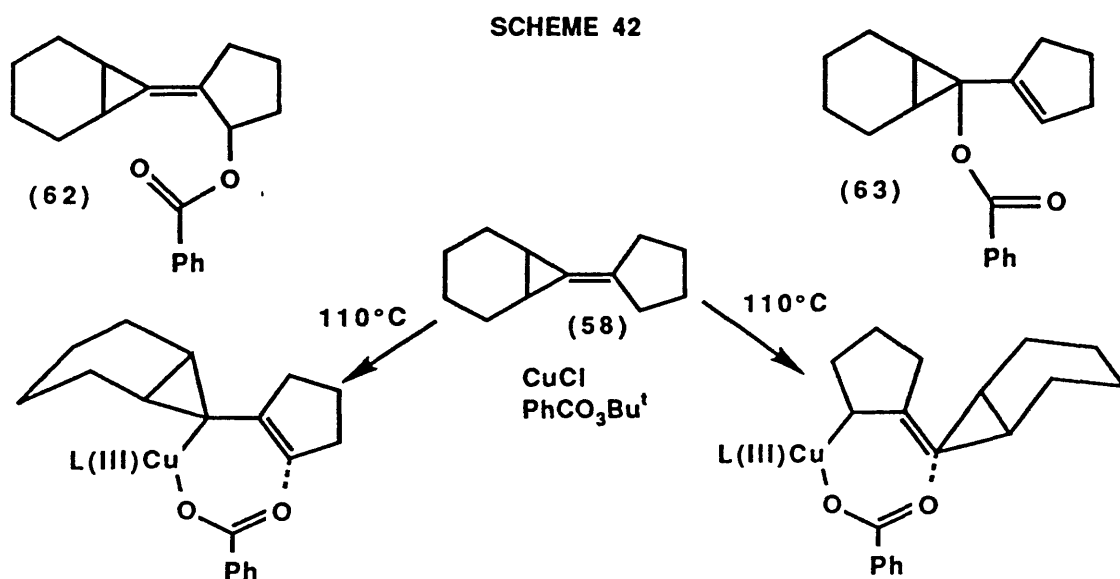
Beckwith concluded the mechanism (Scheme 41) of the reaction between *t*-butyl perbenzoate and olefins to proceed by abstraction of an allylic proton by the *t*-butoxy radical generated by copper (I) cleavage of the perester to afford an allyl radical, and copper (II) benzoate by transfer of an electron. The allyl radical is then captured by the copper (II) to generate an

organo-copper (III) intermediate which then delivers the allylic benzoate functionality by an intramolecular 7-membered cyclic transition state (Scheme 41).



This mechanism explained the observed formation of the less thermodynamically stable olefin (i.e. terminal or less substituted) by the proposition that this was determined by formation of the more thermodynamically stable allyl-copper intermediate⁶¹.

It was considered that the unique properties of alkylidene cyclopropanes by virtue of the strain energy associated with the double bond, should provide an interesting test of the ability of the intermediate allyl-copper species to re-install the cyclopropylidene moiety. Consequently, a mixture of 7-cyclopentylidene-norcarane (58) and catalytic cuprous chloride in benzene at reflux was treated with *t*-butylperbenzoate, to afford a 1:1 mixture of the two allylic perbenzoates (62) and (63) (Scheme 42). The non-predominance of the expected (62) perhaps illustrates the influence of the double bond strain energy on the course of the reaction. In view of this result, it was



postulated that an increase in reaction time might favour formation of the desired thermodynamic product, either on initial reaction, or perhaps by a subsequent rearrangement.

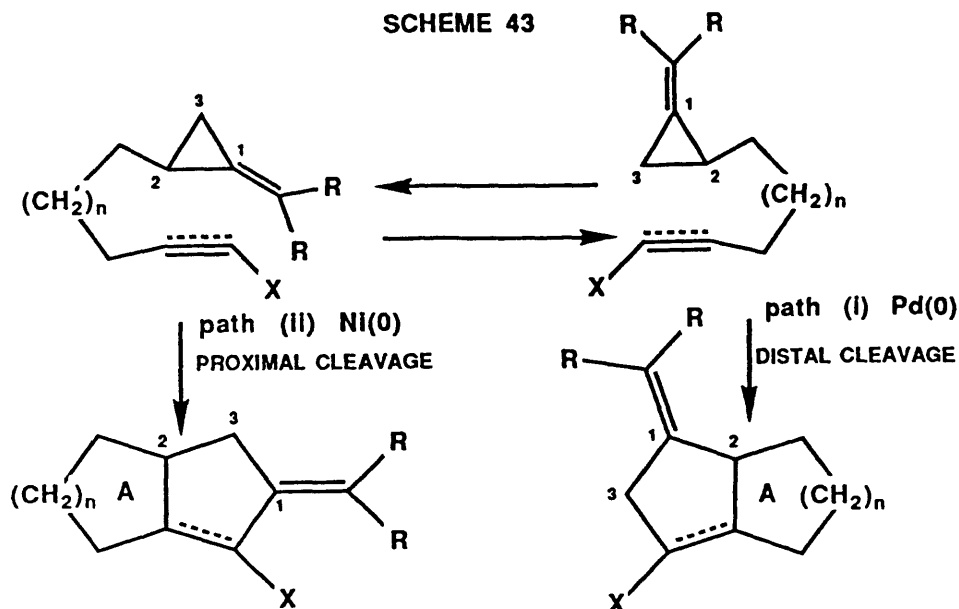
Accordingly, slow addition of the *t*-butylperbenzoate to the olefin via a syringe pump afforded after extended heating a 70:30 mixture of allylic benzoates (41%) in favour of the undesired isomer (62), in accord with Beckwith's mechanistic proposals. Although isomerisation to the required isomer (63) is in principle possible by palladium (II) catalysed rearrangement,⁶² this was not investigated. The low yields of the reaction with *t*-butylperbenzoate do not recommend them for stoichiometric reactions with relatively precious olefins because side reactions become increasingly important. In view of more promising leads elsewhere, no further investigation of these and related routes to vinyl cyclopropanols was undertaken.

4.0) THE SYNTHESIS OF POLYQUINANE SKELETONS BY APPLICATION OF THE [2 σ +2 π] TRANSITION METAL CATALYSED CODIMERISATION OF ALKYLIDENE CYCLOPROPANES WITH OLEFINS AND ACETYLENES

INTRODUCTION

The transition metal catalysed cyclodimerisation of alkylidene cyclopropanes with olefins pioneered by Noyori,⁶⁶ and subsequently developed by Binger⁶⁷ offers great potential in synthetic organic chemistry for the construction of the increasingly important cyclopentane moiety. A particularly attractive feature of the reaction is the incredibly wide variety of π -systems which have been induced to react; ranging from carbon dioxide through electron rich and electron poor olefins to acetylenes. In contrast the alternative Khand-Pauson cobalt octacarbonyl cyclisation of olefins with acetylenes⁷⁶ is sensitive to the substitution pattern at the reacting termini, whilst the trimethylenemethane methodology of Trost³ is applicable only to activated electron deficient π -systems.

Despite extensive investigation of the reaction, a number of anomalies exist, as outlined in the review section above. In particular the apparent dichotomy of reactivity between the parent methylenecyclopropanes and their alkylidene cyclopropane analogues has intriguing mechanistic and synthetic implications. Control of distal or proximal cyclopropyl bond cleavage, selectively induced by suitable choice of catalyst, is the ultimate goal.

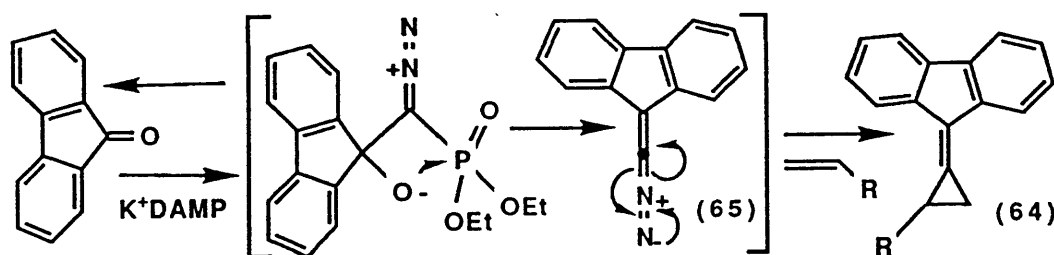


Incredibly, there has been no report of an intramolecular version of this reaction. Intramolecular cyclisation has clear advantages in terms of reducing the regiochemical and stereochemical complications associated with the intermolecular version, which have perhaps hitherto deterred its application in organic synthesis. The possibility of constructing polycyclic skeletons efficiently is also introduced. Employment of a suitably designed link between the reacting centres could conceivably force cleavage of the cyclopropane bond which leads to the less strained ring system irrespective of the catalyst employed. These are the ultimate aims of the project.

In view of Binger's recently reported work on the reaction^{67d}, (diphenylmethylene)cyclopropanes appeared most attractive for initial studies in this field. There exist relatively few concise approaches to the required functionalised systems principally because application of vinylidene carbene methodology is precluded by the Wolff rearrangement. This problem does not apply with fluorenylidene carbene, although steric hindrance has been reported as a problem of carbene

insertion reactions with this moiety⁶⁸.

Nevertheless, in view of previous experience obtained with the one-pot alkylidenecyclopropane synthesis of Gilbert *et al*³⁰ this approach merited investigation. Reaction of fluorenone with the potassium salt of diethyl diazomethyl phosphonate (28) and olefin (74) gave none of the alkylidene cyclopropane (64) (Scheme 44). Recovery of the ketone in high yield indicates that carbene formation does not appear to occur to any significant extent under these conditions. This may be ascribed to the known reversibility of the initial betaine formation³⁰ since attack of the phosphonate anion at the carbonyl introduces a strained sp^3 centre into the ring system. The betaine apparently prefers to revert to the less strained sp^2 hybridised ketone (Scheme 44), rather than proceed to the diazoethene (65).

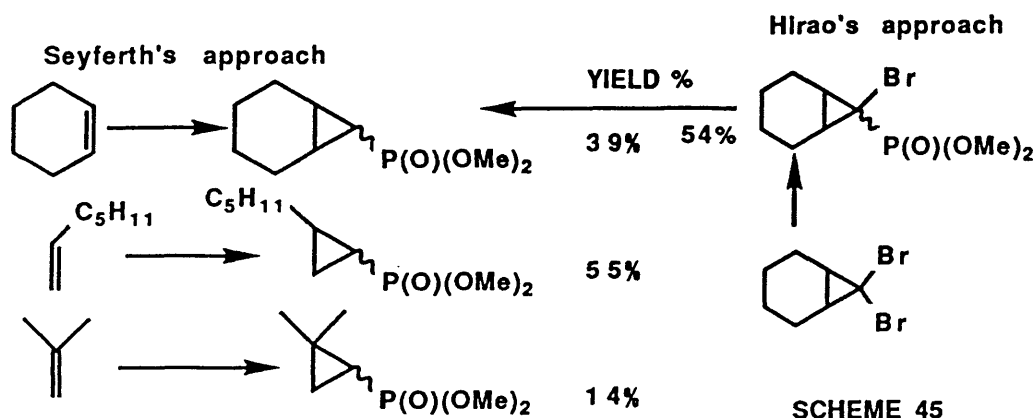


SCHEME 44

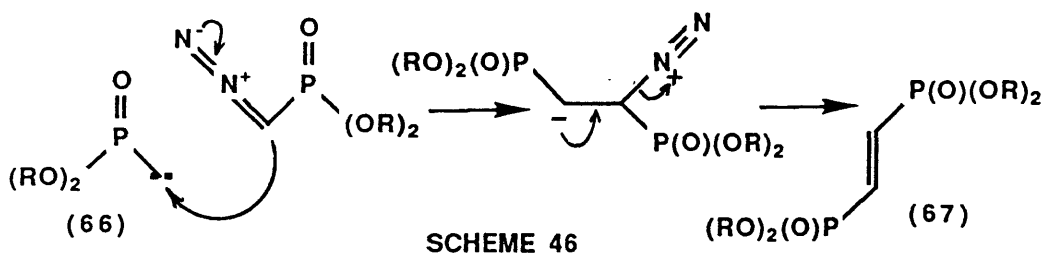
4.1) A WADSWORTH-EMMONS APPROACH TO (DIPHENYLMETHYLENE)CYCLOPROPANES

At this juncture, the early studies of Seyferth³³ on the insertion of carbenes generated by copper catalysed decomposition of diazomethyl phosphonates into olefins, stimulated speculation on a possible Wadsworth-Emmons approach to (diphenylmethylene)-cyclopropanes. Dimethyl diazomethyl phosphonate had been induced

to form low yields of cyclopropyl phosphonates in the presence of a vast excess of olefin and metallic copper³³ (Scheme 45).



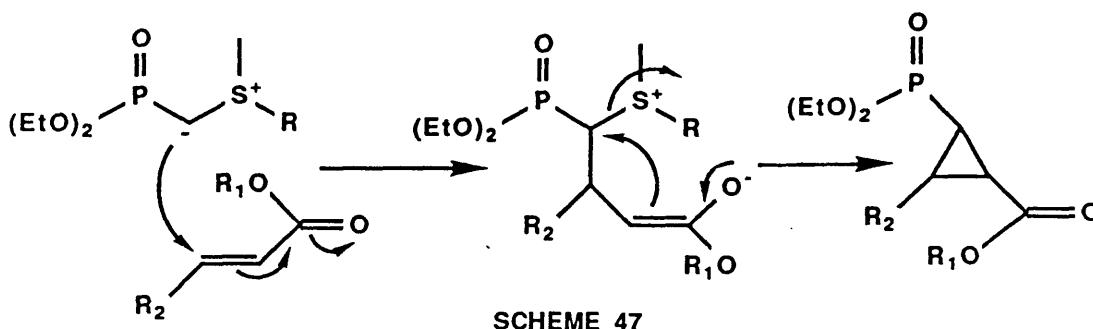
The formal "dimerisation" of the phosphorus substituted methylene carbene (66) to form 1,2-bis(dimethylphosphono)ethylene (67) was known to be the major competing side reaction. This "carbene dimer" arises from attack of the carbene on an unreacted molecule of diazomethyl phosphonate, expelling nitrogen (Scheme 46).



Subsequent to the original reports, it is apparent that no further development of the procedure has been made. Other workers have preferred to employ photolytic methods of carbene generation, which do not appear to offer significant advantages⁷¹.

A reinvestigation of the original reaction was undertaken as a preliminary to development of an efficient approach to the cyclopropyl phosphonates required for the Wadsworth-Emmons step. The only alternative strategy for preparing cyclopropyl

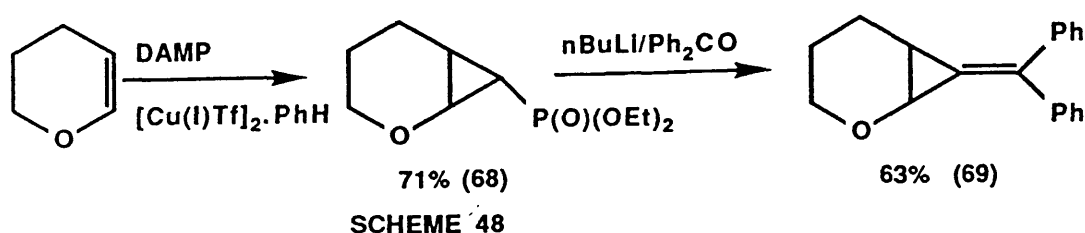
phosphonates from olefins, due to Hirao *et al*⁷², was not considered because of its pedestrian approach to the problem. The Hirao method involves Michaelis-Arbuzov reaction of triethyl phosphite with a gem-dibromo cyclopropane followed by debromination, a three step process which has no advantage over the original one-step procedure of Seyferth (Scheme 45). Cyclopropyl phosphonates are also available by reaction of phosphorus substituted sulphonium ylids with Michael acceptors⁹⁶, (Scheme 47). We, however, required electron rich olefins as our precursors.



3,4-Dihydro-2H-pyran was chosen for initial studies in this area because of its n.m.r spectroscopic characteristics. Following the original Seyferth procedure³³, a 2:1 mixture of olefin and DCM was treated with diethyl diazomethyl phosphonate (28) (DAMP) and copper powder, when a slow rate of diazomethyl phosphonate decomposition was indicated by nitrogen evolution. The major product from this reaction proved to be 1,2-bis(diethyl phosphono)ethene (67) as anticipated. Rhodium acetate and rhodium pivalate catalysis⁶⁹ initiated smooth decomposition of DAMP at room temperature, but again gave predominantly the dimeric product. A rapid deactivation of the catalyst was

observed, with repeated additions of fresh catalyst being necessary to drive phosphonate decomposition to completion. Cuprous trifluoromethanesulphonate (cuprous triflate) held particular attractions in that its reported high activity and ability to co-ordinate olefins with selectivity⁷⁰ seemed ideal. Olefin co-ordination should favour insertion over "dimerisation" of the carbene generated, since the two reacting species are brought into close proximity on the metal. Also attractive was the possibility of exploiting the known affinity for coordinating the most electron rich and least sterically encumbered bond of a poly-olefinic substrate. The cuprous triflate catalysed reaction of DAMP proceeded with rapid, almost violent evolution of nitrogen at room temperature, again yielding predominantly the dimeric product, although more cyclopropyl phosphonate was obtained than was the case with other catalysts. By cooling the reaction to between 0°C and 10°C, the phosphonate decomposition could be conducted at a reasonable rate. The "dimerisation" problem was solved by slow addition of the DAMP via a syringe pump, to a mixture of olefin, DCM, and catalyst at 4°C to 8°C. The activity of the copper catalyst is such that it allows reaction to be faster than the rate of addition; the DAMP exists only at high dilution (provided stirring is efficient). The "dimeric" product is much less likely to form, and good yields of cyclopropanes are thus obtainable. It transpires that the reaction is very clean, with the "dimer" as the only, and readily separable contaminant. Indeed dimer formation was almost totally suppressed in the presence of a large excess of olefin. Hence cyclopropanation of dihydropyran with DAMP in DCM at 8°C afforded

exo,endo DIETHYL (2-OXABICYCLO[4.1.0]HEPT-7-YL)PHOSPHONATE (68) (Scheme 48) in 71% yield. Wadsworth-Emmons reaction was achieved by deprotonation at -78°C with $n\text{-BuLi}$, and quenching with benzophenone. Upon warming to room temperature, the desired (diphenylmethylene)cyclopropane (69) was formed directly in 63% yield.



The reaction is particularly noteworthy on two counts when compared with the literature precedent⁷². Firstly, in contrast, acetone was reported not to participate in the Wadsworth-Emmons reaction of cyclopropyl phosphonates. This difference may be attributable to the inability of benzophenone to enolise. However, a particularly characteristic mark of the reaction of the yellow or orange lithium salts of cyclopropyl phosphonates with benzophenone is the rapid generation and slow fading of an intense blue or green colouration upon addition of the benzophenone, indicative of the benzophenone ketyl radical anion. This suggests that the reaction may proceed by a mechanism involving a degree of electron transfer, a mode to which benzophenone would be eminently suited. Moreover, previous precedents suggested that oxaphosphetane formation did not occur with the lithium salts of the betaine; β -hydroxy phosphonates were apparently, isolated exclusively and in good yield⁷². In this case, however

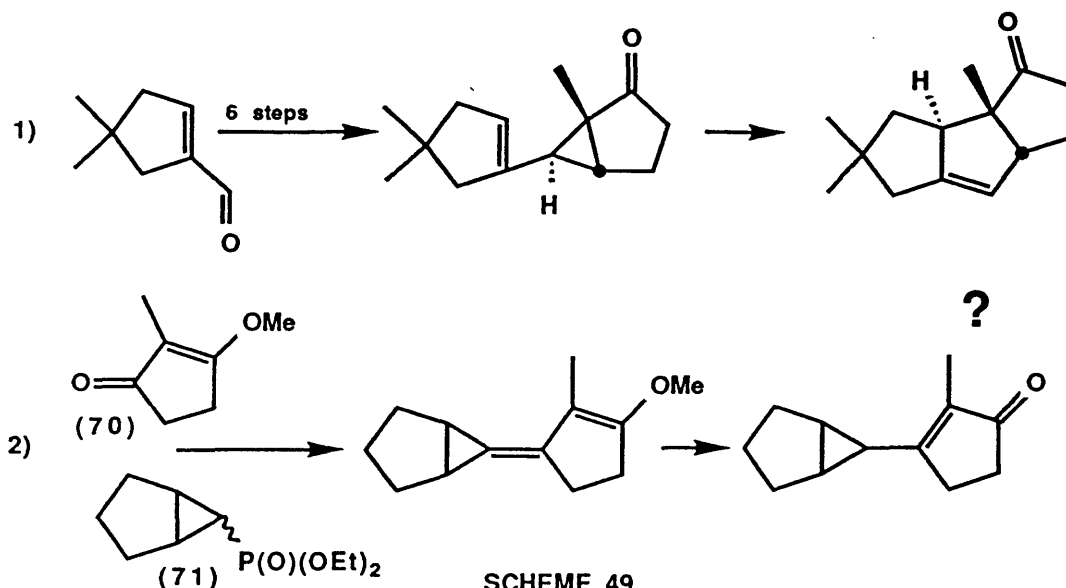
concurrent olefin formation was observed simply on allowing the reaction to reach room temperature.

Encouraged by these results, the Wadsworth-Emmons reactions of cyclopropyl phosphonates with some other ketones were investigated. Wadsworth-Emmons reactions with 2-phenylseleno-ketones might be a more successful approach to selenium substituted alkylidenecyclopropanes inaccessible by the previously explored route. Not suprisingly, in view of the greater basicity expected of the cyclopropyl phosphonate (28) anion compared with that of DAMP, in conjunction with seleno-ketone acidity, the reaction was unsuccessful. Employment of the corresponding organocerium reagent was thought to hold more promise since the initially formed cyclopropyllithium was assumed to be more stable than its diazomethyl phosphonate counterpart, and would thus facilitate preparation of the organocerium reagent. This strategy was equally unsuccessful, perhaps as a result of cerium counterion incompatibility with oxephosphetane formation.

Also attractive was the approach to linear triquinanes via a rhodium catalysed vinyl cyclopropane rearrangement adopted by Hudlicky⁷⁴, (Scheme 49 equation 1). An alternative highly convergent approach to analogous precursors appeared very attractive, (Scheme 49 equation 2). The required ketone (70), is the readily prepared enol ether of 2-methyl-1,3-cyclopentanedione⁷⁵. The cyclopropyl phosphonate (71) was obtained in 62% yield by reaction of DAMP with cyclopentene in the presence of cuprous triflate. We were again thwarted by the apparent

impotence of the cyclopropyl phosphonate anion towards ketone (70).

None of the desired adduct was observed.



SCHEME 49

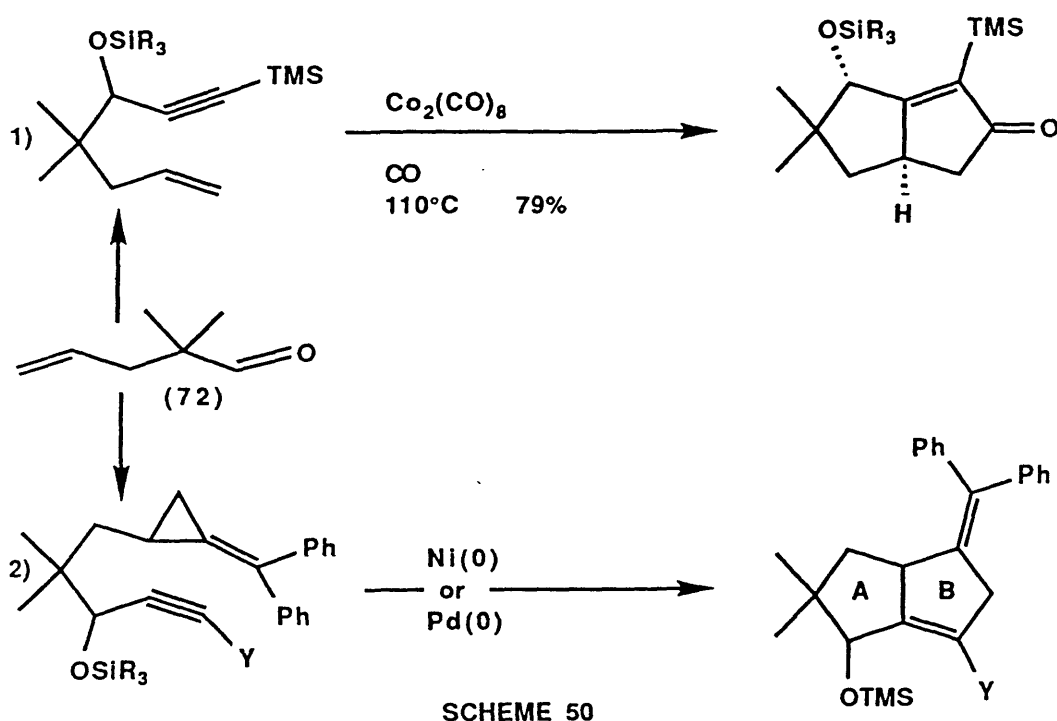
The observations reported above serve to support the suggested rather unique Wadsworth-Emmons reactivity of benzophenone towards cyclopropyl phosphonates.

Having established that cyclopropyl phosphonates were readily available from olefins, and that Wadsworth-Emmons reaction with benzophenone gave access to diphenylmethylene cyclopropanes, attention was focused on the synthesis of suitable substrates for the proposed study of the intramolecular "Binger" reaction. Two molecules were sighted as targets based on the versatility they offered in testing the reaction, and on their relevance to natural product synthesis. The adopted approaches to these targets are described below.

4.2) A MODEL APPROACH TO LINEAR TRIQUINANES

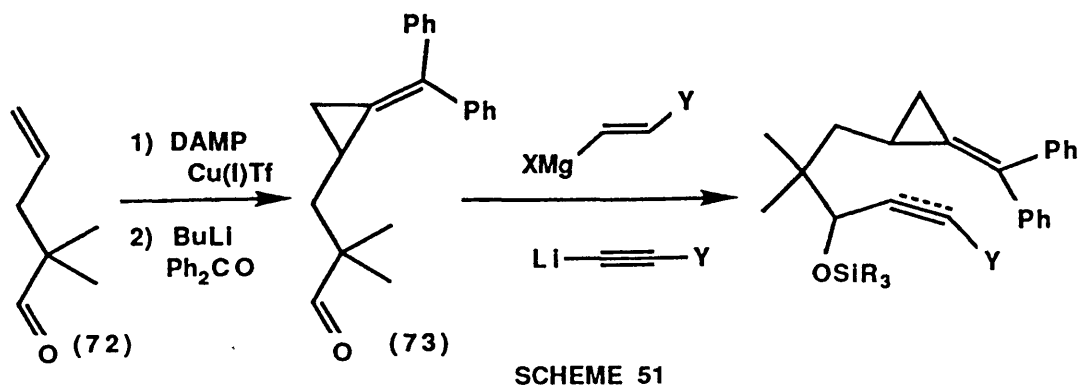
4.2.1) SYNTHESIS OF THE PRECURSOR

The inspiration for this approach came from the impressive work of Magnus *et al* on the development of the Khand-Pauson strategy of cyclopentaannulation and its application to the synthesis of the linear triquinane Coriolin⁷⁶ (Scheme 50), equation 1).



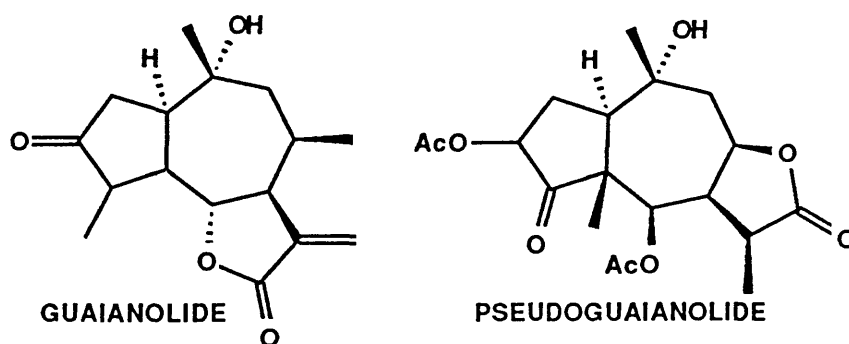
The substrate required for the analogous "Noyori-Binger" reaction was considered to be available from the Magnus aldehyde⁷⁷ (2,2-dimethyl-4-pentenal) (72) by the cyclopropyl phosphonate methodology we had developed, as shown in (Scheme 51). Aldehyde (73) thus became the synthetic target since this versatile building block would provide access to a variety of olefinic and acetylenic substrates for studying the cyclisation

reaction, by addition of readily available acetylide or vinyl anions.



SCHEME 51

This approach also allowed for variation of the size of ring A (Scheme 50 equation 2) of the expected bicyclic product, introducing, at a later date, the possibility of application to the synthesis of bicyclo[5.3.0]decane analogues of, for example, pseudoguaianolides (which possess important biological activity)⁷⁸ (Scheme 52).



SCHEME 52

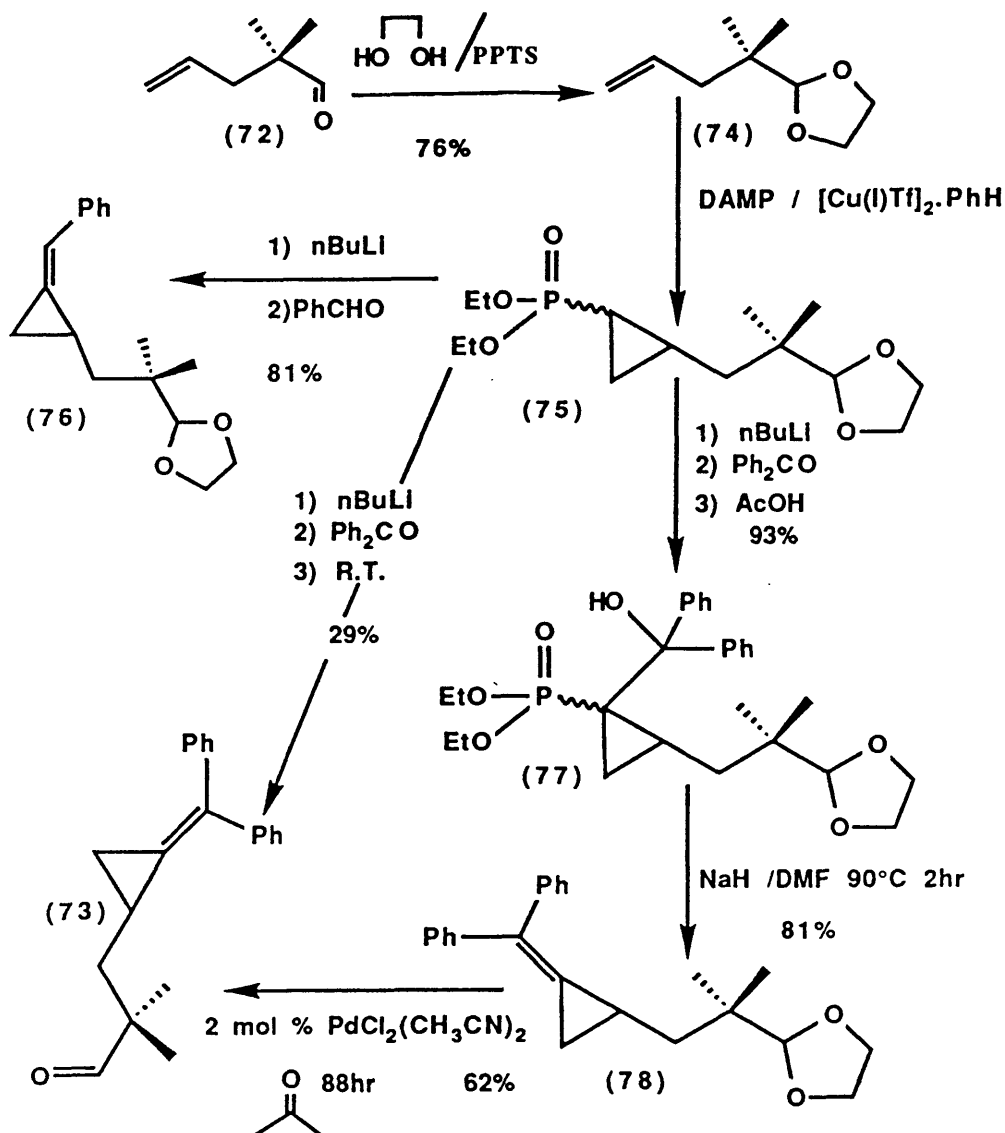
2,2-Dimethyl-4-pentenal (72) was readily prepared by acid catalysed Claisen alkylation of isobutyraldehyde with allyl alcohol according to the procedure of Magnus and Nobbs⁷⁷. To avoid possible competition from attack of DAMP at the aldehyde⁷⁹ it was protected as the 1,3-dioxolane (74)⁸⁰. The dioxolane (74) was treated with cuprous triflate and DAMP to afford the required

cyclopropyl phosphonate (75) as a cis,trans mixture in 73% yield. The experimental technique, applied to all subsequent cyclopropyl phosphonate preparations, involved slow addition of a DCM solution of DAMP to a mixture of olefin, catalyst and DCM at $4-8^{\circ}\text{C}$ over 72 hours (longer periods gave only marginal improvement in yield). This technique permitted a significant reduction in the excess of olefin employed, to the order of 2-4 equivalents, without significantly affecting the yield. The excess olefin was readily recoverable and was routinely recycled.

Deprotonation with *n*-BuLi and quenching with benzophenone gave the same initial dark blue or green colouration which slowly discharged to yellow in accordance with previous observations. On warming to room temperature, the olefin (73) was isolated in a rather disappointing 29% yield. TMEDA, added to stabilise the cyclopropyl phosphonate anion did not improve this result. It was discovered that by quenching the anion with benzaldehyde, the corresponding benzyliidenecyclopropane (76) was obtained in an excellent 81% yield.

This prompted a closer examination of the reaction with benzophenone and it was subsequently determined that on quenching the reaction at low temperature by addition of acetic acid, the intermediate β -hydroxyphosphonate (77) (Scheme 53) could be isolated in 94% yield. The ability to isolate the β -hydroxyphosphonate is in accord with the observations of Hirao⁷². However, contrary to his reports, complete suppression of olefin formation was only achieved when the reaction was quenched at low temperature as described. The β -hydroxy-cyclopropyl phosphonate

(77) was obtained as a separable mixture of two diastereoisomers



SCHEME 53

in a 7.3 : 1 ratio. The major isomer, assumed to possess trans-disposition of the diphenylhydroxymethyl moiety with respect to the alkyl chain on steric grounds, was crystalline, and could be purified by crystallisation from hot petrol. The minor diastereoisomer was a colourless oil. Treatment with potassium hydride in DME to effect oxaphosphetane formation and collapse to the olefin rapidly resulted in a 10% yield of olefin (78) and

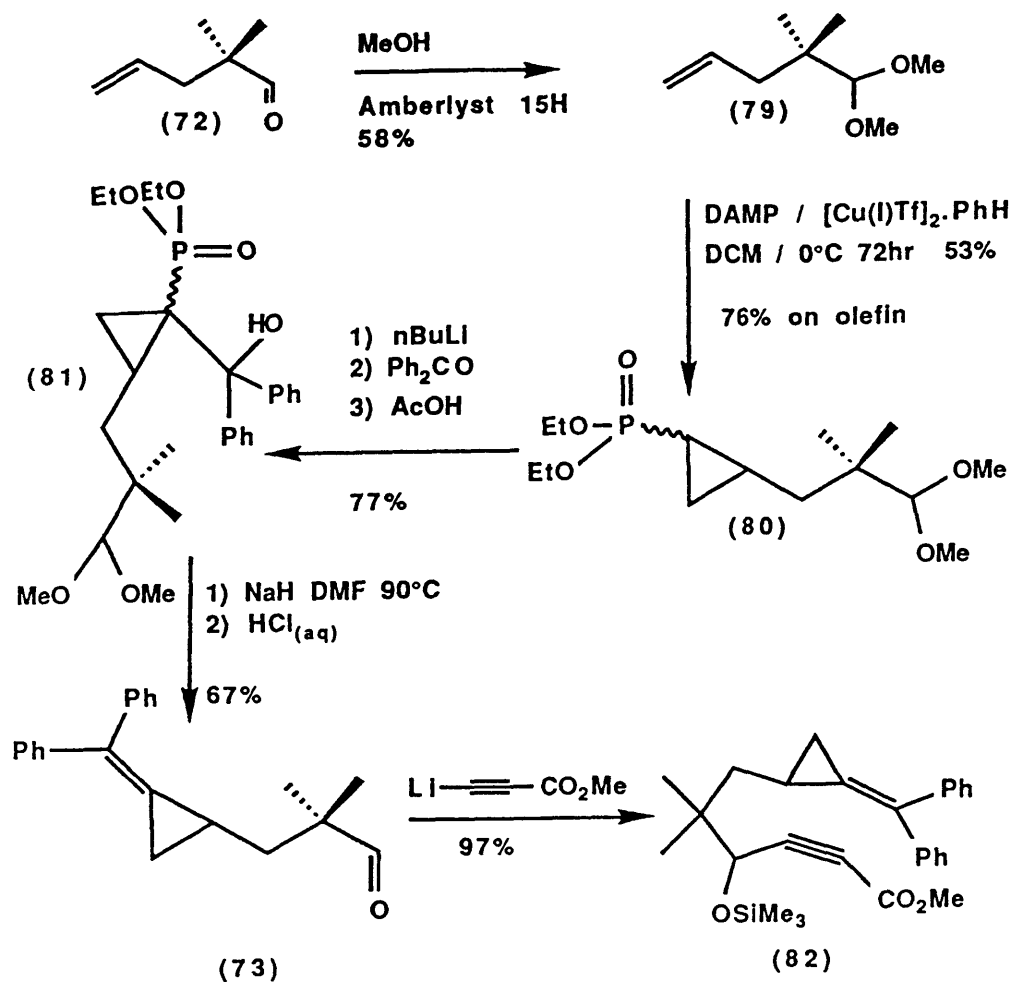
extensive cleavage of the β -hydroxy-phosphonate to liberate benzophenone (40%).

Treatment with sodium hydride in DMF at 90-100°C, however, resulted in a much slower reaction to afford 1-(diphenylmethylene)cyclopropane (78) in 81% yield. No benzophenone formation was observed by t.l.c. This method gives superior results to those reported with sodium hydride-18-crown-6 in THF by Hirao⁷². The dramatic difference in the reactivity of the potassium and sodium betaines is ascribed to achievement of the correct balance of covalent and ionic properties with the sodium salt. Presumably the greater ionic nature of the potassium salt encourages the reversibility of betaine formation, whilst the lithium salt is too strongly covalent to favour a reasonable rate of oxaphosphetane formation. Despite adding an extra step to the reaction sequence, isolation of the β -hydroxy phosphonate (77) is recommended on practical grounds.

(Diphenylmethylene)cyclopropane (78) is of similar polarity to benzophenone, ensuring a tedious chromatographic separation from the excess of benzophenone normally employed, in the one-pot process. This is particularly undesirable on a preparative scale. In contrast, the β -hydroxyphosphonates are readily liberated from the benzophenone due to their greater polarity. On a large scale, crystallisation from hot petrol allows isolation of the major diastereoisomer.

Removal of the 1,3-dioxolane protection proved to be capricious. A variety of acid catalysed trans-ketalisation and hydrolytic methods were explored. The best appeared to be use of

silica supported sulphuric acid in DCM⁸¹, or of dichlorobis(acetonitrile)palladium in acetone⁸². With acid catalysed hydrolysis, rapid partial deprotection was followed by extensive decomposition on standing. Palladium (II) catalysed trans-ketalisation with acetone proceeded to a point beyond which it could not be persuaded to continue by further addition of catalyst or replacement of solvent. In order to cope with these problems, separation of the protected material from the free aldehyde was necessary after reaction had proceeded to ca. 40% conversion. The recovered 1,3-dioxolane could then be recycled. This situation was far from satisfactory principally because chromatographic separation of the aldehyde from the dioxolane was tedious owing to their similar polarity. These difficulties were circumvented by protecting the Magnus aldehyde as the dimethylacetal by treatment with Amberlyst 15H in methanol⁸³ to afford 1,1-dimethoxy-2,2 dimethyl-4-pentene (79) (Scheme 54) in 58% yield. Copper (I) catalysed cyclisation proceeded smoothly as before, to afford a similar diastereoisomeric mixture of cyclopropyl phosphonates (80) in 53% yield. Fortuitously, acetal cleavage under the cyclopropanation conditions was not a problem⁸⁴. Wadsworth-Emmons reaction of (80) with benzophenone allowed isolation of the β -hydroxyphosphonate (81) in 77% yield as a separable 4:1 mixture of diastereomers. The major diastereoisomer was again crystalline. Treatment with sodium hydride in DMF, followed by acidic workup with aqueous HCl afforded directly, in 67% yield, the desired key aldehyde (73). Thus was developed a route amenable to the preparation of the key aldehyde (73) (Scheme 54).



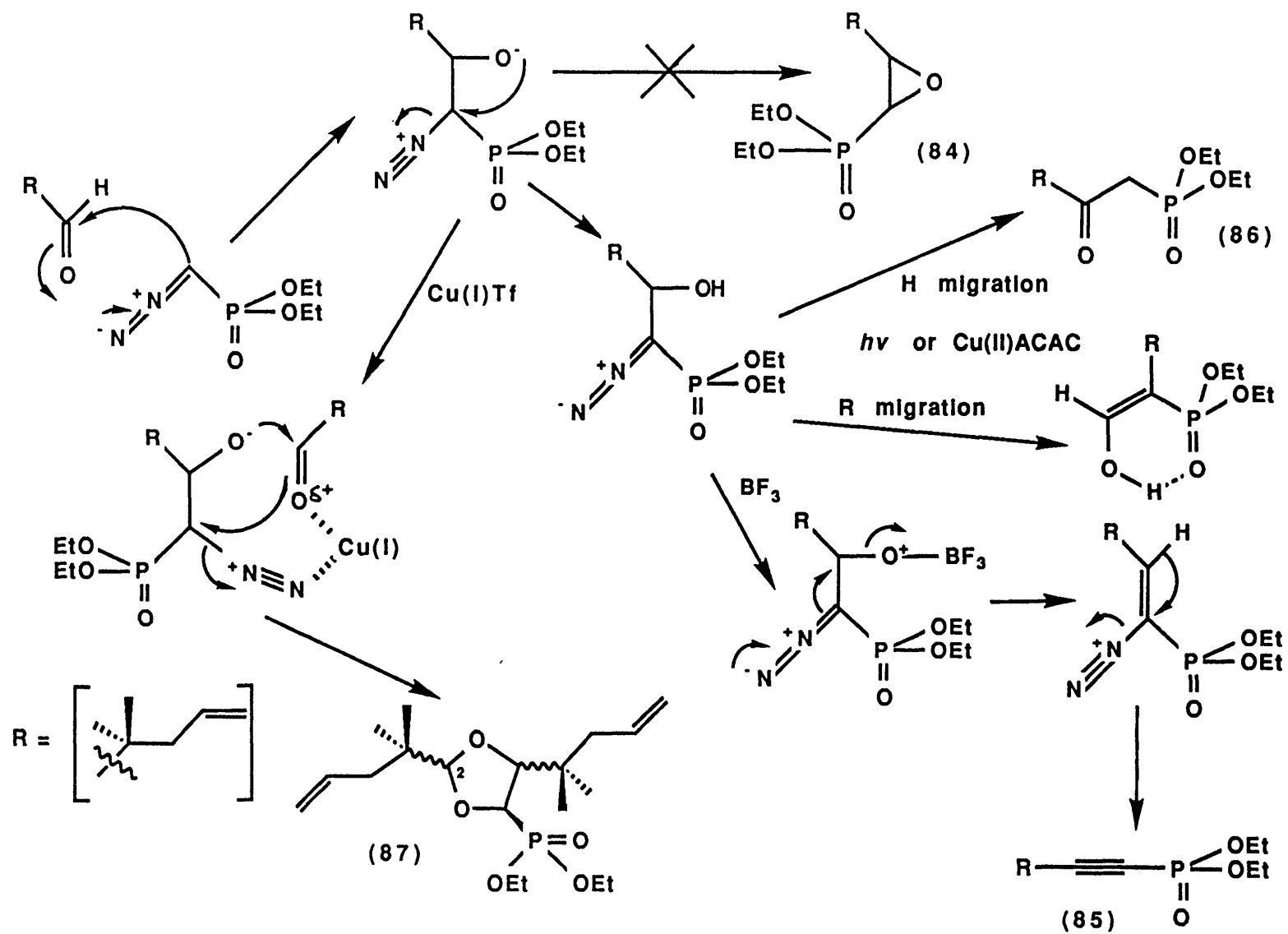
SCHEME 54

An inspection of the recently reported nickel(0) and palladium(0) mediated cyclisation reactions of (diphenylmethylene)cyclopropanes⁸⁵ suggested that, for initial investigations, an acetylenic ester would be the best choice as the second component of the formal $[2\pi+2\sigma]$ reaction, since high yields and clean reaction had previously been obtained with the intermolecular version. (See Schemes 59 and 61, Review Section 2.1). Consequently, the key aldehyde (73) was treated with an excess of lithium(methyl propiolate), and after quenching with

chlorotrimethylsilane, (82), the substrate required for initial study of the intramolecular "Binger-Noyori" reaction, was obtained in 97% yield as a 1:1 mixture of diastereoisomers.

In view of early difficulties experienced with removing the 1,3-dioxolane protecting group, the possibility of avoiding aldehyde protection entirely simply by changing the order of the synthetic sequence appeared attractive. It was rationalised that cuprous triflate should favour olefin insertion over attack at the aldehyde by virtue of its ability to co-ordinate selectively to the electron rich olefin.

Subjection of the Magnus aldehyde (72) to copper(I) catalysed cyclopropanation with DAMP realised, in addition to an 18% yield of the required cyclopropyl phosphonate (83), two other diastereoisomerically related products which proved not to be the expected epoxide (84), acetylene (85) or β -hydroxy ketone (86)⁷⁹ (Scheme 55).

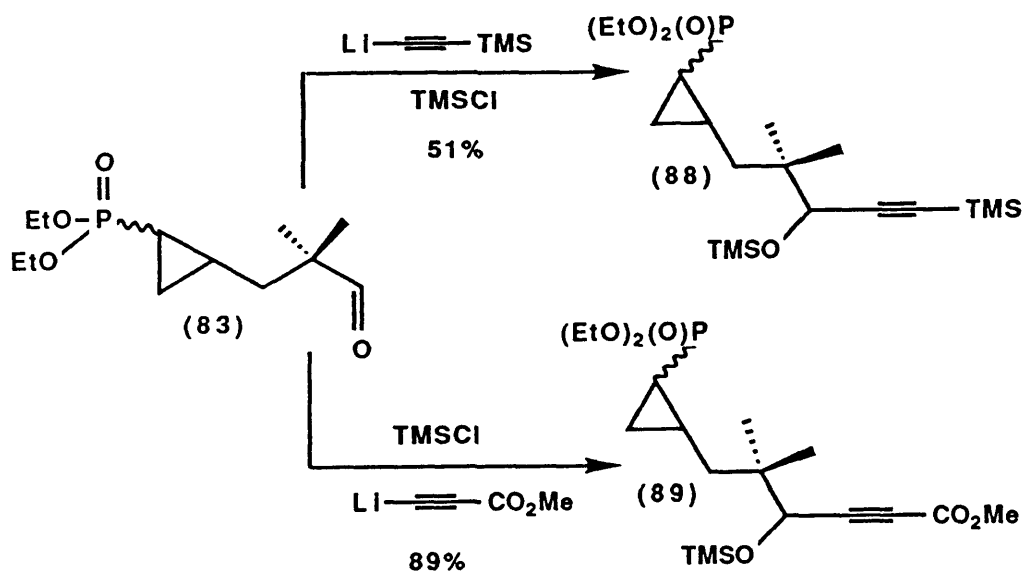


SCHEME 55

These compounds, arising from an unprecedented trapping of two aldehyde molecules and one of diazomethylphosphonate to form 1,3-dioxolanes (87), were identified principally on the basis of mass spectral and ^{13}C n.m.r data. Particularly characteristic of 1,3-dioxolanes is the C-2 signal at 109ppm. Although the geometry of the diastereoisomers was not determined, it is notable that only two are observed. A mechanism for the formation of these compounds is proposed (Scheme 55) in an attempt to account for this unusual result. The presence of high concentrations of the aldehyde, and the Lewis acidic copper catalyst are undoubtedly contributory factors in their formation. One might perhaps consider the unusual outcome of the reaction to be due to chelation of copper causing a template effect. This does not seem unreasonable considering the lability of the trifluoromethanesulphonate ligands, and known copper(I) macrolactonisation procedures⁹⁷. That only two diastereoisomers are observed suggests that steric interactions play a role in the ring closure step to preclude all three bulky substituents from occupying the same face of the ring.

The greater acidity of acetylenic protons ($\text{pK}_\text{a} = 18.5$)⁸⁶ when compared with those α - to a ketone (pK_a acetone = 20), with which protons α - to phosphonates are generally considered to be comparable⁸⁷, suggests that no difficulty should exist in obtaining nucleophilic attack of acetylide anions at the aldehyde as opposed to deprotonation α - to the phosphonate. Indeed Paquette⁷³ has found cyclopropane protons similarly activated by carbonyl, nitro or sulphone substituents to have decreased

acidity compared with acyclic analogs because of the increase in ring strain associated with the re-hybridisation necessary to achieve charge delocalisation. (Once formed, however, these anions are more reactive due to the contribution derived from release of the strain energy). In consequence, no problems were encountered when aldehyde (83) was treated with lithium (trimethylsilylacetylide). On quenching with chlorotrimethylsilane a diastereoisomeric mixture of chain extended cyclopropyl phosphonates (88) was isolated in 51% yield. Similar reaction with lithium(methyl propiolate) afforded the corresponding adduct (89) in 89% yield (Scheme 56).



SCHEME 56

Attempted Wadsworth-Emmons reaction of ester (89) with benzophenone failed to yield more than a trace of the desired olefin, perhaps due to the incompatibility of the ester moiety with the reactive phosphonate anion. Wadsworth-Emmons reaction of the trimethylsilylacetylene analog was not investigated.

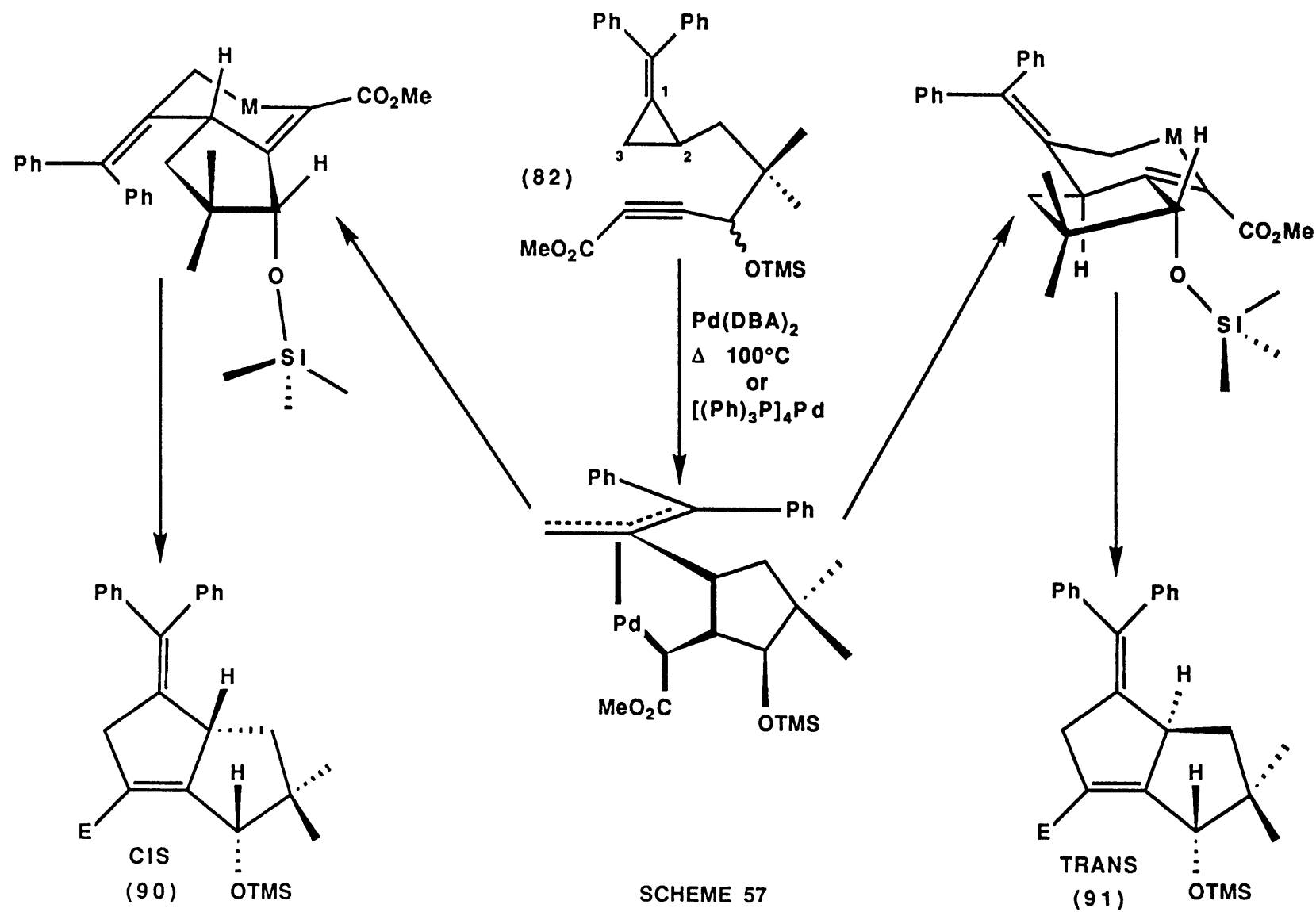
4.2.2) PALLADIUM(0) CATALYSED CYCLISATION OF
(DIPHENYLMETHYLENE)CYCLOPROPANE (82)

A study of the work of Binger and of Noyori concerning the $[2\pi+2\sigma]$ transition metal catalysed cyclisation suggests the wide range of temperatures employed to initiate reaction to be substrate or catalyst dependent, or perhaps arbitrary. Temperatures between 0° and 130°C have been employed⁶⁷. Binger considered from his study on the temperature dependence of the reaction that higher temperatures and shorter reaction times gave cleaner product distributions⁸⁸. Nevertheless, in view of the relatively low activation energy required to initiate reaction, the possibility of using ultrasonication to provide the energy input was intriguing. If successful, such an approach would allow milder conditions for reaction than hitherto employed, and would dispense with the necessity of using Carius tubes.

Investigation into the influence of catalyst ligands on the course of the reaction suggested that catalysts possessing greater than a stoichiometric ratio of phosphine ligands gave much poorer results than those of less than stoichiometric proportions⁸⁸. Tetrakis(triphenylphosphine)palladium(0) was stated to be particularly inefficient for the task in hand. The ligand dependency of catalyst activity is rationalised in terms of the necessity of co-ordinating the π -bond prior to cyclisation. However, on the basis that the intramolecular variant should be much more facile, and with the additional impetus to cyclisation afforded by the Thorpe-Ingold effect of

the gem-dimethyl substituents⁷⁶, we were tempted to try both of these modifications to the standard reaction conditions.

A dilute solution of (diphenylmethylene)cyclopropane (82) in dry degassed toluene under argon was treated with 5 mol% tetrakis(triphenylphosphine)palladium(0) and the mixture subjected to ultrasonication for 100h (an arbitrary period). T.l.c of the mixture at this point indicated clean reaction to give, in addition to what appeared to be recovered starting material, a slightly more polar compound. Spectroscopic examination of these materials showed the more polar product to be the cis or endo diastereoisomeric cyclised product (90), confirmed by nOe studies described below. The less polar fraction was shown to be the other expected diastereoisomeric bicycle (91), contaminated with traces of starting material with which it co-runs on silica gel chromatography. The majority of the acyclic starting material was removed by re-subjecting this upper fraction to the reaction conditions. This allowed characterisation of the exo-diastereoisomer without recourse to HPLC techniques. Thus was achieved the first example of an intramolecular [2 π +2 σ] cyclisation reaction of an alkylidenecyclopropane, under ultrasonication, with a tetrakis(triphenylphosphine)palladium(0) catalyst. (Scheme 57)



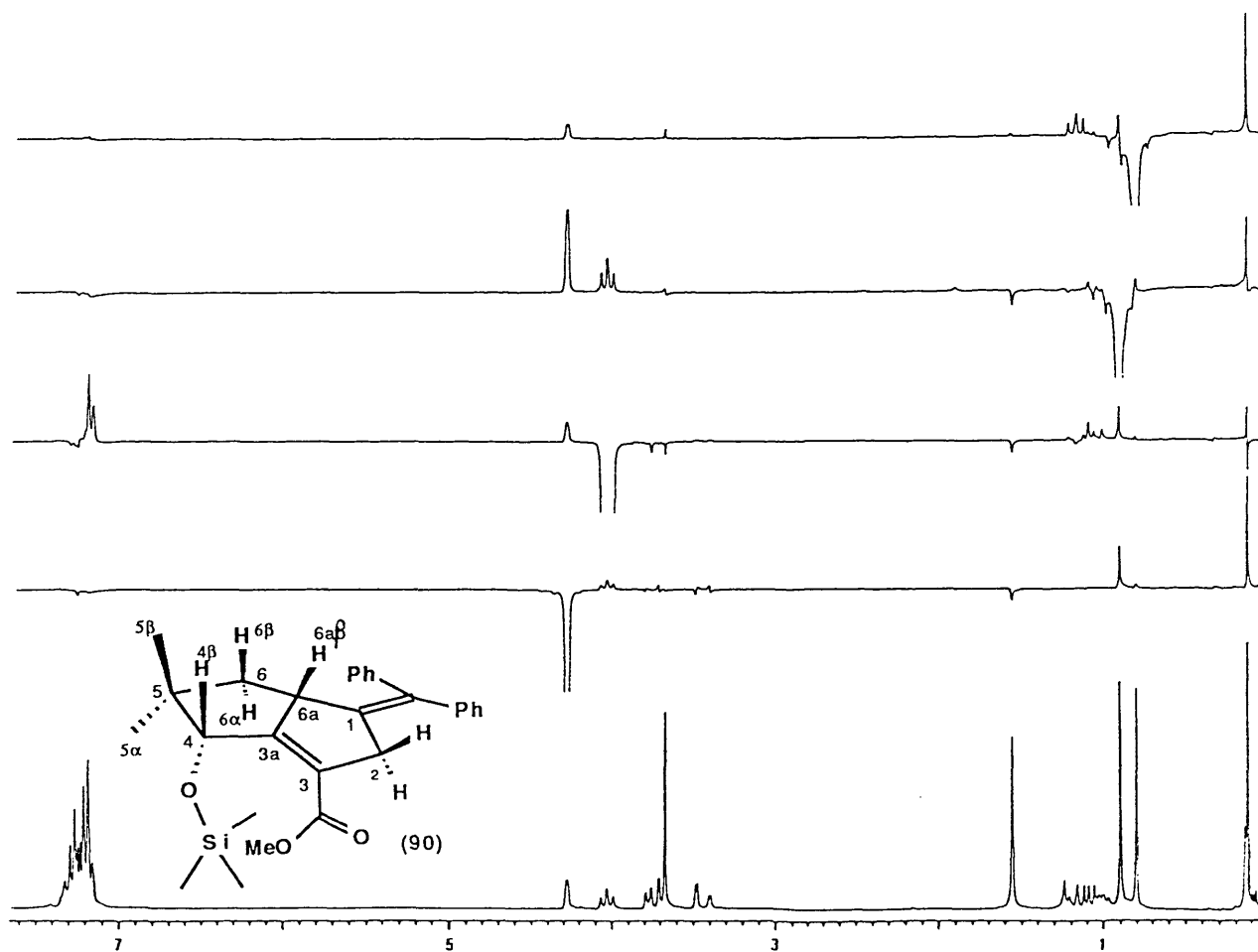
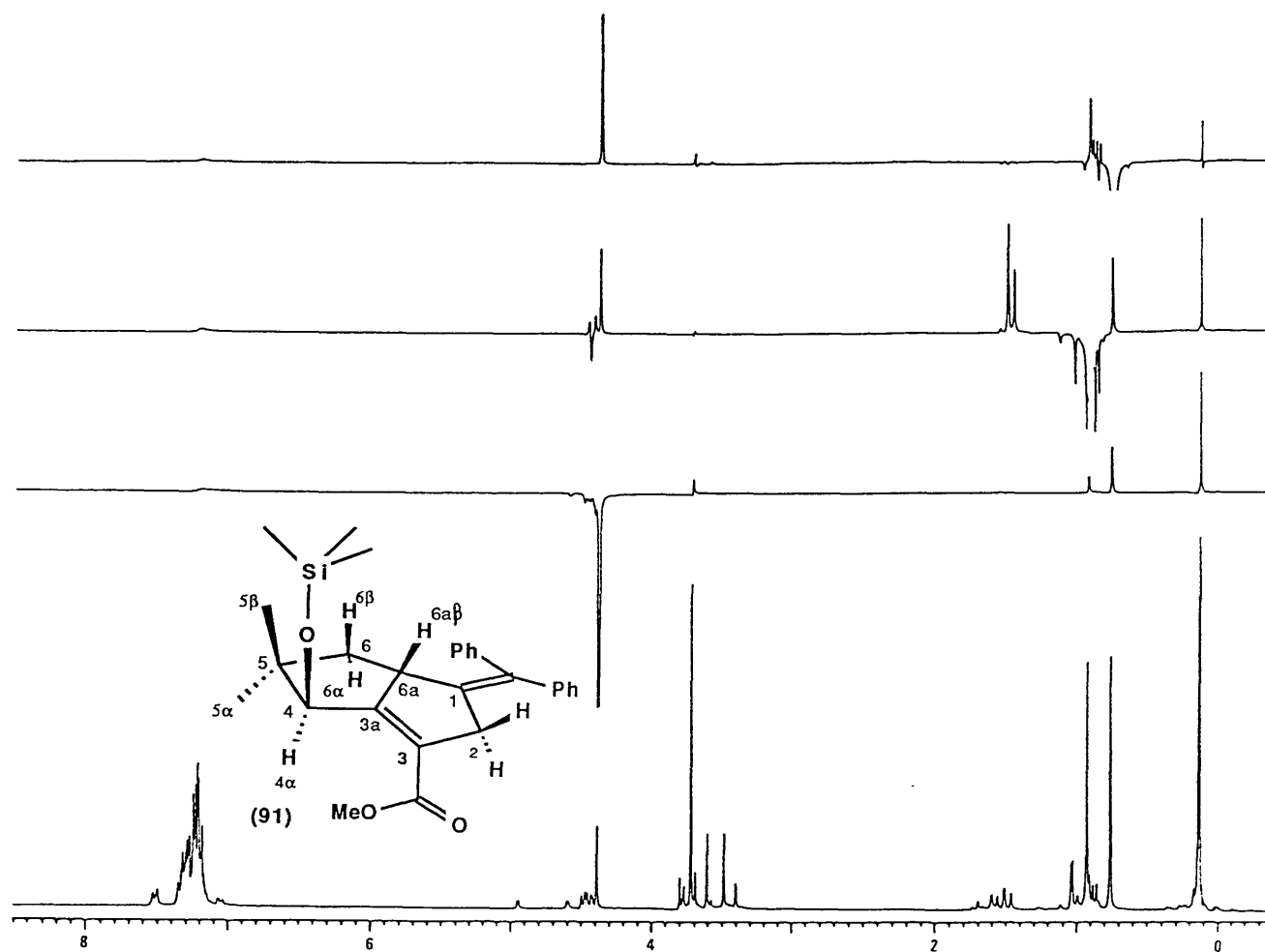
SCHEME 57

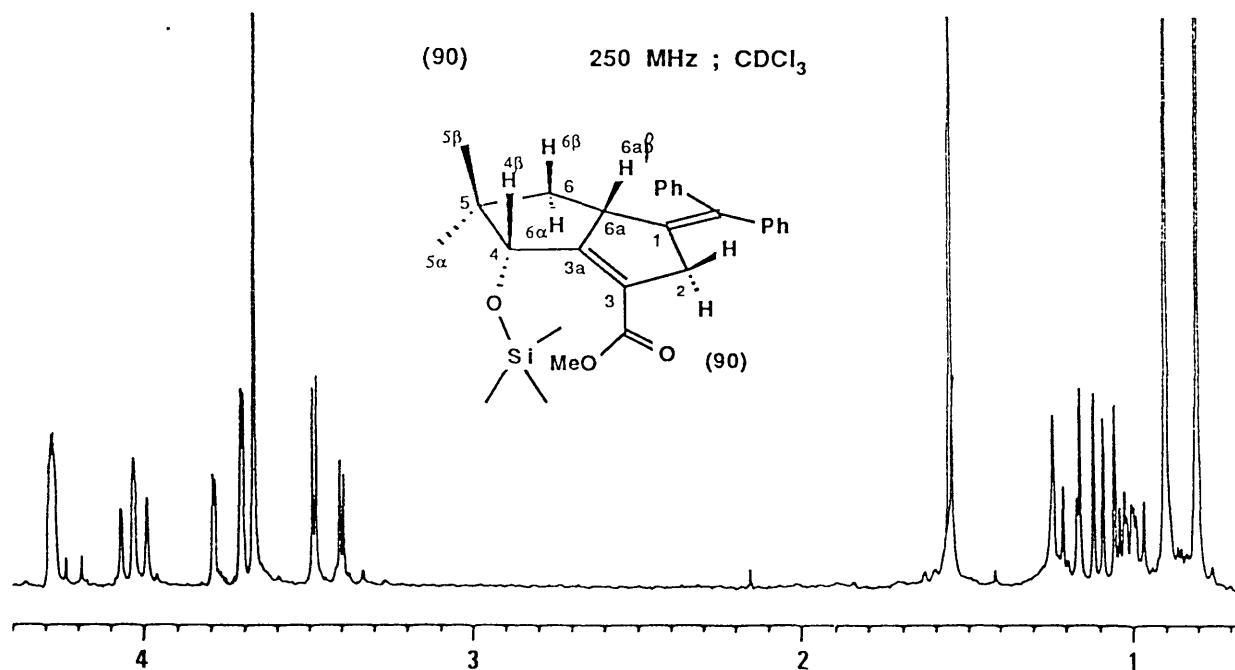
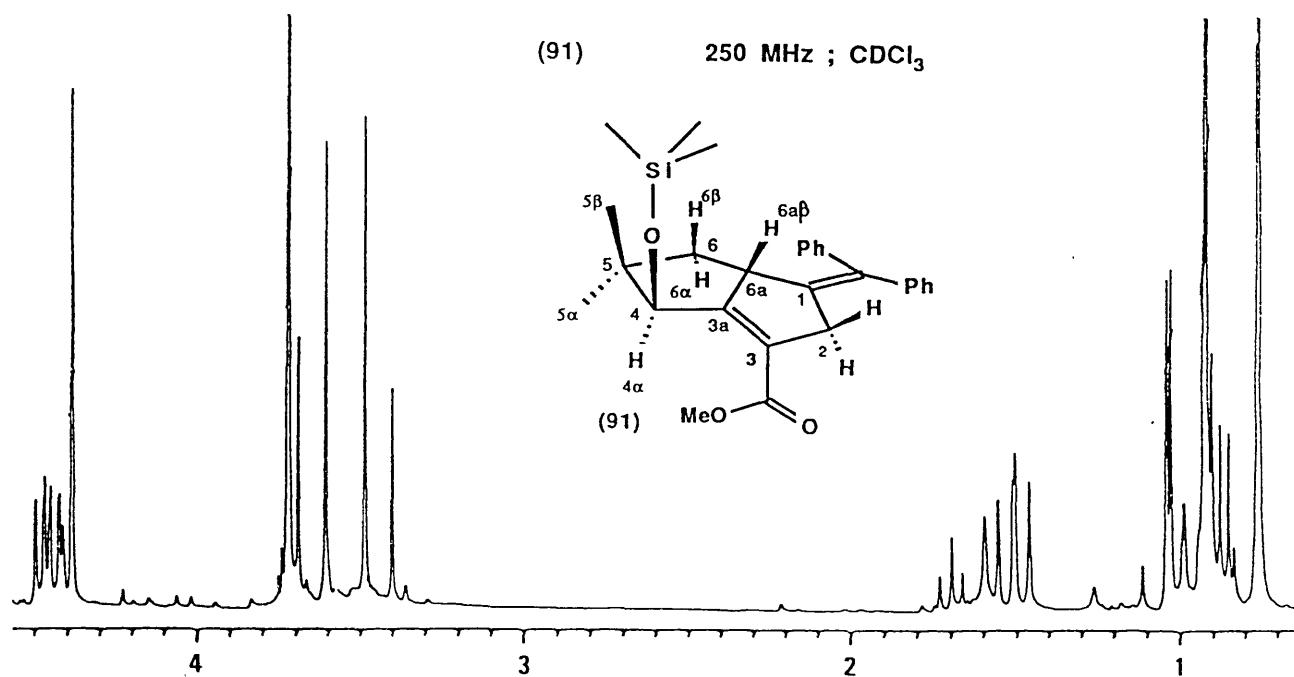
Spurred on by this success, the analogous thermally induced reaction at 110°C in the presence of the more conventional bis (dibenzylidene acetone)palladium(0)-stoichiometric triisopropyl phosphite catalyst was investigated. This reaction gave results identical with the previous findings.

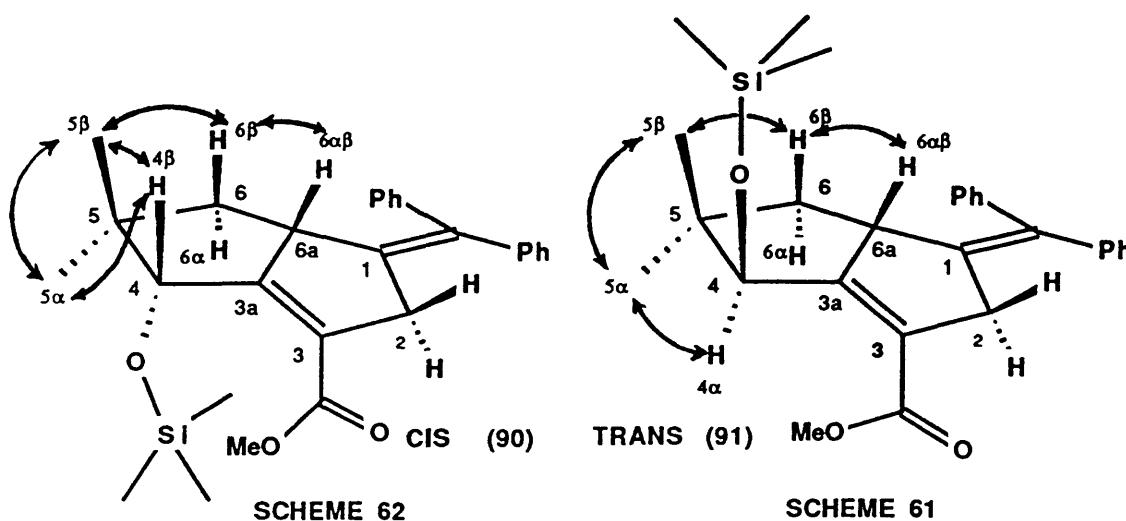
As a preliminary to conducting sealed n.m.r. tube experiments to determine the reaction time, the n.m.r spectrum of cis-bicycle (90) in d_6 benzene was recorded. Dramatic changes in chemical shifts, and slight changes in coupling constants of those protons on the same side of the bicycle as the diphenyl-methylene moiety were observed. Nuclear Overhauser effect studies showed the compound to bear a pendant endo trimethylsilyloxy group as before, but closer examination showed that different parts of the aromatic resonances showed nOe with the proton at the bridge head (6-H_{α}), when compared with the nOe experiment performed in CDCl_3 . The nOe experiments are reproduced in Schemes 58 and 59. The region 3-5ppm in the proton spectra of these compounds holds the key to identification of each isomer, (Scheme 60 .See also Appendix)

n.O.e studies

(a) Taking the trans isomer (91) first (CDCl_3) irradiation of the 4-H_{α} shows strong nOe's with the high field (5_{α})-methyl and TMS signals. Weak effects are also observed to the ester methyl and (5_{β})-methyl. No positive nOe is observed with the 6a-H_{β} . The 5_{α} -methyl shows very strong nOe with the 4-H_{α} and weak effects with the 5_{β} -methyl and TMS. These observations (Scheme 58) are in accordance with the assigned trans geometry. (Scheme 61)



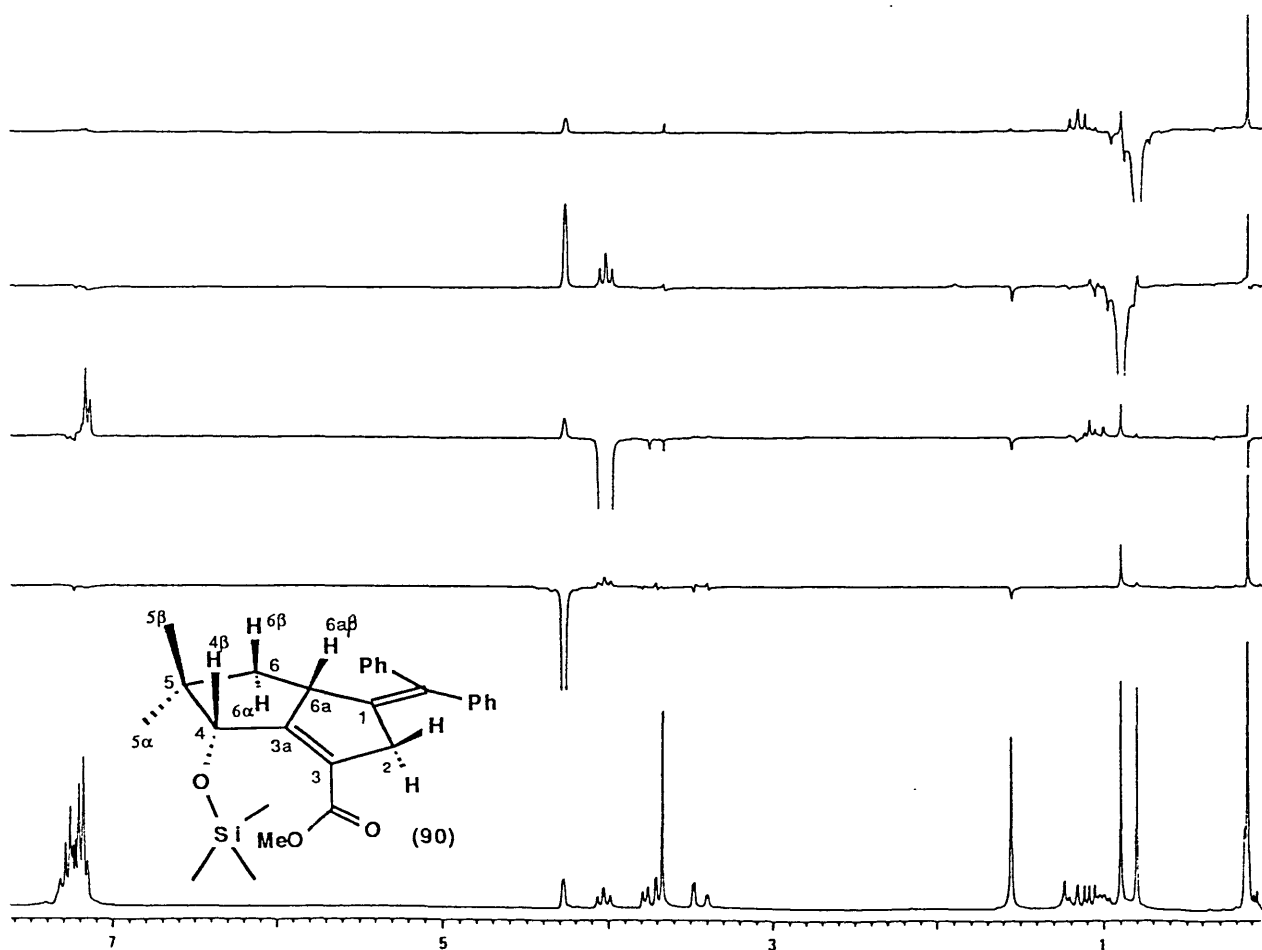
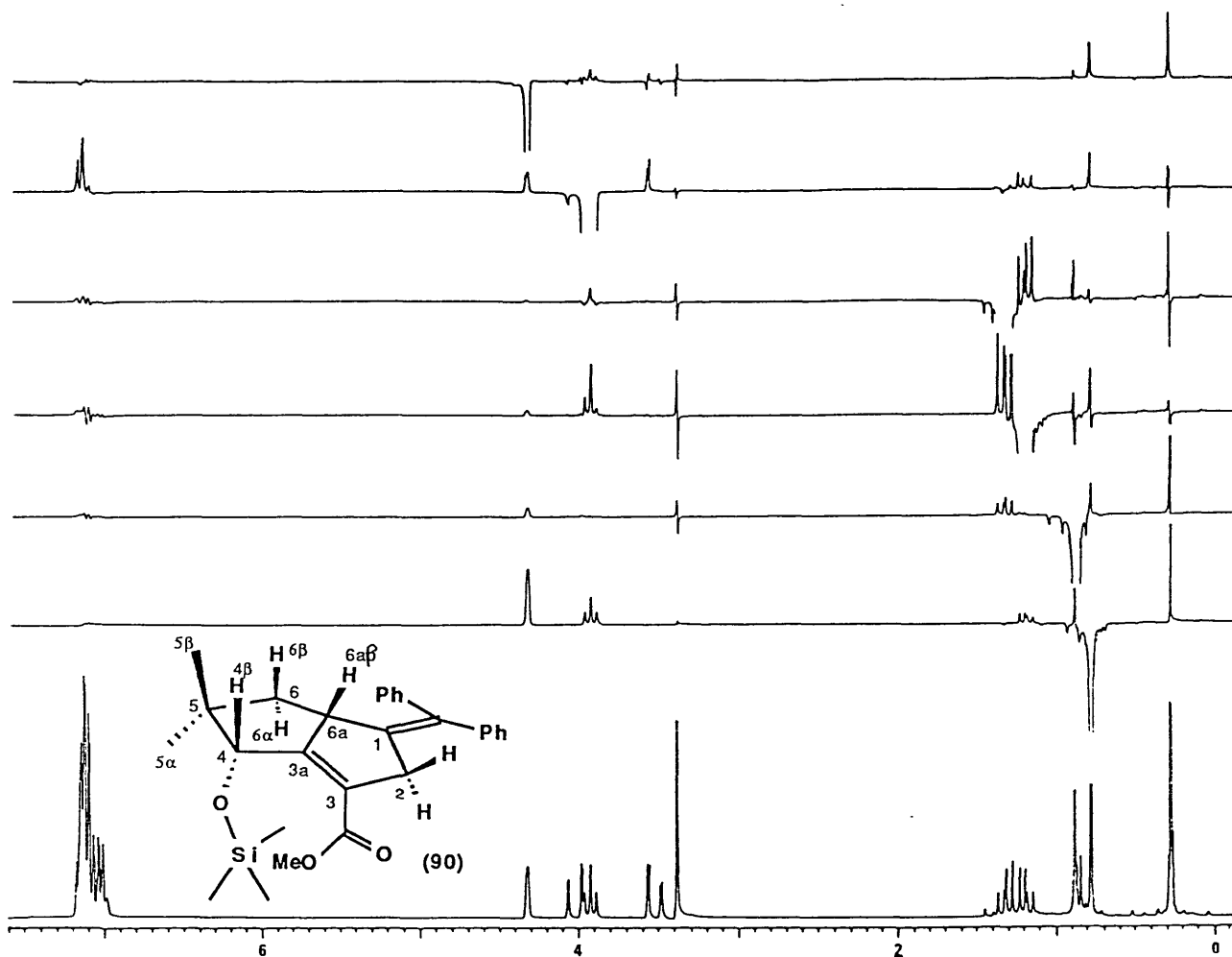
60a) ^1H N.M.R SPECTRA OF THE CIS AND TRANS BICYCLO[3.3.0]OCTANES



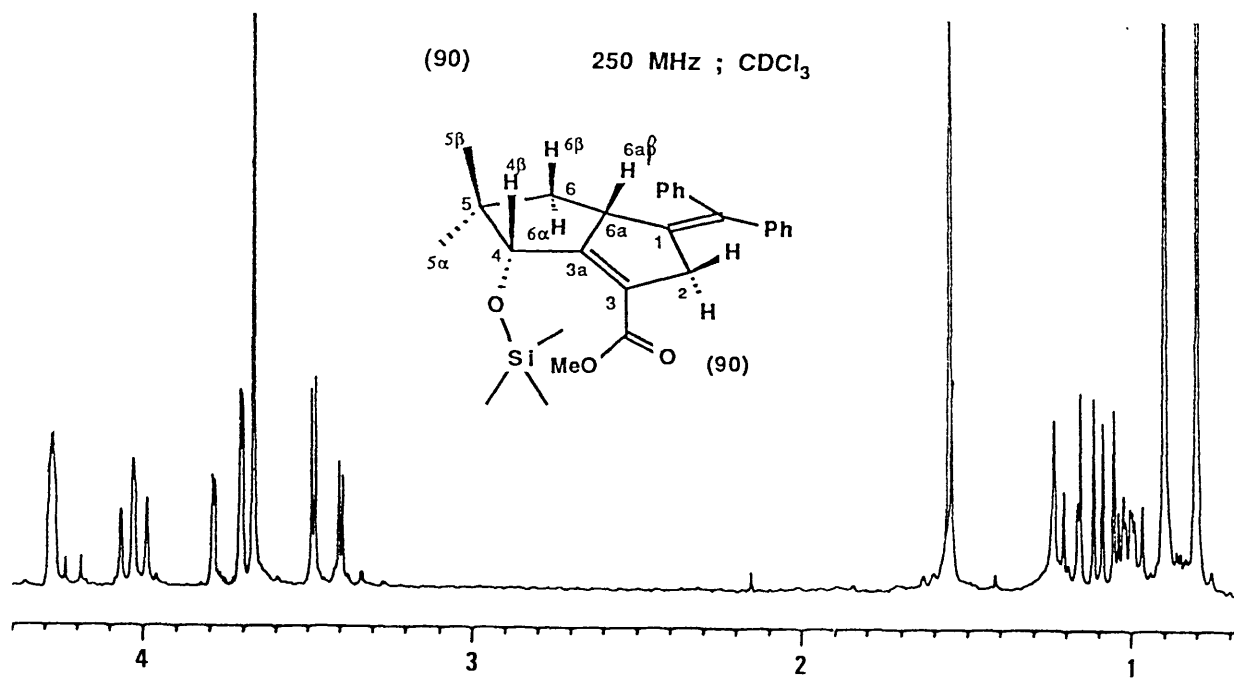
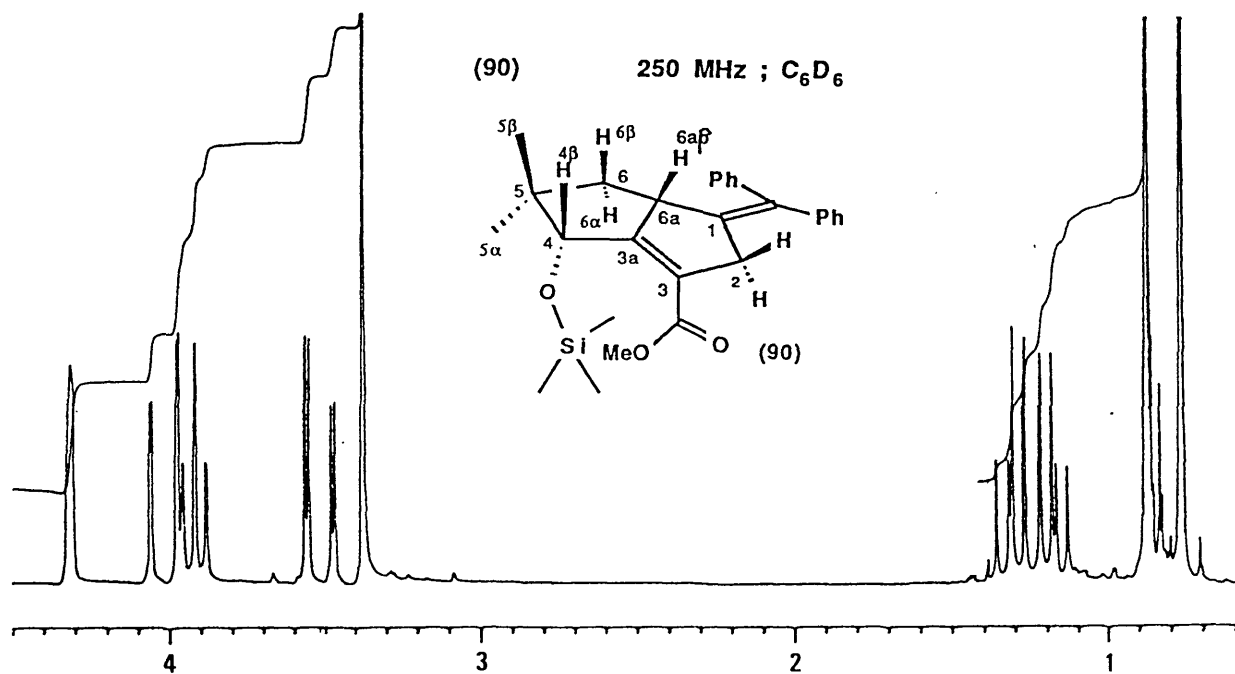
(b) Considering the cis isomer (90) (CDCl_3) irradiation of 4- H_β shows a weak nOe towards 6a- H_β , and stronger nOe's towards the 5- β (low field) methyl and TMS signals. Irradiation of 6a- H_β shows clear nOe's with 4- H_β , 5 β methyl and the high field portion of the aromatic signals. Irradiation of the 5 β (low field) methyl shows strong nOe's with 4- H_β , 6a- H_β and TMS. Irradiation of the 5 α -(high field) methyl shows a strong nOe with TMS, and a weak nOe with 4- H_β . These features (Scheme 58) are consistent with the assigned cis geometry (Scheme 62).

(c) Solvent effects

While the nmr properties of the trans isomer were not studied in d_6 benzene, those of the cis (90) isomer show a strong solvent effect. This is not entirely surprising in view of the possibility of π -stacking of solvent molecules with the phenyl groups and the α,β -unsaturated ester moiety. Particularly noticeable is the downfield shift in chemical shift of the protons at C_2 , C_{6a} and to a lesser extent C_6 . Slight changes in



60b) ^1H N.M.R. SPECTRA OF THE CIS BICYCLO[3.3.0]OCTANES
IN CDCl_3 , AND C_6D_6 SHOWING SOLVENT EFFECTS



coupling constants for these protons are observed. (The relevant regions of the spectra are juxtaposed in Scheme 60.)

Most intriguing, however, is the comparison between the NOE experiments run in CDCl_3 and C_6D_6 for this isomer (these results are juxtaposed in Scheme 59). It is interesting to note that the high field methyl resonance is now the 5_β -methyl, in contrast with the situation in CDCl_3 . Irradiation of the 5_β methyl shows strong NOE's with both the 4-H_β and 6a-H_β and the high field double doublet of the 6-H_2 resonance. The low field 5_α methyl shows strong NOE's with TMS, the low field double doublet of the 6-H_2 resonance, and a weak effect with 4-H_β . Irradiation of 6a-H_β shows NOE's with 4-H_β methyl, the high field part of 6-H_2 and part of the aromatic resonance. Similarly 4-H_β shows NOE's with 6a-H_β , 5_β -methyl and TMS. This data is consistent with the cis structure as previously proposed.

Fascinating, however, is the observation that, depending on the solvent, the 6a-H shows NOE's with different parts of the aromatic resonances. In CDCl_3 it is the high field portion, whilst in C_6D_6 the low field portion. This odd observation may be explicable solely in terms of solvent effects, but taken in conjunction with slight changes in coupling constants, an upfield shift of the 5_β methyl and downfield shift of the 5_α -methyl causing a reversal of their order of appearance in the spectrum, 0.3ppm shift upfield for the ester methyl resonance, and dramatic downfield shifts for the 2-H_2 resonances, it suggests a possible solvent induced change in conformation of the molecule. Twisting of the phenyl rings of the diphenylmethylene moiety can be expected to cause changes of chemical shift in those protons

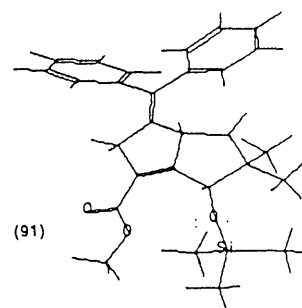
under the influence of their ring currents. It is notable in this respect that 4-H_β the only proton sufficiently remote not to be influenced in this respect, (although in close proximity to the αβ-unsaturated ester and therefore under the influence of effects due to π stacking of the solvent molecules), exhibits a downfield shift of only 0.04ppm in C₆D₆.

In view of the possibility that a change of solvent to benzene might be favouring an alternative rotameric form to that adopted in chloroform, the existence of stable rotameric forms was investigated by molecular mechanics studies utilising the Clark-Still macromodel programme. Although unable to consider solvent effects as complicated and clearly important in this case as the π-stacking of benzene molecules, modelling studies on the cis and trans isomers indicated in each case the presence of two possible rotameric forms, differing in energy (on the programme's arbitrary scale), by of the order of 4kJ mol⁻¹. This result, though necessarily crude and imprecise due to the neglected solvent interactions, is nevertheless encouraging. The four possible rotameric forms picked out by the programme are illustrated in Scheme 63. Scheme 64 shows a partial overlap of each pair, in an attempt to illustrate the change in orientation of the benzene rings. Although not strictly analogous, two rotameric forms of a biphenyl moiety were observed during a synthesis of steganone⁸⁹ arising by rotation about the phenyl-phenyl bond. In this case, however, the rotameric forms were isolable and interconvertible.

MacroModel
Version 1.5
Energy = 199.37 Kjoule (47.65 Kcal)

Str=	8.2	Bnd=	74.0	S-B=	0.0	HBd=	0.0
VDW=	10.4	Tor=	87.3	Imp=	0.3	Ele=	19.2

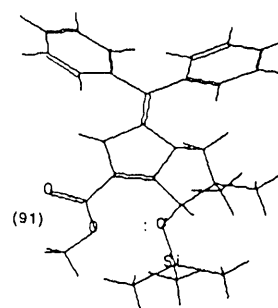
TRANS (91)



MacroModel
Version 1.5
Energy = 195.43 Kjoule (46.71 Kcal)

Str=	8.5	Bnd=	74.4	S-B=	0.0	HBd=	0.0
VDW=	11.8	Tor=	81.3	Imp=	0.3	Ele=	19.1

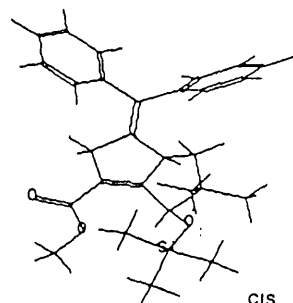
TRANS (91)



MacroModel
Version 1.5
Energy = 187.24 Kjoule (44.75 Kcal)

Str=	7.3	Bnd=	66.9	S-B=	0.0	HBd=	0.0
VDW=	6.0	Tor=	84.6	Imp=	0.1	Ele=	22.4

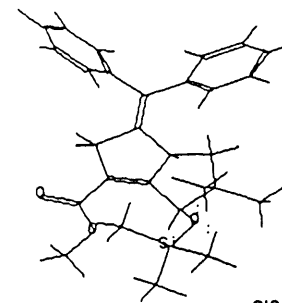
CIS (90)



MacroModel
Version 1.5
Energy = 183.17 Kjoule (43.78 Kcal)

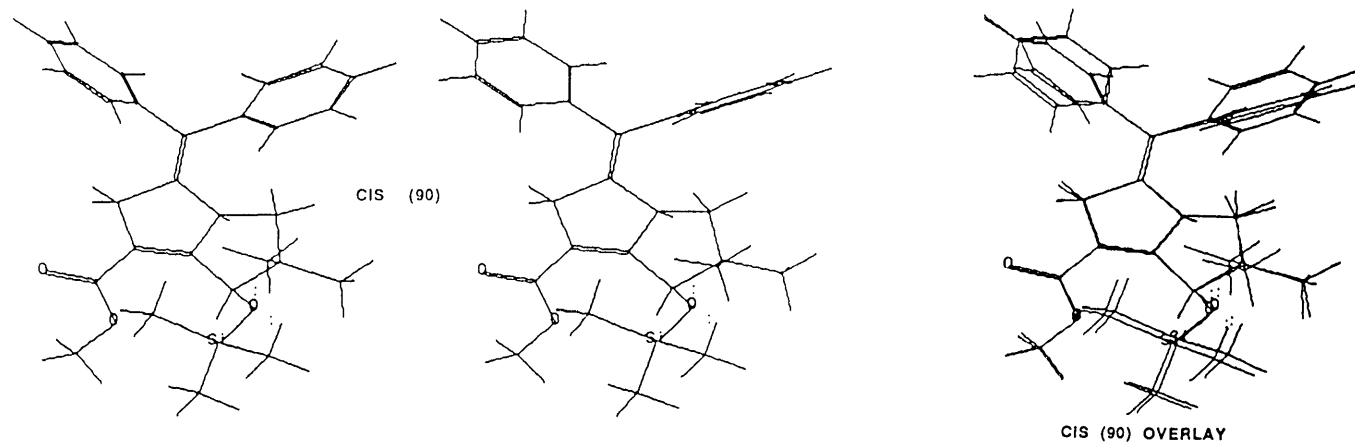
Str=	7.3	Bnd=	67.9	S-B=	0.0	HBd=	0.0
VDW=	6.8	Tor=	79.0	Imp=	0.1	Ele=	22.1

CIS (90)

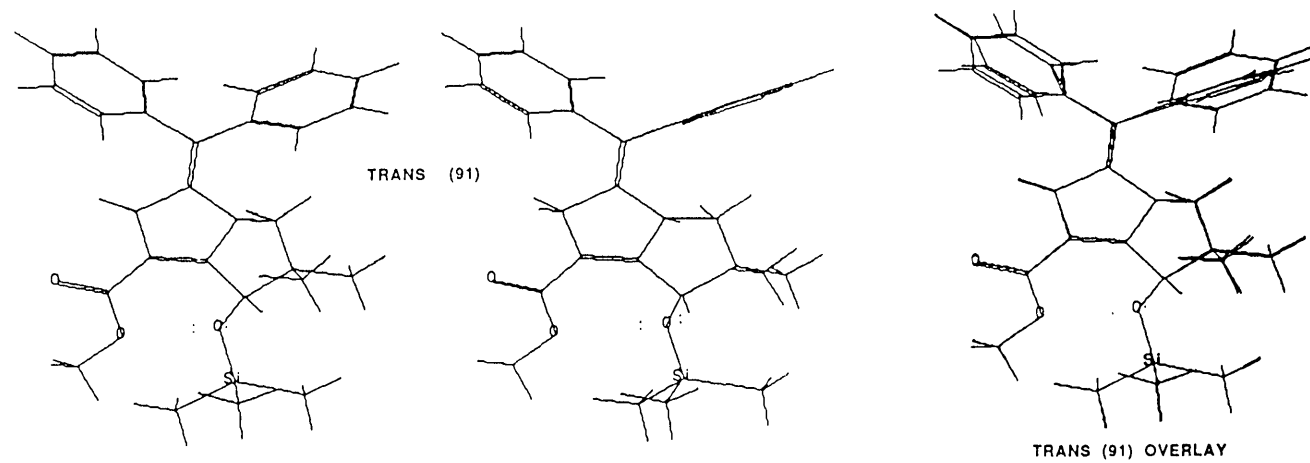


SCHEME 63

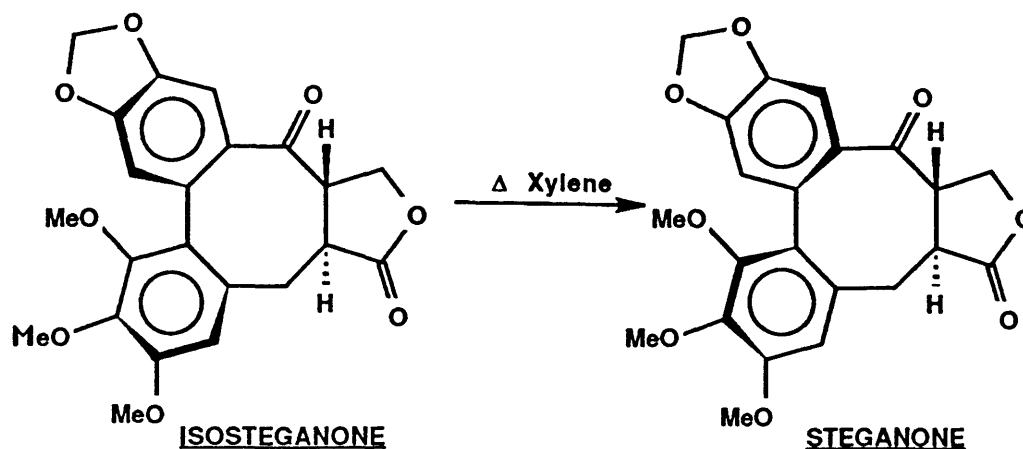
ROTAMERS OF THE CIS AND TRANS CYCLISATION PRODUCTS
GENERATED BY MACROMODEL



ROTAMERS OF THE CIS AND TRANS CYCLISATION PRODUCTS
GENERATED AND SUPERIMPOSED BY MACROMODEL



SCHEME 64



The above discussion pertaining to the possible existence of separate rotameric forms may be of interest, but the stereochemical outcome of the cyclisation is of greater importance. Having chosen to start with a diastereoisomeric mixture of the substrate, it is not possible to tell whether the cyclisation is stereospecific. However, the isolation of both cis and trans products in virtually identical yield is encouraging and, it should now be possible to examine this question if the diastereoisomeric acyclic precursors are separable by HPLC.

The instability of the components, particularly when neat, is notable. This is not surprising in view of the strain inherent in the cyclopentene ring of the bicycle. Mass spectral evidence, which shows peaks at $M^+ + 16$ and $M^+ + 32$ suggests the instability to arise from aerial oxidation. Migration of the exocyclic double bond into the ring precedes endoperoxide formation from the convex face of the molecule resulting in a considerable release of strain. Further circumstantial evidence supporting this postulate is the marginally greater resistance to oxidation

of the diastereoisomer (91) bearing the *exo*- trimethylsilyloxy moiety . The bulky pendant silyloxy substituent is suitably placed to shield the convex face from the approaching oxygen molecule. Additionally, removal of the TMS protecting group by treatment with TBAF to obtain crystalline material gave very complex results with poor recovery of material, suggesting an increase in instability on deprotection, consistent with the other observations.

Comparison of our initial results with the Khand-Pauson approach of Magnus suggests a possible complementarity of the two cyclisation strategies.

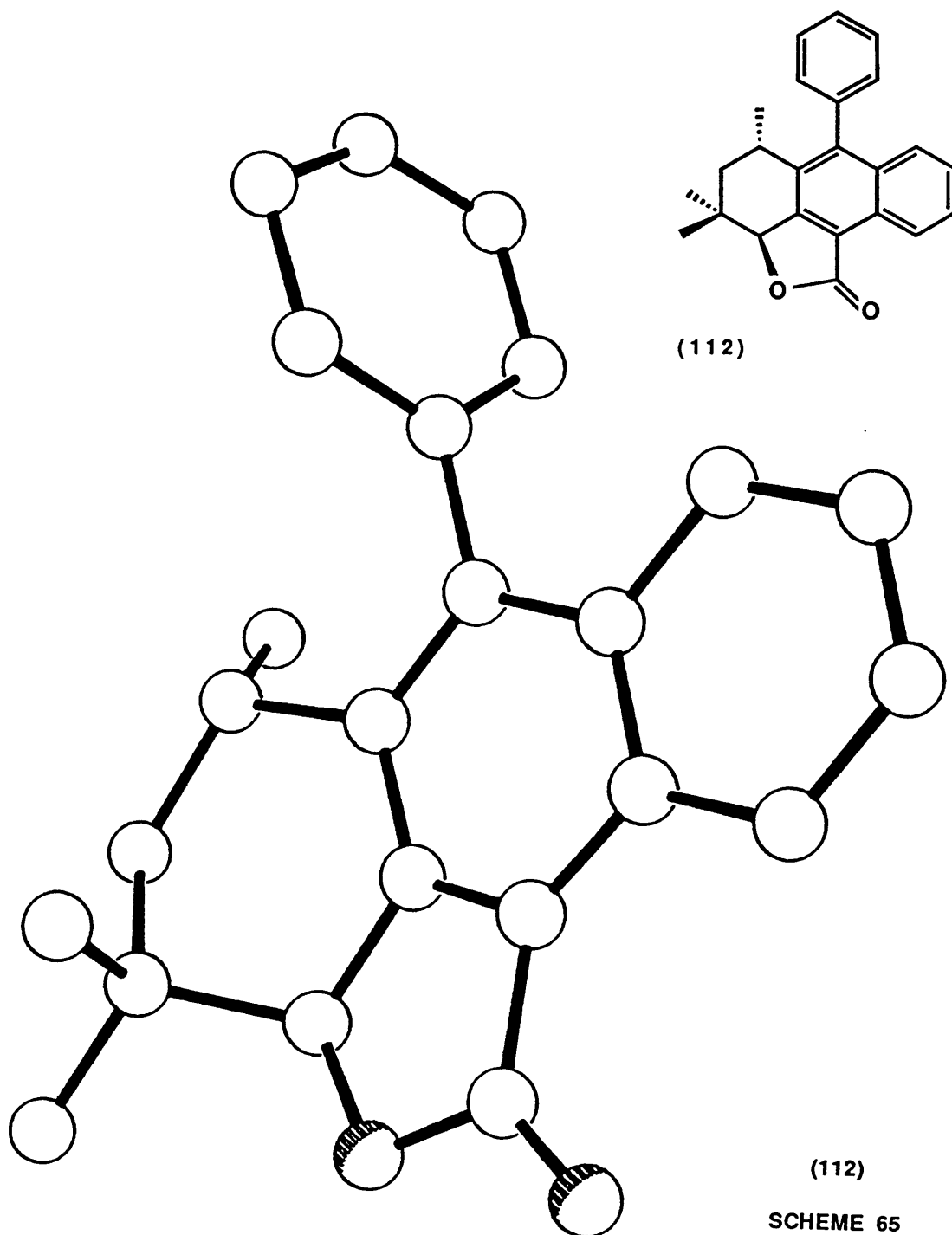
Thus Magnus⁷⁶ observed stereoselectivity in the cobalt octacarbonyl mediated cyclisation to be strongly influenced by the bulk of the acetylenic terminus, and to be somewhat sensitive to the nature of this substituent (Scheme 50 equation 1).

Whether or not the $[2\pi+2\sigma]$ reaction is also stereoselective remains to be seen. It does, however, allow access to the cis isomer, which is always the minor component obtained from the Khand-Pauson route. The gem-diphenylmethylene moiety may be considered as a masked ketone, freed by ozonolysis allowing a further complementarity. From existing literature precedent, the substituent at the acetylenic terminus is unlikely to

affect significantly the intramolecular reaction, and a variety of olefins are also compatible⁶⁷. Consequently this methodology should be applicable to a range of functionalised bicyclo[3.3.0]octanes not available by the Magnus strategy.

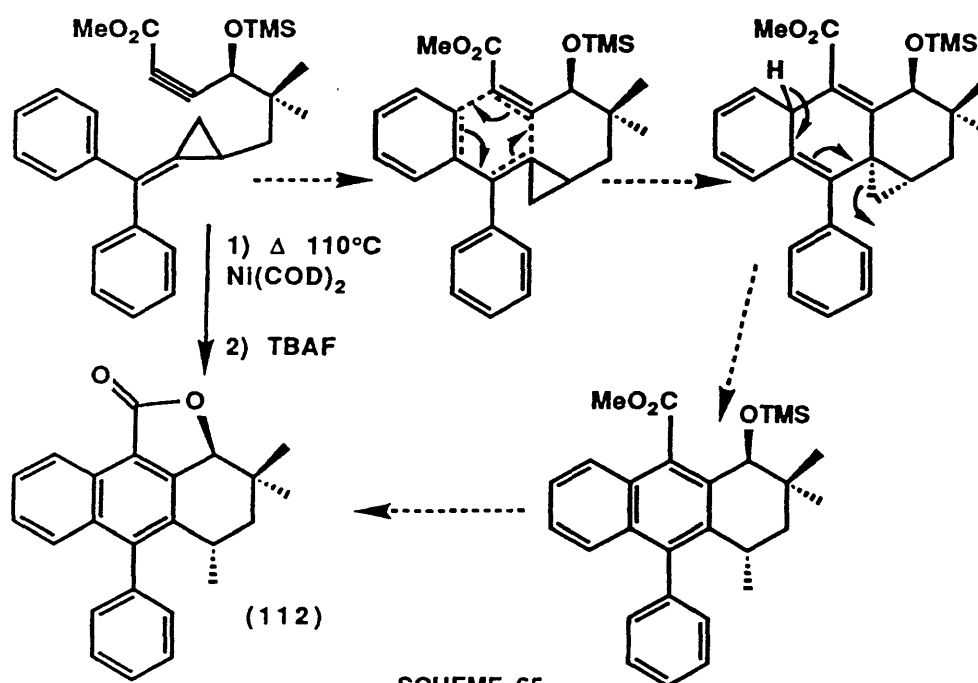
4.2.3) NICKEL(0) CATALYSED REACTION OF
(DIPHENYLMETHYLENE)CYCLOPROPANE (82)

Preliminary studies with thermally induced bis(1,5-cyclooctadienyl)nickel(0)⁹⁰ / triphenylphosphite catalysed cyclisation gave a more complicated product distribution than was observed with palladium catalysis. Furthermore ,in contrast with the palladium catalysed reaction there was no indication of bicyclo[3.3.0]octane formation. These observations strongly suggest the existence of a dichotomy of reactivity as postulated at the onset of this investigation. Upon deprotection of the main component (aproximately 20% of the material recovered) a low yield of a colourless solid was obtained. Recrystallisation of this material from hot petrol (60-80 b.p), afforded rhombohedral colourless crystals. X ray analysis established the structure as the novel lignan derivative (112) illustrated in Scheme 65. This unusual fused array arises by an intramolecular Diels-Alder reaction. Examples of templated nickel(0) induced cyclotrimerisations are known⁶³⁻⁶⁵. If nickel is implicated in the reaction then there is an apparant coordination of nickel to the acyclic precursor in a mode very similar to that desired for cleavage of the proximal bond. It is speculated that alkylidene cyclopropanes incapable of participating in the Diels-Alder sence may indeed form cyclopentenenes by the proximal mode. Further studies in this area will also address the problems with controlling the product distribution in order to obtain more preparatively useful results.



The original reaction conditions, at 110°C were probably too harsh. Lower temperatures or ultrasonication may be more beneficial. Nickel(COD)₂ is not an easy catalyst to handle due to its propensity to undergo autocatalytic decomposition. Other nickel(0) catalysts, particularly the bis(acrylonitrile)nickel(0) originally employed by Noyori⁶⁶, merit investigation.

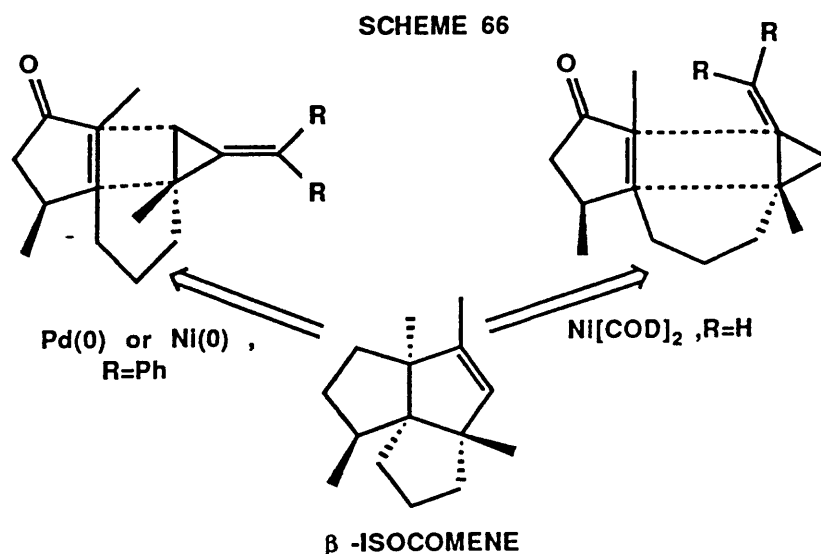
The possibility of development of a route to the lignan skeleton by exploitation of the Diels-Alder reaction deserves consideration.



4.3)

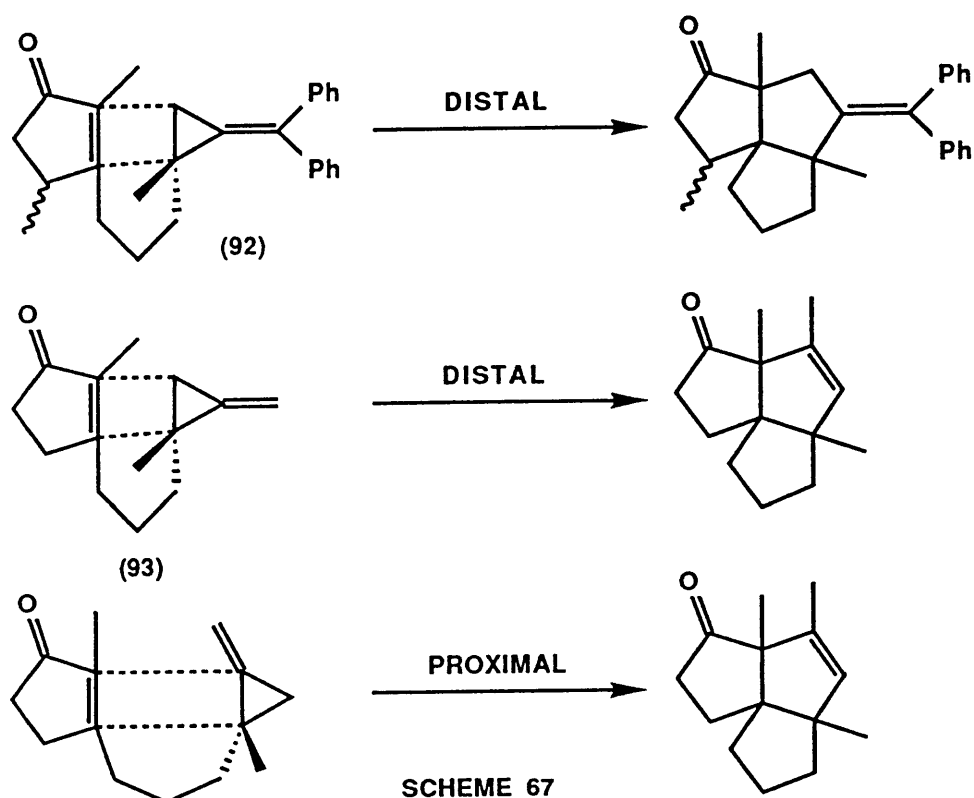
AN APPROACH TO ANGULAR TRIQUINANES

Isocomene, a member of the family of angular triquinane sesquiterpenes, was considered to offer an alternative and perhaps more demanding test of the utility of the intramolecular variant of the "Noyori-Binger" cyclisation methodology. Particularly attractive in this case, was the possibility of cyclopropane cleavage by the proximal mode, since the entire carbon framework could then be constructed in a single step from a monocyclic precursor. (Scheme 66).



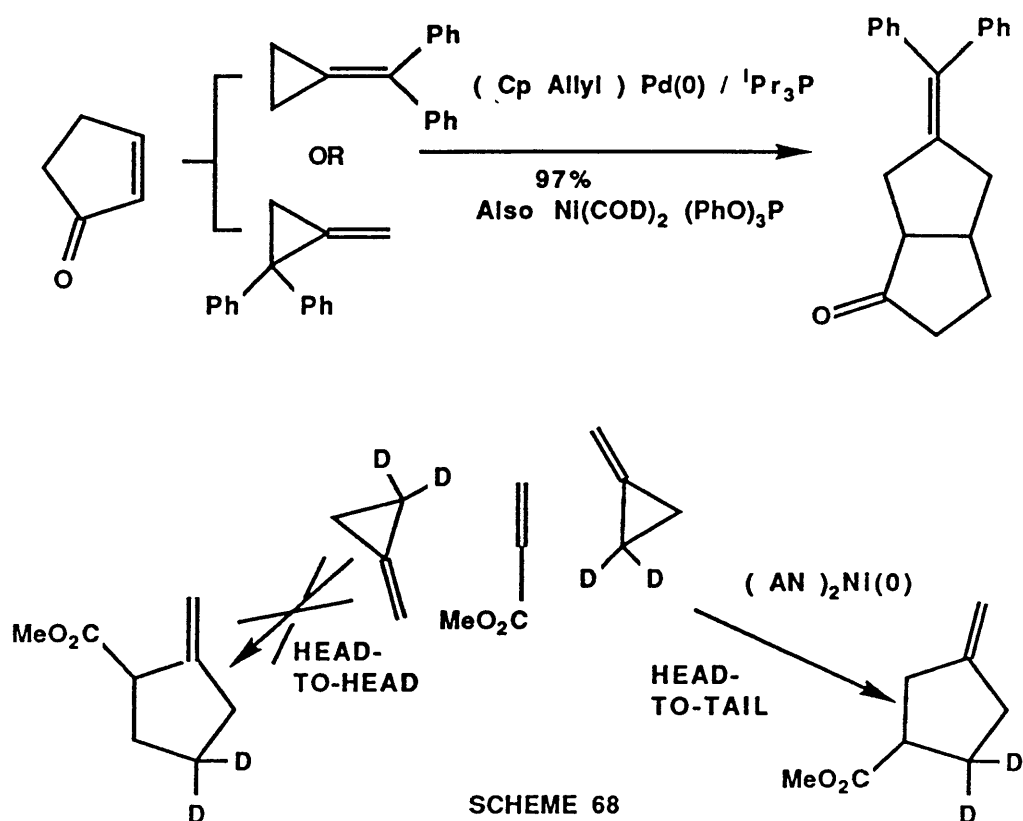
More speculatively, if the intermediate metallocycle was influenced by a product-like transition state, then control of the stereochemistry of the ring closure process might be influenced by the remote methyl substituent. Apart from these considerations, a number of other problems present themselves. Judging by the literature precedent⁶⁶, predicting whether proximal or distal cyclopropane bond cleavage would occur is at best precarious. When the well documented unpredictability in behaviour of

methylene cyclopropanes under these cyclisation reactions is taken in conjunction with the unusual substitution pattern⁶⁶, and the conformational and steric constraints imposed on the intermediate metallocycle by the 3-carbon link and the vinylic methyl, the outcome of the reaction becomes totally imponderable. In fact such a system seems an ideal test of whether nickel(0) always cleaves the proximal bond of methylene cyclopropanes, or whether palladium can also achieve this result. This target is obviously too loaded with imponderables to be suitable for preliminary investigations. Consequently two simpler analogs were considered (Scheme 67).



The greater predictability of distal cleavage under palladium catalysis with substrate (92)⁸⁵ should allow the question of the stereoselectivity of the ring closure to be studied. Whether nickel(0) would promote similar reaction would

also be determined. Substrate (93), without the stereochemical complications imposed by a second chiral centre, would be used to test the regiochemistry of the transition metal catalysed cyclisations in this less predictable system. An additional problem with the cyclisation of (93) is the lack of precedent concerning the co-dimerisation of a methylenecyclopropane with an $\alpha\beta$ -unsaturated ketone. Previous attempts at the intermolecular version were reported to give oligomers⁸⁵, although (diphenylmethylene)cyclopropane reacted smoothly. In the present case, however, intramolecular reaction would allow high dilution techniques to favour the desired pathway. Noyori's original cyclodimerisation of methylenecyclopropane with acrylate esters was observed to proceed with exclusive head-to-tail regiochemistry⁷ as shown in Scheme 68.



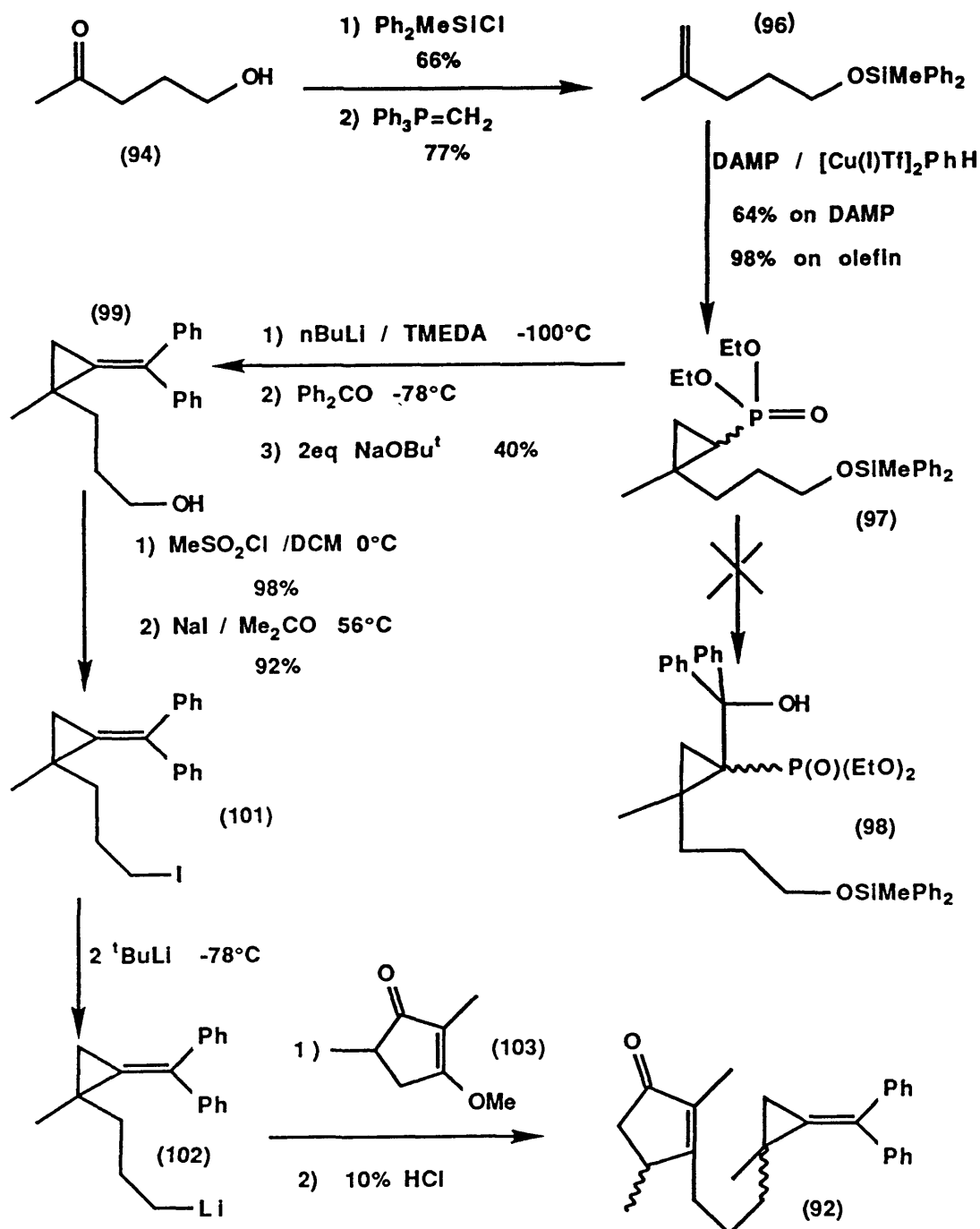
Provided proximal bond cleavage occurred, the head-to-head regiochemistry would be demanded by the restraining 3-carbon link in our case, and would therefore constitute an interesting test of the importance of π - system polarity on the course of the reaction.

4.3.1) SYNTHESIS OF (DIPHENYLMETHYLENE)CYCLOPROPANE (92)

The strategy proposed for preparation of (diphenylmethylene)-cyclopropane (92), outlined in Scheme 69, employed the Wadsworth-Emmons approach developed for the linear triquinanes.

Disconnection of the cyclopentenone reduces the problem to preparation of the key iodide (100). 5-diphenylmethoxysilyloxy-2-methyl-1-pentene (96) was prepared in two steps from commercially available 3-acetyl-propan-1-ol (94) by protection of the alcohol as the diphenylmethoxysilylether (95) (59%) and Wittig reaction with methylenetriphenylphosphorane (77% yield). The protection step is not particularly efficient owing to the presence of an equilibrium between the open chain keto-alcohol and the γ -lactol. Silicon protection apparently did not displace the equilibrium in favour of the open form. If the order of steps was switched, then the olefin, on protection, could not be rendered free from the disiloxane, hydrolysis product of excess chlorosilane. A heavy protecting group was chosen to allow work to be carried out on a small scale. Less bulky protecting groups gave olefins which were too volatile. The olefin obtained by methylenation of commercially available 5-chloro-2-pentanone shared this disadvantage. Copper (I) triflate catalysed

SCHEME 69

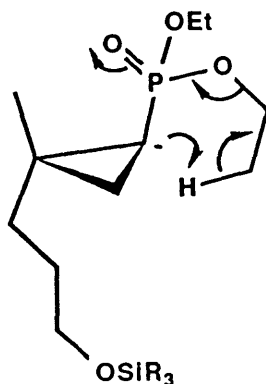


cyclopropanation reaction with **DAMP** at high dilution proceeded smoothly to afford the desired cis, trans- mixture of cyclopropyl phosphonates (97) in 64% yield (98% on recovered olefin). On

deprotonation of the phosphonate with n -BuLi and quenching with benzophenone as previously described, the β -hydroxy-phosphonate (98) could not be isolated.

Recourse was made to a one pot method in which a solution of sodium t -butoxide was added prior to warming to ambient temperature. It was hoped that sodium-lithium exchange, on the apparently unstable betaine would allow oxaphosphetane formation and collapse to the olefin directly. Thus was obtained the required diphenylmethylenecyclopropane (99) albeit in a poor 40% optimal yield. A variety of solvents, reaction temperatures and counter ions were investigated in order to improve this result. At an early stage, the yields were found to be temperamental, often dropping below 25% under similar reaction conditions. The cyclopropyl phosphonate was not recovered from these reactions, dropping to baseline material by t.l.c analysis. Examination of the crude products by ^{31}P nmr showed a veritable forest of peaks indicative of extensive decomposition. These two observations led to speculation on a possible side reaction of the phosphonate anion, which appeared ideally set up to deprotonate one of the ethoxy ligands intramolecularly via a 6-centre transition state (Scheme 70).

SCHEME 70



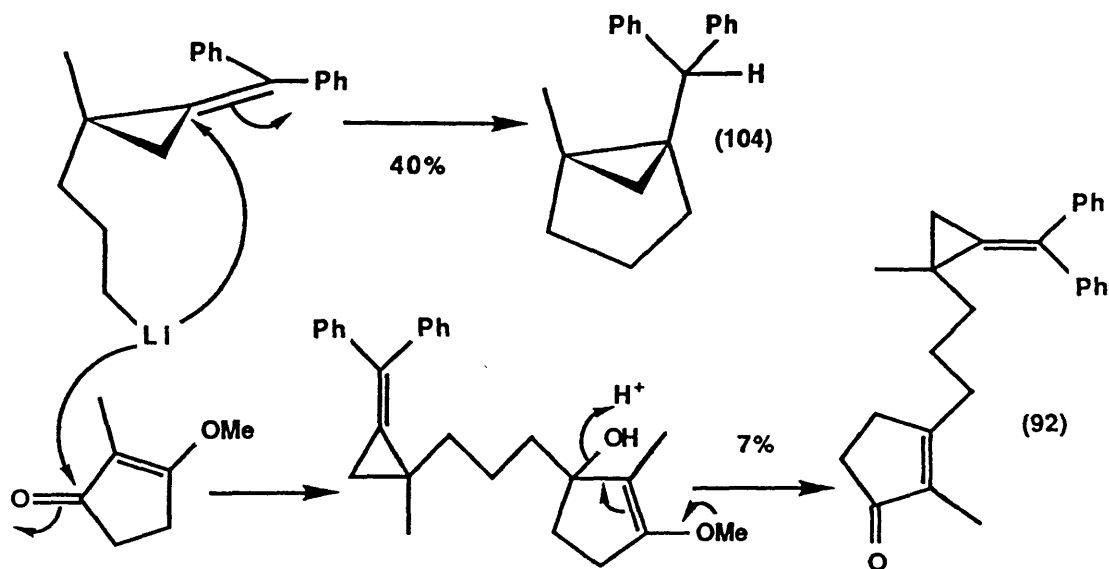
Extrusion of ethene results in a phosphate, accounting for the observed polarity of the products. Polymerisation of such species should also be possible. The most plausible reason why this competing reaction, not observed previously, should become important arises from the steric congestion of the cyclopropyl phosphonate. Betaine formation by reaction with benzophenone introduces extensive eclipsed interactions between the four bulky groups appended to the cyclopropane, thus favouring the reversibility of the initial step and accounting for failure to observe the betaine. The variation in yields of olefin suggests a strong temperature dependency of cyclopropyl anion stability: best results were obtained below -110°C , as long as the solvent could be prevented from freezing. Non-polar solvents gave poorer yields presumably due to an inability to stabilise the cyclopropyl phosphonate anion by solvation. The addition of TMEDA helped in this respect. Clearly if the foregoing hypothesis is true then employment of the known dimethyl diazomethyl phosphonate³³ under our cyclopropanation conditions should form the less sterically congested dimethyl cyclopropyl phosphonate analogue. Elimination of ethene would also be precluded, favouring the desired Wadsworth-Emmons reaction.

An attempt to apply the methodology developed for production of diethyl diazomethyl phosphonate to the methyl analog was unsuccessful. This unanticipated failure is principally due to practical difficulties associated with handling the methyl analogs which are considerably more water soluble than their ethyl counterparts. This institutes considerable difficulties in isolating the free amine after hydrogenolysis of the benzylamine

hydrochloride precursor. Furthermore, the free amine is reportedly unstable³³. Attempted direct diazotisation of the hydrochloride salt of the debenzylated amine failed to yield any significant quantity of the diazomethyl phosphonate due to the presence of traces of palladium salts leached from the hydrogenation catalyst. These caused catalytic decomposition of the diazomethyl phosphonate as fast as it formed, as evidenced by continuous and voluminous evolution of nitrogen during the course of the diazotisation procedure! This is not a problem with the ethyl analog since neutralisation with 0.880 ammonia converts these trace contaminants to water soluble amine complexes which are readily washed out. Attempted preparation by diazo-transfer from diphenyl phosphonic azide to the lithium anion of methyl dimethyl phosphonate was equally unproductive. At this juncture, we did not have sufficient time or resources to resort to the method developed by Seyferth³³. Consequently this hypothesis remains to be tested.

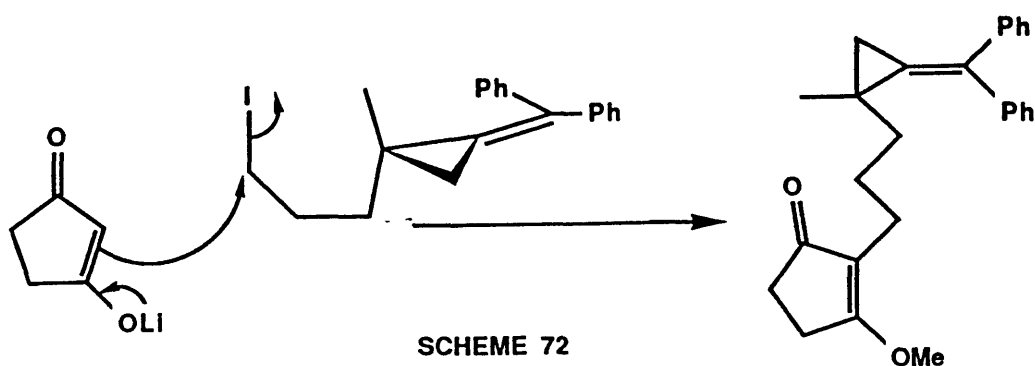
Despite the limited quantities of alcohol (99) available the remainder of the sequence was executed. The alcohol (99) upon deprotection (TBAF) was converted in an uneventful and high yielding sequence via the mesylate (100) to the required key iodide (101) in 88% overall yield. Lithium halogen exchange with *t*-BuLi at -78^oC according to the procedure of Corey,⁹³ and addition of the resulting alkyllithium species (102) to a solution of ketone ((103), (readily available by methylation of the enolate anion of ketone (70) afforded only a trace of the desired alkylated ketone (92). The principal product proved to

be that derived from intramolecular attack of the alkyllithium at the diphenylmethylene moiety to afford the strained 1-diphenylmethylene-5-methyl-bicyclo[3.1.0]hexane system (104) (Scheme 71).



SCHEME 71

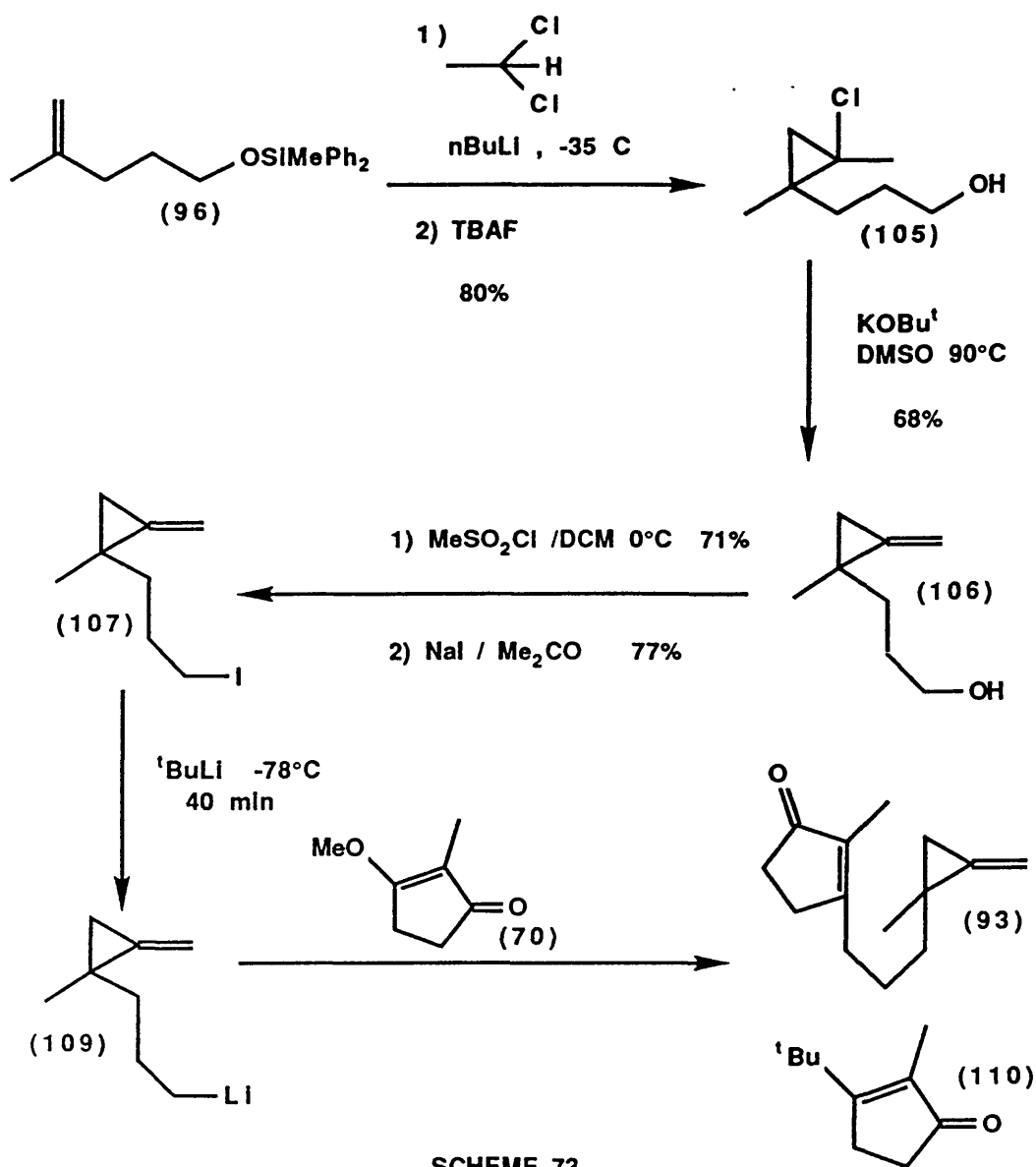
Such reaction is not entirely without precedent, although it is debatable whether the reaction proceeds by an ionic or electron transfer mechanism in this instance. Unfortunately, this second failure left us without sufficient material to merit investigation of the key cyclisation step! Provided that the problems with preparation of the diphenylmethylenecyclopropane may be solved by the suggestions outlined above, this final difficulty should be surmountable by alkylation of the lithium enolate of cyclopentan-1,3-dione with the iodide (102), followed by formation of the methyl enol ether to afford a slightly different but equally effective probe for the cyclisation strategy (Scheme 72).



4.3.2) SYNTHESIS OF METHYLENECYCLOPROPANE (93)

A strategy similar to that adopted previously was employed for the synthesis of ketone (93), but cyclopropanation was achieved employing methodology developed by Binger⁹⁵ as outlined in Scheme 73.

Cyclopropanation of the olefin (96) under the original experimental conditions proceeded poorly. Superior results were obtained by employing a 3-fold excess of 1,1-dichloroethane, added in 3 equal portions at 1 hour intervals whilst simultaneously adding 2 equivalents of *n*-BuLi dropwise via a syringe pump over 3 hours. Adding a large excess of dichloroethane to the reaction in one portion gave inferior yields (ca. 50%). By the modified method, 1-chloro-1,2-dimethyl-2-(1-hydroxylprop-3-yl)cyclopropane (105) was obtained in 80% yield. Separation of (105) from residual olefin was achieved by TBAF deprotection to liberate the alcohol followed by distillation.



SCHEME 73

Dehydrochlorination was effected with potassium-*t*-butoxide in DMSO at 90°C as previously described,⁹⁵ to furnish the methylenecyclopropane (106). Due to the volatility of this material, the crude mixture was directly transformed into the less volatile mesylate (107) isolated in 71% yield. Treatment with sodium iodide in acetone afforded the volatile iodide (108) in 77% yield. Lithium-halogen exchange with 2 equivalents of *t*-butyllithium by analogy with the Cory method⁹⁰ afforded the

desired alkylated ketone (93) upon acid hydrolysis, but contaminated by a substantial quantity (ca. 50%) of the ketone (110) arising from nucleophilic attack by *t*-butyllithium in a combined yield of 51%.

Unfortunately these compounds were inseparable by flash chromatography, but were readily distinguished by analytical GLC on a polydimethylsiloxane capillary column at 70°C. Preparative GLC was not available and the compounds were considered to be too volatile and apolar for successful HPLC separation. It should be possible to reduce the problem in future studies by employing only a single equivalent of *t*-BuLi, although the offending contaminant is always likely to be present to some extent. The intramolecular cyclisation product was not observed. This may be due to its expected volatility. However, the absence of the gem-diphenyl substituents on the methylene group, which provide an excellent electron sink, must be disfavouring the intramolecular attack, thus allowing the desired intermolecular reaction to compete. Activation of the ketone by prior addition of a Lewis acid should assist this competition further in favour of the desired pathway, and increase the yield.

In view of the weak ability of the double bond of $\alpha\beta$ -unsaturated ketones to co-ordinate with palladium or nickel, and the further hindrance provided by a *t*-butyl substituent, it is rationalised that the 3-*t*-butyl cyclopentenone contaminant should not interfere unduly with the cyclisation reaction. However, in view of the speculative nature of the cyclisation reaction, it was not considered wise to proceed further until pure material

became available, or until model studies with the (diphenylmethylene)cyclopropane had been carried out.

PERSPECTIVES AND CONCLUSION

1-Vinyl-1-cyclopropanols were demonstrated to undergo an oxy-anion assisted ring cleavage reaction as predicted, but apparently by an ionic mechanism leading to acyclic ketones rather than the desired radical pathway leading to cyclopentanones. During attempts to prepare the required vinyl-cyclopropanols by oxidative functionalisation with allylic transposition of alkylidene cyclopropanes, a number of unusual reactions of these systems were observed. Over oxidation of allyl selenide systems, with hydrogen peroxide, afforded the important oxaspiropentane systems in reasonable yield, by mild phenylseleninic acid catalysed epoxidation of alkylidene cyclopropanes under effectively neutral conditions. This result deserves further investigation as a potentially mild and direct route to oxaspiropentanes of diverse substitution patterns, perhaps circumventing problems currently encountered with the acid lability of these species under peracid epoxidation.

Also of potential interest, from a mechanistic point of view, is the observed extrusion of cyclohexene upon singlet oxygenation of a substituted alkylidene cyclopropane at low temperature. (Further study is necessary to elucidate the mechanism of the process). If it transpires that the proposed mechanism is correct, then the reaction represents a rare example

of attack of an oxygen centred radical on a carbonyl moiety.

The studies on cyclopropyl phosphonates have also exposed a number of interesting phenomena. The methodology developed for the construction of gem-diphenylmethylene cyclopropanes by a Wadsworth-Emmons approach constitutes a versatile extension to the currently available routes to these important systems. Not only is the Wadsworth-Emmons reactivity of these cyclopropyl phosphonates with benzophenone apparently unique amongst the ketones currently investigated, but the method of cyclopropyl phosphonate synthesis also compares extremely favourably with any previously available method. Although cuprous trifluoromethanesulphonate has proved an excellent and readily handleable catalyst in our group, alternative choice of catalyst for effecting decomposition of the diazomethyl phosphonate may prove worth developing for use by less able experimentalists. In this regard, problems experienced with decomposition of dimethyl diazomethyl phosphonate (during diazotisation of the crude amine obtained by hydrogenolytic debenzylation) may have proved useful. These problems have been ascribed to leaching of palladium chloride from the hydrogenation catalyst, and suggest that palladium chloride or acetate may be suitable alternative choices. Cuprous triflate is known⁶⁹ to possess properties analogous to these compounds as regards catalytic decomposition of diazo-compounds, and co-ordination of olefins. Problems encountered with low yields in the Wadsworth-Emmons reaction of highly substituted cyclopropyl phosphonates are under active investigation in our group. It is hoped that the corresponding

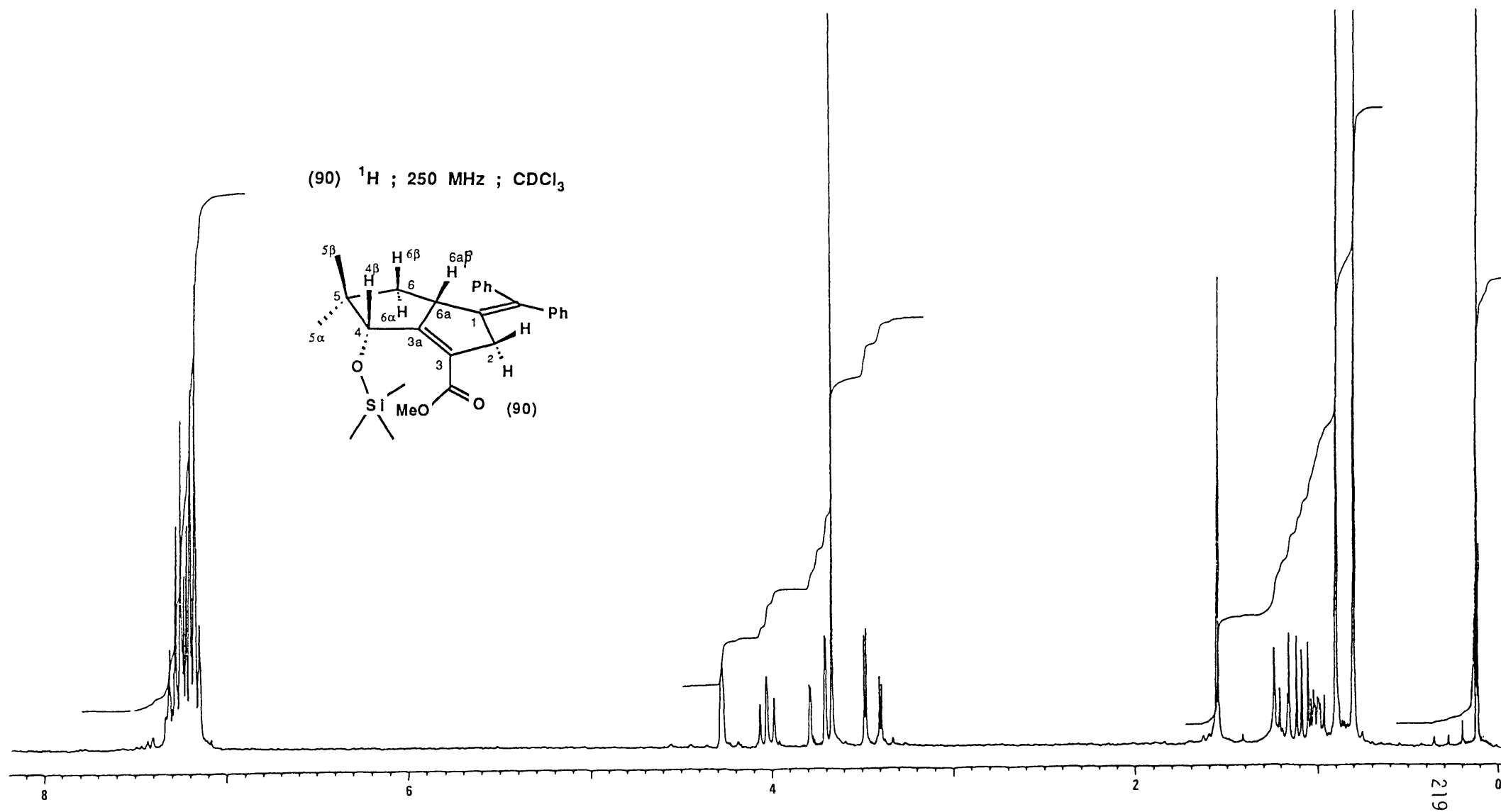
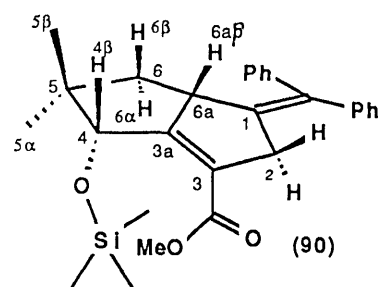
dimethyl cyclopropyl phosphonates will prove more satisfactory with regard to phosphonate anion stability, and relief of steric congestion at the betaine stage.

Finally initial studies of the first reported "Noyori-Binger" reaction have provided encouraging results. Palladium catalysts under thermal or novel ultrasonication conditions have resulted in high yields of bicyclo[3.3.0]octane systems. The stereospecificity of the reaction has not yet been determined, but is under current investigation.

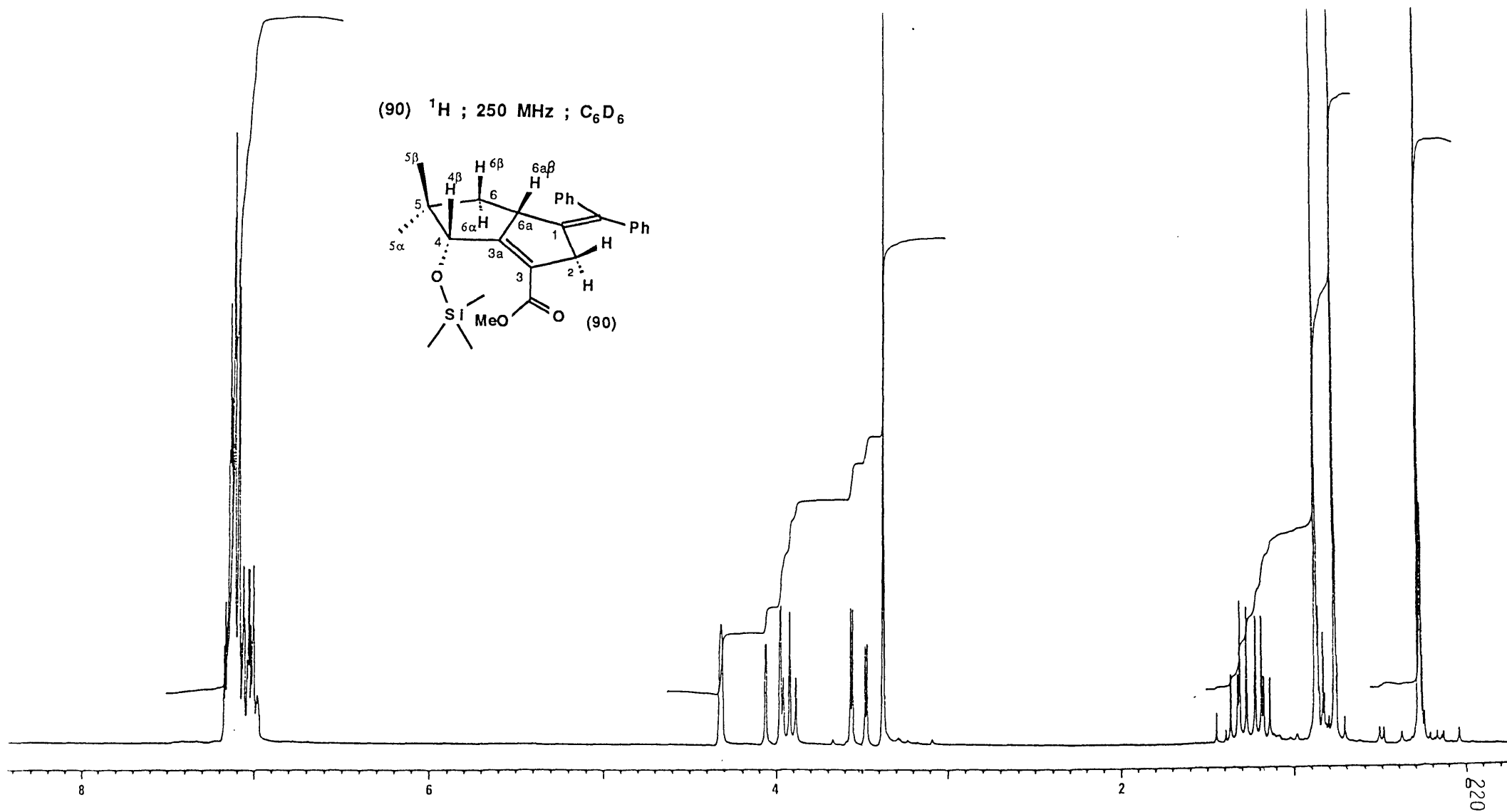
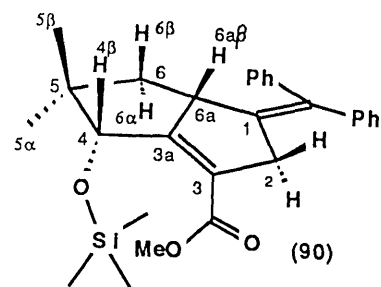
Initial investigations into the dichotomy observed in other systems when nickel catalysis is employed has also proved valuable. Under nickel catalysed conditions the reaction is not nearly as clean as previously observed with palladium. It is abundantly clear, however, that the reaction pathway is entirely different in this case, none of the previously observed bicyclic compounds being obtained. In fact, after deprotection a low yield of the novel lignan (112), was obtained. This formal Diels-Alder adduct may illustrate the dichotomy of reactivity between palladium and nickel catalysis outside the confines of methylene cyclopropanes, as we had originally hoped. The further study of these and related systems should prove extremely fruitful.

APPENDIX

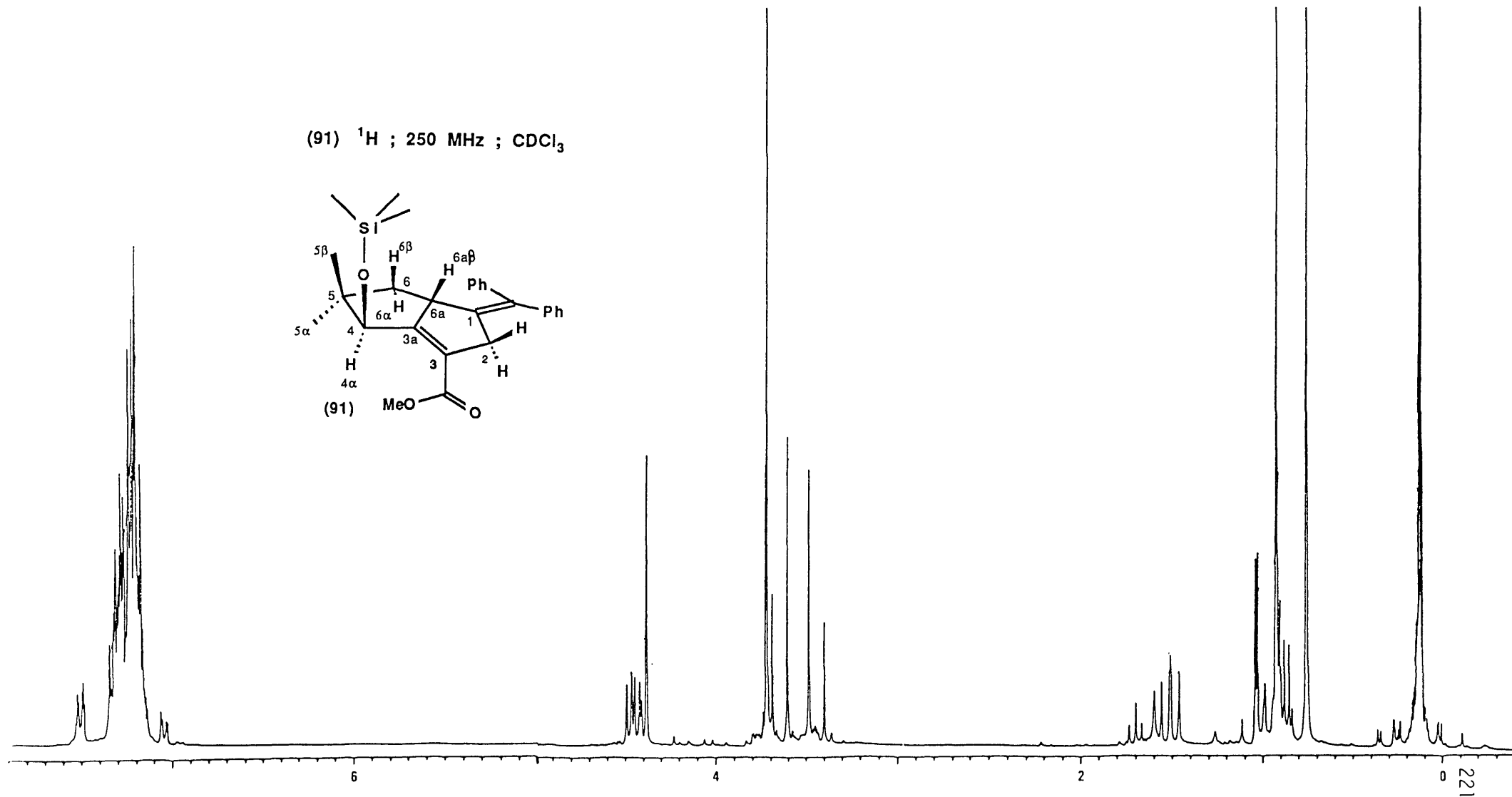
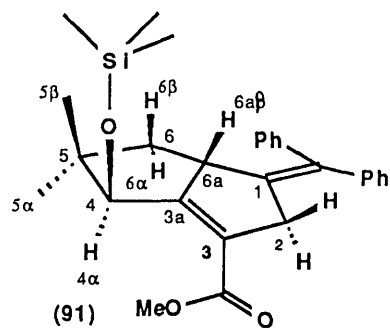
(90) ^1H ; 250 MHz ; CDCl_3



(90) ^1H ; 250 MHz ; C_6D_6



(91) ^1H ; 250 MHz ; CDCl_3



Crystal Data (112)

$C_{24}H_{22}O_2$, $M = 342.4$, monoclinic, $a = 16.487(12)$, $b = 12.654(10)$, $c = 19.595(14)$ Å, $\beta = 111.10(5)^\circ$, $V = 3814$ Å³, space group $P2_1/c$, $Z = 8$ (2 crystallographically independent molecules), $D_c = 1.19$ g cm⁻³, $\mu(\text{Cu-K}\alpha) = 6$ cm⁻¹, $F(000) = 1480$. 3917 independent reflections ($\theta \leq 50^\circ$) were measured on a Nicolet R3m diffractometer with Cu-K α radiation (graphite monochromator) using ω -scans. Of these 3034 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; no absorption correction was applied. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically. The positions of the hydrogen atoms were idealised, C-H = 0.96 Å, assigned isotropic thermal parameters, $U(H) = 1.2 U_{eq}(C)$, and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade full-matrix least-squares and converged to give $R = 0.054$, $R_w = 0.063$. The maximum residual electron density in the final ΔF map was 0.54 e Å⁻³ and mean and maximum shift/error in final refinement were 0.011 and 0.047 respectively.

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Kofler-hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 983 G grating infrared spectrophotometer as thin films, or as dichloromethane or carbon tetrachloride solutions. ^1H , and ^{13}C n.m.r spectra were recorded at 90 MHz and 22.5 MHz respectively on a Jeol FX 90 Q; at 250 MHz and 62.9 MHz respectively on a Bruker WM-250; and at 500 MHz and 125.8 MHz respectively on a Bruker AM-500, with tetramethylsilane as internal standard. ^{31}P n.m.r spectra were recorded at 36.2 MHz on a Jeol FX 90 Q with 85% aqueous phosphoric acid in deuterium oxide as external reference. Spectra were recorded in deuteriochloroform, deuteriobenzene, or deuterium oxide as specified. ^{13}C assignments were routinely confirmed by J-modulated spin echo and/or off resonance pulse decoupled experiments as appropriate. Mass spectra were recorded on a VG Micromass 7070B instrument. Elemental microanalysis was performed by the staff of the Imperial College Chemistry department microanalysis laboratory.

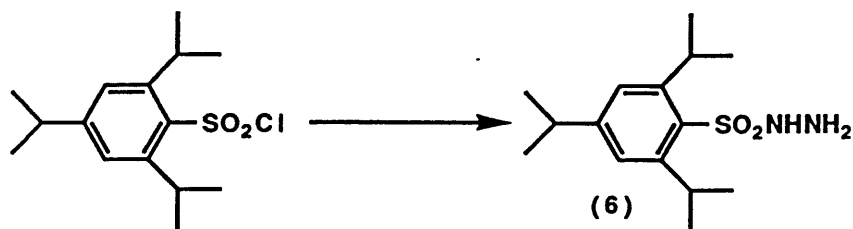
Analytical thin layer chromatography was performed on pre-coated glass-backed plates (Merck Kieselgel 60 F₂₅₄). Preparative thin layer chromatography was performed on (20x20 cm) glass plates coated with Merck Kieselgel 60 GF₂₅₄. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230-400 mesh); "Silica" refers to this grade of Kieselgel.

"Petrol" refers to redistilled light petroleum ether with b.p 40-60^oC unless otherwise indicated. "Ether" refers to diethyl ether. Ether, tetrahydrofuran, dimethoxyethane, toluene, and benzene were distilled from sodium - benzophenone ketyl under argon immediately prior to use. Dimethylformamide was distilled from calcium hydride at reduced pressure, and stored over 4 A molecular sieves under an argon atmosphere prior to use. Dimethylsulphoxide, distilled from 4 A molecular sieves was stored likewise. Dichloromethane was freshly distilled from phosphorus pentoxide under an argon atmosphere prior to use. 1,1-dichloroethane was passed through a pad of neutral alumina prior to distillation from 4 A sieves under an argon atmosphere. All other solvents and reagents were purified by standard methods^{*}.

Unless stated otherwise, all reactions were performed under an atmosphere of dry argon in degassed solutions. The transition metal catalysts were stored and handled under an argon atmosphere. Glassware was oven dried at 150^oC before use.

Solutions were concentrated with a rotary evaporator at water pump pressure, followed by static evaporation at an oil pump.

1) PREPARATION OF 2,4,6-TRIISOPROPYLBENZENESULPHONYL HYDRAZINE (6)

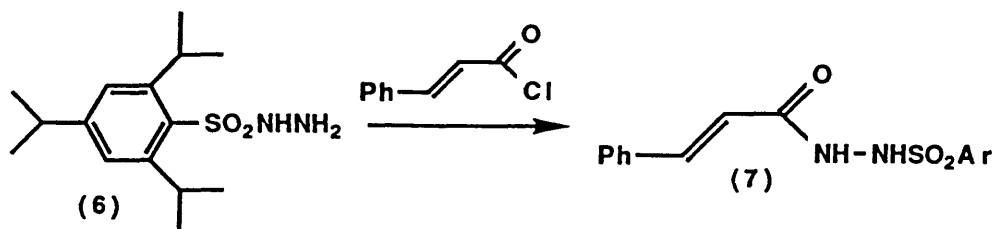


85% Hydrazine hydrate (25.5 g, 435 mmol) was added dropwise over 0.5 h to a stirred solution of 2,4,6-triisopropylbenzenesulphonyl chloride (53.0 g, 175 mmol) in THF (200 ml) at -5°C . After stirring for 3 h at 0°C , the hydrazine hydrochloride was filtered, the filtrate washed with brine (3x75ml) at 0°C , and dried (MgSO_4) at 0°C . The solvent was stripped at reduced pressure below 25°C until crystallisation began. Petrol (500 ml) was added, the precipitate collected, and dried at 0°C in vacuo to afford

2,4,6-TRIISOPROPYLBENZENESULPHONYL HYDRAZINE (6), (51.0 g, 97%) as colourless plates. m.p. $118-120^{\circ}\text{C}$; ν_{max} (DCM) 3367, 3314, 2962, 2930, 2870, 1598, 1462, 1363, 1325, 1164, 1153, 909, 884, 652, and 633 cm^{-1} ;

δ_{H} (90 MHz; CDCl_3) 1.28 (18H, d, J 7.2 Hz, $(\text{Me})_2\text{CH-Ar}$) ,
2.93 (1H, h, J 7.2 Hz, $(\text{Me})_2\text{CH-Ar[para]}$) , 3.65 (2H, bs, NH_2) ,
4.18 (2H, h, J 7.2 Hz, $(\text{Me})_2\text{CH-Ar[ortho]}$) , 5.17 (1H, bs, NH) ,
7.21 (2H, s, m-Ar-H) .

(Found : C, 60.40 ; H, 8.70. $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$ requires : C, 60.36 ; H, 8.78 %)

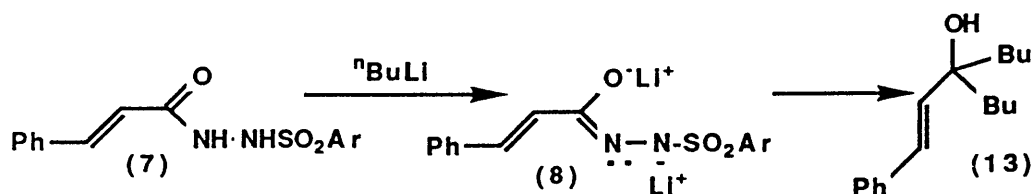
2) PREPARATION OF N'-2,4,6-TRIISOPROPYLBENZENESULPHONYLCINNAMOHYDRAZIDE (7)

To a stirred solution of 2,4,6-triisopropylbenzenesulphonylhydrazine (6) (18.0 g, 60 mmol), and pyridine (5.36 g, 66 mmol) in dry DCM (140 ml) at 0°C was added a solution of cinnamoyl chloride (10.06 g, 60 mmol) in DCM (70 ml) dropwise over 1.5 h. The mixture was stirred at 0°C for 2 h, then allowed to stand at 4°C for 48 h. Ethyl acetate (100 ml) was added, the mixture warmed to room temperature and stirred until all the precipitate dissolved. The yellow solution was washed with 5% aqueous HCl (100 ml), water (3x60 ml), brine, and dried (Na_2SO_4). The solvents were stripped at reduced pressure, and the residue dissolved in acetone. An equal volume of petrol (60–80 b.p.) was added, the solution concentrated to 1/3 volume, then chilled to -5°C . The colourless solid was filtered, and the mother liquor concentrated to afford a second crop. The solid was dried in vacuo over P_2O_5 to yield N'-2,4,6-TRIISOPROPYLBENZENESULPHONYL CINNAMOHYDRAZIDE (7) (23.86 g, 93%). m.p. 192°C ; ν_{max} (DCM) 3378, 2963, 1687 (C=O), 1622 (C=C), 1466, 1334, 1171, 1151, 1035, 981, 909, and 651 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.23 (6H, d, J 7.6 Hz, $\text{p-CH}(\text{Me})_2$), 1.32 (12H, d, J 7.6 Hz, $\text{p-CH}(\text{Me})_2$), 2.89 (1H, h, J 7.6 Hz, $\text{p-CH}(\text{Me})_2$), 4.07 (2H, h, J 7.6 Hz, $\text{p-CH}(\text{Me})_2$), 6.36 (1H, d, J 15.2 Hz, PhCHCHCO-), 7.17 (2H, s, m-CH-Ar), 7.40 (5H, m, Ph-H), 7.53 (1H, br d, J 5 Hz, NH-CO-),

7.61 (1H,d,J 15.2Hz,PhCHCHCO) , 7.95 (1H,br d,J 5Hz,NH-SO₂-) ;
 m/z 429(MH⁺), 364, 319, 291, 267(SO₂Ar), 162(M-267), 132(PhCHCHCO),
 103(PhCHCH), 77, 43 ; $\lambda_{\max}$ 285nm , $\epsilon_{\max}$ 9800. (Found: C, 67.39 ; H, 7.57 ;
 N, 6.36 . C₂₄H₃₂N₂SO₃ requires : C, 67.20 ; H, 7.53 ; N, 6.53 %)

3) ATTEMPTED FORMATION OF TRISYL CINNAMO HYDRAZIDE DIANION (8)

WITH n-BUTYLLITHIUM



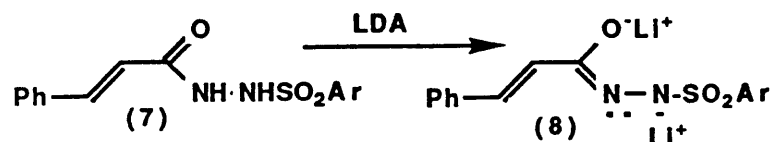
To a suspension of hydrazide (7) (560 mg, 1.17 mmol) in toluene (100 ml), and THF (15 ml) at -40°C was added *n*-BuLi (1.86 ml of a 1.4 M solution in hexanes, 2.6 mmol, 2.2 eq) dropwise with stirring over 0.5 h, when a dark red solution formed. On warming to room temperature, methyl iodide (4 ml, 64 mmol), was added and the solution became yellow. The mixture was poured into water and the layers separated. The organic phase was washed with 0.1 M aqueous sodium thiosulphate, brine, and dried (Na₂SO₄). The solvents were stripped at reduced pressure, and the residue chromatographed (SiO₂-DCM). No methylated material was isolated, and the only non-polar product was

1,1-DI-*n*-BUTYLCINNAMYL ALCOHOL (13) . $\nu_{\max}$ (DCM) 3596(OH), 3051, 2959, 2935, 2863, 1449, 1420, , 1257, 973, 896, 754, and 713 cm⁻¹ ;

δ_{H} (250MHz ; CDCl₃) 0.9 (6H,m,CH₃(CH₂)₃-) , 1.3 (8H,m,CH₃(CH₂)₂-) ,
 1.6 (4H,m,CH₃(CH₂)₂CH₂COH-) , 6.21 (1H,d,J 14.5Hz,PhCHCHCOH) ,
 6.58 (1H,d,J 14.5Hz,PhCHCHCOH) , 7.3 (5H,m,Ph) ; m/z 246(M⁺) ,

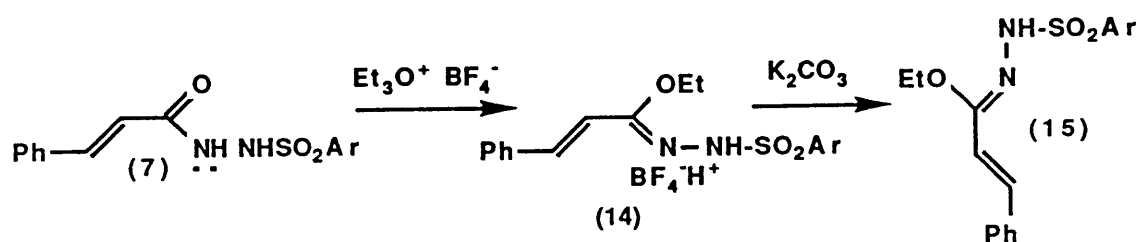
228(M-H₂O), 189(M-Bu), 146(M-2Bu)

4) INVESTIGATION INTO THE STABILITY OF THE HYDRAZIDE DIANION (8)



To a solution of the hydrazide (7) (540 mg, 1.26 mmol) in THF (5 ml) and cyclohexene (5 ml) at -78°C, was added with stirring a 1M solution of LDA (2.20 ml, 2.5 mmol) in THF dropwise. After stirring at -78°C for 1h, an aliquot was removed by syringe, and quenched with glacial acetic acid. T.l.c showed recovery of starting material. After warming to room temperature a second similarly treated aliquot also showed only starting material by t.l.c. At 60°C initiation of decomposition was evident. No carbene adducts could be isolated from the complex product distribution.

5) PREPARATION OF ETHYL CINNAMATE-2,4,6-TRIISOPROPYLBENZENESULPHONYL HYDRAZONE (15)



To a stirred suspension of N'-trisyl cinnamohydrazide (7) (2.85 g, 6.65 mmol) in DCM (60 ml) was added a solution of triethyloxonium tetrafluoroborate (2.37 g, 1.2 equiv), in DCM (2 ml). The mixture was stirred at room temperature for 3 h when a pale yellow solution of the hydrofluoroborate salt (14) formed.

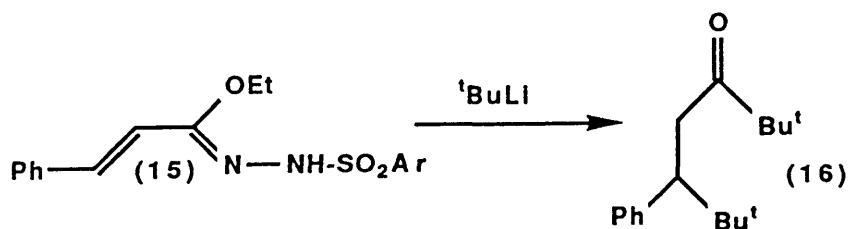
Anhydrous potassium carbonate (11 g, 10 equiv) was added, and the mixture stirred for 0.3 h. The solid was allowed to settle, and the solution transferred via a catheta to a dry flask. The solvent was removed at reduced pressure at an oil pump, to yield a pale yellow foam. Dissolution in dry ether and filtration under argon removed excess Meerwein salt and starting hydrazide. The solvent was stripped as before to afford

ETHYL CINNAMATE 2,4,6-TRIISOPROPYLBENZENESULPHONYL HYDRAZONE (15)

as a pale yellow foam, (2.60 g, 86%). $\nu_{\max}$ (DCM) 2963, 2931, 1708 (C=N), 1672, 1634, 1596, 1449, 1368, 1324, 1296, 1203, 1183, 1048, and 979 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.26 (16H, m, Me_2CH), 1.34 (3H, t, J 6.7 Hz, MeCH_2O), 2.95 (1H, h, J 7 Hz, p-Ar- CHMe_2), 4.02 (2H, m, o-Ar- CHMe_2), 4.27 (2H, q, J 6.7 Hz, MeCH_2O), 6.45 (1H, d, J 17.8 Hz, PhCHCHCOEtN), 7.17 (2H, s, m-Ar SO_2), 7.38 (3H, m, m,p-PhH), 7.54 (2H, m, o-PhH), 7.70 (1H, d, J 17.8 Hz, PhCHCHCOEtN); m/z 456 (M^+), 267 (Ar SO_2), 204 (267- SO_2), 189 ($\text{C}_{11}\text{H}_{13}\text{ON}_2$, base), 161 ($\text{C}_{11}\text{H}_{13}\text{O}$), 131 ($\text{C}_9\text{H}_7\text{O}$), 103 ($\text{C}_8\text{H}_7\text{O}$), 91, 77. (Found: M^+ , 456.2454. $\text{C}_{26}\text{H}_{36}\text{O}_3\text{N}_2\text{S}$ requires: M^+ , 456.2447).

6) TREATMENT OF ETHYL CINNAMATE TRISYL HYDRAZONE (15) WITH

t-BUTYLLITHIUM

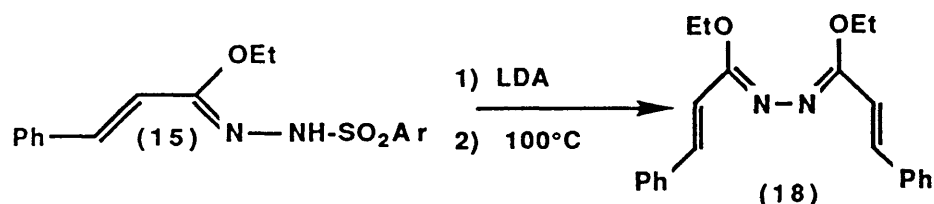


To a solution of hydrazone (15) (800 mg, 1.8 mmol) in cyclooctene (5 ml) at -40°C was added $t\text{-BuLi}$ (1.40 ml of a 1.8M

solution in hexanes, 2.5 mmol, 1.4eq). The dark red solution was stirred for 10 min, allowed to warm to room temperature, then heated at reflux for 48 h. On cooling the mixture was poured into saturated ammonium chloride, and extracted with ether. The organic phase was washed with water, brine, and dried (Na_2SO_4). The solvent was stripped at reduced pressure, and a portion of the residue subjected to P.L.C (silica-DCM) to afford 3,3-DIMETHYL-2-PHENYL-1-BUTYL-t-BUTYL KETONE (16), as the major component of a complex product product distribution, a colourless crystalline solid (petrol 60-80 b.p), m.p $95-97^\circ\text{C}$. ; ν_{max} (DCM) 3028, 2958, 2870, 1702 (C=O), 1491, 1476, 1392, 1366, 1296, 1227, 1090, 1071, and 993 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.88 (9H, s, $\text{PhCH}(\text{CMe}_3)$) , 1.00 (9H, s, $\text{CO}(\text{CMe}_3)$) , 2.72 (1H, m, PhCH-) , 3.14 (2H, m, $-\text{CH}_2\text{CO}$) , 7.18 (5H, m, Ph) ; δ_{C} (22.5 MHz ; CDCl_3) 26.2, 27.8, (C-1' & C-3 Me) , 34.2 (C-1) , 38.0 (C-3) , 50.4 (C-2) , 66.0 (C-1') , 126.0, 127.7, 129.4 (Ar C-H) , 143.1 (Ar C-C) , 213.8 (C=O) ; m/z 246 (M^+), 190 (M-tBu), 133 (M-2tBu), 105, 91, 85 (tBuCO), 57 (tBu) .

(Found : C, 82.87 ; H, 10.61 . $\text{C}_{17}\text{H}_{26}\text{O}$ requires : C, 82.87 ; H, 10.64 %).

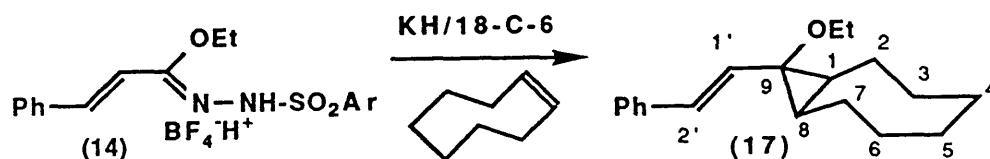
7) DEPROTONATION OF ETHYL CINNAMATE TRISYL HYDRAZONE (15) WITH L.D.A



To a solution of imino ether (15) (1.20 g, 2.6 mmol) in toluene (6 ml) and cyclohexene (4 ml) at -78°C was added L.D.A

(3.12 ml of a 1.0 M solution in THF, 3.12 mmol, 1.2 equiv) dropwise with stirring. After stirring for 0.5 h at -78°C , rhodium acetate (4 mg) was added via a solid addition tube. After stirring an additional 0.6 h, the mixture was warmed to room temperature, and stirred 14 h. T.l.c analysis showed predominantly starting material. The mixture was heated at reflux (100°C) for 4 h. On cooling, water was added and the mixture extracted with ether. The organic layer was washed (brine) and dried (Na_2SO_4). The solvent was stripped at reduced pressure, and a portion of the residue subjected to P.L.C (Silica-20% DCM/toluene). The major component of the non polar material separated proved to be ETHYL CINNAMATE AZINE (18), identical in all respects to material obtained by other means. The more polar fractions consisted predominantly of hydrazide (7).

8) DEPROTONATION OF ETHYL CINNAMATE 2,4,6-TRIISOPROPYLBENZENESULPHONYLHYDRAZONE HYDROFLUOROBORATE (14)
WITH POTASSIUM HYDRIDE 18-CROWN-6



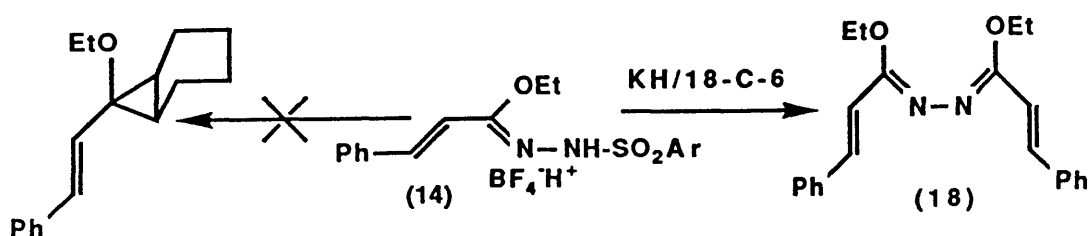
To a stirred slurry of potassium hydride (5.10 g of a 35% oil dispersion, 44.6 mmol, 7 equiv) in dry cyclooctene (15 ml), was added rhodium acetate (5 mg), 18-crown-6 (500 mg, 1.9 mmol), DME (12 ml), followed by a solution of crude hydrazone hydrofluoroborate salt* (14) (3.26 g, 6 mmol) in DME (7 ml)

dropwise over 25 min, when evolution of gas with concomitant darkening of the mixture was observed. After 4 h the reaction mixture was rapidly heated to reflux, and reflux maintained for 2 h. On cooling to 0°C saturated aqueous ammonium chloride was added cautiously, the organic layer separated, and the aqueous layer extracted with ether. The combined organic phases were dried (MgSO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-2% ether/petrol) to afford the desired 9-ETHOXY-9-(2-PHENYLETHENYL)-BICYCLO[6.1.0]NONANE (17)

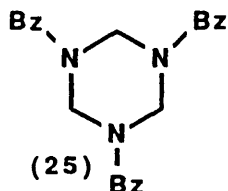
(65 mg, 4%) as a pale yellow oil. ν_{max} (DCM) 2926, 2854, 1597, 1492, 1464, 1445, 1388, 1331, 1254, 1121, 1073, 1045, 970, and 692 cm^{-1} ;

δ_{H} (250 MHz ; CDCl_3) 0.88 (2H, m, 1-H, 8-H) ,
 1.0-2.0 (15H, 2-7-H₂ ; 1.20, t, J 6.4 Hz, OCH_2Me) ,
 3.53 (2H, q, J 6.4 Hz, MeCH_2O) , 6.50 (1H, d, J 14.7 Hz, 1'-H) ,
 6.73 (1H, d, J 14.7 Hz, 2'-H) , 7.30 (5H, m, Ph) ; δ_{C} (62.9 MHz ; CDCl_3)
 15.60 (OCH_2Me , q) , 23.11 (C-2, C-7, t) , 26.41 (C-3, C-6, t) ,
 29.15 (C-4, C-5, t) , 30.98 (C-1, C-8, d) , 62.17 (MeCH_2O , t) ,
 65.83 (C-9, s) , 126.01, 126.92, 128.51, 130.16, (Ar) , 136.57 (C-2') ,
 137.66 (C-1') ; m/z 270 (M^+) , 241 (M-Et) , 227, 213, 199, 185, 171,
 131 (PhCHCHO) , 103, 91, 77.

(Found : M^+ , 270.1982 . $\text{C}_{19}\text{H}_{26}\text{O}$ requires : M^+ , 270.1984).

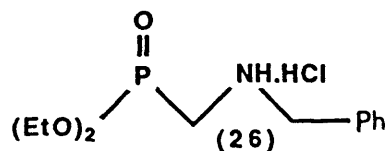
9) ATTEMPTED PREPARATION OF 7-ETHOXY-7(1-PHENYLETHEN-2-YL)-BICYCLO[4.1.0]HEPTANE

To a suspension of potassium hydride (1.90 g of a 35% oil dispersion, 16.6 mmol, 3 equiv) and 18-crown-6 (790 mg, 3 mmol) in DME (5 ml) and cyclohexene (5 ml) at -50°C , was added a solution of crude hydrazone hydrofluoroborate salt^{*} (14) (2.46 g, 5.4 mmol) in DME (7 ml), and the mixture allowed to warm to room temperature when a bright yellow solution formed with concomitant evolution of gas. Catalytic rhodium pivalate (20 mg) was added and the solution stirred a further 4 h when gas evolution ceased. The mixture was then heated at reflux for 1 h, cooled, and quenched by cautious addition of saturated aqueous ammonium chloride. The mixture was extracted from water with ether, the extracts dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography of the residue (Silica-gradient 3 to 30% ether/petrol) afforded ETHYL CINNAMATE AZINE (18) as yellow plates (60–80 b.p petrol) m.p. $147\text{--}148^{\circ}\text{C}$; ν_{max} (DCM) 2977, 1627 (C=N), 1580, 1565, 1492, 1448, 1365, 1305, 1278, 1202, 1045, 974, 753, and 690 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 1.45 (3H, t, J 7.26 Hz, OCH_2CH_3), 4.38 (2H, q, J 7.26 Hz, OCH_2CH_3), 7.4 (7H, m, Ph and A:B system- CHCH -); m/z 348 (M^+), 319 (M-Et), 277, 189, 174 (PhCHCHC(OEt)N), 146, 131 (PhCHCHCO), 103, 77. (Found: C, 75.45; H, 6.86; N, 7.88. $\text{C}_{22}\text{H}_{24}\text{O}_2\text{N}_2$ requires: C, 75.83; H, 6.94; N, 8.04 %)

10) PREPARATION OF 1,3,5-TRI-N-BENZYLHEXAHYDRO-S-TRIAZINE(25)

To benzylamine (41.4 g, 386 mmol) at 0°C was added with stirring a 40% solution of formalin (38.8 ml 400 mmol) slowly, such that the temperature remained below 10°C. To the precipitated gum was added 3M aqueous sodium hydroxide (40 ml), and the mixture stirred briefly with a glass rod. After standing in ice for 0.3 h ether (100 ml), was added, and the mixture stirred until all precipitate dissolved. The aqueous phase was separated and extracted with ether. The combined organic layers were washed with brine. The solvents were stripped at reduced pressure to afford the s-triazine as a colourless oil. Crystallisation from ethanol (450 ml per mol) at -10°C by addition of water (in 30 ml portions per 450 ml), afforded after drying at 0.1 torr

TRI-N-BENZYLHEXAHYDRO-S-TRIAZINE (25) (39.7 g, 86%) as colourless rods. m.p. 50°C (lit 50°C^{*}) ; ν_{max} (film) 2861, 1360, 1168, 1118, 1072, 1016, 982, 739, and 699 cm⁻¹ ; δ_{H} (60 MHz ; CDCl₃) 3.45 (6H, s, N-CH₂-N), 3.7 (6H, s, Ph-CH₂) , 7.37 (15H, m, PhH) ; m/z 357 (M⁺), 267 (M-Ph-CH₂), 178 (M-2(Ph-CH₂)), 164, 119, 91.

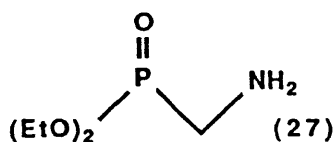
11) PREPARATION OF N-BENZYLAMINOMETHYL DIETHYL PHOSPHONATEHYDROCHLORIDE (26)

To a solution of s-triazine (25) (39.7 g, 111 mmol) under argon was added diethyl phosphite (46.1 g, 43 ml, 334 mmol), and the mixture was heated with stirring at 100°C for 6 h. The mixture was then heated at 50°C, 0.1 torr for 18 h to remove volatile impurities. The resulting crude amine was taken up in dry ether (800 ml), cooled to 0°C in an ice/salt bath, and dry HCl gas passed through slowly with stirring, when the colourless hydrochloride salt precipitated. Filtration and drying in vacuo over CaCl₂ afforded N-BENZYLAMINOMETHYL DIETHYL PHOSPHONATE HYDROCHLORIDE (26) (95 g, 83%) m.p. 89-90°C ;

δ_P (36.2 MHz ; D₂O) 18.82 .

(Found : C, 49.28 ; H, 7.32 ; N, 4.74 ; Cl, 11.91 .

C₁₂H₂₁NO₃PCl requires: C, 49.07 ; H, 7.21 ; N, 4.77 ; Cl, 12.07 %)

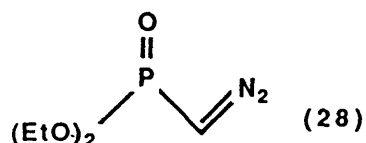
12) PREPARATION OF AMINOMETHYL DIETHYL PHOSPHONATE (27)

To a solution of N-benzylaminomethyl phosphonate hydrochloride (26) (109 g, 379 mmol) in absolute ethanol (500 ml)

was added 10% Pd/carbon catalyst (3 g). The efficiently stirred mixture was exhaustively hydrogenated under a slight positive pressure of hydrogen. Progress was monitored by ^1H , and ^{31}P n.m.r. On completion the catalyst was filtered, and the solvent stripped at reduced pressure. Aqueous (0.880) ammonia solution was added to the residue until well basic, and the free amine was extracted with DCM. The combined extracts were washed with brine and dried (Na_2SO_4). The solvent was stripped at reduced pressure, and the residual oil distilled to afford

AMINOMETHYL DIETHYL PHOSPHONATE (27) (59 g, 95%) as a colourless oil
b.p. 92°C 0.005 torr ; ν_{max} (film) 3370(N-H), 3306, 2982, 2907, 1606, 1443, 1390, 1233, 1164, 1054, 968, and 775 cm^{-1} ; δ_{H} (60 MHz ; CDCl_3) 1.35 (6H, t, J 7Hz, MeCH_2OP) , 1.52 (2H, br s, NH_2) , 3.0 (2H, d, J 10Hz, $\text{P-CH}_2\text{-NH}_2$) , 4.13 (4H, m, MeCH_2OP) ; δ_{P} (36.2 MHz ; CDCl_3) 24.53 free amine , (20.73 hydrochloride)
 Distillation is not normally necessary prior to diazotisation.

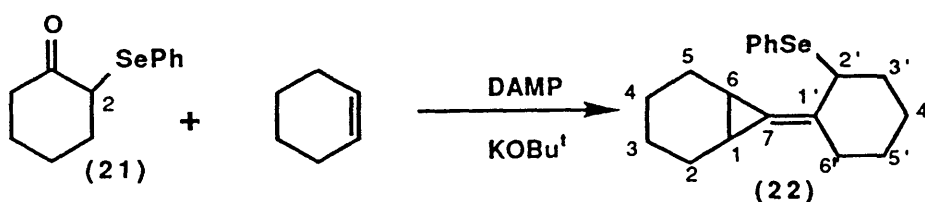
13) PREPARATION OF DIAZOMETHYL DIETHYL PHOSPHONATE (28)



To a solution of aminomethyl phosphonate (27) (39.0 g, 232 mmol), in DCM (217 ml) at -5°C was added with stirring aqueous sodium nitrite (19.33 g, 280 mmol, 108 ml water), followed by glacial acetic acid (28 g, 462 mmol) dropwise over 10 min. On stirring at 0°C for 4h the DCM layer became bright yellow. The

mixture was transferred to a chilled separating funnel, and the DCM layer run into cold aqueous potassium carbonate (75 g in 100 ml water). The aqueous layer was extracted once with DCM, and the combined organic phases shaken with the potassium carbonate until well neutralised. The layers were separated, and the organic phase dried (K_2CO_3), filtered through a short pad of neutral alumina, and the solvent stripped at reduced pressure below $40^\circ C$. Distillation of the residual oil afforded DIAZOMETHYL DIETHYL PHOSPHONATE (28) as a bright yellow liquid (30.5 g, 73%), stable as old boots at $4^\circ C$ under an argon atmosphere. b.p. $86-88^\circ C$, 0.2 torr. ; ν_{max} (film) 3482, 2986, 2103 (N=N=C strong), 1298, 1247, 1025, 970, and 826 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.32 (6H, t, J 7.5 Hz, $MeCH_2OP$) , 3.75 (1H, d, J 11 Hz, P- $\underline{CHN}_2$) , 4.09 (4H, m, $MeCH_2OP$) ; δ_P (36.2 MHz ; $CDCl_3$) 17.36 ; m/z 178 (M^+), 133 (M-OEt), 121 (M- N_2 -Et), 105 (133- N_2), 93, 65 (base).

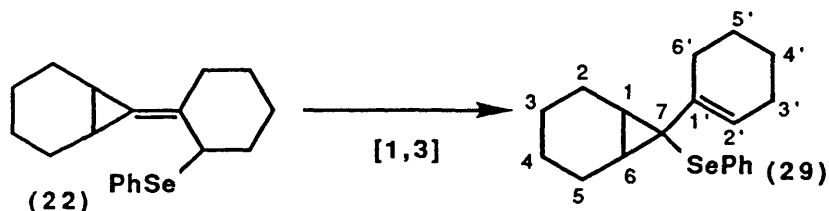
14)

SYNTHESIS OF7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (22)

To potassium t-butoxide (336 mg, 3 mmol) in DME (5 ml) and cyclohexene (5 ml) at $-78^\circ C$ was added a solution of 2-phenylselenocyclohexanone* (21) (630 mg, 2.37 mmol) in DME (1 ml), followed by DAMP (28) (650 mg, 3.65 mmol) dropwise over 1 h, when evolution of nitrogen occurred. The mixture was stirred a further

1 h then allowed to stand at -78°C for 18h. Ether (5 ml) was added, followed by saturated aqueous ammonium chloride (5 ml) and the reaction allowed to warm to room temperature. Extraction from water with petrol, drying (MgSO_4), concentration at reduced pressure, and chromatography of the residue (Silica-5% ether/petrol) were performed rapidly to afford 7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (I) as a pale yellow oil (678 mg, 82%). ν_{max} (film) 3067, 2928, 2852, 1576, 1473, 1443, 1434, 1329, 1250, 1174, 1155, 1064, 1022, 997, 738, 690, and 653 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.72–2.80 (18H, m, all aliphatic-H, except 2'-H), 4.38 (1H, m, 2'-H), 7.25 (3H, m, m,p-Ar-H), 7.53 (2H, m, o-Ar-H); δ_{C} (22.5 MHz; CDCl_3) 12.37, 13.16 (C-1, C-6), 21.10, 21.40 (C-3, C-4), 22.62, 22.74 (C-2, C-5), 27.38, 27.56, 28.72, 30.01 (C-3', 4', 5'), 33.18, 33.49 (C-6'), 48.86, 49.66 (C-2'), 125.76, 126.86 (C-7, C-1'), 130.71 (Se-C_{Ar}), 127.05–135.53 (Ar); m/z 332 (M^+), 251 (M-C₆H₉), 175 (M-SePh), 157 (SePh), 147, 133, 119, 105, 91, 81, 77, 67, 55, 41. (Found: M^+ , 332.1049. $\text{C}_{19}\text{H}_{24}\text{Se}$ requires: M^+ , 332.1043).

15)

ALLYL SELENIDE REARRANGEMENT OF7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (22)

A solution of 7-(2-phenylselenocyclohexylidene)norcarane (22) (100 mg, 0.3 mmol) in CDCl_3 (0.5 ml) was stored at 4°C without shielding from stray light sources for a number of weeks.

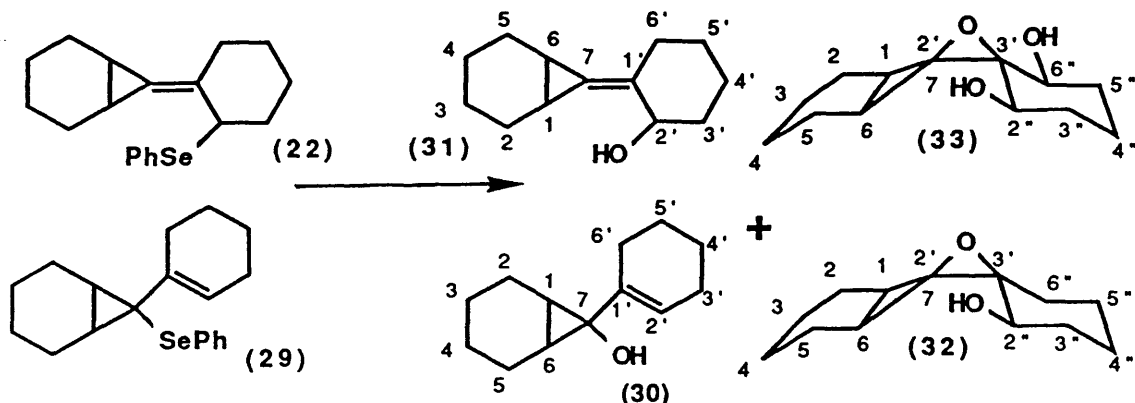
The progress of the allyl selenide rearrangement was followed by ^1H n.m.r since the chemical shift of the 2'-H changes from δ 4.38 to 5.12.

TIME /DAYS	(22)	RATIO :	(29)
0	1	:	0
5	2	:	1
17	1	:	2
30	1	:	6.5
60	0	:	1

The rearrangement proceeds to completion to afford

7-(CYCLOHEXEN-1-YL)-7-(PHENYLSELENO)-BICYCLO[4.1.0]HEPTANE (29)

as a pale yellow oil. $\nu_{(\text{max})}$ film 2930, 2856, 1660, 1575, 1473, 1339, 1299, 1174, 1135, 1064, 1022, 737, and 690 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 0.91 (2H, m, 1-H, 6-H), 1.05-2.35 (14H, m, 2-5- H_2 , 3'-6'- H_2), 5.15 (1H, m, 2'-H), 7.25 (3H, m, m,p-ArH), 7.53 (2H, m, o-ArH); δ_{C} (62.9 MHz; CDCl_3) 21.39 (C-3, C-4), 21.53 (C-2, C-5), 22.42 (C-1, C-6), 23.13 (C-4', C-5'), 25.48 (C-3'), 27.80 (C-6'), 36.95 (C-7), 131.41 (C-2'), 134.28 (C-1'), 127.28 (p-Ar), 128.17 (m-Ar), 128.55 (Se-CAr), 135.20 (o-Ar); m/z 332 (M^+), 251 ($\text{M}-\text{C}_6\text{H}_9$), 175 ($\text{M}-\text{SePh}$), 157 (SePh), 133, 119, 105, 91, 81, 77, 67, 55. (Found: M^+ , 332.1039. $\text{C}_{19}\text{H}_{24}\text{Se}$ requires: M^+ , 332.1043).

16) OXIDATIVE REARRANGEMENT OF ALLYL SELENIDES (22) AND (29)

To a stirred solution of the allyl selenides (22) and (29) (1.40 g, 4.23 mmol) in THF-pyridine (3:1 v/v) (100 ml) at -25°C was added 30% aqueous H_2O_2 (2.6 ml, 23 mmol, 5.4 equiv) dropwise over 3 min. The mixture was stirred at -25°C for 2.3 h, then diluted with ether (100 ml). The aqueous layer was separated, the organic phase washed with water, brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-20% ether/petrol) to afford in order of elution, the allylic alcohols (30) and (31), (354 mg, 44%) as colourless needles, followed by the epoxide (32) contaminated with diol (33) (240 mg, 27%). Epoxy-diol (33) was removed by fractional crystallisation from petrol (40-60 b.p), when it crystallised prior to (32) as colourless rods. Epoxide (32) also crystallised from petrol as colourless rods. The allylic alcohols were inseparable, proton n.m.r of the mixture indicating a ratio (30) : (31) of 1 : 1.8 by integration of peaks at δ 5.79 , 4.24 . The spectroscopic properties were consistent with those of pure materials obtained by other means.

DISPIRO(BICYCLO[4.1.0]HEPTANE-7,2'-OXIRANE-3',1''-

(2''-HYDROXYCYCLOHEXANE)-(32)

Colourless rods (petrol 40-60 b.p) m.p. 81-84°C ;

$\nu_{\max}$ (DCM) 3550, 2934, 2858, 1448, 1073, 1035, 1004, and 860 cm^{-1} ;

δ_{H} (250 MHz ; CDCl_3) 1.0-2.2 (19H, m, all H except 2''-H) ,

3.78 (1H, dd, J 9.4 Hz, 4.7 Hz, 2''-H) ; δ_{C} (62.9 MHz ; CDCl_3)

11.74, 13.75 (C-1, C-6) , 19.99, 20.65 (C-3, C-4) , 21.87, 21.91 (C-2, C-5) ,

23.18 (C-4'') , 23.34 (C-5'') , 31.06 (C-6'') , 33.80 (C-3'') ,

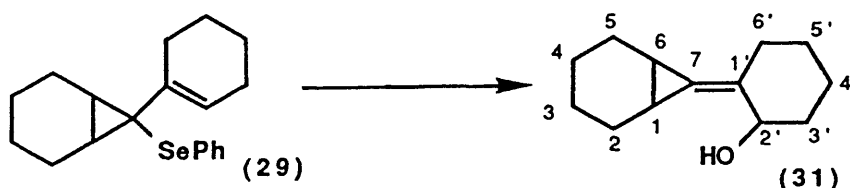
66.88 (C-7) , 68.27 (C-2'') , 68.39 (C-1'') ; m/z 208 (M^+), 190 ($\text{M}-\text{H}_2\text{O}$)

, 162 ($190-\text{C}_2\text{H}_4$ retro D.A), 148, 133, 126 (base), 111, , 98 ($\text{C}_6\text{H}_{10}\text{O}$), 81, 70, 41.

(Found : C, 74.97 ; H, 9.79 . $\text{C}_{13}\text{H}_{20}\text{O}_2$ requires : C, 74.96 ; H, 9.68 %)

DISPIRO(BICYCLO[4.1.0]HEPTANE-7,2' $_{\beta}$ -OXIRANE-3' $_{\beta}$,1''-(2'' $_{\beta}$,6'' $_{\beta}$ -DIHYDROXYCYCLOHEXANE) (33)

This minor artefact, colourless rods (petrol 40-60 b.p) m.p. 83-86°C, was identified solely on the basis of its X-ray crystal structure, and a weak M^+ at 224 as a contaminant of the epoxide (32)

17) OXIDATIVE REARRANGEMENT OF 7-(CYCLOHEXEN-1-YL)-7-PHENYLSELENO-BICYCLO[4.1.0]HEPTANE (29)

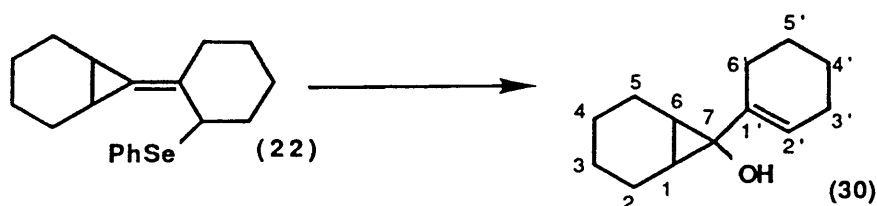
To a solution of the selenide (29) (949 mg, 2.87 mmol) in pyridine (20 ml), was added with stirring a 15% w/w solution of

H_2O_2 (14 ml, 20 equiv), and the mixture stirred 0.5 h. On dilution with ether (20 ml), the mixture was washed with 10% aq. HCl (2x40 ml), brine, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography of the residue (Silica-20% ether/petrol) afforded 7-(2-HYDROXYCYCLOHEXYLIDINE)-BICYCLO[4.1.0]HEPTANE (31)

(292 mg, 53%) as colourless needles, (petrol 40-60 b.p) m.p. 96-99°C

ν_{max} (CCl_4) 3604 (OH), 3470, 2934, 1705 (C=C), 1447, 1379, 1222, 1078, 1034, 1000, and 968 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 4.24 (1H, m, 2'H), 0.8-2.7 (19H, m, all other protons); δ_{C} (22.5 MHz; CDCl_3) 10.11, 12.74 (C-1, C-6), 21.03, 21.22 (C-3, C-4), 22.32, 22.68 (C-2, C-5), 23.35 (C-4'), 27.20 (C-5'), 30.25 (C-6'), 35.81 (C-3'), 71.75 (C-2'), 122.35 (C-7), 129.91 (C-1'); m/z 192 (M^+), 174 ($\text{M}-\text{H}_2\text{O}$), 163, 149, 145, 131, 109, 95 (C_7H_{11}), 81 (C_6H_9), 79 (C_6H_7), 67, 41; (Found: M^+ , 192.1516. $\text{C}_{13}\text{H}_{20}\text{O}$ requires: M^+ , 192.1514)

18)

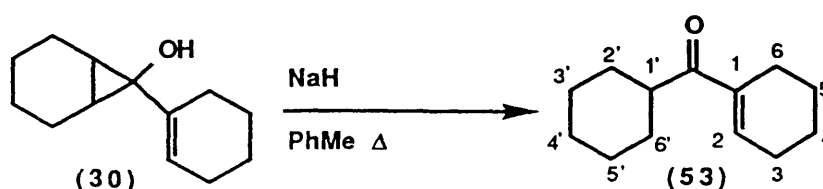
PREPARATION OF7-CYCLOHEXYNYL-7-HYDROXY-BICYCLO[4.1.0]HEPTANE (30)

To potassium t-butoxide (180 mg, 1.60 mmol) in dry DME (2.5 ml) and cyclohexene (2.5 ml) at -78°C was added a solution of 2-phenylselenocyclohexanone (21) (309 mg, 1.21 mmol) in DME (1 ml). To the mixture was added dropwise with stirring over 1 h DAMP (28) (320 mg, 1.8 mmol), when evolution of nitrogen occurred. The mixture was stirred a further 2 h at -78°C, and then quenched by

slow addition of saturated aqueous NH_4Cl (5 ml), and warming to ambient temperature. The mixture was poured into water, and extracted with petrol. After concentration at reduced pressure below room temperature, the crude selenide was taken up in THF:pyridine (3:1) (30 ml), chilled to -25°C (ice/acetone), and 30% aqueous hydrogen peroxide (0.75 ml, 6.6 mmol) added dropwise. After stirring 2 h at -25°C , the mixture was allowed to warm to room temperature, poured into water, and extracted with petrol. The extracts were dried (MgSO_4) and concentrated at reduced pressure, residual pyridine being removed at 0.1 torr. The residue was chromatographed (Silica -20% ether/petrol) to afford 7-(CYCLOHEXEN-1-YL)-7-HYDROXY-BICYCLO[4.1.0]HEPTANE (30)

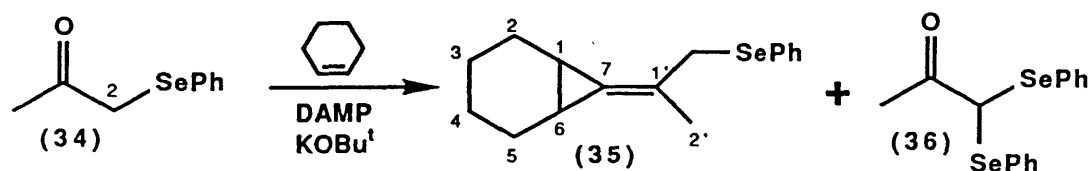
(138 mg, 58%) as colourless needles m.p. $95-98^\circ\text{C}$;
 ν_{max} (CCl_4) 3602(OH), 2934, 2856, 1448, 1379, 1222, 1187, 1078, 1034, and 967 cm^{-1} ; δ_{H} (250 MHz ; CDCl_3) 1.0-2.5 (18H, m, all aliphatic-H), 4.24 (1H, m, OH) , 5.79 (1H, m, 2'-H) ; δ_{C} (62.9 MHz ; CDCl_3) 20.49(C-3, C-4) , 21.28(C-2, C-5) , 21.71(C-1, C-6) , 22.26(C-4') , 22.93(C-5') , 25.25(C-3') , 26.22(C-6') , 63.21(C-7) , 128.69(C-2') , 136.08(C-1') ; m/z 192(M^+), 174($\text{M}-\text{H}_2\text{O}$), 146(174- C_2H_4 , retro D.A.), 131, 109, 91(tropylium), 81(C_6H_9), 41 .
 (Found : M^+ , 192.1516 . $\text{C}_{13}\text{H}_{20}\text{O}$ requires : M^+ , 192.1514)

19) OXY-ANION MEDIATED REARRANGEMENT OF
7-CYCLOHEXEN-1-YL-7-HYDROXY-BICYCLO[4.1.0]HEPTANE (30)



To a stirred slurry of sodium hydride (24 mg of 60% oil dispersion, 0.6 mmol, 2 equiv) in toluene (5 ml) was added a solution of vinyl cyclopropanol (30) (58 mg, 0.3 mmol) in toluene (15 ml), and the mixture stirred 45 min at room temperature. The mixture was then heated at reflux for 2.25 h, cooled, and cautiously quenched with saturated aqueous NH_4Cl . The organic layer was separated, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-10% ether/petrol) to afford CYCLOHEXYL CYCLOHEXENYL KETONE (53) (42 mg, 72%) as a colourless oil. ν_{max} (film) 2930, 2854, 1662, 1633, 1448, 1244, 1197, and 984 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.05–1.85 (14H, m, 2'-6'- H_2 , 4- H_2 , 5- H_2), 2.16 (4H, m, 3- H_2 , 6- H_2), 2.90 (1H, m, 1'-H), 6.83 (1H, m, 2-H); δ_{C} (62.9 MHz; CDCl_3) 21.69 (C-4, C-5), 22.12 (C-4'), 23.45 (C-3), 25.95 (C-3', C-5'), 26.06 (C-6), 29.80 (C-2', C-6'), 44.27 (C-1'), 138.25 (C-2), 138.40 (C-1), 204.80 (C=O); m/z 192 (M^+), 163, 109 ($\text{M}-\text{C}_6\text{H}_{11}$, base), 81 (109-CO), 55, 41. (Found: M^+ , 192.1516. $\text{C}_{13}\text{H}_{20}\text{O}$ requires: M^+ , 192.1514).

20)

PREPARATION OF7-(1-(PHENYLSELENOMETHYL)ETHYLIDENE)BICYCLO[4.1.0]HEPTANE (35)

To freshly sublimed potassium *t*-butoxide (526 mg, 4.7 mmol)

in DME (4 ml) and cyclohexene (6 ml) at -78°C was added a solution of DAMP (28) (876 mg, 4.9 mmol, 1.5 equiv) in DME (2 ml) dropwise with stirring. After 20 min, a solution of 2-phenylselenoacetone (678 mg, 3.18 mmol) in DME (5 ml) was added dropwise over 15 min, and the resulting mixture stirred at -78°C for 48 h with provision for venting of the nitrogen evolved. The mixture was allowed to warm to room temperature, poured into water, and extracted with petrol. The extracts were dried (Na_2SO_4), concentrated at reduced pressure, and chromatographed (Silica-5% ether/petrol) to afford

7-(1-(PHENYLSELENOMETHYL)ETHYLIDENE)-BICYCLO[4.1.0]HEPTANE (35)

(396 mg, 43%) as a pale yellow oil. ν_{max} (film) 2931, 2857, 1576, 1473, 1435, 1369, 1022, 895, 736, and 690 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.0–1.8 (10H, m, 1-H, 6-H, 2-5- H_2), 1.92 (3H, t, J 1.7 Hz, 1'-Me), 3.7 (2H, A:B q, J_{gem} 10.6 Hz, CH_2SePh), 7.23 (3H, m, m,p-Ar-H), 7.50 (2H, m, o-Ar-H); δ_{C} (62.9 MHz; CDCl_3) 12.92, 13.38 (C-1, C-6), 19.04 (C-2'), 21.33, 21.42 (C-3, C-4), 22.59, 22.68 (C-2, C-5), 33.06 (CH_2SePh), 120.87 (C-1'), 130.78 (C-7), 126.81, 128.65, 133.72 (p,m,o-ArC), 131.20 (SeCAr); m/z 292 (M^+), 157 (SePh), 135 (M-SePh), 131, 117, 91, 77, 41.

(Found: M^+ , 292.0729. $\text{C}_{16}\text{H}_{20}\text{Se}$ requires: M^+ , 292.0730).

Also in the product distribution were :-

DIPHENYLDISELENIDE,

2-PHENYLSELENOACETONE (34) ν_{max} (film) 3054, 2998, 1700, 1576, 1476, 1435, 1355, 1229, 738, and 690 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 2.22 (3H, s, Me), 3.54 (2H, s, CH_2SePh), 7.23 (3H, m, p-Ar), 7.46 (2H, o-Ar).

20) OPTIMISATION OF CONDITIONS FOR PREPARATION OF (20)

BASE	No. Equivs.	DAMP (Equivs)	CYCLOHEXENE ETHER RATIO	PHENYSELENO ACETONE (Equivs)	RXN CONCENT (M) (w.r.t ketone)	RXN Time/h	RXN Temp °C	ADDITIVE (Equivs)	YIELD (20)	METH
KO Bu ^t	1.1	1	1 : 2.8 THF	1	0.17	16	-78	-	22	a
KO Bu ^t	1.1	1.2	1 : 2.0 THF	1	0.16	24	-78	-	-	b
KO Bu ^t	1.1	1	1 : 4.5 THF	1	0.18	16	-78	-	7	c
n'BuLi	1.1	1.1	1 : 1.2 DME	1	0.08	16	-78	-	-	c
KH/+OH	1.5	1.5	1 : 1.8 DME	1	0.18	2.5	-78	-	22	c
KH/+OH	2.1	2.9	1 : 1.6 DME	1	0.08	2.5	-78	BF ₃ Et ₂ O (0.1 eq)	7	d
KH/+OH	3.4	4.5	1 : 1.6 DME	1	0.07	16	-78	-	42	c
KH/+OH	1.7	2.2	1 : 3 THF	1	0.11	24	-78	-	-	b
KH/+OH	1.7	2.4	1 : 2 THF	1	0.11	3	-60	-	13	c
KH/+OH	1.2	1.3	1 : 2.4 DME	1	0.17	1	-50	-	19	c
KH/+OH	2.8	2.6	1 : 1.4 DME	1	0.11	1	-55	-	26	c
KH/+OH/ ZnCl ₂	1.2	1.2	1 : 2 DME	1	0.14	24	-78	ZnCl ₂	0	c
CPrMgCl	1.1	1.3	1 : 1.8 THF	1	0.17	7.5	-78	-	11	c
n BuLi	1.2	1.7	1 : 2 THF	1	0.08	1	-78	ZnCl ₂ (1.3)	-	d

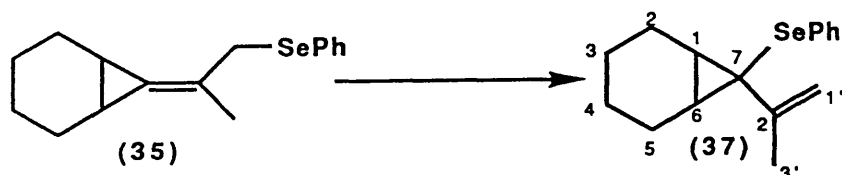
BASE	No. Equivs.	DAMP (Equivs)	CYCLOHEXENE/ETHER RATIO	PHENYSELENO ACETONE (Equivs)	RXN CONCENT (M) (w.r.t ketone)	RXN Time/h	RXN Temp °C	ADDITIVE (Equivs)	YIELD (20)	METHOD
KOBu ^t	1.5	1.6	1 : 8 DME	1	0.19	48	-78		43	c
KOBu ^t	1.5	1.2	1 : 7 DME	1	0.20	6	-78		18	e
nBuLi	1.2	1.3	1 : 2 THF	1	0.10	5	-78	CeCl ₃ (1.2)	4	f
KH-18-C- 6CeCl ₃	1.8	2.0	1 : 1.8 DME	1	0.14	1.5	-78	CeCl ₃ (1.0)	15	c
KH-18-C	1.9	2.0	1 : 1.8 DME	1	3.3	44	-78		64	c
KH-CeCl ₃	3.2	3.3	1 : 1.2 DME	1	0.1	18	-78		36	c

Method: (a) Base added to a mixture of ketone, damp and olefin
 (b) Damp anion added to ketone and olefin
 (c) Ketone added to mix of base, damp and olefin
 (d) L.A. then ketone added to mix of base, damp and olefin
 (e) Damp added to mix base, ketone olefin
 (f) Li anion of damp added to CeCl₃/olefin, ketone added last

2,2-DIPHENYLSELENOACETONE (36) $\nu_{\max}$ (film) 3053, 1695, 1473, 1435, 1352, 1238, 1216, 1021, 740, and 690 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 2.32 (3H, s, Me), 4.95 (1H, s, $\text{CH}(\text{SePh})_2$), 7.25 (6H, m, m, p-Ar), 7.52 (4H, m, o-Ar).

aldol products were not detected

21) ALLYL SELENIDE REARRANGEMENT OF
7-(PHENYLSELENOMETHYLETHYLIDENE)NORCARANE (35)

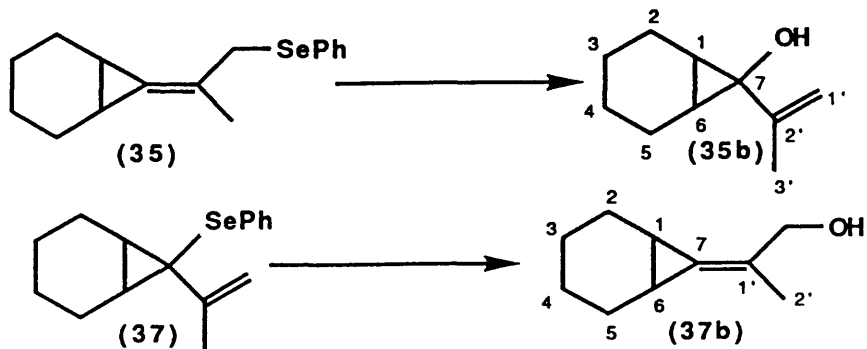


Facile allyl selenide rearrangement occurred on standing, or if the reaction mixture was allowed to stand at room temperature for any length of time prior to workup. The

7-PHENYLSELENO-7-(PROPEN-2-YL)BICYCLO[4.1.0]HEPTANE (37) was obtained in quantitative yield when a concentrated solution was stored at 4°C for prolonged periods, as a pale yellow oil.

$\nu_{\max}$ (film) 2934, 2857, 1474, 1446, 895, and 736 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.5-2.0 (10H, m, 1-H, 6-H, 2-5- H_2), 1.93 (3H, s, C-2'-Me), 4.55 (1H, m, 1'- H_1), 4.85 (1H, m, 1'- H_1), 7.02 (3H, m, m, p-ArH), 7.32 (2H, m, o-Ar); δ_{C} (22.5 MHz; CDCl_3) 21.28 (C-2, 3, 4, 5), 22.19 (C-1, C-6), 23.41 (C-2'-Me), 36.05 (C-7), 116.55 (C-1'), 141.94 (C-2'), 127.23, 128.57, 134.18 (o, m, p-ArC), 131.39 (SeCAr); m/z 292 (M^+), 157 (SePh), 135 (M-SePh), 131, 117, 107, 93, 91, 79, 77, 55.

(Found: M^+ , 292.0734. $\text{C}_{16}\text{H}_{20}\text{Se}$ requires: M^+ , 292.0730).

22) OXIDATIVE REARRANGEMENT OF ALLYL SELENIDES (35) AND (37)

To a solution of mixed allyl selenides (35) and (37) (304 mg, 1.04 mmol) in pyridine (5 ml) at 0°C, was added dropwise with stirring 15% aqueous hydrogen peroxide (4 ml, 17.5 mmol) over 1 min. After stirring an additional 30 min at room temperature, the mixture was diluted with ether, washed with water, and concentrated at reduced pressure. Residual pyridine was removed at 0.1 torr. The residue was chromatographed (Silica-20% ether/petrol) to afford the transposed allylic alcohols (37b) (80.3 mg, 50.7%) and (35b) (12 mg 7.6%), combined yield 58%, as colourless oils.

7-(1-HYDROXYMETHYLETHYLIDENE)-BICYCLO[4.1.0]HEPTANE (37b)

$\nu_{\max}$ (DCM) 3600, 2930, 2856, 1445, 1378, 1054, 1000, and 969 cm^{-1} ;

δ_{H} (250 MHz; CDCl_3) 1.05–1.90 (11H, m, 1-H, 6-H, 2-5-H₂, OH),

1.81 (3H, t, J 1.5 Hz, C-1'-Me), 4.17 (2H, br. s, CH_2 -OH);

m/z 151 ($\text{M}^+ - \text{H}$), 137 (M-Me), 134 (m-H₂O), 119 (134-Me), 109, 95, 93, 91, 81, 67, 55, 41.

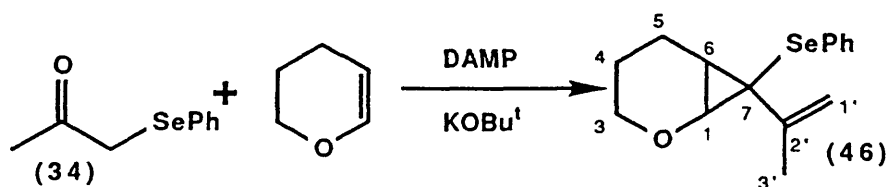
(Found: $\text{M}^+ - \text{H}$, 151.1123. $\text{C}_{10}\text{H}_{16}\text{O}$ requires $\text{M}^+ - \text{H}$, 151.1123).

7-HYDROXY-7-(PROPEN-2-YL)-BICYCLO[4.1.0]HEPTANE (35b)

$\nu_{\max}$ (DCM) 3575, 2934, 2858, 1447, 1202, 1178, 1073, and 913 cm^{-1}

δ_H (250 MHz ; $CDCl_3$) 1.0-1.9 (11H,m,1-H,6-H,2-5- H_2 ,OH) ,
 1.84 (3H,t, J 1.1Hz,C-2'-Me) , 5.03 (2H,t,J 1.1Hz,1'- H_2) ;
 m/z 151(M^+ -H),137(M-Me),135(M-OH),119,111(M- C_3H_5),109,95(C_7H_{11}),
 91,81,69,55,43(base),41(C_3H_5).
 (Found : M^+ -H,151.1123 . $C_{10}H_{16}O$ requires : M^+ -H,151.1123).

23)

PREPARATION OF7-PHENYLSELENO-7-(PROPEN-2-YL)-2-OXABICYCLO[4.1.0]HEPTANE (46)

To a solution of potassium *t*-butoxide (900 mg,8.0 mmol) in DME (10 ml) at $-60^{\circ}C$ was added dihydropyran (5 ml,55 mmol). On cooling to $-70^{\circ}C$ DMP (28) (1.60 g,8.99 mmol) was added dropwise. After stirring for 2.5 h, 2-phenylselenoacetone(34) (400 mg,1.87 mmol) was added dropwise over 5 min. After stirring at $-78^{\circ}C$ for 18 h, the reaction was warmed to room temperature poured into water ,extracted with ether, dried(Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-5% ether/petrol), to afford exclusively

7-PHENYLSELENO-7-(PROPEN-2-YL)-2-OXABICYCLO[4.1.0]HEPTANE (46)

(161 mg,28%) as a low melting pale yellow solid (m.p. $<23^{\circ}C$)
 ν_{max} (film) 2954,2857,1474,1436,1232,1147,1072,1022,884,738,
 and 690 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.30 (1H,m,4- H_{1ax}) ,
 1.44 (1H,m,4- H_{1eq}) , 1.60 (1H,m,6-H) , 1.92 (2H,m,5- H_2) ,

1.95 (3H,t,J 1.3Hz,C-2'-Me) , 3.25 (1H,,ddd,J 11,11,2.6Hz,3-H_{1ax})
 3.60 (1H,dt,J 11,3.6Hz,3-H_{1eq}) , 3.90 (1H,d,J 7.6Hz,1-H) ,
 4.68 (1H,m,1'-H₁) , 4.88 (1H,m,1'-H₁) , 7.27 (3H,m, m,p-Ar) ,
 7.52 (2H,m, o-Ar) , assignments checked by decoupling expts. ;
 δ_C (62.9 MHz ; CDCl₃) 18.34(C-5,t) , 21.66(C-2'-Me,q) , 21.89(C-4) ,
 23.42(C-6,d) , 34.58(C-7,s) , 60.92(C-1,d) , 64.06(C-3,t) ,
 116.87(C-1',t) , 141.81(C-2',s) , 127.67,128.70,134.6(o,m,p-ArC) ,
 130.25(Se-CAr,s) ; m/z 294(M⁺),157(SePh),137(M-SePh),93(C₆H₆O) ,
 79,67,41(C₃H₅) .

(Found : M⁺,294.0536 . C₁₅H₁₈OSe requires : M⁺,294.0523).

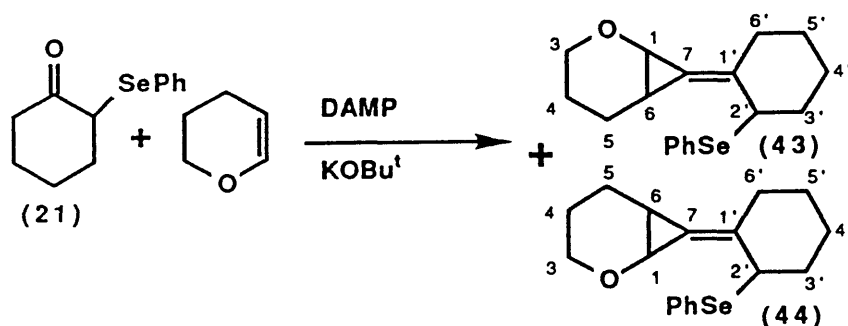
In addition a mixture of starting ketone and

2,2-diphenylselenoacetone (36) (152 mg) was recovered.

24)

PREPARATION OF cis,trans

7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-2-OXABICYCLO[4.1.0]HEPTANE (43) (44)



To potassium hydride (400 mg of 35% oil dispersion, washed with ether,3.6 mmol) suspended in DME (4 ml) at -78^oC was added dihydropyran (5 ml,55 mmol), and t-butanol(200 μ L,2.12 mmol) with stirring.A solution of 2-phenylselenocyclohexanone (660 mg,2.6 mmol) in DME (2 ml) was prepared, and 0.8 ml added to the reaction mixture, followed by a solution of DAMP (28) (660 mg,3.7 mmol), in DME (3 ml) dropwise over 30 min, with the rest of the ketone

solution being added after 15 min. Evolution of nitrogen was observed from the bright yellow solution. The mixture was stirred at -78°C for a further 4h, quenched by cautious dropwise addition of saturated aqueous NH_4Cl (5 ml), and allowed to warm to room temperature. The mixture was extracted from water with ether, the extracts dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-3% ether/petrol), to afford *cis,trans* 7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-2-OXABICYCLO[4.1.0]HEPTANE (43) and (44) in ~2:1 ratio. (combined yield 863 mg, 99%)

(26)

δ_{H} (250 MHz ; CDCl_3) 0.8-2.4 (12H, m, 4- H_2 , 5- H_2 , 6-H, 3'-5'- H_2 , 6- $\text{H}_{1\text{ax}}$) , 2.65 (1H, m, 6- $\text{H}_{1\text{eq}}$) , 3.01 (1H, dd, J 7.5, 1.9 Hz, 1-H) , 3.25 (1H, m, 3- $\text{H}_{1\text{ax}}$) , 3.52 (1H, dt, J 11, 3.8 Hz, 3- $\text{H}_{1\text{eq}}$) , 4.47 (1H, m, 2'-H) , 7.2 (3H, m, m,p-ArH) , 7.47 (2H, m, o-ArH)

(27)

δ_{H} (250 MHz ; CDCl_3) 0.8-2.8 (13H, m, 4- H_2 , 5- H_2 , 6-H, 3'-6'- H_2 , 6- H_1) , 3.27 (1H, m, 3- $\text{H}_{1\text{ax}}$) , 3.53 (1H, m, 3- $\text{H}_{1\text{eq}}$) , 3.68 (1H, d, J 7.7 Hz, 1H) , 4.32 (1H, m, 2'-H) , 7.2 (3H, m, m,p-Ar) , 7.54 (2H, m, o-ArH)

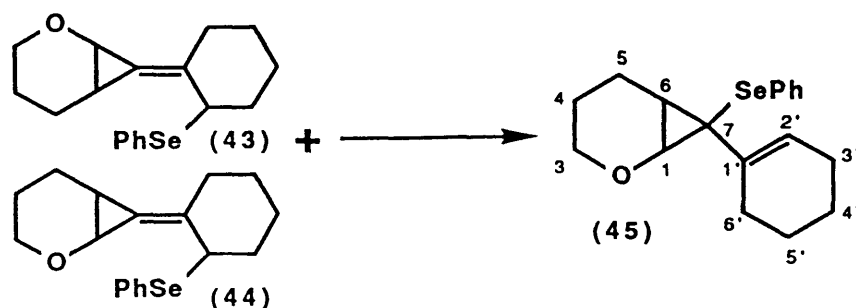
mixture

δ_{C} (62.9 MHz ; CDCl_3) 11.12, 13.47 (C-6) , 48.29, 48.88 (C-1) , 49.09 (C-2') , 63.44 (C-3) , 120.97, 121.79, 132.37, 133.43, (C-7, C-1') ; m/z 334 (M^+), 177 (M-SePh, base), 159, 133, 108, 91, 84, 79, 41.

(Found : M^+ , 334.0841 . $\text{C}_{18}\text{H}_{22}\text{OSe}$ requires : M^+ , 334.0836).

Stereochemistry was not determined.

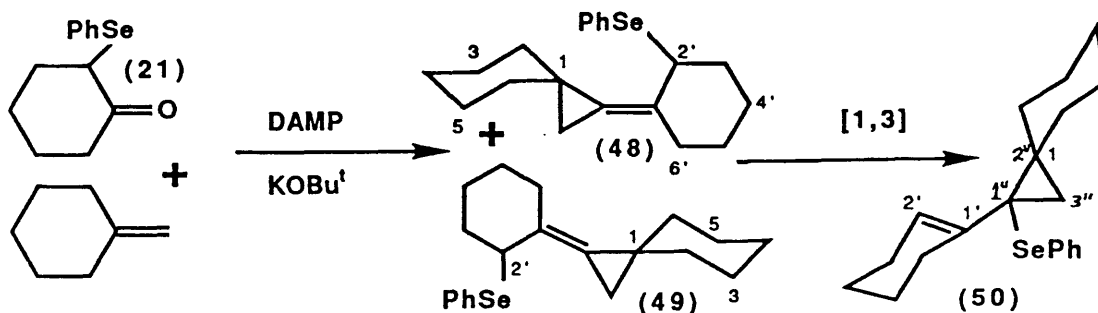
25)

ALLYL SELENIDE REARRANGEMENT OF7-(2-PHENYLSELENOCYCLOHEXYLIDENE)-2-OXABICYCLO[4.1.0]HEPTANE(43) & (44)

Facile allyl selenide rearrangement occurred cleanly and quantitatively on standing, or under the reaction conditions for preparing the alkylidene cyclopropane if allowed to stand for any length of time at room temperature prior to workup, to afford 7-CYCLOHEXYNYL-7-PHENYLSELENO-2-OXABICYCLO[4.1.0]HEPTANE (45) as a pale yellow oil. $\nu_{\max}$ (film) 2926, 2853, 1434, 1136, 1072, 1016, 736, and 691 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.2-2.4 (13H, m, 4- H_2 , 5- H_2 , 6-H, 3'-6'- H_2), 3.25 (1H, ddd, J 10.7, 10.7, 3.0 Hz, 3- $\text{H}_{1\text{ax}}$), 3.57 (1H, dt, J 10.7, 3.6 Hz, 3- $\text{H}_{1\text{eq}}$), 3.87 (1H, d, J 7.4 Hz, 1-H), 5.30 (1H, m, 2'-H), 7.27 (3H, m, m, p-ArH), 7.50 (2H, m, o-ArH); δ_{C} (62.9 MHz; CDCl_3) 18.66 (C-5, t), 22.08, 22.45 (C-4, C-5'), 23.07 (C-6, d, -ve), 23.18 (C-4'), 25.68 (C-3', t), 27.33 (C-6', t), 35.27 (C-7, s), 60.82 (C-1, d, discont), 64.12 (C-3, t), 129.03 (C-2'), 133.93 (C-1'), 127.61, 128.43 (m, p-ArC), 135.28 (o-ArC), 130.31 (Se-Ar); m/z 334 (M^+), 253 ($\text{M}-\text{C}_6\text{H}_9$), 177 ($\text{M}-\text{SePh}$), 159, 133, 105, 91, 79, 41.

(Found : M^+ , 334.0841. $\text{C}_{18}\text{H}_{22}\text{OSe}$ requires : M^+ , 334.0836).

26) REACTION OF METHYLENECYCLOHEXANE WITH
2-PHENYLSELENOCYCLOHEXANONE



To a suspension of potassium hydride (425 mg, 3.7 mmol) in DME (3 ml), and dry methylenecyclohexane (2.5 ml, 21 mmol) was added *t*-butanol (200 μ L, 2.1 mmol), and the mixture was cooled to -78°C . A solution of DAMP (28) (800 mg, 4.49 mmol) in DME (0.5 ml) was added dropwise with stirring. The mixture was stirred for 10 min then 2-phenylselenocyclohexanone (511 mg, 2.03 mmol) in DME (1 ml) was added dropwise over 15 min when the yellow solution became orange and nitrogen was evolved. The mixture was stirred at -78°C for 14 h then allowed to warm to -40°C before quenching by cautious addition of saturated aqueous NH_4Cl (5 ml). The mixture was poured into water, extracted with ether, and the extracts dried (Na_2SO_4). After concentration at reduced pressure, the residue was chromatographed (Silica-2% ether/petrol) to afford a mixture of allylic selenides (48), (49) and (50), (448 mg, 65%) as a pale yellow oil. The ratio was determined to be (48):(49):(50) 1:3:4.4 by ^1H n.m.r integration of the 2'-H of each species at 4.46, 4.33, and 5.12 ppm respectively.

δ_{H} (250 MHz; CDCl_3) 0.08-2.8 (20H, m, all other aliphatics!), 4.33 (0.36H, m, CH-SePh, assigned as (49) on basis of expected major isomer), 4.46 (0.12H, m, CH-SePh, isomer (48)),

5.12 (0.52H,m,2'-H,isomer (50)) , 7.22 (3H,m, m,p-ArH) ,

7.5 (2H,m,o-ArH) ; δ_C (62.9 MHz ; $CDCl_3$)

49.48,49.67(C-2',(48),(49)) , 65.71(C-2',(50))

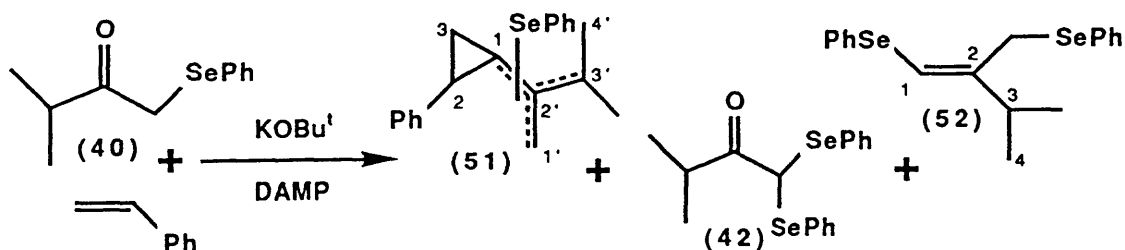
m/z 346(M^+), 189(M-SePh base), 157(SePh), 121, 107(189-

C_6H_{10}), 95, 91, 79, 67, 55, 41 .

(Found : M^+ , 346.1206 . $C_{20}H_{26}Se$ requires : M^+ , 346.1200)

27)

REACTION OF STYRENE WITH
PHENYLSELENOMETHYL ISOPROPYL KETONE (40)



To a suspension of potassium hydride (430 mg of 35% oil dispersion, washed ether, 3.76 mmol) in DME (4 ml) and styrene (5 ml, 44 mmol) at $-70^{\circ}C$ was added *t*-butanol (200 μ L, 2.12 mmol), followed by a solution of DAMP (28) (890 mg, 5 mmol), in THF (2 ml) dropwise over 5 min, and the mixture cooled to $-78^{\circ}C$. After stirring an additional 0.5 h a solution of seleno-ketone (40) (486 mg, 2.01 mmol) in DME (3 ml) was added dropwise over 0.5 h. The mixture was stirred 48 h at $-78^{\circ}C$ with provision for venting the nitrogen evolved, then allowed to warm to room temperature. After cautious addition of saturated aqueous NH_4Cl (5 ml), the mixture was diluted with ether, poured into water, and extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. The styrene was removed at 0.1

torr, and the residue chromatographed (Silica-3% ether/petrol) to afford in order of elution :- diphenyldiselenide (44 mg), cyclopropyl selenide (51) (13 mg contaminated with DPDS and (52)), vinyl selenide (52) (127 mg) as a pale yellow oil, and a mixture of mono and diselenated ketones (250 mg, 51% by wt. of starting material).

1-(3-METHYL-BUT-1-EN-2-YL)-2-PHENYL-1-PHENYLSELENOCYCLOPROPANE
& 1-(1-METHYL-BUT-2-EN-3-YL)-2-PHENYL-1-PHENYLSELENOCYCLOPROPANE (51)

Present as trace contaminants of the vinyl selenide (52) in the mass spectrum.

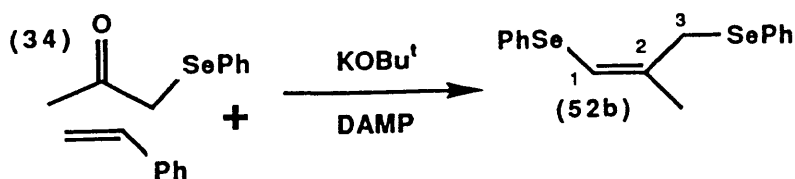
(Found : M^+ , 342.0877 . $C_{20}H_{22}Se$ requires : M^+ , 342.0886)

3-METHYL-1-PHENYLSELENO-2-(PHENYLSELENOMETHYL)-BUT-1-ENE (52)

ν_{max} (film) 3055, 2959, 2927, 2868, 1576, 1474, 1435, 1072, 1022, 808, 736, 690, and 668 cm^{-1} ; δ_H (250 MHz ; $CDCl_3$) 1.10 (6H, d, J 7Hz, Me) , 2.63 (1H, hept, J 7Hz, 3-H) , 3.84 (2H, s, $\underline{CH_2}$ -SePh) , 6.35 (1H, s, 1-H) 7.25 (6H, m, m,p-ArH) , 7.38 (2H, m, o-ArH) , 7.60 (2H, m, o-ArH) ; δ_C (62.9 MHz ; $CDCl_3$) 22.05 (Me, q) , 31.04 ($\underline{CH_2}$ -SePh, t) , 34.97 (C-3, d) , 116.55 (C-1, d) , 126.66, 127.26, 128.91, 129.05, 131.49, 133.92 (o, m, p-ArC, d) , 130.69, 131.93 (SeCAr) , 148.63 (C-2, s) ; m/z 396 (M^+), 239 (M-SePh), 206, 185, 157 (SePh), 143, 129, 115, 105, 91, 77, 58, 43 (C_3H_7 , base), 41.

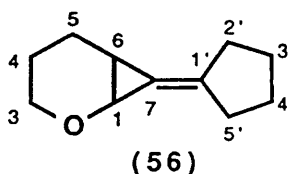
Selenium isotope pattern does not allow accurate mass measurement with available instrumentation. Analysis is precluded by tendency to extrude DPDS. The geometry of (52) was not determined.

28) REACTION OF STYRENE WITH 2-PHENYLSELENOACETONE (34)



Under reaction conditions analogous to those reported above, 2-phenylselenoacetone reacted in the presence of styrene and DAMP (28) to afford 2-METHYL-1,3-DI(PHENYLSELENO)-PROP-1-ENE (52b) m/z 368(M^+), 211(M -SePh), 209, 157(SePh), 130, 91, 77, 51 ; δ_H (250 MHz ; CDCl₃) 2.0 (3H, d, J 1.4 Hz, C-2 Me) , 3.80 (2H, s, 3-H₂) , 6.25 (1H, d, J 1.4 Hz, 1-H) , 7.2-7.65 (10H, m, Ar) .

29)

PREPARATION OF7-CYCLOPENTYLIDENE-2-OXABICYCLO[4.1.0]HEPTANE (56)

To a suspension of potassium hydride (800 mg of a 35% oil dispersion, washed with ether, 7.0 mmol) in DME (5 ml) at -78°C was added a solution of cyclopentanone (420 mg, 5 mmol) in dihydropyran (5 ml, 55 mmol), followed by DAMP (28) (1.62 g, 8 mmol) dropwise with stirring, when gas evolution occurred. The reaction was stirred at -78°C for 18h, warmed to room temperature, poured into saturated aqueous NH_4Cl , and extracted with ether. The extracts were dried (MgSO_4), concentrated at reduced pressure and the residue chromatographed, (Silica-27 ether/petrol(30-40 b.p)),

to afford 7-CYCLOPENTYLIDENE-2-OXABICYCLO[4.1.0]HEPTANE (56)

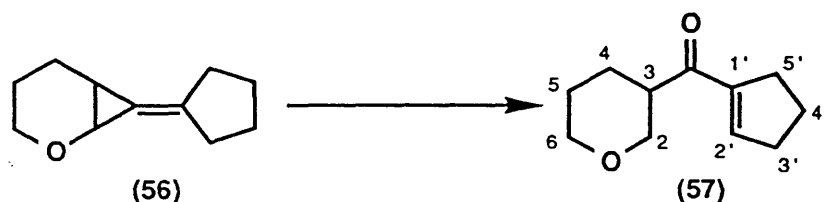
(247 mg, 30%) as a colourless aromatic oil.

$\nu_{\max}$ (film) 2953, 2860, 1450, 1432, 1226, 1192, 1139, 1106, 1063, and 845 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.85 (1H, m, 6-H), 1.0–2.0 (8H, m, 4-H₂, 5-H₂, 3'-H₂, 4'-H₂), 2.3 (4H, m, 2'-H₂, 5'-H₂), 3.4 (2H, m, 3-H₂), 3.82 (1H, m, 1-H); δ_{C} (22.5 MHz; CDCl_3) 14.5 (C-6, d), 19.64 (C-5, t), 22.56 (C-4, t), 26.71 (C-3', C-4', t), 31.22 (C-5', t), 32.2 (C-2'), 49.80 (C-1, d), 63.85 (C-3, t), 116.21 (C-1', s), 136.71 (C-7, s); m/z 164 (M^+), 136, 107, 97 ($\text{M}-\text{C}_5\text{H}_7$), 91, 85, 79, 67 (C_5H_7), 57, 41. (Found: M^+ , 164.1200. $\text{C}_{11}\text{H}_{16}\text{O}$ requires: M^+ , 164.1201).

30)

SINGLET OXYGENATION OF

7-CYCLOPENTYLIDENE-2-OXABICYCLO[4.1.0]HEPTANE (56)



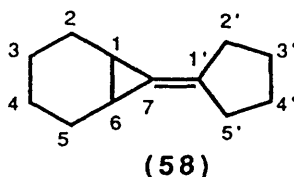
Dry oxygen was passed through a solution of the alkylidenecyclopropane (56) (168 mg, 1.02 mmol) and meso-tetraphenylporphrin (4 mg) in benzene (20 ml), whilst irradiating with a 650 W tungsten-halogen lamp for 3 h. On cooling in ice, triphenylphosphine (280 mg, 1.07 mmol) in ether (10 ml) was added, and the mixture stirred 1.5 h. The solvents were stripped at reduced pressure, and the residue chromatographed (Silica-15% ether/petrol) to afford

3,4-DIHYDRO-2H-PYRAN-3-YL (1-CYCLOPENTENYL) KETONE (57)

(77 mg, 42%) the only isolable product, as a colourless oil.

$\nu_{\max}$ (film) 2950, 1618 (s, br), 1388, 1343, 1304, 1266, 1230, 1173, 996, 937, 754, and 729 cm^{-1} ; δ_{H} (90 MHz ; CDCl_3) 1.8 (4H, m, 5- H_2 , 4'- H_2) , 2.4 (6H, m, 4- H_2 , 5'- H_2 , 3'- H_2) , 4.03 (2H, t, J 5.4 Hz, 6- H_2) , 6.14 (1H, m, 2'-H) , 7.48 (1H, s, 2-H) : δ_{C} (22.5 MHz ; CDCl_3) 18.41 (C-4) , 20.91 (C-5) , 22.56 (C-4') , 32.81, 33.49 (C-3', C-5') , 66.87 (C-6) , 116.73 (C-3) , 138.82 (C-2') , 143.65 (C-1') , 157.80 (C-2) , 193.14 (C=O) ; m/z 178 (M^+), 150, 122, 111 ($\text{M}-\text{C}_5\text{H}_7$) , 95 ($\text{M}-\text{C}_5\text{H}_7\text{O}$), 83, 67, 41, 28 .
(Found : M^+ , 178.0990 . $\text{C}_{11}\text{H}_{14}\text{O}_2$ requires : M^+ , 178.0994).

31) PREPARATION OF 7-CYCLOPENTYLIDENE-BICYCLO[4.1.0]HEPTANE (58)



To a solution of potassium *t*-butoxide (672 mg, 6 mmol) in DME (7 ml) and cyclohexene (7 ml) at -78°C was added cyclopentanone (0.5 g, 6 mmol), followed by DAMP(28) (1.09 g, 6.1 mmol) dropwise with stirring. The mixture was stirred at -78°C for 4 h when gas evolution ceased. On warming to room temperature the mixture was poured into water, and extracted with petrol (30-40 b.p). The extracts were dried (MgSO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-2% ether/petrol(30-40 b.p)),

to afford 7-CYCLOPENTYLIDENE-BICYCLO[4.1.0]HEPTANE (58)

(863 mg, 89%) as a colourless oil. $\nu_{\max}$ (film) 2930, 2834, 1449, 1340,

1328, 1170, 940, 845, and 690 cm^{-1} ; δ_{H} (90 MHz; CDCl_3)

0.90 (2H, m, 1-H, 6-H), 1.2 (4H, m, 3-H₂, 4-H₂),

1.70 (8H, m, 2-H₂, 5-H₂, 3'-H₂, 4'-H₂), 2.3 (4H, m, 2'-H₂, 5'-H₂);

δ_{C} (22.5 MHz; CDCl_3) 12.86 (C-1, C-6), 21.52 (C-3, C-4),

22.26 (C-2, C-5), 26.71 (C-3', C-4'), 31.23 (C-2', C-5'), 120.51 (C-1')

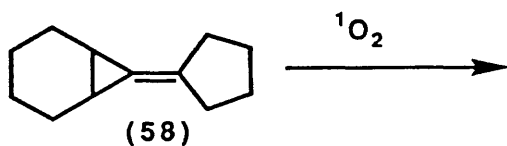
130.89 (C-7); m/z 162 (M^+), 147, 133, 119, 105, 91, 79, 67 (C_5H_7).

(Found: M^+ , 162.1406. $\text{C}_{12}\text{H}_{18}$ requires: M^+ , 162.1408).

32)

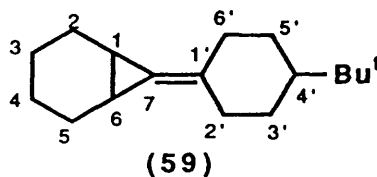
SINGLET OXYGENATION OF

7-CYCLOPENTYLIDENE-BICYCLO[4.1.0]HEPTANE (58)



Singlet oxygenation of (58) by the method described in experiment (30) resulted in reaction of the starting material. After triphenylphosphine workup, evaporation and flash chromatography as before only 20% of the mass was recovered, as a mixture of several compounds, none of which proved to be the expected ketone by mass spectroscopy. Further identification was not pursued.

33)

SYNTHESIS OF7-(4-*t*-BUTYLCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (59)

To a solution of potassium *t*-butoxide (725 mg, 6.5 mmol) in DME (7 ml) and cyclohexene (7 ml, 69 mmol) at -78°C was added a solution of 4-*t*-butyl-cyclohexanone (926 mg, 6 mmol) in DME (1 ml), followed by DAMP (28) (1.09 g, 6.12 mmol) dropwise with stirring when gas was evolved. The mixture was allowed to warm to -70°C , and stirred a further 2 h before warming to room temperature. The reaction was poured into water and extracted with petrol. The extracts were dried (MgSO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-2% ether/petrol) to afford 7-(4-*t*-BUTYLCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (59)

(996 mg, 67%) as a colourless solid . m.p. $63-65^{\circ}\text{C}$;

ν_{max} (CCl_4) 2938, 2856, 1479, 1442, 1364, 1240, and 1187 cm^{-1} ;

δ_{H} (90 MHz ; CDCl_3) 0.88 (9H, s, *t*Bu) , 1.0-2.7 (19H, m, all other H) ;

δ_{C} (22.5 MHz ; CDCl_3) 12.37 (C-1, C-6, -ve) , 21.52 (C-3, C-4) ,

22.99 (C-2, C-5) , 27.69 (Me_3C) , 28.48, 28.91 (C-3', C-5') ,

32.81, 33.12 (C-2', C-6') , 48.32 (C-4') , 135.22, 135.35 (C-7, C-1') ;

m/z 232 (M^+) , 217 (M-Me) , 175 (M-*t*Bu, base) , 161, 147, 133, 123, 107, 93, 79, 67, 57 (*t*Bu).

(Found : C, 87.60 ; H, 12.26 . $\text{C}_{17}\text{H}_{28}$ requires : C, 87.86 ; H, 12.14 %)

34)

SINGLET OXYGENATION OF7-(4-*t*-BUTYLCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (59)

Dry oxygen was passed through a solution of the olefin (59) (95.5 mg, 0.38 mmol), and meso-tetraphenylporphyrin (4 mg) in dry benzene (5 ml) and pyridine (50 μ L, 0.62 mmol), whilst irradiating with a 650 W tungsten halogen lamp for 10 h, further portions of benzene being added periodically to maintain concentration. The mixture was chilled to 4 $^{\circ}$ C and a solution of triphenylphosphine (150 mg, 0.57 mmol, 1.5 eq) in ether (5 ml) was added. After standing 12 h at 4 $^{\circ}$ C, the solvent was stripped at reduced pressure, and the residue chromatographed (Silica-gradient 0-5% ether/petrol), to afford in order of elution, triphenylphosphine (126 mg), and a number of products of total mass 45 mg.

No 4-*t*-butyl-cyclohexanone was observed by t.l.c. The major product (20 mg), a colourless oil was identified as

(4-*t*-BUTYL-1-CYCLOHEXENYL) 1-CYCLOHEXENYL KETONE (60)

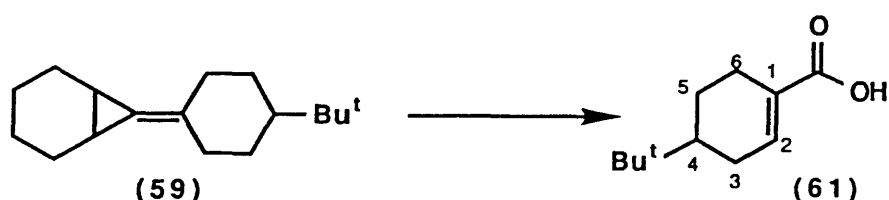
ν_{max} (film) 2941, 2866, 1630 (s, br), 1365, 1249, 919, and 733 cm^{-1} ;
 δ_{H} (90 MHz ; CDCl_3) 0.88 (9H, s, Me_3C) , 1.0-2.7 (15H, m, all other H) ,
 6.42 (2-H, m, 2-H, 2'-H) ; δ_{C} (22.5 MHz ; CDCl_3) 21.77, 22.13 (C-4', C-5')
 23.60 (C-3') , 24.33 (C-6) , 25.67 (C-6') , 25.86 (C-3) , 27.14 (Me_3C) ,
 27.50 (C-5) , 32.14 (Me_3C) , 43.62 (C-4) , 138.09, 138.34 (C-1, C-1') ,
 138.70, 139.19 (C-2, C-2') , 199.73 (C=O) ; m/z 246 (M^+), 231 (M-Me) ,
 218 (M-28, retro D.A), 189 (M- ^tBu), 162 (M-84, retro D.A), 133, 109 ($\text{C}_7\text{H}_9\text{O}$) ,

84,81,57(^tBu) .

Derivative 2,4-dinitrophenylhydrazone m.p. 144-146°C.

(Found : M^+ , 426.2239 . $C_{23}H_{30}O_4N_4$ requires M^+ , 426.2267).

35) LOW TEMPERATURE SINGLET OXYGENATION REACTION OF
7-(4-*t*-BUTYLCYCLOHEXYLIDENE)-BICYCLO[4.1.0]HEPTANE (59)



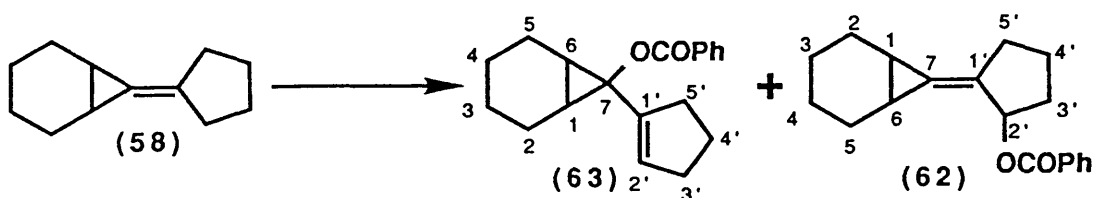
Dry oxygen was passed through a solution of the olefin (59) (68.5 mg, 0.28 mmol) and tetraphenylporphyrin (4 mg) in toluene (4.5 ml) at -78°C whilst irradiating with a 650 W tungsten-halogen lamp for 18 h. (The reaction vessel is immersed in acetone/CO₂, contained in a non-silvered dewar). A solution of triphenylphosphine (80 mg, 0.304 mmol, 1.1 eq) in toluene (2 ml) at -78°C was then added, the mixture agitated for 0.5 h, then allowed to warm to room temperature. The solvent was stripped at reduced pressure, and the residue chromatographed (Silica-100% ether), to afford in addition to recovered olefin (7 mg), 4-*t*-BUTYL-1-CYCLOHEXENE CARBOXYLIC ACID (61) (33 mg, 65%) as colourless plates (hexane) m.p. 189-191°C ; $\nu_{\max}$ (film) 2953, 2925, 2852, 1675, 1639, and 1274 cm⁻¹ ; δ_H (90 MHz ; CDCl₃) 0.92 (9H, s, Me₃C) , 0.9-2.8 (8H, m, OH, 3-H₂, 4-H, 5-H₂, 6-H₂) , 7.13 (1H, m, 2-H) ; δ_C (22.5 MHz ; CDCl₃) 23.54 (C-3) , 25.25 (C-6) , 27.08 (Me₃C) , 27.75 (C-5) , 32.08 (Me₃C) , 43.25 (C-4) , 129.67 (C-1) , 142.85 (C-2) , 172.82 (CO₂H) ; m/z 182 (M^+) , 167 (M-Me) , 139, 126, 111,

84(C₆H₁₂), 57(^tBu, base) .

(Found : C, 72.50 ; H, 10.11 . C₁₁H₁₈O₂ requires : C, 72.48 ; H, 9.95 %)

36) COPPER (I) CATALYSED REACTION OF OLEFIN (58)

WITH t-BUTYLPERBENZOATE



To a mixture of olefin (58) (145 mg, 0.89 mmol) and cuprous chloride (0.6 mg, 6 μmol) in benzene (10 ml) at reflux was added dropwise over 30 min *t*-butyl perbenzoate (120 mg, 0.62 mmol). After a further 1.5 h at reflux t.l.c. indicated complete consumption of the perbenzoate. On cooling the solvent was stripped at reduced pressure, and the residue chromatographed (Silica-3% ether/petrol), to obtain in order of elution, recovered olefin (60 mg, 41%), and two major products (62) (32 mg, 12.8%), and (63) (23 mg, 9.2%), respectively as colourless oils, with an additional (6 mg, 2.4%) of mixture.

2-[7-BICYCLO[4.1.0]HEPTYLIDENE]CYCLOPENTYL BENZOATE (62)

$\nu_{\max}$ (film) 2938, 2854, 1718, 1450, 1314, 1272, 1107, 1069, 734, & 712 cm⁻¹

δ_{H} (250 MHz ; CDCl₃) 1.0-2.7 (16H, m, all other H) , 5.88 (1H, m, 1-H)

7.45 (3H, m, m, p-Ar) , 8.02 (2H, m, o-Ar) ; δ_{C} (22.5 MHz ; CDCl₃)

12.31, 13.34 (C-1', C-6', -ve) , 21.22, 21.46 ((C-3', C-4')) ,

21.71, 22.01 (C-2', C-5') , 23.23 (C-4) , 29.46 (C-5) , 33.67 (C-3) ,

76.57 (C-1) , 128.2 (Ar, m) , 128.75 (C-2, +ve) , 129.55 (Ar, o) ,

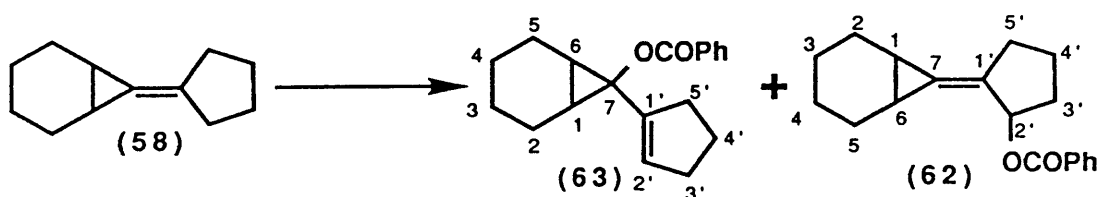
132.48(Ar-CO,+ve) , 132.60(Ar,d) , 134.12(C-7',+ve) ,
 166.35(CO₂R,+ve) ; m/z 282(M⁺),176(M-PhCOH),
 160(M-PhCO₂H,Mclafferty),105(PhCO),95,91,77,67(C₅H₅) .
 (Found : M⁺,282.1614 . C₁₉H₂₂O₂ requires : M⁺,282.1620 .)

7-(1-CYCLOPENTENYL)-BICYCLO[4.1.0]HEPT-7-YL BENZOATE (63)

δ_H (90 MHz ; CDCl₃) 0.8-2.3 (16H,m, all aliphatics) ,
 6.0 (1H,m,2'-H) , 7.45 (3H,m, m,p-Ar) , 8.02 (2H,m, o-Ar) ;
 δ_C (22.5 MHz ; CDCl₃) 19.56(C-1,C-6) , 20.97(C-3,C-4) ,
 21.10(C-2,C-5) , 22.87(C-4) , 32.69,33.55(C-3',C-5') ,
 62.78(C-7) , 130.95(C-2') , 137.42(C-1') , 128.08,129.43,132.42,
 134.55(ArC) , 165.56(CO₂R) .
 (Found : M⁺,282.1617 . C₁₉H₂₂O₂ requires : M⁺,282.1620 .)

37) COPPER (I) CATALYSED REACTION OF OLEFIN (58) WITH SLOW

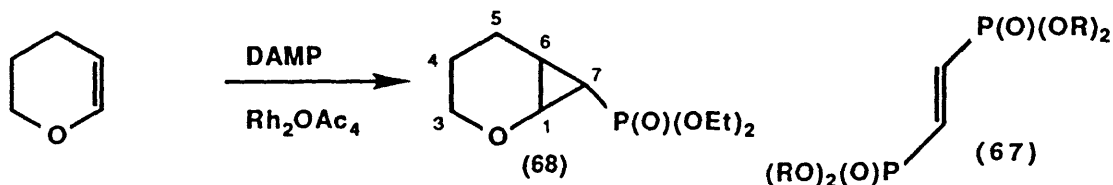
ADDITION OF t-BUTYL PERBENZOATE



To a solution of olefin (58) (265 mg,1.64 mmol) in dry benzene (20 ml) and cuprous chloride (4 mg ,40 μ mol), at reflux was added a solution of t-butyl perbenzoate (317 mg , 311 μ L,1.64 mmol) in benzene (0.6 ml) dropwise over 40h via a syringe pump. The mixture was heated a further 8 h, cooled and poured into saturated aqueous NaHCO₃). The organic phase was dried (MgSO₄), the solvent

stripped, and the residue chromatographed (Silica-4% ether/petrol) to afford in order of elution, recovered olefin (118 mg, 44%), and the allylic benzoate isomers (62) and (63) (191 mg, 41%) in a ratio (42):(43) of 70:30, identical in all respects with materials prepared previously.

38) RHODIUM CARBOXYLATE CATALYSED DECOMPOSITION OF
DIAZOMETHYL DIETHYL PHOSPHONATE (28)

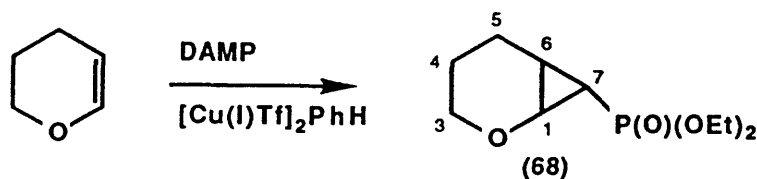


To rhodium acetate (100 mg, 0.22 mmol) in THF (5 ml), and dihydropyran (5 ml, 55 mmol) was added with stirring DMP (28) (1.11 g, 6.23 mmol) dropwise over 0.5 h. The initial green colouration slowly discharged. When nitrogen evolution ceased, a further portion of catalyst (100 mg, 0.22 mmol) was added, and the mixture stirred a further 3 h. The mixture was concentrated in vacuo, the residue taken up in ether, washed with water, brine, dried (Na₂SO₄), and concentrated. The residue was distilled, (short path, oven 150°C, 0.1 torr) to yield exo,endo-DIETHYL (2-OXABICYCLO[4.1.0]HEPT-7-YL) PHOSPHONATE (68) (748 mg, 50.5%), as a colourless oil identical in all respects to material synthesised by alternative means. The residue consisted the "carbene dimer",

1,2-DI(DIETHYL PHOSPHONO)ETHENE (67)

$\nu_{\max}$ (film) 2982, 2934, 2908, 1392, 1253, 1165, 1099, 1025, 968, 815, & 732 cm⁻¹; δ_{H} (90 MHz; CDCl₃) 1.25 (12H, t, J 7.0 Hz, POCH₂CH₃) 4.05 (8H, m, POCH₂CH₃), 6.7 (2H, t(dd), J 23.9, 25.7 Hz, PCHCHP); δ_{P} (36.2 MHz; CDCl₃) 11.47; δ_{C} (22.5 MHz; CDCl₃) 16.15 (Me), 62.35 (t, J 2.75 Hz, OCH₂), 132.29, 136.44, 140.35 (t(dd), J 90.77 Hz).

39) CUPROUS TRIFLUOROMETHANESULPHONATE CATALYSED DECOMPOSITION OF DIAZOMETHYL DIETHYL PHOSPHONATE (28)

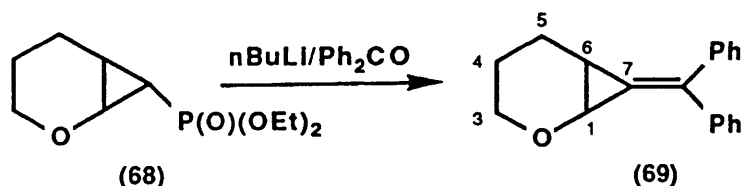


To a stirred mixture of cuprous triflate.benzene complex (58 mg , 0.11 mmol) in dry THF (5 ml) and dihydropyran (5 ml, 55 mmol), under argon was added DAMP (28) (1.03 g, 5.78 mmol) dropwise over 1 h. Nitrogen evolution was vigorous. The mixture was stirred until nitrogen evolution ceased, was diluted with ether and poured into water. The ether layer was dried (MgSO_4), concentrated, and the residue subjected to short path distillation (150°C , 0.1 torr) to afford

exo,endo-DIETHYL (2-OXABICYCLO[4.1.0]HEPT-7-YL) PHOSPHONATE (68)

(950 mg , 71%) as a colourless oil. ν_{max} (film) 2981, 2934, 1239, 1106, 1029, 960, & 860 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.9 (2H, m, 6-H, 7-H), 1.3 (8H, t on m; t, J 7.2 Hz, MeCH_2O ; m, 4-H₂), 2.1 (2H, m, 5-H₂), 3.2-4.3 (7H, m, 1-H, 3-H₂, MeCH_2O); δ_{P} (36.2 MHz; CDCl_3) 25.12; m/z 234 (M^+), 206 ($\text{M}-\text{C}_2\text{H}_4$, McLafferty), 178 ($\text{M}-2(\text{C}_2\text{H}_4)$), 138 ($\text{HOP}(\text{OEt})_2$), 97 ($\text{M}-138$).

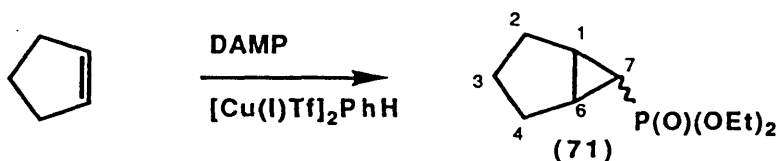
(Found : M^+ , 234.1028 . $\text{C}_{10}\text{H}_{19}\text{O}_4\text{P}$ requires M^+ , 234.1021)

40) WADSWORTH-EMMONS REACTION OF CYCLOPROPYL PHOSPHONATE (68) WITHBENZOPHENONE

To a solution of cyclopropyl phosphonate (68) (243 mg, 1.04 mmol) in THF (5 ml) at -78°C was added with stirring $n\text{-BuLi}$ (0.820 ml of a 1.4 M solution in hexanes, 1.1 eq). The orange solution was stirred 0.3 h, then a solution of benzophenone (206 mg, 1.1 mmol) in THF (2 ml) was added dropwise over 2 min, when the mixture became green. The mixture was stirred at -78°C for 1.5 h when the colour slowly discharged to yellow, then allowed to warm to room temperature, and quenched with saturated aqueous ammonium chloride (5 ml). The mixture was extracted from water with ether, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-2% ether/petrol), to afford 7-(DIPHENYLMETHYLENE)-2-OXABICYCLO[4.1.0]HEPTANE (69) (170 mg, 63%) as a colourless oil. ν_{max} (film) 2942, 2858, 1614, 1247, 1169, 1137, 764, 733, 700, & 631 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.48 (2H, m, 4- H_2), 1.82 (2H, m, 5- H_2), 2.13 (1H, m, 6-H), 3.51 (1H, m, 3- H_{ax}), 3.75 (1H, dt, J 3.8, 11.4 Hz, 3- H_{eq}), 4.20 (1H, d, J 7.6 Hz, 1-H), 7.38 (8H, m, Ar), 7.6 (2H, m, Ar); δ_{C} (250 MHz; CDCl_3) 15.95 (C-6), 19.03 (C-5), 22.36 (C-4), 50.17 (C-1), 63.85 (C-3), 140.08, 140.30 (C-7, C-8), 128.13-134.77 (Ar); m/z 262 (M^+), 233, 219, 205, 191, 165 (fluorene), 152, 77.

(Found : M^+ , 262.1358 . $\text{C}_{19}\text{H}_{18}\text{O}$ requires M^+ , 262.1357).

41)

PREPARATION OFexo,endo-DIETHYL (BICYCLO[3.1.0]HEX-6-YL) PHOSPHONATE

To cuprous trifluoromethanesulphonate (200 mg, 0.38 mmol) and cyclopentene (5 ml) at 0°C under argon was added dropwise via a syringe pump with stirring, a solution of DMP (28) (2.65 g, 14.88 mmol) in DCM (3 ml) over 36 h. After stirring a further 18 h at room temperature, the mixture was concentrated at reduced pressure, and the residue chromatographed (Silica-100% ether), to afford the diastereoisomeric.

exo,endo-DIETHYL (BICYCLO[3.1.0]HEX-6-YL) PHOSPHONATE (71)

(1.99 g, 62%) as a colourless oil, in 3:1 ratio by ^{31}P nmr.

ν_{max} (film) 2937, 2865, 1381, 1246, 1165, 1028, 961, 860, & 795 cm^{-1} ;

δ_{H} (90 MHz ; CDCl_3) 1.25 (6H, t, J 7.2 Hz, MeCH_2O) ,

1.75 (6H, m, 2- H_2 , 3- H_2 , 4- H_2) , 0.3-2.2 (3H, m, 6-H, 1-H, 5-H) ,

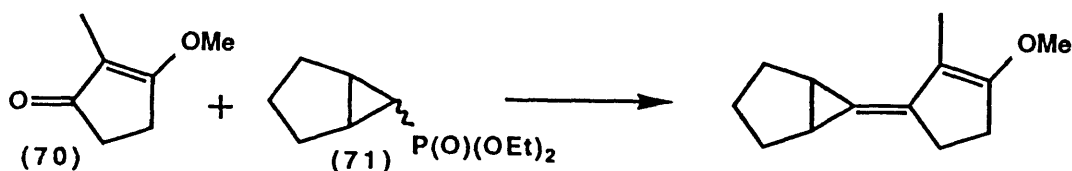
4.0 (4H, m, MeCH_2O) ; δ_{P} (36.2 MHz ; CDCl_3) 28.64, 29.30 (75:25 ratio);

m/z 218(M^+), 190(M-28, McLafferty), 173(M-OEt), 162(M-56

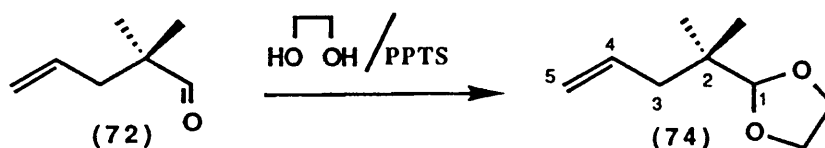
2xMcLafferty), 152, 139($\text{HOP}(\text{OEt})_2$), 111($139-\text{C}_2\text{H}_4$), 80(M-138).

(Found : M^+ , 218.1069 . $\text{C}_{10}\text{H}_{19}\text{O}_3\text{P}$ requires : M^+ , 218.1072 .)

42)

ATTEMPTED WADSWORTH-EMMONS REACTION OFCYCLOPROPYL PHOSPHONATE (71) WITH 3-METHOXY-2-METHYL-CYCLOPENTENONE (70)

To a solution of the cyclopropyl phosphonate (71), (246 mg, 1.13 mmol) and TMEDA (340 μ L, 2.3 mmol, 2 eq) in THF (8 ml) at -100°C , was added *n*-BuLi (0.500 ml of a 2.5 M solution in hexanes, 1.25 mmol, 1.1 eq), and the orange solution was stirred 0.5 h. A solution of the ketone (70) (285 mg, 2.26 mmol) in THF (2 ml) was then added dropwise, when a bright orange-red colouration resulted. The mixture was allowed to warm slowly to -78°C over 1 h, then stirred at -78°C for 3 h. A freshly prepared solution of sodium *t*-butoxide (NaH, 98 mg of 60% oil dispersion, 2.45 mmol; 4 ml THF; 0.650 ml, 6.9 mmol *t*-butanol; stirred 1 h at room temperature) was then added dropwise and the mixture allowed to warm slowly to room temperature. After stirring an additional 18 h the reaction was poured into saturated aqueous NH_4Cl , and extracted with ether. The extracts were dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-5% ether/petrol), to afford 8 mg of non-polar material. Mass spectroscopy did not suggest this to be the desired Wadsworth-Emmons adduct.

43) SYNTHESIS OF 2,2-DIMETHYL-4-PENTENAL ETHYLENE ACETAL (74)

A mixture of 2,2-dimethyl-4-pentenal, (8.16 g, 72.7 mmol), ethylene glycol (22.44 g, 362 mmol, 5eq), benzene (370 ml), and pyridinium p-toluene sulphonate (1.08 g, 4.3 mmol, 3.6 mol%), was heated at reflux under Dean-Stark conditions until water evolution ceased (6 h). On cooling, the reaction was poured into saturated aqueous NaHCO_3 (200 ml), the organic phase separated, washed with brine (100 ml), and dried (MgSO_4). After concentration at reduced pressure the residue was distilled to afford 2,2-DIMETHYL-4-PENTENAL ETHYLENE ACETAL (74)

(8.66 g, 76 %) as a colourless liquid. b.p $177-178^\circ\text{C}$ 1 atm ;

ν_{max} (film) 2974, 2877, 1472, 1395, 1111, 997, 962, 947, & 914 cm^{-1} ;

δ_{H} (90 MHz ; CDCl_3) 0.90 (6H, s, C-2-Me) , 2.20 (2H, d, J 7.2 Hz, 3- H_2)

3.88 (4H, m, O- CH_2CH_2 -O) , 4.56 (1H, s, 1-H) , 5.0 (2H, m, 5- H_2) ,

5.8 (1H, m, 4-H) ; δ_{C} (22.5 MHz ; CDCl_3) 21.16, 21.46 (C-2 Me) ,

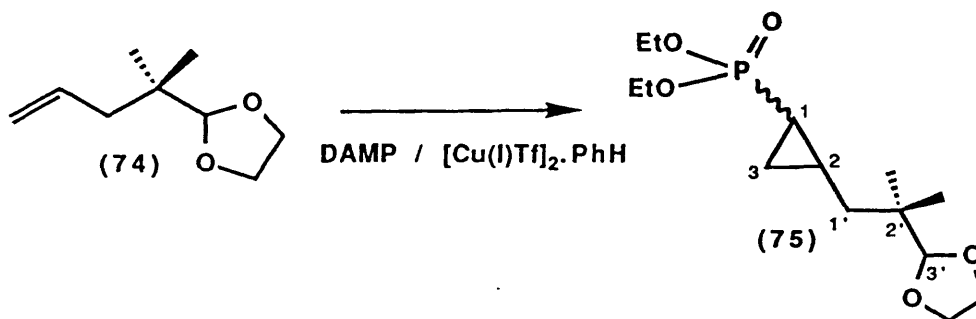
37.27 (C-2) , 41.85 (C-3) , 65.16 (O- CH_2CH_2 -O) , 109.53 (C-1) ,

116.98 (C-5) , 134.74 (C-4) ; m/z 115 (M-H) , 141 (M-Me) , 113, 99, 81,

73 ($\text{C}_3\text{H}_5\text{O}_2$) .

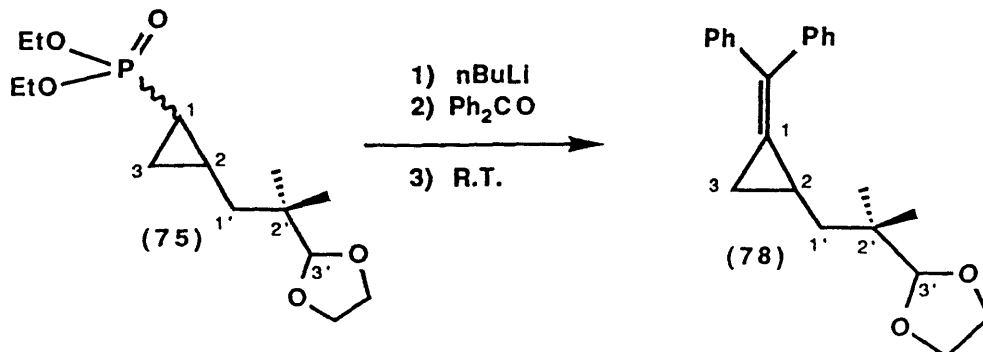
(Found : C, 69.33 ; H, 10.42 . $\text{C}_9\text{H}_{16}\text{O}_2$ requires : C, 69.19 ; H, 10.32 %)

44)

SYNTHESIS OF cis,trans-DIETHYL[2-(2,2-DIMETHYL-PROPAN-3-AL ETHYLENEACETAL)CYCLOPROPYL]PHOSPHONATE (75)

To a mixture of dioxolane (74) (1.87 g, 12 mmol), DCM (3 ml) and cuprous triflate (80 mg, 0.16 mmol) at 8°C under argon was added a solution of DAMP(28) (820 mg, 4.6 mmol) in DCM (3 ml) dropwise with stirring via a syringe pump over 30 h, with provision for venting the nitrogen evolved. The solution, initially green, became yellow. After stirring for a further 18 h at room temperature, the solvent was stripped at reduced pressure and the residue chromatographed (Silica-100% ether) to afford cis,trans-DIETHYL [2-(2,2-DIMETHYL-PROPAN-3-AL ETHYLENE ACETAL)CYCLOPROPYL] PHOSPHONATE (75), a colourless oil, as a 1:1 mixture of diastereoisomers (1.03 g, 73%). $\nu_{\max}$ (film) 2978, 2878, 1244, 1108, 1033, 959, & 731 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.64 (6H, s, C-2'-Me), 1.0 (6H, t, J 7.2 Hz, $\text{MeCH}_2\text{O}-$), 0.3-1.6 (6H, m, 1-H, 2-H, 3-H₂, 1'-H₂), 3.53 (4H, m, O-(CH_2)₂-O), 4.28 (1H, s, 3'-H); δ_{P} (36.21 MHz; CDCl_3) 29.4, 29.2 (diastereoisomers ~1:1 ratio); m/z 306 (M^+), 234 ($\text{M}-\text{C}_3\text{H}_5\text{O}_2$), 163, 153, 134, 73 ($\text{C}_3\text{H}_5\text{O}_2$). (Found: M^+ , 306.1606. $\text{C}_{14}\text{H}_{27}\text{O}_5\text{P}$ requires: M^+ , 306.1596).

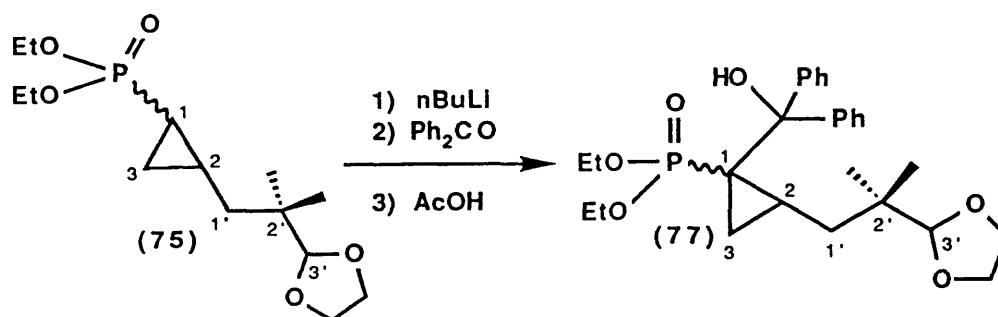
45)

ONE POT WADSWORTH-EMMONS REACTION OFCYCLOPROPYL PHOSPHONATE (75) WITH BENZOPHENONE

To a solution of cyclopropyl phosphonate (75) (136 mg, 0.44 mmol) in THF (1 ml) at -78°C was added with stirring *n*-BuLi, (0.355 ml of a 2.5 M solution in hexanes, 0.88 mmol, 2 eq). After stirring the orange solution at -78°C 1 h, benzophenone (243 mg, 1.33 mmol) in THF (0.5 ml) was added dropwise. After stirring at -78°C for 3 h, the mixture was allowed to warm slowly to room temperature. Potassium *t*-butoxide (149 mg, 1.33 mmol) was added and the mixture stirred 18 h at room temperature. The reaction was poured into saturated aqueous NH_4Cl and extracted with ether. After drying (Na_2SO_4) and concentration at reduced pressure, the residue was chromatographed (Silica-2% ether/petrol) to afford 2-(2,2-DIMETHYLPROPAN-3-AL ETHYLENE ACETAL)-1-(DIPHENYLMETHYLENE)-CYCLOPROPANE (78) as a colourless oil, (43 mg, 29 %). ν_{max} (film) 2967, 2876, 1491, 1106, 771, & 697 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.9 (3H, s, C-2'-Me), 0.94 (3H, s, C-2'-Me), 0.7-1.9 (5H, m, 2-H, 3-H₂, 1'-H₂), 3.78 (4H, m, O-(CH₂)₂-O), 4.54 (1H, s, 3'-H), 7.25 (10H, m, Ph); δ_{C} (22.5 MHz; CDCl_3) 11.76 (C-2), 12.03 (C-3), 21.52, 21.89 (C-2'-Me), 38.18 (C-2'), 39.89 (C-1'), 65.16 (O-(CH₂)₂-O), 109.53 (C-3').

140.71, 141.08 (C-1, C-4) , 126-129 (Ar) ; m/z 334 (M^+), 257 (M-Ph),
 180 (M-2Ph), 165 (fluorene), 105, 91, 77, 73 ($C_3H_5O_2$) .
 (Found : C, 82.43 ; H, 7.89 . $C_{23}H_{26}O_2$ requires : C, 82.59 ; H, 7.84 %)

46) PREPARATION OF cis,trans-DIETHYL [2-(2,2-DIMETHYLPROPAN-3-AL
ETHYLENE ACETAL)-1-(DIPHENYLHYDROXYMETHYL)-CYCLOPROPYL]
PHOSPHONATE (77)

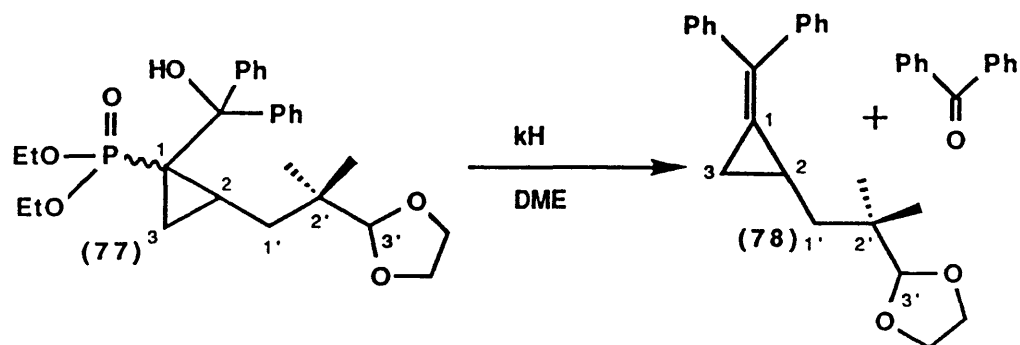


To a solution of cyclopropyl phosphonate (75) (599 mg, 1.92 mmol) in THF (12 ml) and TMEDA (0.330 ml, 2.19 mmol, 1.1eq) at $-78^{\circ}C$ was added *n*-BuLi (0.850 ml, of a 2.5 M solution in hexanes, 2.13 mmol, 1.1 eq), with stirring. After stirring the orange solution for 25 min, a solution of benzophenone (764 mg, 4.2 mmol, 2.2 eq) in THF (3 ml) was added dropwise over 5 min, when a green solution formed. The mixture was stirred at $-78^{\circ}C$ a further 5 h ; the resulting yellow solution quenched by addition of glacial acetic acid (0.250 ml, 4.4 mmol), and allowing to warm to room temperature. The solution was poured into saturated aqueous NaHCO₃, and extracted with ether. The extracts were dried (MgSO₄), and concentrated at reduced pressure .Chromatography of

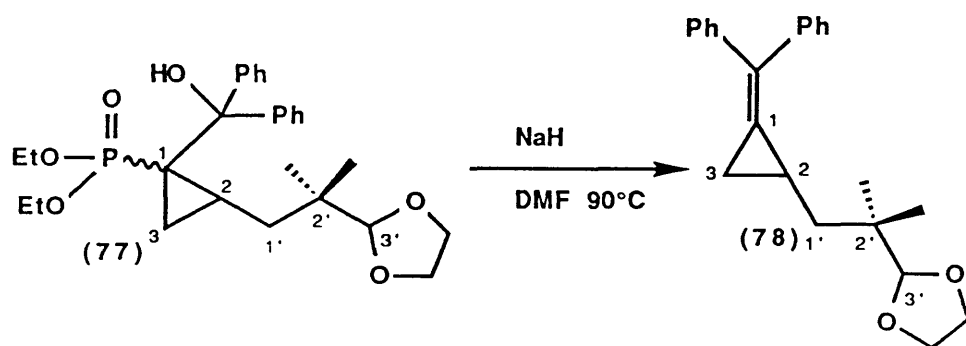
the residue (Silica-100% ether) afforded *cis,trans*-DIETHYL
 [2-(2,2-DIMETHYLPROPAN-3-AL ETHYLENE ACETAL)-1-(DIPHENYLHYDROXYMETHYL)
 -CYCLOPROPYL] PHOSPHONATE (77) (877 mg, 94%) in a 7.3 : 1
 diastereoisomeric ratio, the minor isomer (105 mg) as a colourless
 oil, the major diastereoisomer (772 mg) as a colourless
 crystalline solid, m.p. 114-116.5°C ; $\nu_{\max}$ (DCM)
 3353, 2956, 2878, 1473, 1391, 1208, 1108, 1054, and 805 cm^{-1} ;
 δ_{H} (90 MHz ; CDCl_3) 0.7 (3H, s, C-2'-Me) , 0.82 (3H, s, C-2'-Me) ,
 1.13 (6H, q, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{-O-}$) , 0.5-1.8 (5H, m, 2-H, 3-H₂, 1'-H₂) ,
 3.76 (4H, m, O-(CH_2)₂-O) , 3.3-4.1 (4H, m, $\text{CH}_3\text{CH}_2\text{-O-}$) , 4.36 (1H, s, 3'-H)
 5.6 (1H, brs, OH) , 7.0-7.8 (10H, m, Ar) ; δ_{P} (36.2 MHz ; CDCl_3) 30.44 ;
m/z 448 (M^+) , 471 (M-OH) , 442, 411 (M-Ph) , 398, 373 (M-C₆H₁₁) , 330 ,
 305 (M-Ph₂COH) , 254, 234, 226, 191, 178, 165 (fluorene) , 114 (C₆H₁₀) ,
 105 (PhCO) , 77, 73 (C₃H₅O₂) , 57 .
 (Found : C, 66.29 ; H, 7.58 . C₂₇H₃₇O₆P requires : C, 66.37 ;
 H, 7.63 %) .

MINOR DIASTEREOISOMER

δ_{H} (90 MHz ; CDCl_3) 0.80 (3H, s, C-2'-Me) , 0.83 (3H, s, C-2'-Me) ,
 1.03 (3H, t, J 7 Hz, $\text{CH}_3\text{CH}_2\text{-O-}$) , 1.25 (3H, t, J 7 Hz, $\text{CH}_3\text{CH}_2\text{-O-}$) ,
 0.5-1.7 (4H, m, 3-H₂, 1'-H₂) , 2.12 (1H, d, J 12.8 Hz, 2-H) ,
 3.5 (2H, m, $\text{CH}_3\text{CH}_2\text{-O-}$) , 4.05 (2H, m, $\text{CH}_3\text{CH}_2\text{-O-}$) ,
 3.83 (4H, m, O-(CH_2)₂-O) , 4.49 (1H, s, 3'-H) , 6.42 (1H, brs, OH) ,
 7.05-7.9 (10H, m, Ar) ; δ_{P} (36.2 MHz ; CDCl_3) 31.40 ;

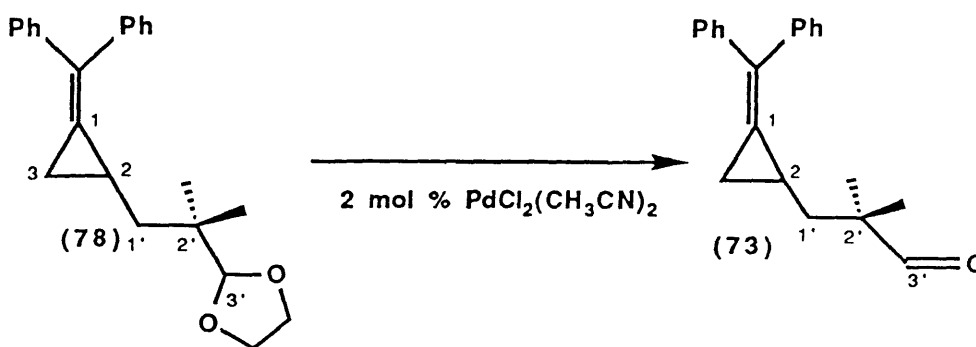
47) BREAKDOWN OF THE POTASSIUM SALT OF β -HYDROXY PHOSPHONATE (77)

To a slurry of potassium hydride (60 mg of 35% oil dispersion, 0.52 mmol, 1.9 eq) in DME (10 ml) at 0°C was added a solution of β -hydroxy phosphonate (77) (132 mg, 0.27 mmol) in DME (2 ml). When hydrogen evolution subsided (0.3 h), the mixture was stirred at room temperature for 1 h, then cautiously quenched by addition of 10% aqueous HCl (2 ml). The mixture was poured into water and extracted with ether. The extracts were dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-5% ether/petrol), to afford the (diphenylmethylene)cyclopropane (78) (9 mg, 10%), as a colourless oil, identical in all respects to previously synthesised material. In addition, benzophenone (20 mg, 40.9%) was isolated.

48) BREAKDOWN OF THE SODIUM SALT OF β -HYDROXY PHOSPHONATE (77)

To a slurry of sodium hydride (16 mg of a 60% dispersion in oil, 0.4 mmol, 1.8 eq) in dry DMF (8 ml) at room temperature was added a solution of β -hydroxy phosphonate (77) (107 mg, 0.219 mmol) in DMF (2 ml). When hydrogen evolution subsided, the mixture was heated at 90–100°C for 2h, cooled and the dark solution quenched with 10% aqueous HCl (2 ml). The reaction was poured into water (25 ml), extracted with petrol, the extracts dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-5% ether/petrol) to afford the (diphenylmethylene)cyclopropane (78) (55 mg, 81%), as a colourless oil, identical in all respects to an authentic sample. No benzophenone was observed.

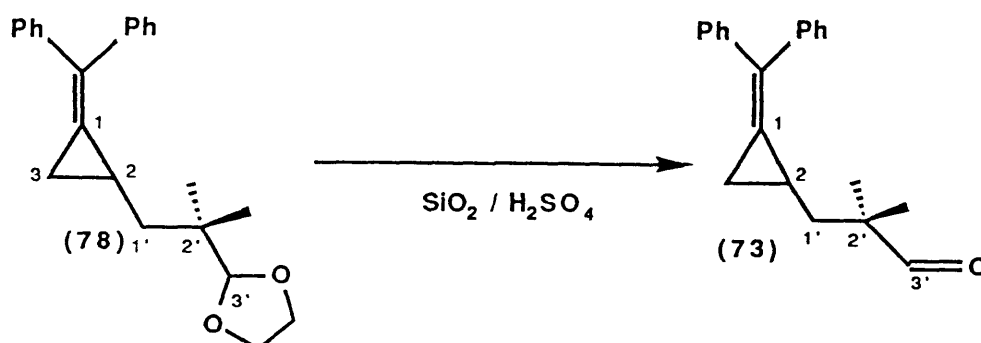
49) PALLADIUM (II) CATALYSED TRANS-KETALISATION
OF DIOXOLANE (78) WITH ACETONE



To a solution of the 1,3-dioxolane (78) (234 mg, 0.7 mmol) in acetone (40 ml) was added dichlorobis(acetonitrile)palladium(II) (4 mg, 1.4×10^{-5} mol, 2 mol%) and the mixture stirred for 72 h in a blacked out vessel. Evaporation at reduced pressure and chromatography of the residue (Silica-5% ether/petrol), afforded

the aldehyde (73) (97 mg, 48%) as a colourless oil. An additional 53 mg of the dioxolane (78) was recovered, a 62% yield of aldehyde based on recovered starting material. The product was identical in all respects with aldehyde (73) obtained by other means.

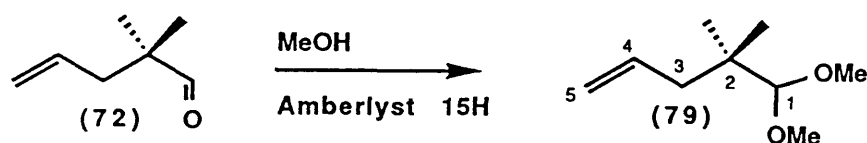
50) ACID CATALYSED HYDROLYSIS OF DIOXOLANE (78)



To a slurry of silica gel (1.0 g chromatography silica) in DCM (20 ml) was added 10% w/w aqueous sulphuric acid (0.1 ml). The mixture was stirred until a uniform consistency was obtained. A solution of the dioxolane (78) (455 mg, 1.36 mmol) in DCM (2 ml) was added and the mixture stirred 48 h at room temperature. The silica was filtered and washed with DCM (5 ml). The filtrate was washed with saturated aqueous NaHCO₃, dried (MgSO₄), and concentrated at reduced pressure. The residue was chromatographed (Silica-2% ether/petrol) to afford 2-(2,2-DIMETHYLPROPAN-3-AL)-1-(DIPHENYLMETHYLENE)-CYCLOPROPANE (73) (280 mg, 71%) as a colourless oil. $\nu_{\max}$ (film) 3059, 1725, 1599, 1447, 1318, 1278, 942, 920, and 700 cm⁻¹; δ_{H} (90 MHz; CDCl₃) 1.0 (6H, s, C-2' Me), 0.5-2.5 (5H, m, 2-H, 3-H₂, 1'-H₂).

7.4 (10H,m,Ph) , 9.4 (1H,s,CHO) ; δ_C (22.5 MHz ; $CDCl_3$) 11.88(C-2),
 12.00(C-3) , 21.16,21.52(C-2'Me) , 39.65(C-1') , 46.54(C-2') ,
 137.48,140.47(C-1,C-4) , 126.8-132.2(Ph) , 205.59(C-3') ;
 m/z 290(M^+),272,219($M-C_4H_7O$),206,182,165(fluorene),105,91,77 .
 (Found : M^+ ,290.1669 . $C_{21}H_{22}O$ requires : M^+ ,290.1671 .) .

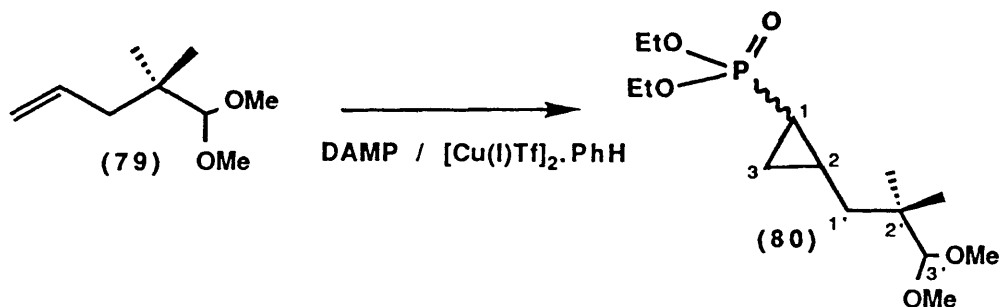
51) SYNTHESIS OF 1,1-DIMETHOXY-2,2-DIMETHYL-4-PENTENE (79)



To a solution of 2,2-dimethyl-4-pentenal (8.44 g, 75 mmol) in methanol (120 ml) was added acidic resin Amberlyst 15H (2.5 g) and the reaction stirred at room temperature for 18 h. After filtration, the solvent was removed at reduced pressure. Distillation of the residue afforded

1,1-DIMETHOXY-2,2-DIMETHYL-4-PENTENE (79) (6.88 g ,58%),
b.p. 164 $^{\circ}$ C 1atm ; $\nu_{\max}$ (film) 2977,2830,1386,1186,1112,1078,
 and 967 cm^{-1} ; δ_H (90 MHz ; $CDCl_3$) 0.70 (6H,s,C-2-Me) ,
 1.87 (2H,d,J 7.7Hz,3-H₂) , 3.35 (6H,s,OMe) , 3.66 (1H,s,1-H) ,
 4.82 (2H,m,5-H₂) , 5.65 (1H,m,4-H) ; δ_C (22.5 MHz ; $CDCl_3$)
 21.70(C-2 Me) , 39.47(C-2) , 42.40(C-3) , 58.14(OMe) ,
 113.31(C-1) , 116.79(C-5) , 134.98(C-4) ; m/z 157(M-H),143(M-Me),127(M-MeO),117(M-CH(OMe)₂),75(CH(OMe)₂) .
 (Found : C,68.28 ; H,11.44 . $C_9H_{18}O_2$ requires : C,68.31 ; H,11.46 %))

52)

PREPARATION OF cis,trans-DIETHYL[2-(3,3-DIMETHOXY-2,2-DIMETHYLPROPYL)-CYCLOPROPYL] PHOSPHONATE (80)

To a solution of acetal (79) (5.50 g , 34.8 mmol) , DCM (2 ml) , and cuprous triflate (100 mg 0.2 mmol) , at 8°C under argon was added dropwise with stirring via a syringe pump a solution of DAMP (28) (2.19 g, 12.3 mmol) in DCM (2 ml) over 22 h with provision for venting the nitrogen evolved. After a further 2 h the homogenous green solution was allowed to warm to room temperature. The DCM was stripped at reduced pressure, and the residue was chromatographed (Silica, neat ether) , to give in order of elution , recovered olefin (79) (4.13 g 75%) , and the diastereoisomeric mixture of cis,trans-DIETHYL

[2-(3,3-DIMETHOXY-2,2-DIMETHYLPROPYL)-CYCLOPROPYL] PHOSPHONATE (80)

(1.73 g , 53% on DAMP , 76 % on recovered olefin) , as a colourless oil , ν_{max} (film) 2979, 1244, 1108, 1071, 1030, and 962 cm^{-1} ;

δ_{H} (90 MHz ; CDCl_3) 0.90 (6H, s, C-2' Me) ,

1.27 (6H, t, J 7Hz, $\text{CH}_3\text{CH}_2\text{O}$) , 0.5-2.0 (6H, m, 1-H, 2-H, 3-H₂, 1'-H₂) ,

3.44 (6H, s, OMe) , 4.0 (5H, m, $\text{CH}_3\text{CH}_2\text{O}$, 3'-H) ; δ_{P} (36.2 MHz ; CDCl_3)

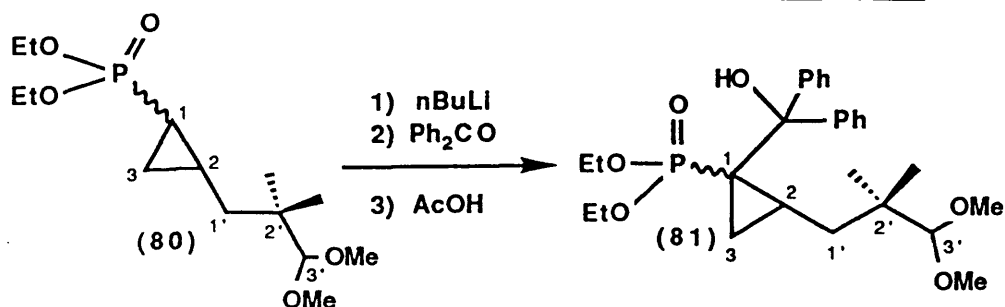
29.0 , 29.3 (1:1) ; m/z 308 (M^+) , 293 (M-Me) , 277 (M-MeO) , 248 ,

233 (M- $\text{C}_3\text{H}_7\text{O}_2$) , 208, 195, 166, 139, 107, 75 ($\text{C}_3\text{H}_7\text{O}_2$) .

(Found : C, 54.42 ; H, 9.70. $\text{C}_{14}\text{H}_{29}\text{O}_5\text{P}$ requires : C, 54.53 ; H, 9.48 %)

Phosphonate dimer (67) (1.18 g) was also recovered.

53) WADSWORTH-EMMONS REACTION OF CYCLOPROPYL PHOSPHONATE (80) WITH BENZOPHENONE : ISOLATION OF THE β -HYDROXY-PHOSPHONATE (81)



To a solution of cyclopropyl phosphonate (80) (1.20 g, 3.84 mmol) in THF (25 ml) and TMEDA (0.640 ml, 4.37 mmol, 1.1 eq) at -78°C was added *n*-BuLi (1.70 ml of a 2.5 M solution in hexanes 4.25 mmol, 1.1 eq), and the orange solution stirred 0.3 h. A solution of benzophenone (1.50 g, 8.24 mmol, 2.1 eq) in THF (6 ml) was added dropwise, the solution becoming green, and the mixture was stirred a further 2.5 h. To the resulting yellow solution at -78°C was added glacial acetic acid (0.70 ml, 12 mmol), the solution warmed to room temperature, poured into saturated aqueous NaHCO₃, and extracted with ether. The extracts were dried (MgSO₄), concentrated at reduced pressure, and the residue chromatographed (Silica-80% ether/petrol) to afford *cis,trans*-DIETHYL [2-(3,3-DIMETHOXY-2,2-DIMETHYLPROPYL)-1-

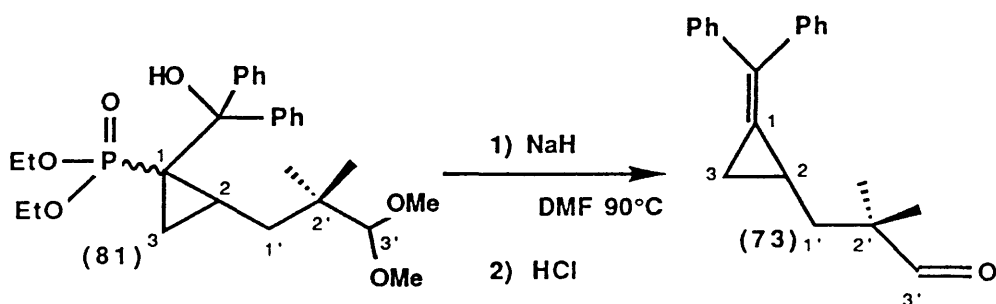
(DIPHENYLHYDROXYMETHYL)-CYCLOPROPYL] PHOSPHONATE (81)

(1.44 g, 77%) in a 4:1 diastereoisomeric ratio; the minor diastereoisomer (286 mg) as a colourless oil, the major diastereoisomer (1.156 g) as a colourless crystalline solid. Crystallisation from hot petrol (b.p 40-60) afforded diastereoisomerically pure material. m.p. $124-125.5^{\circ}\text{C}$;

ν_{max} (film) 3353, 2977, 2829, 1491, 1449, 1388, 1363, 1209, 1053, 964, 759, & 704 cm^{-1} ; δ_{H} (90 MHz; CDCl₃) 0.4-1.4 (3H, m, 2-H, 3-H₂),

1.4-2.2 (8H,m, $\underline{\text{CH}_3\text{CH}_2\text{O}}$,1'-H₂) , 1.14 (3H,s,C-2' Me) ,
 1.24 (3H,s,C-2' Me) , 3.80 (3H,s,OMe) , 3.83 (3H,s,OMe) ,
 4.0-4.5 (5H,m, $\underline{\text{CH}_3\text{CH}_2\text{O}}$,3'-H) , 6.14 (1H,s,OH) ,
 7.5-8.2 (10H,m,Ph) ; δ_p (36.2 MHz ; CDCl₃) 30.55 ; m/z
 490(M⁺), 473(M-OH), 427, 412, 398(M-OH-C₃H₇O₂), 373(M-C₆H₁₃O₂) ,
 330, 276, 191, 165(Fluorene), 105(PhCO), 91, 86, 75(C₃H₇O₂) .
 (Found : C, 66.02 ; H, 8.05. C₂₇H₃₉O₆P requires : C, 66.10 ; H, 8.01 %))
 Minor diastereoisomer δ_p (36.2 MHz ; CDCl₃) 31.47 :

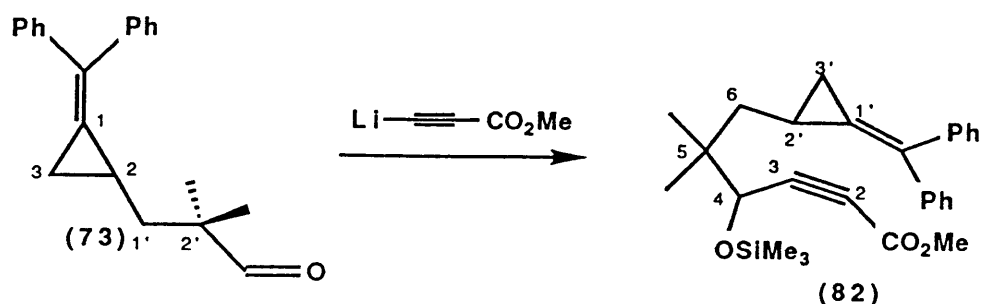
54)

PREPARATION OF2-(2,2-DIMETHYL-PROPAN-3-AL)-1-(DIPHENYLMETHYLENE)-CYCLOPROPANE (73)

To a slurry of sodium hydride (272 mg , of a 60% oil dispersion, 6.8 mmol, 1.2 eq) in dry DMF (100 ml), was added with stirring a solution of β -hydroxy phosphonate (81) (2.78 g, 5.67 mmol) in DMF (50 ml) . When rate of hydrogen evolution subsided, the alkoxide was heated at 90°C for 2.5 h. On cooling to 0°C , a solution of 10% w/w aqueous HCl (20 ml) was added cautiously with stirring, when the dark red colour rapidly discharged. Acetal cleavage was completed on stirring at room temperature overnight. The mixture was poured into an equal volume of ice-water, and extracted with ether. The extracts were

washed with aqueous NaHCO_3 , dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-5% ether/petrol) to yield the aldehyde (73) (1.10 g, 67%) as a colourless oil identical in all respects to previously synthesised material.

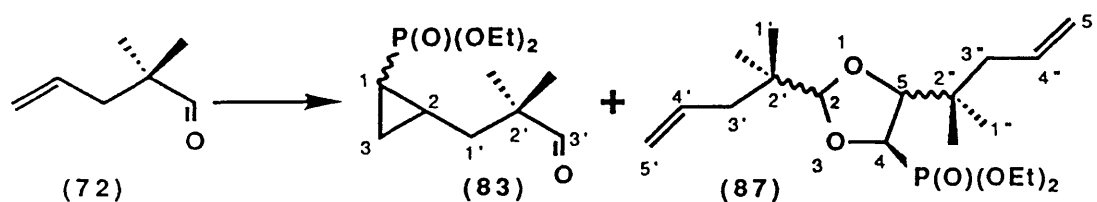
55) PREPARATION OF METHYL 5,5-DIMETHYL-6-[1-(DIPHENYLMETHYLENE)-CYCLOPROP-2-YL]-4-TRIMETHYLSILYLOXY-2-HEXYNOATE (82)



To a solution of methyl propiolate (96 mg, 1.14 mmol, 4 eq) in THF (3 ml) at -78°C was added *n*-BuLi (0.760 ml of a 1.5 M solution in hexanes, 1.14 mmol), and the mixture stirred for 1.5 h. To the resulting solution was added a solution of the aldehyde (73) (83 mg, 0.286 mmol) in THF (2 ml) at -78°C , and the mixture stirred for 1 h. Freshly distilled chlorotrimethylsilane (145 μL , 1.14 mmol, 4 eq) was then added and the mixture allowed to warm to room temperature. The reaction was poured into water (20 ml), extracted with ether, washed with brine, and dried (Na_2SO_4). Concentration at reduced pressure and chromatography of the residue (Silica-5% ether/petrol) afforded METHYL 5,5-DIMETHYL-6-[1-(DIPHENYLMETHYLENE)-CYCLOPROP-2-YL]-4-TRIMETHYLSILYLOXY-2-HEXYNOATE (82), a 1:1 mixture of diastereoisomers as a colourless oil (124 mg, 97%).

$\nu_{\max}$ (film) 2959, 2234, 1718, 1253, 1063, 875, 846, and 699 cm^{-1} ;
 δ_{H} (250 MHz ; CDCl_3) 0.17 (9H, s, TMS) , 0.94 (1H, m, 3'-H₁) ,
 1.22 (1H, m, 3'-H₁) , 1.01, 1.10, 1.40, 1.50 (6H, 4x s, C-5 Me
 diastereotopic, diastereoisomeric) , 1.6 (2H, m, 6-H₂) ,
 1.90 (1H, m, 2'-H) , 3.78, 3.80 (3H, 2x s, CO₂Me diastereoisomeric),
 4.20, 4.26 (1H, 2x s , 4-H, diast.) , 7.2-7.5 (10H, m, Ph) ;
 δ_{C} (22.5 MHz ; CDCl_3) 1.38 (TMS) , 11.88 (C-2') , 12.00 (C-3') ,
 22.56, 22.93, 23.11 (C-5-Me) , 40.01 (C-6) , 40.26 (C-5) ,
 52.59, 52.71 (CO₂Me) , 69.98, 70.30 (C-4) , 77.37, 87.74, 87.92 (C-2, C-3)
 126-128.5 (Ph) , 140.66, 140.84 (C-1') , 144.74 (C-4') ,
 153.35, 153.72 (C-1) ; m/z 446 (M^+), 431 (M-Me), 387 (M-CO₂Me),
 372 (M-TMS), 356 (M-OTMS), 338, 323, 306, 279 (M-fluorene), 261, 249, 189,
 165 (fluorene), 105, 73 .
 (Found : M^+ , 446.2260 . $\text{C}_{28}\text{H}_{34}\text{O}_3\text{Si}$ requires : M^+ , 446.2277 .)

56)

PREPARATION OF cis,trans-DIETHYL [2-(2,2-DIMETHYL-PROPAN-3-AL)-CYCLOPROPYL] PHOSPHONATE (83)

To a mixture of cuprous triflate (280 mg, 0.56 mmol),
 2,2-dimethyl-4-pentenal (6.93 g, 61.8 mmol) and DCM (3 ml) at 4°C
 under argon was added slowly with stirring over 38 h via a
 syringe pump a solution of DAMP (28) (2.32 g, 13 mmol) in DCM
 (3 ml), with provision for pressure relief. The reaction was then

allowed to warm to room temperature, and stirred a further 2 h. The solvent and excess olefin were removed (into a cold trap at 0.2 torr), and the residue was chromatographed (Silica-80% ether/petrol) to afford 2 fractions. The more polar fraction, (600 mg, 18%) a colourless oil consisted of the *cis,trans*-DIETHYL [2-(2,2-DIMETHYL-PROPAN-3-AL)-CYCLOPROPYL] PHOSPHONATE (83) in a diastereoisomeric ratio of 1.4 : 1

Major diastereoisomer

$\nu_{\max}$ (film) 2979, 1725 (CO), 1244, 1098, 1030, 964, and 795 cm^{-1} ;
 δ_{H} (90 MHz ; CDCl_3) 0.52 (2H, m, 3-H₂) , 1.05 (6H, s, C-2'-Me) ,
 1.20 (6H, t, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$) , 0.7-2.0 (4H, m, 1-H, 2-H, 1'-H₂) ,
 4.0 (4H, m, $\text{CH}_3\text{CH}_2\text{O}$) , 9.48 (1H, s, 3'-H) ; δ_{P} (36.2 MHz ; CDCl_3)
 28.17 ; m/z 262 (M^+), 247 (M-Me), 234 (M-CO), 191 (M-C₄H₇O McLafferty) ,
 165, 152, 135, 125, 109, 95, 81 .
 (Found : C, 55.00 ; H, 9.10 . $\text{C}_{12}\text{H}_{23}\text{O}_4\text{P}$ requires : C, 54.95 ; H, 8.84 %).

Minor diastereoisomer

δ_{H} (90 MHz ; CDCl_3) 0.62 (2H, m, 3-H₂) , 1.14 (6H, s, C-2'-Me) ,
 1.32 (6H, t, J 7.2 Hz, $\text{CH}_3\text{CH}_2\text{O}$) , 0.8-1.65 (4H, m, 1-H, 2-H, 1'-H₂) ,
 4.10 (4H, m, $\text{CH}_3\text{CH}_2\text{O}$) , 9.51 (1H, s, 3'-H) ; δ_{P} (36.2 MHz ; CDCl_3)
 27.85 .

The less polar fraction (782 mg, 16%) contained two diastereoisomers, chromatographically separable (Silica-30% ether/petrol), identified as

DIETHYL [2,5-DI(2-METHYL-4-PENTEN-2-YL)-1,3-DIOXOLAN-4-YL] PHOSPHONATE (87)

$\nu_{\max}$ (film) 2976, 1466, 1391, 1366, 1253, 1164, 1109, 1031, 967, and 914 cm^{-1} ;

(A) δ_{H} (90 MHz ; CDCl_3) 0.96 (6H, s, C-2' Me) , 1.13 (6H, d, J

1.5Hz, C-2" Me) , 1.33 (6H, td, J 2.4, 7.0Hz, POCH₂CH₃) ,
 2.13 (2H, d, J 7.4Hz, 3"-H₂, or 3'-H₂) ,
 2.27 (2H, d, J 7.4Hz, 3"-H₂, or 3'-H₂) ,
 3.69 (1H, d, J 7.4Hz, 5-H) , 4.18 (5H, m, POCH₂CH₃, 4-H) ,
 4.48 (1H, d, J 1.5Hz, 2-H) , 5.0 (4H, m, 5'-H₂, 5"-H₂) ,
 5.8 (2H, m, 4'-H, 4"-H) : δ_p (36.2 MHz ; CDCl₃) 17.38 ;
 δ_c (22.5 MHz ; CDCl₃) 16.33 (d, J 5.5 Hz, POCH₂CH₃) ,
 21.83, 22.01, 22.74, 23.90 (C-2'-Me, C-2"-Me) , 35.93, 36.72 (C-2', C-2") ,
 42.52, 44.65 (C-3', C-3") , 62.23 (m, POCH₂CH₃) , 73.28 (d, J 173Hz, C-4) ,
 87.19 (C-5) , 109.0 (d, J 2.8Hz, C-2) , 117.10, 117.46 (C-5', C-5") ,
 134.86 (C-4', C-4") .

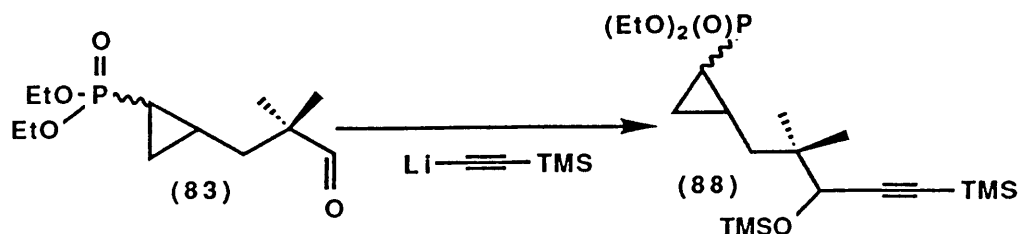
(B)

δ_H (90 MHz ; CDCl₃) 0.83 (6H, s, C-2' Me) ,
 0.85 (6H, d, J 1.5Hz, C-2" Me) , 1.25 (6H, dt, J 2.4, 7.0Hz, POCH₂CH₃) ,
 2.02 (4H, d, J 7.4Hz, 3"-H₂, 3'-H₂) , 4.1 (6H, m, POCH₂CH₃, 4-H, 5-H) ,
 4.72 (1H, br s , 2-H) , 5.0 (4H, m, 5'-H₂, 5"-H₂) ,
 5.8 (2H, m, 4'-H, 4"-H) : δ_p (36.2 MHz ; CDCl₃) 19.65 ;
 δ_c (22.5 MHz ; CDCl₃) 71.61 (d, J 169 Hz, C-4) ,
 83.44 (d, J 6.9Hz, C-5) , all other peaks correspond substantially to
 those reported for the other isomer.

m/z 374 (M⁺) , 291 (M-C₆H₁₁) , 251, 205, 164, 107, 91, 83 (C₆H₁₁) , 55, 41 .

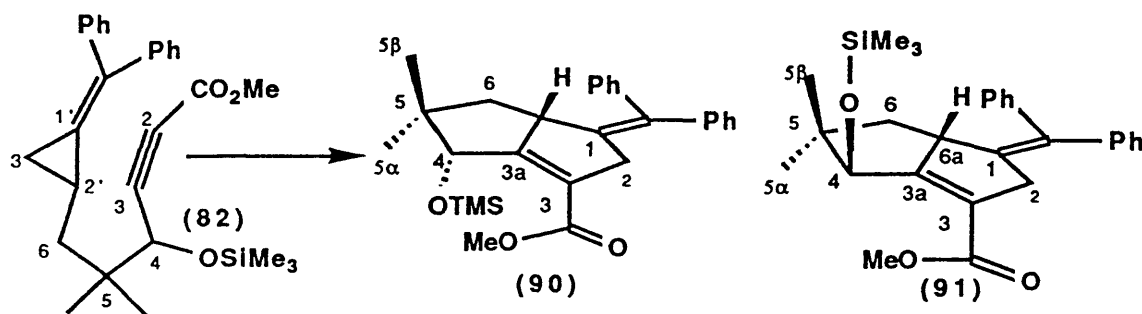
(Found : M⁺, 374.2213 . C₁₉H₃₅O₅P requires : M⁺, 374.2222 .).

57) PREPARATION OF cis,trans-DIETHYL [2-(2,2-DIMETHYL-5-TRIMETHYLSILYL-3-TRIMETHYLSILOXY-PENT-4-YNE-1-YL)-CYCLOPROPYL] PHOSPHONATE (88)



To trimethylsilylacetylene (196 mg, 2.0 mmol) in THF (8 ml) at -78°C was added $n\text{-BuLi}$ (0.800 ml of a 2.4 M solution in hexanes, 1.92 mmol), and the solution stirred 1 h. The solution was then cannulated into a solution of the aldehyde (83) (335 mg, 1.27 mmol) in THF (5 ml) at -78°C , and the mixture stirred at -78°C for 2 h. Chlorotrimethylsilane (1.0 ml, 8 eq), was added and the mixture allowed to warm to room temperature. The solvents were stripped at reduced pressure, and the residue chromatographed (Silica-100% ether) to afford, in order of elution the desired diastereoisomeric cis,trans-DIETHYL [2-(2,2-DIMETHYL-5-TRIMETHYLSILYL-3-TRIMETHYLSILOXY-PENT-4-YNE-1-YL)-CYCLOPROPYL] PHOSPHONATE (88) (281 mg, 51%) as a colourless oil, and recovered aldehyde (47 mg, 14%). ν_{max} (film) 2962, 2902, 2171 (weak), 1250, 1061, 1033, 962, 844, & 760 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.0 (18H, s, TMS), 0.83 (6H, s, C-2'-Me), 1.17 (6H, t, J 7 Hz, POCH_2CH_3), 0.5-2.0 (6H, m, 1-H, 2-H, 3-H₂, 1'-H₂), 3.93 (5H, m, 3'-H, POCH_2CH_3); δ_{P} (36.2 MHz; CDCl_3) 28.90, 28.83; m/z 432 (M^+), 417 (M-Me), 334, 327 (M-Me-TMSOH), 306, 279, 237, 179 ($\text{C}_3\text{H}_4\text{P}(\text{O})(\text{OEt})_2$, base), 151 (179- C_2H_4), 125, 95, 91, 41, . (Found: M^+ , 432.2283. $\text{C}_{20}\text{H}_{41}\text{O}_4\text{PSi}_2$ requires: M^+ , 432.2281).

58) TETRAKIS(TRIPHENYLPHOSPHINE)PALLADIUM(0) CATALYSED CYCLISATION
OF (82) INDUCED BY ULTRASONICATION



To a solution of (diphenylmethylene)cyclopropane (82) (65 mg, 0.146 mmol) in toluene (10 ml) under argon was added $(\text{Ph}_3\text{P})_4\text{Pd}(0)$ (10 mg), and the mixture was subjected to ultrasonication for 100 h (arbitrary period), and the solvents were then stripped at reduced pressure. The residue was chromatographed (Silica-5% ether/petrol), to afford the two diastereoisomeric bicycles, the less polar of which co-runs by t.l.c with the starting material, (42 mg, 64.6%), in addition to the more polar isomer (23 mg, 35.4%), as colourless oils.

The more polar isomer was identified on the basis of n.o.e experiments (See discussion section) as

METHYL 5,5-DIMETHYL-1-(DIPHENYLMETHYLENE)-4_α-TRIMETHYLSILYLOXY-1,4,6-HEXAHYDRO-3-PENTALENE CARBOXYLATE (90)

δ_{H} (250 MHz ; CDCl_3) 0.13 (9H, s, TMSO) , 0.80 (3H, s, endo C-5-Me) , 0.92 (3H, s, exo C-5-Me) , 1.04 (1H, dd, J 12.6, 8.5 Hz, 6-H₁ exo) , 1.13 (1H, dd, J 12.6, 10.1 Hz, 6-H₁ endo) , 3.44 (1H, dd, J 21.5, 3.2 Hz, 2-H₁) , 3.68 (3H, s, CO_2Me) , 3.75 (1H, dd, J 21.5, 1.6 Hz, 2-H₁) , 4.03 (1H, br t, J 9.5 Hz, 6_a-H) , 4.28 (1H, br s, 4-H) ,

7.24 (10H,m,Ph) ; δ_C (22.5 MHz ; $CDCl_3$) 0.47(TMS) ,
 24.76,27.93(C-5 Me) , 41.24(C-6) , 43.56(C-2) , 45.39(C-5) ,
 51.37(CO_2 Me) , 51.92(C-6_a) , 77.49(C-4) , 124.30(C-3) , 126.01-
 128.88(Ar) , 135.83(C-1) , 139.86(C-7) , 142.30(C-3_a) ,
 164.76(CO_2 Me) ; m/z 446(M^+), (478 $m+32$, 462 $m+16$ -endoperoxide from
 aerial oxidation), 431(M-Me), 390, 373(M-TMS), 356(M-TMSOH), 331,
 279(M- Ph_2CH), 241, 186, 180, 167(Ph_2CH), 144, 105, 91, 83, 73(TMS) .
 (Found : M^+ , 446.2278 . $C_{28}H_{34}O_3Si$ requires : M^+ , 446.2277.)

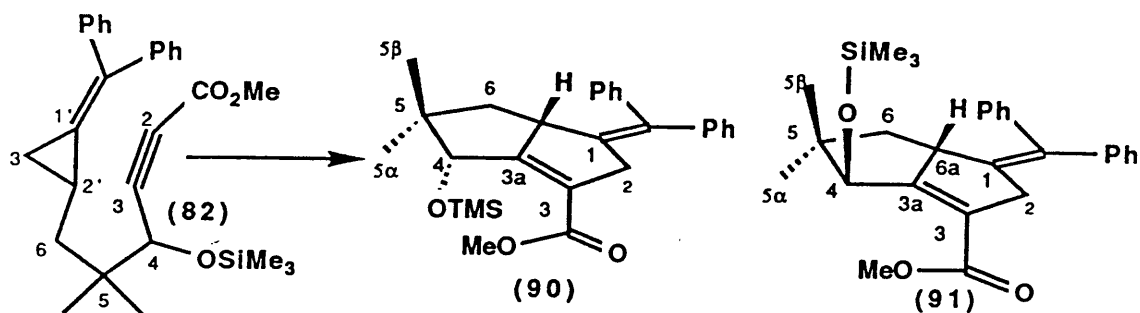
The upper fraction containing the diastereoisomeric bicycle contaminated with traces of starting material, was taken up in toluene (2 ml), catalyst (5 mg) added, and the mixture subjected to ultrasonication for a further 48 h. Isolation by chromatography as above afforded the trans diastereoisomer (91), as a colourless oil free from starting material.

METHYL 5,5-DIMETHYL-1-(DIPHENYLMETHYLENE)-4- β -TRIMETHYLSILOXY-1,4,6-HEXAHYDRO-3-PENTALENE CARBOXYLATE (91)

ν_{max} (film) 2954, 1714, 1441, 1250, 1112, 1075, 1031, 909, 881, 844, 734, &
 701 cm^{-1} ; δ_H (500 MHz ; $CDCl_3$) 0.13 (9H,s,TMS) ,
 0.750 (3H,s,C-5-Me endo) , 0.884 (1H,dd,J 6.5,13Hz,6-H₁ exo) ,
 0.914 (3H,s,C-5-Me exo) , 1.496 (1H,dd,J 13,11Hz,6-H₁ endo) ,
 3.446 (1H,d,J 22Hz,2-H₁) , 3.648 (1H,d,J 22Hz,2-H₁) ,
 3.725 (3H,s, CO_2 Me) , 4.378 (1H,s,4-H) ,
 4.444 (1H,dd,J 6.5,11Hz,6_a-H) , 7.26 (10H,m,Ar) ;
 δ_C (22.5 MHz ; $CDCl_3$) 0.104(TMS -ve) , 23.66,28.91(C-5-Me,-ve),
 41.36 (C-6) , 42.09(C-2) , 44.78(C-5) , 51.06(C-6_a) ,
 52.65(CO_2 Me,-ve) , 75.66(C-4) , 123.02(C-3,+ve) , 126.07,126.43,

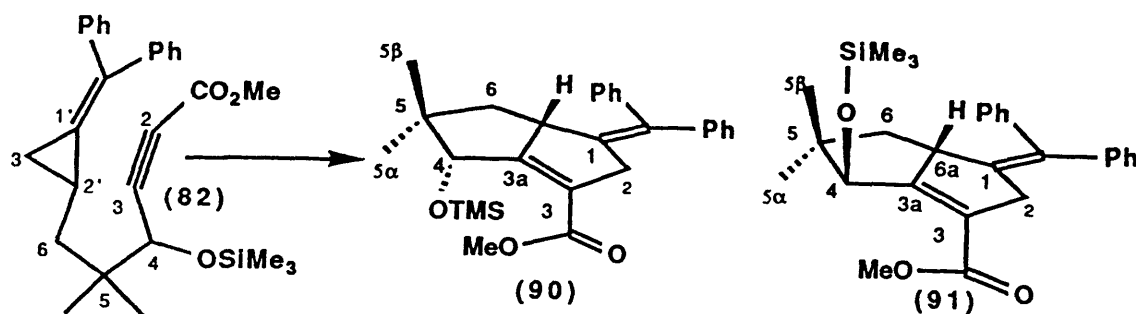
127.96, 128.14, 128.39, 128.57, 128.82(Ar) , 136.20(C-1, +ve) ,
 141.33(C-7, +ve) , 142.18(C-3_a, +ve) , 165.68(CO₂Me) ;
 (Found : M⁺, 446.2278 . C₂₈H₃₄O₃Si requires : M⁺, 446.2277.)

**59) BIS(DIBENZYLIDENEACETONE)PALLADIUM(0) CATALYSED CYCLISATION OF
 DIPHENYLMETHYLENECYCLOPROPANE (60) UNDER ULTRASONICATION**



To bis(dibenzylideneacetone)palladium (0) (1 mg, 1.7×10^{-6} mol) and diphenylmethylenecyclopropane (82) (50 mg, 0.12 mmol) in toluene (2 ml) was added a solution of triisopropylphosphite (0.250 ml of a 0.010 M solution in toluene, 1.7×10^{-6} mol). The mixture was sealed in an ampoule and ultrasonicated for 4 days, when the ampoule cracked. The solvent was stripped at reduced pressure, and the residue chromatographed to afford in addition to recovered starting material (25 mg, 50%), the more polar cis diastereoisomer (90) (6 mg, 12%) identical in all respects to previously synthesised material. No attempt was made to isolate the trans isomer (91).

60) BIS(DIBENZYLIDENEACETONE)PALLADIUM(0) CATALYSED CYCLISATION OF
DIPHENYLMETHYLENECYCLOPROPANE (82) UNDER THERMAL CONDITIONS

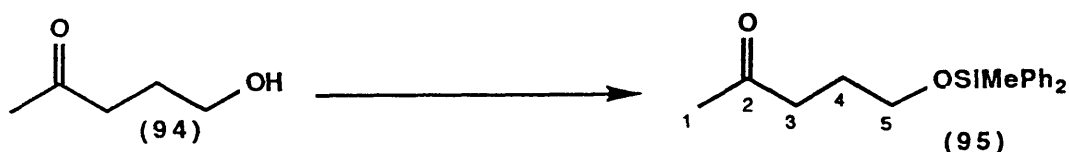


To bis(dibenzylideneacetone)palladium (0) (6 mg , $1.0 \times 10^{-5} \text{ mol}$) and diphenylmethylenecyclopropane (82) (206 mg , 0.46 mmol) in toluene (5 ml) was added a solution of triisopropylphosphite (1.00 ml of a 0.010 M solution in toluene, $1.0 \times 10^{-5} \text{ mol}$). The mixture was stirred briefly, then transferred to a Carius tube and sealed under argon. The tube was heated at $105\text{--}110^\circ\text{C}$ for 24 h , cooled, the tube opened, and the contents concentrated at reduced pressure. The residue was chromatographed (Silica, 2% ether/petrol), to afford two fractions, the less polar of which (104 mg , 50.5%) consisted predominantly of the trans bicycle (91), identical with material previously obtained, contaminated with traces of starting material.

The cis bicycle constituted the more polar fraction as before (78 mg , 38%), a colourless oil. ν_{max} (film) $2954, 1725, 1491, 1441, 1324, 1297, 1248, 1191, 1092, 1030, 878, 844, 786, \& 701 \text{ cm}^{-1}$; δ_{H} (250 MHz ; C_6D_6) $0.27 (9\text{H}, \text{s}, \text{TMS})$, $0.77 (3\text{H}, \text{s}, \text{C-5 Me exo})$, $0.88 (3\text{H}, \text{s}, \text{C-5 Me endo})$, $1.17 (1\text{H}, \text{dd}, J 12.0, 9.0 \text{ Hz}, 6\text{-H}_1 \text{ exo})$, $1.32 (1\text{H}, \text{dd}, J 12.0, 10.0 \text{ Hz}, 6\text{-H}_1 \text{ endo})$, $3.38 (3\text{H}, \text{s}, \text{CO}_2\text{Me})$, $3.52 (1\text{H}, \text{dd}, J 21.5, 3.0 \text{ Hz}, 2\text{-H}_1 \text{ exo})$, $3.92 (1\text{H}, \text{t}, J 9.5 \text{ Hz}, 6\text{-H})$, $4.02 (1\text{H}, \text{dd}, J 21.5, 1.5 \text{ Hz}, 2\text{-H}_1 \text{ endo})$, $4.32 (1\text{H}, \text{br s}, 4\text{-H})$, $7.1 (10\text{H}, \text{m}, \text{Ph})$; δ_{C} (22.5 MHz ; C_6D_6) $0.57 (\text{TMS})$, $24.80, 27.67 (\text{C-5-Me})$, $41.58 (\text{C-6})$, $43.84 (\text{C-2})$,

45.18(C-5) , 50.80(CO₂Me) , 51.65(C-6_a) , 77.90(C-4) ,
 124.82(C-3) , 126.5-129.28(Ar) , 136.36(C-1) , 140.57(C-7) ,
 142.77(C-3_a) , 164.56(CO₂Me) ; m/z 446(M⁺), 431(M-Me), 390, 356(M-TMSOH), 331, 279(M-Ph₂CH), 241, 167(Ph₂CH), 144, 115, 91, 84, 73, 59(CO₂Me)
 (Found : M⁺, 446.2287 . C₂₈H₃₄O₃Si requires : 446.2277.)

61) PREPARATION OF 5-DIPHENYLMETHYLSILYLOXY-2-PENTANONE (95)

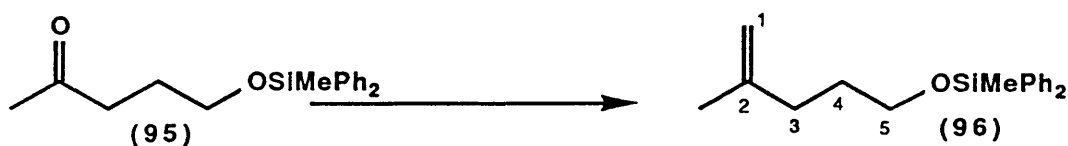


To a solution of chlorodiphenylmethylsilane (25.6 g, 110 mmol, 1.1 eq), 4-DMAP (0.50 g, 4.0 mmol, 0.04 eq), and triethylamine (11.11 g, 15.3 ml, 120 mmol, 1.2 eq) in DCM (250 ml) at 0°C was added 5-hydroxy-2-pentanone (10.2 g, 100 mmol), and the reaction stirred briefly before standing at 4°C for 24 h. On pouring into water (250 ml) the organic phase was separated, and the aqueous phase extracted with DCM. The combined extracts were washed with brine, dried (Na₂SO₄), and concentrated at reduced pressure. The residue was chromatographed (Silica-15% ether/petrol) to yield 5-DIPHENYLMETHYLSILYLOXY-2-PENTANONE (95)

(17.48 g, 59%) as a colourless oil. $\nu_{\max}$ (film) 2956, 1714, 1428, 1255, 1118, 791, 765, 733, & 700 cm⁻¹ ; δ_{H} (90 MHz ; CDCl₃) 0.0 (3H, s, TMS) , 1.19 (2H, m, 4-H₂) , 1.43 (3H, s, 1-H₃) , 1.86 (2H, t, J 7.2 Hz, 3-H₂) , 3.07 (2H, t, J 6 Hz, 5-H₂) , 6.77 (6H, m, m, p-Ar) , 6.94 (4H, m, o-Ar) ; δ_{C} (22.5 MHz ; CDCl₃)

-3.26(TMS) , 26.47(C-1) , 29.76(C-4) , 39.89(C-3) , 62.35(C-5) ,
 127.78-135.83(Ar),208.46(C-2) ; (Found : C,76.62 ; H,7.48 .
 $C_{18}H_{22}O_2Si$ requires : C,72.43 ; H,7.43 %) .

62) PREPARATION OF 5-DIPHENYLMETHYLSILOXY-2-METHYL-1-PENTENE (96)

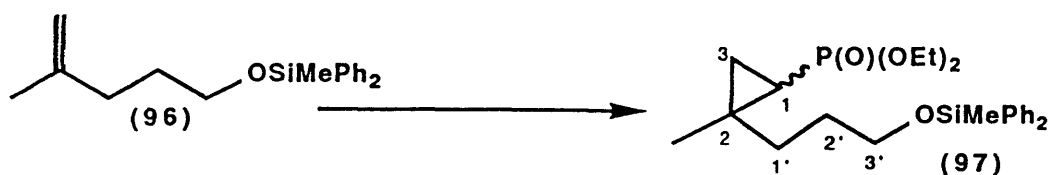


To a slurry of methyltriphenylphosphonium bromide (8.93 g, 25 mmol) in THF (100 ml) at $-78^{\circ}C$ was added n -BuLi (20.0 ml of a 1.25 M solution in hexanes, 25 mmol), and the yellow mixture allowed to warm to room temperature when a red homogeneous solution formed. Ketone (70) (6.77 g, 22.73 mmol) in THF (5 ml) was then added and the mixture stirred 0.5 h at room temperature. Benzoic acid (300 mg, 2.46 mmol, 10 mol%) was added and the reaction stirred a further 18 h. Petrol (150 ml) was added, the reaction filtered through a glass wool plug, and the filtrate washed with water, brine, dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-5% ether/petrol) to afford (5.20 g, 77%) of the 5-DIPHENYLMETHYLSILOXY-2-METHYL-1-PENTENE (96)

as a colourless oil . ν_{max} (film) 2941, 2857, 1640, 1420, 1253, 1118, 790, 734 and 699 cm^{-1} ; δ_H (90 MHz ; $CDCl_3$) 0.0 (3H, s, SiMe) , 1.04 (3H, s, C-2-Me) , 1.08 (2H, m, 4-H₂) , 1.40 (2H, br t, J 7.2 Hz, 3-H₂) , 3.07 (2H, t, J 7 Hz, 5-H₂) , 4.04 (2H, br s, 1-H₂) , 6.7 (6H, m, m, p-Ar) , 6.9 (4H, m, o-Ar) ; δ_C (22.5 MHz ; $CDCl_3$) -3.01(SiMe) , 22.38(C-2-Me) , 30.56(C-4) , 33.91(C-3) , 63.08(C-5) , 109.89(C-1) ,

127.77-136.14(Ar) , 145.48(C-2) ; m/z 296(M^+), 281(M-Me), 255(M- C_3H_5), 240, 203, 199(Ph_2SiOH), 137($PhMeSiOH$), 105, 82, 67, 56, 41 .
 (Found : C, 77.16 ; H, 8.39 . $C_{19}H_{24}OSi$ requires : C, 76.97 ; H, 8.16 %).

63)

PREPARATION OF cis,trans-DIETHYL [2-(3-DIPHENYLMETHYLSILOXYPROP-1-YL)-2-METHYL-CYCLOPROPYL]PHOSPHONATE (97)

To olefin (96) (3.00 g, 10.1 mmol) and cuprous triflate (190 mg, 0.38 mmol) in DCM (2.5 ml) under argon at 0°C was added with stirring a solution of DAMP (28) (3.0 g, 16.85 mmol, 1.6 eq) in DCM (7.5 ml) dropwise over 72 h via a syringe pump. After standing a further 18 h at room temperature, the reaction was concentrated at reduced pressure, and the residue chromatographed (Silica gradient 30% ether/petrol-100% ether), to afford recovered olefin (1.06 g, 35%) and cis,trans- DIETHYL [2-(3-DIPHENYLMETHYLSILOXYPROP-1-YL)-2-METHYL-CYCLOPROPYL] PHOSPHONATE (97) (2.86 g, 64%, 98% on recovered olefin), as a colourless oil .

LESS POLAR diastereoisomer: ν_{max} (film) 2978, 2958, 1428, 1246, 1118, 1094, 1059, 1030, 958, 791, 737, and 701 cm^{-1} ; δ_H (90 MHz ; $CDCl_3$) 0.0 (3H, s, SiMe) , 0.45 (3H, d, J 3Hz, C-2-Me) , 0.1-0.5 (3H, m, 1-H, 3-H₂) , 0.65 (6H, t, J 7.2Hz, $\underline{CH_3CH_2O}$) , 1.06 (4H, m, 2'-H₂, 1'-H₂) , 3.08 (2H, m, 3'-H₂) , 3.40 (4H, m, $\underline{CH_3CH_2O}$) .

6.75 (6H,m, m,p-Ar) , 6.95 (4H,m, o-Ar) ; δ_p (36.2 MHz ; CDCl_3)
 28.54 ; m/z 446(M^+), 431(M-Me), 403(M- C_2H_4 , McLafferty), 369(M-
 Ph), 232(M- Ph_2MeSiOH), 197, 95 .

MORE POLAR diastereoisomer: δ_H (90 MHz ; CDCl_3) 0.0 (3H,s, SiMe) ,

0.1-0.5 (3H,m, 1-H, 3- H_2) , 0.68 (9H,m, C-2-Me, $\text{CH}_3\text{CH}_2\text{O}$) ,

1.0 (4H,m, 2'- H_2 , 1'- H_2) , 3.08 (2H,t, J 6.6Hz, 3'- H_2) ,

3.40 (4H,m, $\text{CH}_3\text{CH}_2\text{O}$) , 6.75 (6H,m, m,p-Ar) , 6.95 (4H,m, o-Ar) ;

δ_p (36.2 MHz ; CDCl_3) 28.66 ;

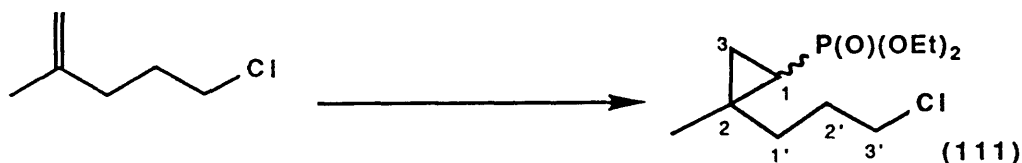
MIXTURE diastereoisomers

(Found : C, 64.45 ; H, 8.16 . $\text{C}_{24}\text{H}_{35}\text{O}_4\text{PSi}$ requires : C, 64.54 ; H, 7.90 % .)

64)

PREPARATION OF cis,trans-DIETHYL

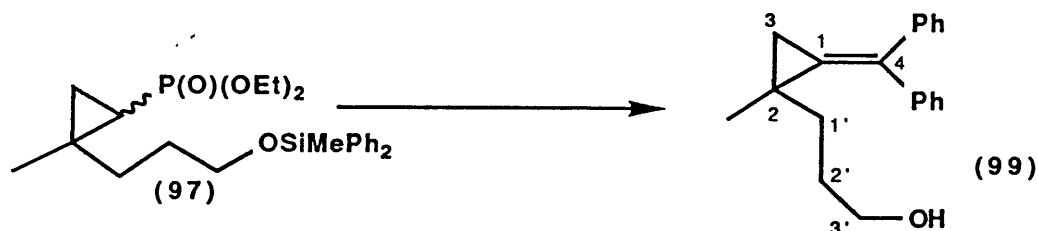
[2-(3-CHLOROPROP-1-YL)-2-METHYL-CYCLOPROPYL] PHOSPHONATE (111)



To cuprous triflate (300 mg, 1.03 mmol) , 5-chloro-2-methyl-
 1-pentene (2.39 g, 20.13 mmol) and DCM (1 ml) at 5°C was added
 dropwise with stirring over 72 h via a syringe pump a solution of
 DAMP (28) (2.0 g, 11.23 mmol) in DCM (2 ml) dropwise . After stirring
 an additional 18 h at room temperature the mixture was
 concentrated at reduced pressure, and the residue chromatographed
 (Silica-80% ether/petrol) to afford *cis,trans*-
 DIETHYL [2-(3-CHLOROPROP-1-YL)-2-METHYL-CYCLOPROPYL] PHOSPHONATE (111)
 (2.39 g, 79%) as a colourless oil . ν_{max} (film) 2981, 2933, 2907, 1388, 1245,
 1097, 1031, 961, 793, and 763 cm^{-1} ; δ_H (90 MHz ; CDCl_3)

0.5-2.3 (16H,m,1-H,3-H₂,C-2-Me,1'-H₂,2'-H₂; 1.27 ,6H,t,J 7Hz,OCH₂CH₃)
 3.5 (2H,m,3'-H₂) , 4.04 (4H,p,J 7Hz,OCH₂CH₃) ; δ_p (36.2 MHz ; CDCl₃)
 28.07 ; m/z 268(M⁺),233(M-Cl,base),205(233-C₂H₄,McLafferty),
 177(205-C₂H₄),163,149,135,138((EtO)₂POH),111,95 .
 (Found : M⁺,268.0990 .C₁₁H₂₂O₃PCl requires : M⁺,268.0995).

65)

PREPARATION OF1-DIPHENYLMETHYLENE-2-METHYL-2-(3-HYDROXYPROP-1-YL)CYCLOPROPANE (99)

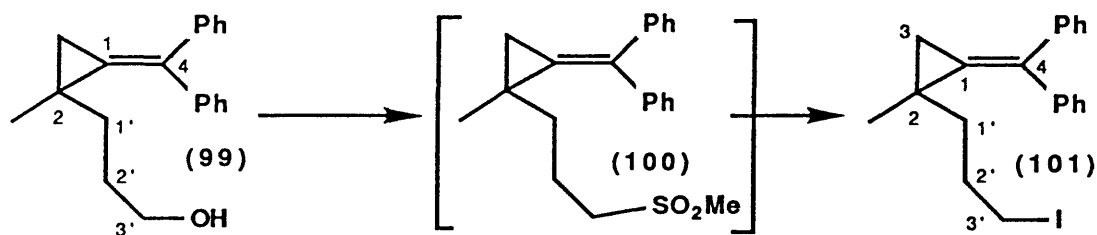
To a solution of the phosphonate (97) (213 mg, 0.477 mmol) in THF (8 ml) and TMEDA (80 μ L, 0.53 mmol) at -125^oC was added *n*-BuLi (210 μ L of a 2.5 M solution in hexanes, 0.525 mmol, 1.1 eq) dropwise .After stirring at -120^oC for 15 min, benzophenone (184 mg, 1 mmol, 2.1 eq) in THF (2 ml) was added dropwise ,the mixture allowed to warm to -100^oC, and stirred 2 h. On warming to -78^oC the solution was stirred a further 3 h. A solution of sodium *t*-butoxide (10 mmol) (NaH, 40 mg of 60% oil dispersion; 225 mg *t*-butanol; 2 ml THF ; stirred 1 h R.T.), was then added dropwise and the mixture allowed to warm slowly to room temperature. After 36 h at room temperature, extensive cleavage of the silyl protection was evident by t.l.c. Deprotection was completed by addition of TBAF (1.0 ml of a 1 M solution in THF, 1.0 mmol).

After a further 3 h, the mixture was quenched by cautious addition of 5% aqueous acetic acid (3 ml), poured into water and extracted with ether. The extracts were dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-40% ether/petrol) to afford

1-DIPHENYLMETHYLENE-2-METHYL-2-(3-HYDROXYPROP-1-YL)CYCLOPROPANE (99)

as a colourless oil (53 mg, 40 %). On other occasions yields varied between 18-40%. ν_{max} (film) 3360, 2935, 2865, 1598, 1491, 1443, 1059, 771, 755, 697, and 610 cm^{-1} ; δ_{H} (250 MHz; CDCl_3) 1.1-1.8 (10H, m, OH, 3-H₂, 1'-H₂, 2'-H₂; 1.29, s, C-2-Me), 3.55 (1H, t, J 6.1 Hz, 3'-H₂), 7.3 (10H, m, Ar); δ_{C} (22.5 MHz; CDCl_3) 16.82 (C-3), 20.06 (C-2), 22.50 (C-2-Me), 29.52 (C-1'), 33.67 (C-2'), 62.90 (C-3'), 126.68-130.46 (Ar), 135.83, 140.90 (C-1, C-4); m/z 278 (M^+), 245, 233, 219 ($\text{M}-\text{C}_3\text{H}_7\text{O}$), 204, 165 (fluorene), 105, 91, 86, 84; (Found: M^+ , 278.1674. $\text{C}_{20}\text{H}_{22}\text{O}$ requires: M^+ , 278.1670).

66)

PREPARATION OF1-DIPHENYLMETHYLENE-2-(3-iodoprop-1-yl)-2-methyl-cyclopropane (101)

To a solution of the alcohol (99) (50 mg, 0.18 mmol) in dry DCM (5 ml) at 0°C was added triethylamine (100 μL , 0.72 mmol, 4 eq), followed by methanesulphonyl chloride (16 μL , 22.7 mg, 1.1

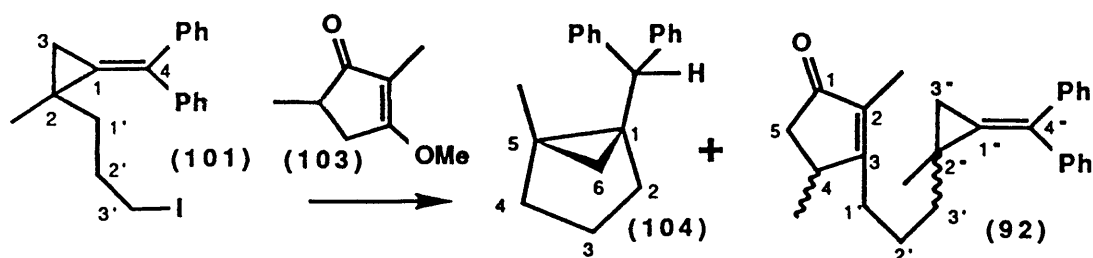
eq). The reaction was stirred at 0°C for 1 h, poured into water and the layers separated. The aqueous layer was extracted with ether, and the extracts dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica, 70% ether/petrol) to afford the mesylate (100) (63 mg, 98%) as a colourless oil.

To the mesylate (100) (63 mg, 0.176 mmol) was added a solution of sodium iodide (110 mg, 0.72 mmol, 4 eq) in acetone (1.5 ml), and the mixture allowed to stand at room temperature in the dark for 24 h, when a precipitate of sodium mesylate formed. The acetone was stripped at reduced pressure, the residue partitioned between ether and water, the organic phase separated, dried (MgSO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-10% ether/petrol) to afford 1-DIPHENYLMETHYLENE-2-(3-iodoprop-1-yl)-2-methyl-cyclopropane (101) (63 mg, 90%) as a colourless foam. Alcohol (99) (3 mg) was also isolated.

ν_{max} (film) 2954, 1599, 1491, 1444, 1032, 770, 700, and 600 cm^{-1} ;
 δ_{H} (90 MHz ; CDCl_3) 1.1-2.0 (9H, m, $1'\text{-H}_2, 2'\text{-H}_2$; 1.26, s, C-2-Me) ,
 3.09 (2H, t, J 6.6 Hz, $3'\text{-H}_2$) , 7.3 (10H, m, Ph) ; δ_{C} (22.5 MHz ; CDCl_3)
 6.81 (C-3') , 17.13 (C-3) , 19.51 (C-2) , 22.56 (C-2-Me) , 30.62 (C-1')
 38.37 (C-2') , 126.80-132.54 (Ar) , 135.10, 140.72 (C-1, C-4) ;
 m/z 388 (M^+), 373 (M-Me), 260 (M-HI), 219 (M- $\text{C}_3\text{H}_6\text{I}$), 204 (219-Me), 141,
 165 (fluorene), 105, 91, 77.

(Found : M^+ , 388.0685 . $\text{C}_{20}\text{H}_{21}\text{I}$ requires : M^+ , 388.0688).

67)

LITHIUM-HALOGEN EXCHANGE OF1-DIPHENYLMETHYLENE-2-(3-iodoprop-1-yl)-2-methyl-cyclopropane (101)

To a solution of the iodide (101) (78 mg, 0.2 mmol) in pentane (0.8 ml) at -78°C was added $t\text{-BuLi}$ (0.22 mmol, 130 μL of a 1.7 M solution in hexanes, 1.1 eq), and the mixture stirred 0.7 h. A solution of the ketone (103) (41 mg, 0.29 mmol, 1.5 eq) in THF (1 ml) was then added dropwise, when the reaction became red. After standing 20 min at -78°C , the mixture was allowed to warm to room temperature, poured into saturated aqueous NH_4Cl , and extracted with ether. The extracts were dried (Na_2SO_4), concentrated at reduced pressure, and the residue chromatographed (Silica-gradient 100% petrol to 30% ether/petrol), to afford in order of elution, the bicycle (104) (21 mg, 40% on iodide), recovered iodide (101) (15 mg, 19%), and the desired adduct (5 mg, 7%) as colourless oils.

1-(DIPHENYLMETHYL)-5-METHYL-BICYCLO[3.1.0]HEXANE (104)

ν_{max} (film) 3057, 3025, 2955, 2869, 1598, 1491, 1446, 1032, 769, 745, and 699 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.17 (1H, d, J 5 Hz, 6- H_1), 0.66 (1H, d, J 5 Hz, 6- H_1), 0.7–2.0 (10H, m, all aliphatics, ; 1.3, s, C-5-Me) 3.8 (1H, s, PhCHPh), 7.25 (10H, m, Ar); δ_{C} (22.5 MHz; CDCl_3) 19.33 (C-5-Me, -ve), 19.63 (C-6), 19.94 (C-5), 29.58, 30.19, 35.44 (C-2, C-3, C-4), 39.89 (C-1), 53.44 (PhCHPh , -ve), 125.7–129.55 (ArC-H), 143.22, 144.99 (ArC-C); m/z 262 (M^+), 247 (M-

Me), 233, 219, 205, 191, 167 (PhCHPh, base), 152, 115, 95 (M-167), 91, 77 ;

(Found : M^+ , 262.1717 . $C_{20}H_{22}$ requires M^+ , 262.1721).

**2,4-DIMETHYL-3-[3-(1-DIPHENYLMETHYLENE)-2-METHYL-CYCLOPROP-2-YL]
CYCLOPENTENONE (92)**

$\nu_{\max}$ (CCl₄) 3058, 3026, 2961, 2868, 1700 (s, C=O), 1642, 1491, 1443, 1411, 1382, 1340, 1297, 1096, 1074, 1033, 727, 697, and 618 cm^{-1} ;

δ_H (250 MHz ; CDCl₃) 1.03 (3H, 2x d, J 7Hz, diast. C-4-Me) ,

1.1-1.7 (17H, m, 3"-H₂, 3'-H₂, 2'-H₂, 1-H₂, ; 1.31, 2x s, diast. C-2"-Me;

1.58, s, C-2-Me) , 1.91 (1H, m, 4-H) , 2.56 (2H, m, 5-H₂) ,

7.30 (8H, m, Ar) , 7.44 (2H, m, Ar) ; m/z 370 (M^+), 332, 293 (M-Ph),

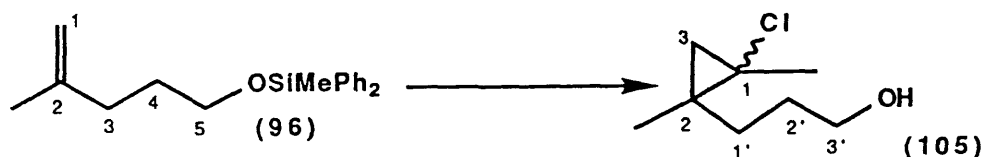
278 (293-Me), 260 (M-C₇H₉OH), 245 (260-Me), 231, 220 (Ph₂C₆H₈, base),

205 (M-fluorene), 191, 178, 165 (fluorene), 151, 137, 110, 91, 77, 69, 57, 41 ;

(Found : M^+ , 370.2307 . $C_{27}H_{30}O$ requires : M^+ , 370.2297).

68) PREPARATION OF 1-CHLORO-1,2-DIMETHYL-2-(3-HYDROXYPROP-1-YL)

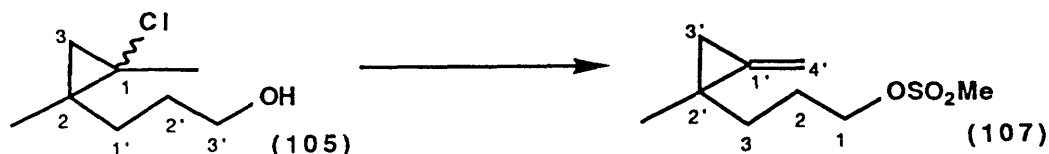
CYCLOPROPANE (105)



To a solution of the olefin (96) (2.59 g, 8.74 mmol) and 1,1-dichloroethane (1.124 g, 11.36 mmol, 0.960 ml) in ether (4 ml) at $-35^{\circ}C$ was added *n*-BuLi, (9.36 ml of a 2.1M solution in hexanes, 19.66 mmol, 2.25 eq) dropwise with stirring over 3 h via a syringe pump . The solution rapidly became orange. Further portions (0.5 ml, 5.9 mmol) of 1,1-dichloroethane were added 1 h, and 2h after commencement of base addition . On completion of

base addition the mixture was allowed to warm to room temperature, poured into water and extracted with petrol. The extracts were dried (MgSO_4), concentrated at reduced pressure, and the residue taken up in THF (5 ml). TBAF (10.0 ml of a 1.1 M solution in THF, 11 mmol) was added and the solution stirred at room temperature for 18 h. On pouring into water, the reaction was extracted with ether, the extracts dried (MgSO_4), and concentrated. Kugelrohr distillation of the residue (70°C , 1 torr) afforded 1-CHLORO-1,2-DIMETHYL-2-(3-HYDROXYPROP-1-YL) CYCLOPROPANE (105) as a colourless oil, (1.13 g, 80%). ν_{max} (film) 3338, 2937, 1438, 1381, 1130, 1057, 796, 738, and 700 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.59 (1H, d, J 6.5 Hz, 3- H_1), 0.80 (1H, d, J 6.5 Hz, 3- H_1), 1.32 (3H, s, C-2-Me), 1.62 (3H, s, C-1 Me), 1.0-2.0 (5H, m, 1'- H_2 , 2'- H_2 , OH), 3.64 (2H, t, J 6 Hz, 3'- H_2); δ_{C} (22.5 MHz; CDCl_3) 18.78 (C-3), 21.03 (C-2), 24.94 (C-2-Me), 28.79 (C-1-Me), 30.07 (C-1'), 33.73 (C-2'), 50.45 (C-1), 62.96 (C-3'); m/z 145 (M-OH), 127 (M-Cl), 126 (M-HCl), 116 ($\text{C}_6\text{H}_9\text{Cl}$), 81, 67, 55, 41. (Found: M-HCl, 126.1044. $\text{C}_8\text{H}_{15}\text{ClO}$ requires: M-HCl, 126.1045).

69) PREPARATION OF 3-(2-METHYL-1-METHYLENE-CYCLOPROP-2-YL)PROPYL METHANESULPHONATE (107)



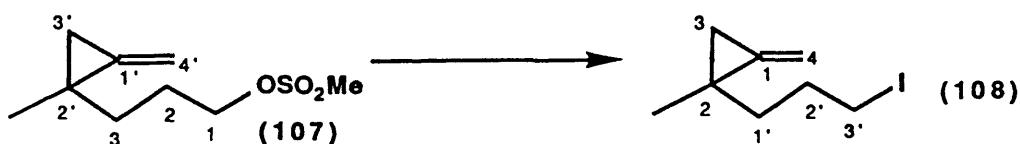
To a solution of potassium *t*-butoxide (1.14 g, 7.6 mmol, 2 eq),

in dry DMSO (5 ml) at 90°C was added with stirring a solution of the cyclopropyl chloride (105) (617 mg, 3.79 mmol) dropwise via a syringe pump over 2 h. On cooling the resulting dark red mixture was poured into water (25 ml), and extracted with ether (40 ml). The extracts were dried (MgSO₄), filtered and the crude ethereal solution was treated at 0°C with triethylamine (3.2 ml, 22.7 mmol, 6 eq) and methanesulphonyl chloride (870 mg, 0.590 ml, 7.59 mmol) for 18 h. The mixture was poured into water (25 ml), and extracted with ether (40 ml). The extracts were dried (MgSO₄), and concentrated at reduced pressure. Chromatography of the residue (Silica, 20% ether/petrol) afforded

3-(2-METHYL-1-METHYLENE-CYCLOPROP-2-YL)PROPYL METHANESULPHONATE (107)

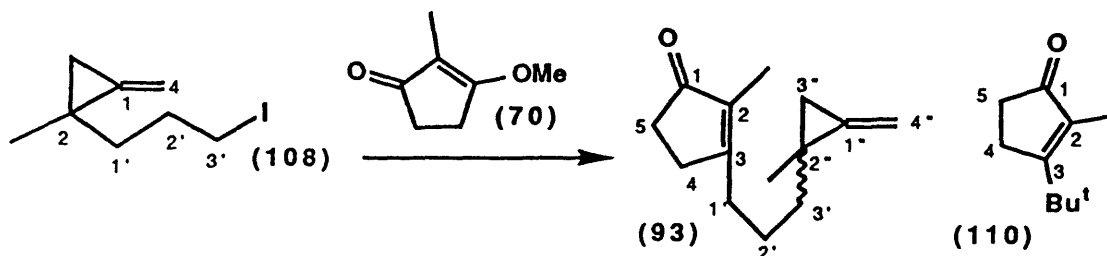
(550 mg, 71%) as a colourless oil. $\nu_{\max}$ (film) 2966, 1449, 1353, 1174, 954, and 817 cm⁻¹; δ_{H} (90 MHz; CDCl₃) 0.86 (2H, m, 3'-H₂), 1.08 (3H, s, C-2'-Me), 1.2-2.0 (4H, m, 3-H₂, 2-H₂), 2.90 (3H, s, SO₂Me), 4.13 (2H, t, J 6.8 Hz, 1-H₂), 5.25 (2H, m, 4'-H₂); δ_{C} (22.5 MHz; CDCl₃) 16.40 (C-3'), 18.84 (C-2'), 21.16 (C-2'-Me), 26.34 (C-3), 33.24 (C-2), 36.90 (SO₂Me), 69.92 ((C-1), 101.53 (C-4'), 141.88 (C-1'); m/z 108 (M-MeSO₃H), 93 (108-Me), 82, 79 (MeSO₂), 67 (C₅H₇), 41 (C₃H₅). (Found: C, 53.04; H, 7.85. C₉H₁₆O₃S requires C, 52.91; H, 7.90 %)

70)

PREPARATION OF2-(3-iodoprop-1-yl)-2-methyl-1-methylenecyclopropane (108)

To a solution of the mesylate (107) (200 mg, 1.27 mmol) in acetone (5 ml) was added sodium iodide (760 mg, 5.07 mmol, 4eq), and the solution stood at room temperature in darkness for 24 h. Silica (1.5 g) was then added and the mixture evaporated to dryness at reduced pressure. The pre-adsorbed residue was chromatographed (Silica-5% ether/petrol[30-40 bp]) to afford 2-(3-iodoprop-1-yl)-2-methyl-1-methylenecyclopropane (108) (180 mg, 77%) as a colourless oil. $\nu_{\max}$ (film) 2958, 2869, 1452, 1375, 1254, 1205, 1172, 1055, 917, 886, and 700 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 0.92 (2H, m, 3-H₂), 1.13 (3H, s, C-2-Me), 1.3-2.2 (4H, m, 1'-H₂, 2'-H₂), 3.18 (2H, t, J 6.8 Hz, 3'-H₂), 5.35 (2H, m, 4-H₂); δ_{C} (22.5 MHz; CDCl_3) 6.57 (C-3'), 16.76 (C-3), 19.02 (C-2), 21.65 (C-2-Me), 31.23 (C-1'), 38.61 (C-2'), 101.72 (C-4), 142.24 (C-1); m/z 235 (M-H), 109 (M-I), 95 (M-CH₂I), 79, 67, 41 (C₃H₅). (Found: M-H, 234.9988. C₈H₁₃I requires: M-H, 234.9984.)

71)

LITHIUM-HALOGEN EXCHANGE REACTION OF2-(3-iodoprop-1-yl)-2-methyl-1-methylenecyclopropane (108)

A solution of the iodide (108) (961 mg, 4.07 mmol) in pentane (9 ml) was added slowly to a stirred solution of *t*-BuLi (5.27 ml of a 1.7 M solution in hexanes, 8.95 mmol, 2.2 eq) at -78°C , and the colourless solution was stirred a further 0.7 h. The solution was then rapidly cannulated into a stirred solution of the ketone (70) (803 mg, 6.4 mmol) in THF (15 ml) at -78°C , when the mixture became yellow. After stirring an additional 10 min at -78°C , the reaction was permitted to warm to room temperature, and 10% w/w aqueous HCl (6 ml) added slowly. The mixture was stirred vigorously for 8 h, water was added and the organic phase separated. The aqueous phase was extracted with ether, the combined organic layers washed with aqueous NaHCO_3 , dried (Na_2SO_4), and concentrated at reduced pressure. The residue was chromatographed (Silica-40% ether/petrol) to afford

2-METHYL-3-[3-(2-METHYL-1-METHYLENE-CYCLOPROP-2-YL)PROP-1-YL] CYCLOPENTENONE (93) as a colourless aromatic oil (420 mg, 51%)

ν_{max} (film) 2923, 2863, 1697, 1643, 1618, 1442, 1380, 919, 733, and 646 cm^{-1} ; δ_{H} (90 MHz; CDCl_3) 1.17 (3H, s, C-2-Me), 1.50 (3H, s, C-2''-Me), 0.5-2.6 (12H, m, 3''-H₂, 3'-H₂, 2'-H₂, 1'-H₂, 4-H₂, 5-H₂), 5.0 (2H, m, 4''-H₂); in a 60:40 ratio with

3-t-BUTYL-METHYLCYCLOPENT-2-ENONE (110)

δ_{H} (90 MHz ; CDCl_3) 1.17 (3H, s, C-2-Me) , 1.6 (9H, s, ^tBu) , 1.9-2.6 (4H, m, 4-H₂, 5-H₂) ;

m/z 204 (M^+) , 189 (M-Me) , 176, 163 (M-C₃H₅) , 137 (M-C₅H₇) , 123, 110, 95,

67 (C₅H₇) , 41 (C₃H₅) ;

(Found : M^+ , 204.1518 . C₁₄H₂₀O requires : M^+ , 204.1514) .

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