RHODIUM CATALYSED TANDEM HYDROSILYLATION CYCLISATION REACTIONS

A thesis presented by

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In partial fulfilment of the requirements
for the award of the degree of

Master of Philosophy of The University of London

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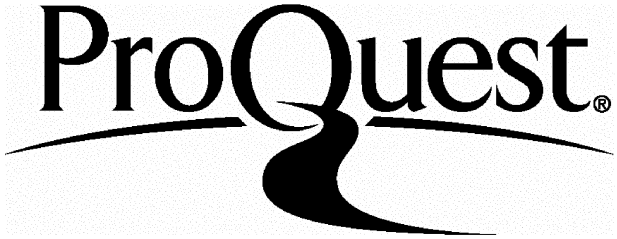
April 2000

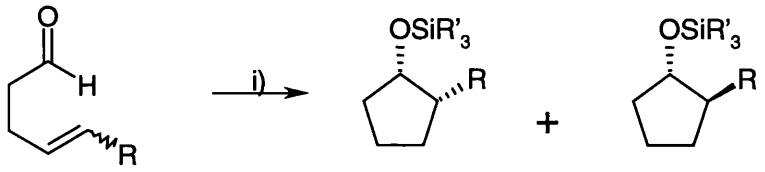


To John and Deanna with all my love

ABSTRACT

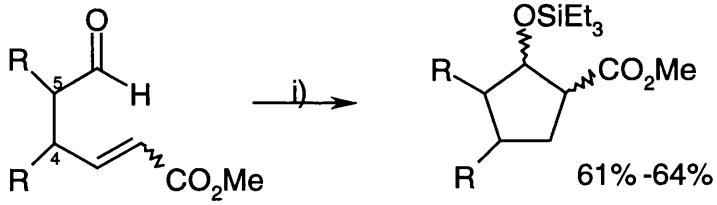
Work has begun on defining the scope of a novel tandem hydrosilylation cyclisation reaction as a general method for the synthesis of substituted carbocycles.

Part I: Substituted cyclopentanols are accessible from 4-pentenals in moderate yield and *cis* selectivity. When R=CO_2Me, a reversal in selectivity can be effected through the choice of the catalytic system.



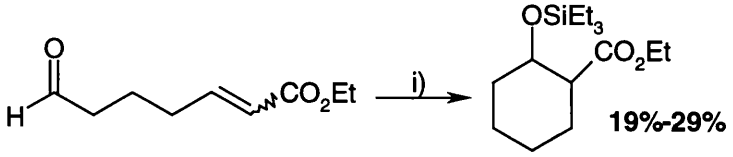
R=CO_2Me: Yield 81%
R=CN: Yield 10%
i)catalytic Rh(I), excess R_3SiH, toluene, heat

Part II: This methodology is compatible with 4, 5-substitution of the parent substrate,
generating functionalised cyclopentanols in moderate selectivity and good yield.



R, R=isopropylidenedioxy, phenyl
i) catalytic $RhCl(PPh_3)_3$, Et_3SiH, heat

Part III: Tandem hydrosilylation cyclisation chemistry is applicable to the synthesis of substituted cyclohexanols.



i) 3%mol $RhCl(PPh_3)_3$, Et_3SiH, toluene, 70°C, 16hr

Conclusion: This novel chemistry provides a simple entry from lactols to highly substituted cyclopentanols and cyclohexanols in moderate yield and selectivity.

CONTENTS

ACKNOWLEDGEMENTS

I would like to thank Professor W.B. Motherwell for allowing me the opportunity to work in his research group and for all of his advice and encouragement throughout the year. I would also like to thank my industrial supervisor, Mr. Andrew Whitehead for his constant enthusiasm, ideas and much appreciated literature references.

I am grateful to all of the technical staff at UCL for their hard work and co-operation and especially to Mrs. Jane Hawkes for the specialist NMR work that she so willingly undertook on my behalf.

Finally, a big thank-you to everybody in the room 459 for being such an enjoyable group to work with.

ABBREVIATIONS

The following abbreviations have been used throughout this thesis:

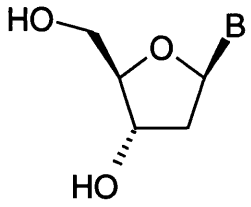
Ac	Acetyl
AIBN	2, 2'-Azobis-*iso*-butyronitrile
Ar	Aryl
BINAP	2, 2'-Bis(diphenylphosphino)-1, 1'-binaphthyl
Bn	Benzyl
Bu	Butyl
^{t}Bu	*tert*-Butyl
COSY	Correlation Spectroscopy
DCM	Dichloromethane
DIBAL	Di-*iso*-butylaluminium hydride
Diphos	1, 2-Bis(diphenylphosphino)ethane
DMAP	4-N, N'-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
Ee	enantiomeric excess
Eq	Molar equivalents
Et	Ethyl
EtOAc	Ethyl Acetate
Hr	hours
IR	Infrared
Me	Methyl
Min	minutes
NBD	Norbornadiene
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
P	Protecting group
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
P.E.	Petroleum Ether
Ph	Phenyl

PPTS	Pyridinium *p*-toluenesulphonate
PTSA	*p*-Toluenesulphonic acid
Pr	Propyl
^{i}Pr	*iso*-Propyl
Pyr	Pyridine
S.G.	Silica Gel
TBAF	Tetra-butylammonium fluoride
TBDMS	tert-Butyldimethylsilyl
Tf	Trifluoromethylsulphonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilane
TPAP	Tetrapropylammonium perruthenate
TPP	Triphenylphosphine

CHAPTER ONE: INTRODUCTION

1.1 Carbocylic Nucleosides: Biological Activity

The chemistry of naturally occurring nucleosides (**1**) and their analogues has been widely studied as a potential source of anti-viral, fungicidal and anti-cancer agents.[1]



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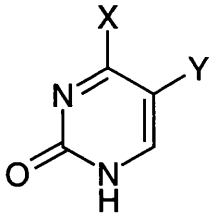
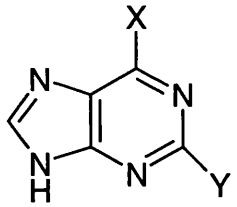


Pyrimidines

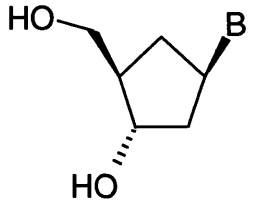


Purines

$X=NH_2$, Y=H Cytosine
X=OH, $Y=CH_3$ Thymine
X=OH, Y=H Uracil

$X=NH_2$, Y=H Adenine
X=OH, $Y=NH_2$ Guanine
X=OH, Y=H Hypoxanthine

Carbocylic nucleosides, where the furanose oxygen has been replaced by a methylene group (**2**), are structurally analogous to natural or synthetic nucleosides.



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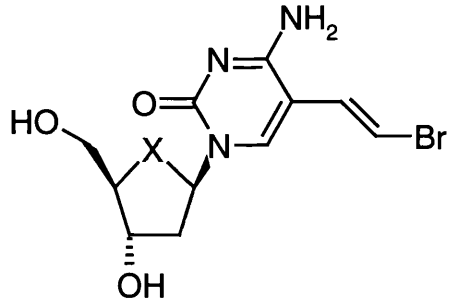
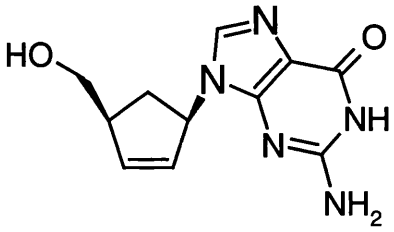
This isosteric replacement often results in enhanced activity, increased metabolic stability,[2] better enzymatic resistance[3] and a relative decrease in the toxicity of the carbocyclic analogue.[4] The mode of action is considered to occur mainly in the inhibition of a replication step of the virus, by direct inhibition of a viral polymerase as a chain terminator and/or by competitive inhibition.[1]

Research on carbocyclic nucleoside analogues has recently been directed towards the development of agents showing activities against HIV (Human Immuno-deficiency Virus), HSV types I and II (Herpes Simplex Virus), VZV (Varicella Zoster Virus), HCMV (Human CytoMegaloVirus) and EBV (Epstein-Barr Virus).

The carbocyclic analogue (**3**) of BVDU (5-bromovinyl-2'-deoxyuridine, (**4**) has some activity against HSV and VZV.[5] Carbovir (C-2',3'-didehydro-2',3'-dideoxyguanosin, (**5**)[6] shows interesting anti-HIV activity *in-vitro*, while Neoplacin A (**6**) is an antibiotic with anti-cancer activity (particularly for leukaemia).[7]



3 X=CH_2
4 X=O



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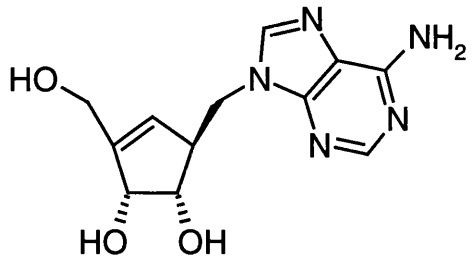

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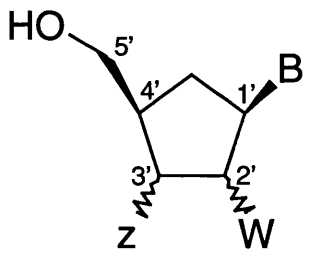
1.2 Existing stereoselective methodology for the synthesis of carbocyclic nucleosides

1.2.1 Introduction

All of the existing syntheses of carbocyclic nucleosides are carried out by prior formation of a functionalised cyclopentane and then by introduction of the purine or pyrimidine heterocycle or an appropriate precursor. The functionalised cyclopentane, by analogy with a β-D-nucleoside, must have certain structural features which will direct the design of the precursor (**7**). It must have:

- a hydroxymethyl group in the 4' position,

- in the 1' position, a group which can react either with a precursor of the heterocycle or with the heterocyclic base directly.



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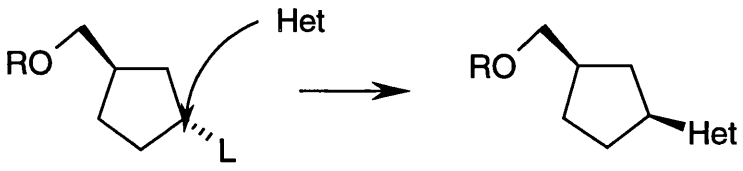
Two approaches can be used to construct the appended purine or pyrimidine heterocycle viz:

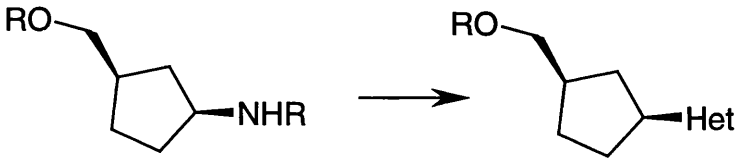
the **CONVERGENT APPROACH**, which involves nucleophilic substitution of a labile α-(*trans*) group on the carbocycle by the heterocycle moiety (Scheme 1),



L=leaving group
Het=heterocyclic base

Scheme 1

or the **LINEAR APPROACH**, which requires construction of a heterocyclic base around a 1' β-(*cis*) amino function (Scheme 2). A 1' β-acidic function on the carbocycle has also been used as a precursor via the Curtius Schmidt reaction.



Het=heterocyclic base

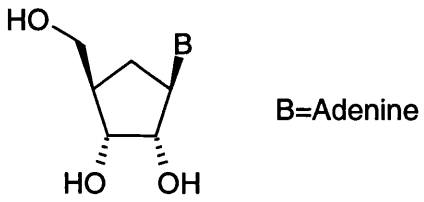
Scheme 2

1.2.2 Existing methodology for the synthesis of functionalised cyclopentanes in C-nucleosides

The diversity and differing successes of existing strategies for the synthesis of various functionalised cyclopentyl moieties is best illustrated by a close

examination of the various approaches to one such carbocyclic nucleoside analogue.

Carbocyclic adenosine, (-)-β-D-aristeromycin (**8**) is believed to exhibit antiviral activity by inhibiting *S*-adenosyl-L-homocysteine hydrolase, an important enzyme in RNA methylation. [8]



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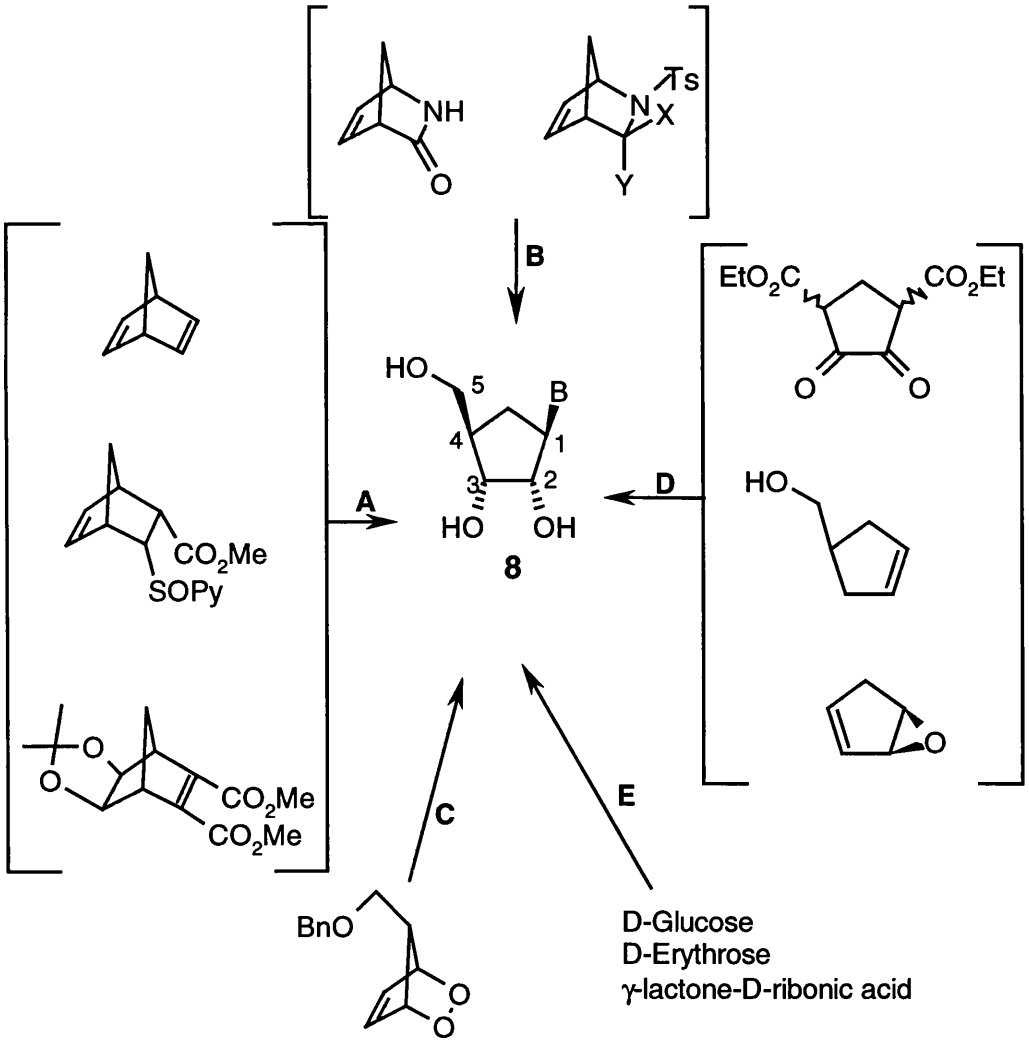
Various strategies have been developed to synthesise this compound (Scheme 3).



Scheme 3

The precursors of these syntheses fall into five categories that define the strategic approach taken.

ROUTE A: Utilizes a bicyclic system of type [C-C] obtained from a Diels-Alder cycloaddition of dienophile of type [C=C] and cyclopentadiene. [9, 10]

ROUTE B: Utilizes a bicyclic system of type [C-N] obtained from a Diels-Alder cycloaddition of an azadienophile of type [C=N] and cyclopentadiene.[11,12]

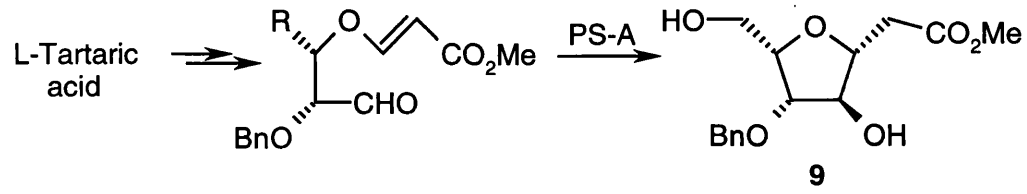
ROUTE C: Utilizes a bicyclic system of type [O-O] obtained from a Diels-Alder cycloaddition of singlet oxygen $^1O_2$ and cyclopentadiene.[13]

ROUTE D: Utilizes a routinely accessible functionalised cyclopentane.[14, 15, 16]

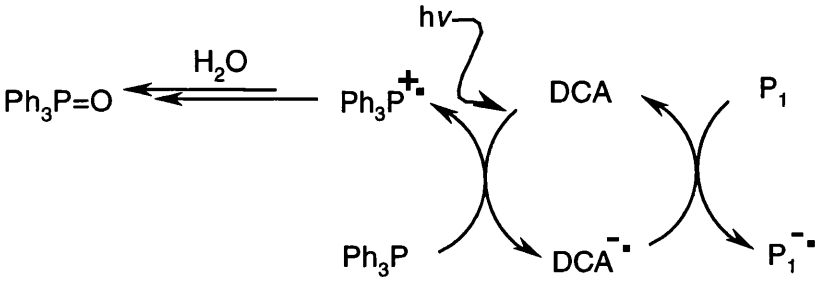
ROUTE E: Uses substrates from the carbohydrate pool such as D-glucose and its derivatives.[17]

As can be seen from Scheme 3, the majority of the literature methods start with rigid bicyclic systems, thereby taking advantage of fixing the configuration at C-1' and C-4' (routes A, B and C). When the synthesis of carbocyclic-ribo-NH_2 involves a functionalised cyclopentane (route D) as a precursor, the main synthetic problem is to control the regiostereoselectivity of the various steps required to produce the desired *cis* configuration of the substituents at C-1' and C-4'.

The approach of starting from the "chiral pool" of natural carbohydrates (and amino acids) to accomplish the synthesis of C-nucleosides has recently received much attention.[18] Pandey *et al.*[19] provide one such example in their synthesis of the C-furanoside (**9**), a precursor to C-nucleosides, as well as many other natural products (Scheme 4).[20]



where PS-A represents photosystem-A shown below

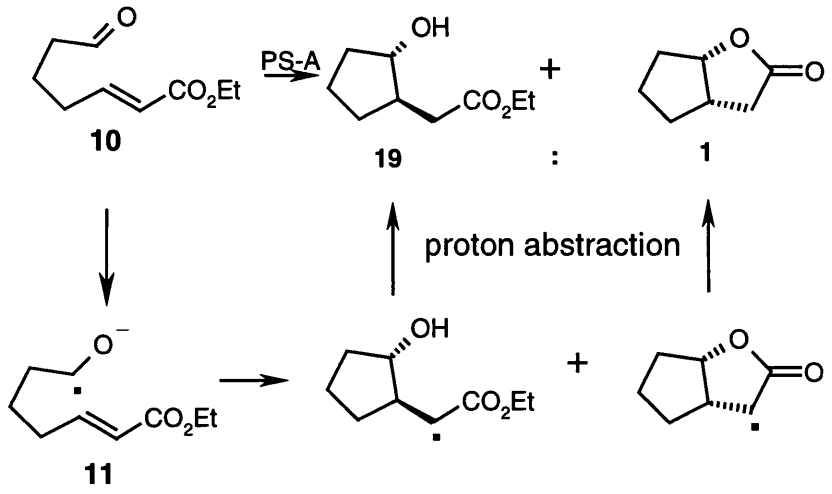


DCA- 9, 10 dicyanoanthracene

P_1- Carbonyl compound

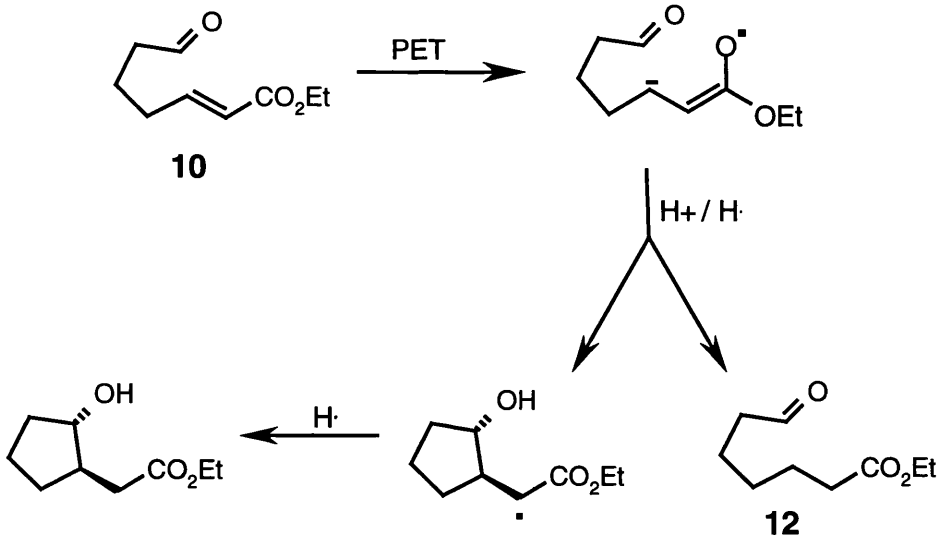
Scheme 4

The key step in their strategy involves the photosensitised one electron transfer cyclisation of an aldehyde tethered to an α, β-unsaturated ester (Scheme 5). Mechanistically, it is believed that this cyclisation involves reduction of the aldehyde (**10**) to a ketyl radical anion intermediate (**11**) followed by intramolecular addition to the electron deficient olefin and H-abstraction.



Scheme 5

The authors consider that the alternative possibility of these cyclisations involving one electron reduction of the α, β-unsaturated ester (**10**) can be dismissed due to the absence of the corresponding olefin reduction product (**12**, Scheme 6).



Scheme 6

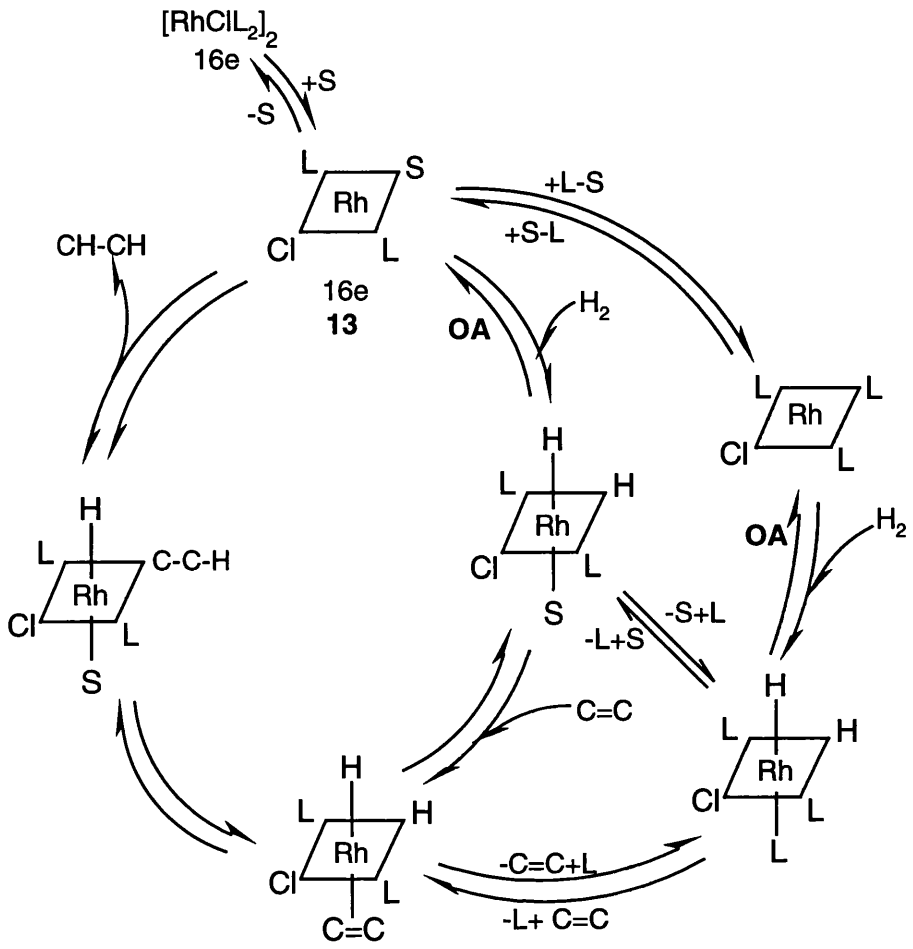
In contrast to the mixtures of *cis* and *trans* cyclopentanols previously reported by other groups[21] working on the cyclisation stereochemistry of ketyl radicals, Pandey *et al.*[19] reports high *trans* diastereoselectivity (>90%). It should be recognised however that the product **9** (Scheme 4) is only isolated in the low yield of 25% following the cyclisation, due to competing pathways available from the ketyl radical intermediate.

1.3 Preparation of Carbocyclic Nucleoside Precursors via Rhodium Catalysed Intramolecular Hydroacylation of Substituted 4-Pentenals

1.3.1 Introduction : Wilkinson's catalyst as the precursor for the active catalytic species

Before discussing the intramolecular variant of hydroacylation in detail, it is pertinent to first examine the role of Wilkinson's catalyst in such a mechanism. In this respect, two reactions of relevance related to hydroacylation are hydrosilylation and alkene hydrogenation.

The catalytic cycle of alkene hydrogenation in particular has been the subject of intense experimental interest. The idealised mechanism of alkene hydrogenation belies a more complex system (Scheme 7).[22] The inner circle represents the major catalytic cycle.



OA- oxidative addition
L= Ph_3P
S=solvent or possibly loosely bonded tertiary phosphine

Scheme 7

The active catalytic species appears to contain two tertiary phosphine ligands but how such a species is actually formed from the tri-tertiary phosphine complex is still open to question. The original suggestion that $RhClL_3$ rapidly dissociates in solution to form the solvated species **13** was somewhat discredited when it was shown, using molecular weight and ^{31}P NMR measurements, that, in the absence of oxygen, $RhClL_3$ is essentially undissociated ($K=3x10^{-3}M$) in benzene

solution. This fits in with Tolman's 16/18 electron rule in that the equilibrium so suggested would involve a 16 to 14 electron species transformation:

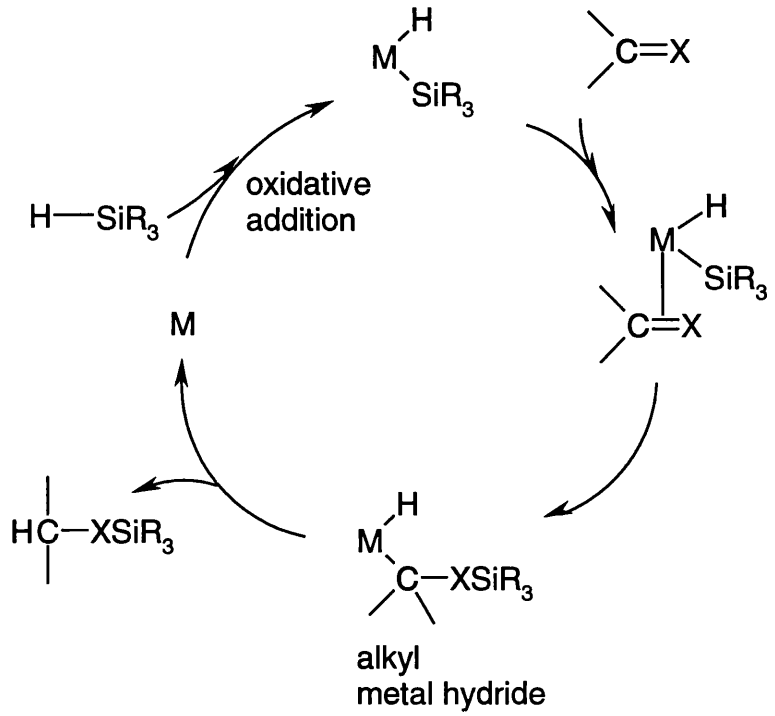
$$\underset{16e}{RhClL_3} \rightleftharpoons \underset{14e}{RhClL_2} + L$$

In the presence of a suitable co-ordinating solvent, eg. EtOH or indeed O_2, this objection could be overcome via a sequence of the type:

$$\underset{16e}{RhClL_3} + S \rightleftharpoons \underset{18e}{RhClL_3S} \rightleftharpoons \underset{\mathbf{13}}{\overset{16e}{RhClL_2S}} + L$$

Thus, the solvated di-tertiary phosphine species [$RhClL_2S$] (**13**) is the true catalyst, [$RhClL_3$] being merely the precursor. This solvated di-tertiary phosphine species (**13**) can also dimerize to form a chloro-bridged dirhodium complex, which is inactive as a catalyst.[23]

The hydrosilylation of alkenes is the process by which a Si-H element is added across an unsaturated bond such as C=C, C=O and C=N. The addition is *cis*, as in hydrogenation. The most frequently employed catalyst precursor for this reaction is H_2PtCl_6, although catalysts such as $Co(CO)_8$, $Ni(COD)_2$, [$NiCl_2(PPh_3)_2$] and [$RhCl(PPh_3)_3$] have also proved to be effective. The catalytic mechanism proposed for hydrosilylation by Ojima[24] is represented in Scheme 8.



Scheme 8

Unfortunately, the reaction mechanism for hydrosilylation is highly controversial.[25] The four main steps in the catalytic cycle proposed by Ojima[24] are as follows:

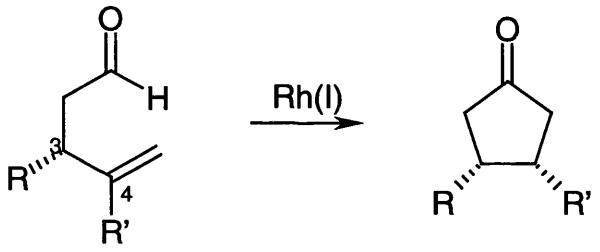
- Initial oxidative addition of the Si-H bond to the low valence transition metal
- Substrate co-ordination
- Insertion of the double bond into Si-M bond forming an alkyl metal hydride
- Reductive elimination of the product to complete the catalytic cycle

The mechanism for hydrosilylation is controversial as the timing of

oxidative addition and substrate interaction with metal is sensitive to the nature of the unsaturated compound. With olefins, the substrate co-ordination to the metallic centre may precede the oxidative addition of Si-H bond. The order of the reaction of Rh-Si and Rh-H is unclear. The Rh-H could react first with C=X bond giving Rh-X linkage.

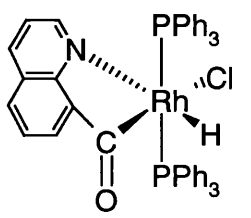
1.3.2 Hydroacylation of substituted 4-pentenals

Rhodium (I) catalysed intramolecular hydroacylations of 3,4-substituted-pentenals have been previously reported by Sakai[246] and other workers[27] as a novel method of cyclopentanone synthesis (Scheme 9). This type of cyclisation has been shown to be highly stereoselective affording the *cis*-substituted products only.[28]



Scheme 9

Labelling work by Miller[29] and isolation of acylrhodium (III) hydride species such as (**14**) by Suggs[30] and (**15**) by Milstein[31] allowed a general mechanism and catalytic cycle for intramolecular hydroacylation to be proposed (Scheme 10).



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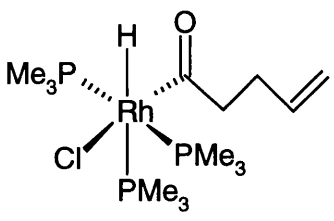

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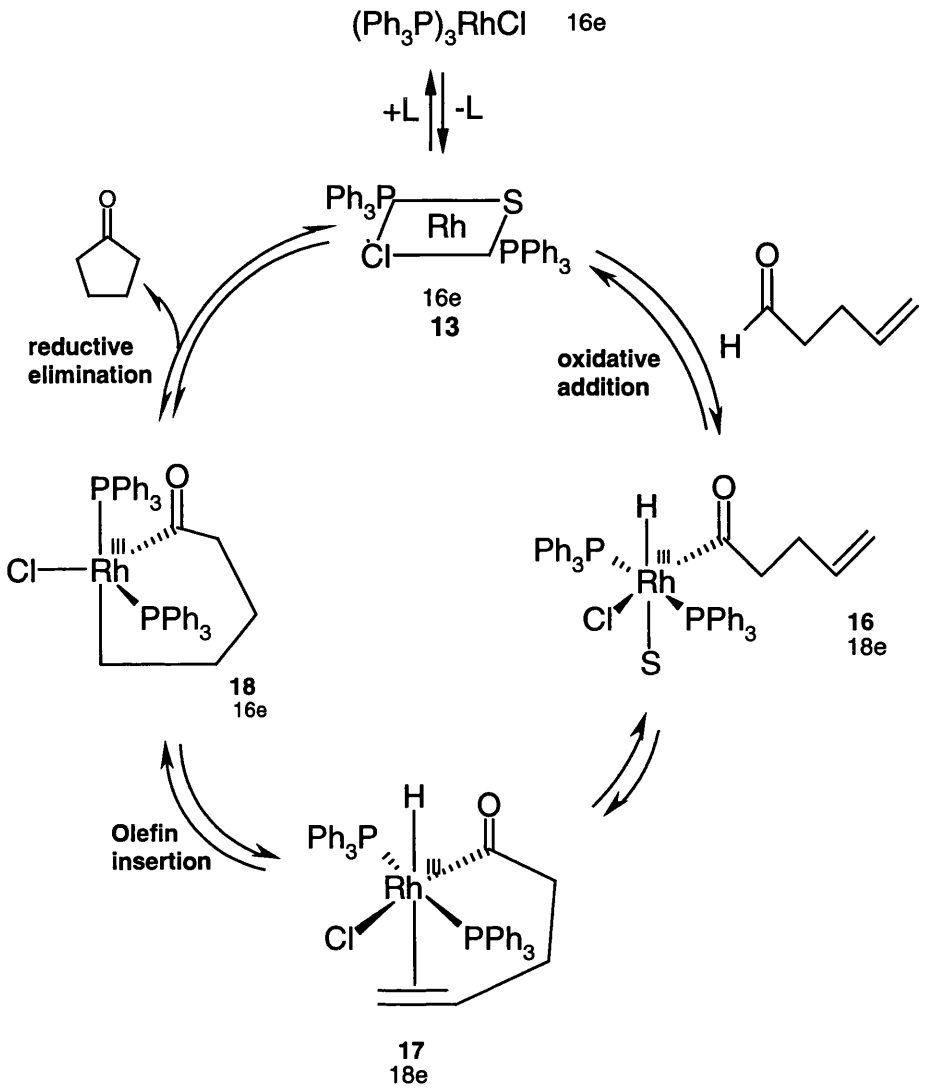


Scheme 10

The key mechanistic steps in the catalytic cycle proposed for rhodium(I) catalysed intramolecular hydroacylation of 4-pentenals are as follows and feature once again the intermediacy of (**13**). Thus:

- Oxidative addition of the aldehyde to the 16e electron Rh(I) catalyst (**13**) generates an 18e hydridoacylrhodium(III) species (**16**).

- The hydride ligand in the hydridoacylrhodium (III) species exerts a strong *trans*[30] effect and thus the *trans* ligand (S in the major catalytic cycle, L=PPh_3 in the minor catalytic cycle) is labilised and replaced by the substrate olefin (**17**).

- Following olefin insertion, the resulting Rh(III) carbometallocycle (**18**) undergoes reductive elimination. This results in carbon-carbon bond formation to generate the cyclopentanone product and also regenerates the Rh(I) catalyst.

By general consensus, the true catalyst is presented as the 16e species $Rh(PPh_3)_2ClS$ (**13**), although this species has proved too reactive and unstable to be detected. As for the case of alkene hydrogenation,[22, 23] this catalytic cycle is idealised and may be sensitive to the nature of the substrate, with $Rh(PPh_3)_3Cl$ possibly involved in a minor catalytic cycle.

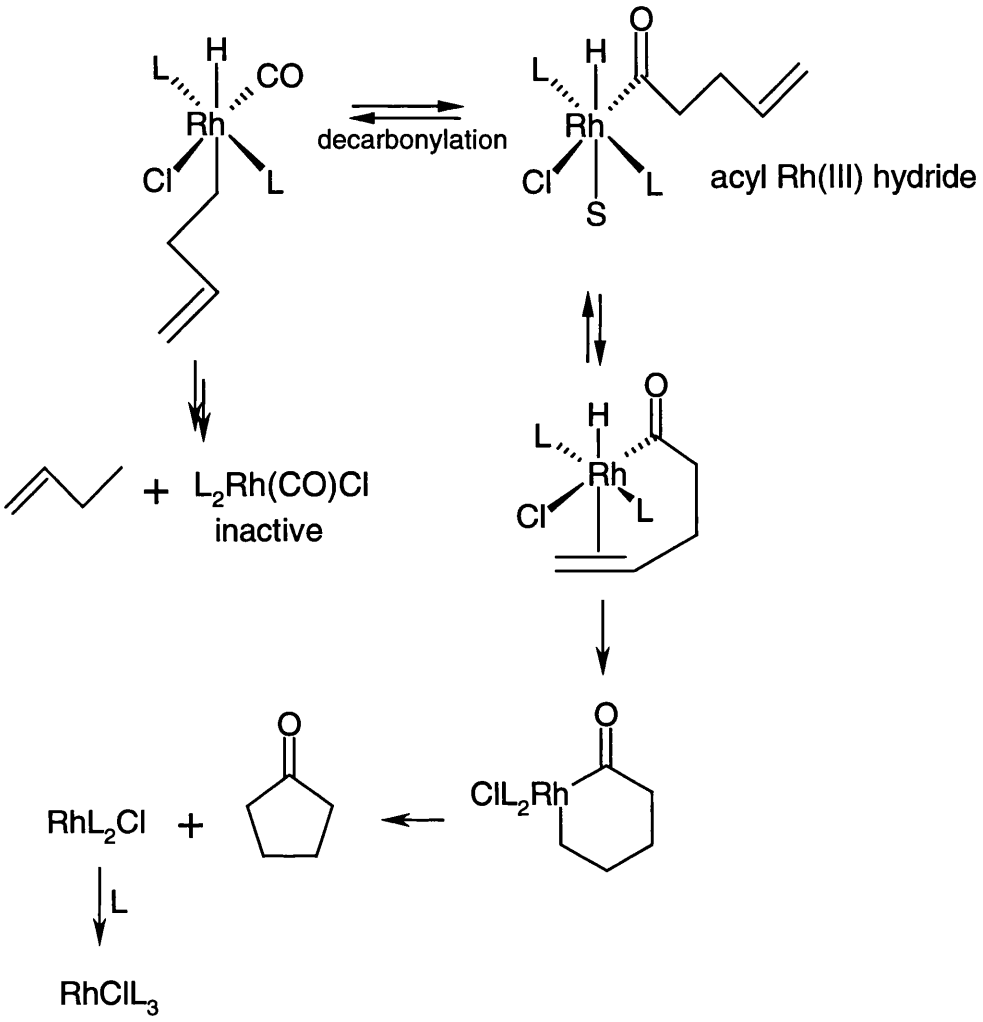
One of the advantages of hydroacylation as a synthetic route to cyclopentanones, is the ease of preparation of the pentenals. The starting materials are readily available from commercial sources and offer the potential to generate highly substituted chiral cyclopentanones from ribose base sugars. The application of such methodology to the construction of carbocyclic nucleosides is accordingly self evident.

1.3.3 Disadvantages of Rh(I) catalysed intramolecular hydroacylation as a means to functionalised cyclopentyl moieties

Although Rhodium (I) catalysed intramolecular hydroacylation appears an attractive method of generating functionalised cyclopentanones, it has a number of limitations. Thus:

- decarbonylation is a competing side reaction which renders the catalyst inactive

(Scheme 11).



Scheme 11

The addition of ethene to simple 4-pentenal mixtures enhances the catalytic activity of the Rh(I) catalyst by pre-empting a metal co-ordination site that is required by the decarbonylation process, thus increasing the yield of the cyclopentanone.[32] However, if co-ordination of the olefin to the Rh(III) species is slow, as in the case of an electron deficient alkene[33] or because of steric interactions of the olefin with surrounding ligands,[27, 34] decarbonylation remains a serious possibility.

Further problems include:

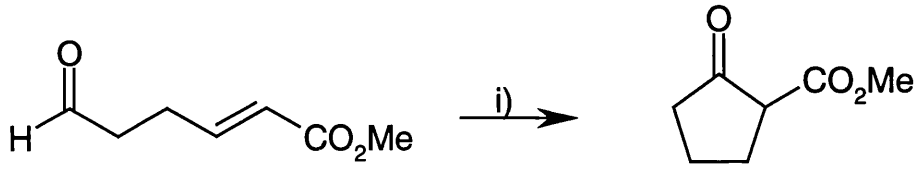
- large amounts of catalyst (20-50 mol%) are needed in many examples.[26, 32]
- alkyl substitution in either the 2 or the 5 position substantially reduces the yield of the ketone.[27]
- it is restricted to the use of an aldehyde functionality since oxidative addition to this group is of course the first step in the catalytic cycle.
- heteroatomic substituents give reduced yields.
- intramolecular hydroacylation is not applicable to the synthesis of larger ring sizes.[27, 35]

1.4 Tandem Hydrosilylation Cyclisation as a means to functionalised cyclopentyl moieties

1.4.1 Introduction

Whitehead[33] determined that the electron deficient terminally substituted 4-pentenal, methyl-6-oxo-2-hexenoate, was incompatible with intramolecular hydroacylation methodology. Large amounts of catalyst were required to achieve only moderate yields, with decarbonylation as the main side reaction (Scheme 12).

An alternative methodology was therefore sought, with the key process being hydrosilylation rather than hydroacylation. The prototypical reaction was first

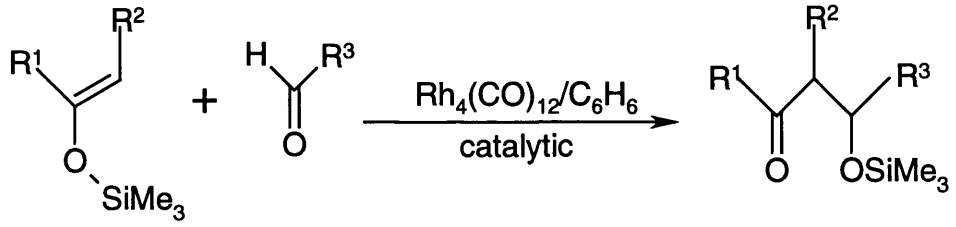


22 69%

i) 25%mol $[RhCl(cyclooctene)_2]_2$, L=tri-*p*-tolylphosphine, 72hr

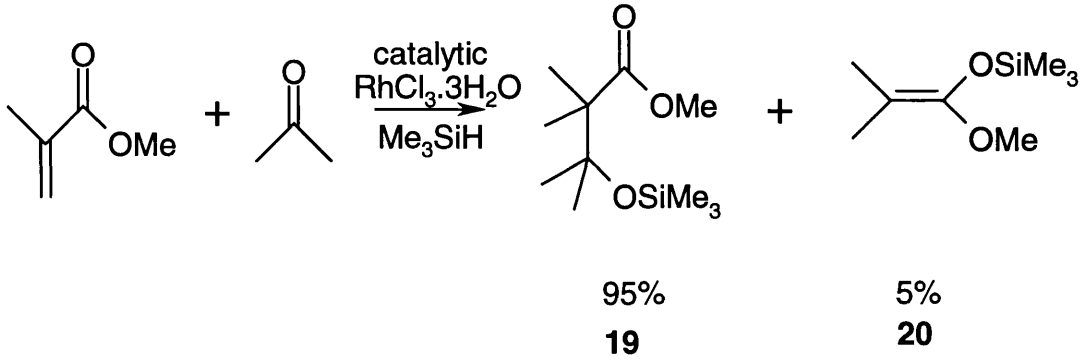
Scheme 12

reported by Matsuda *et al.*[36] in 1986 when they examined the aldol couplings of enol trimethylsilyl ethers with aldehydes in sealed tubes at 100°C for 15 hours, catalysed by rhodium complexes, to yield β-siloxy carbonyls (Scheme 13).



Scheme 13

As a natural progression to this work, Revis and Hilty[37] were the first to report a one-pot reaction of α, β-unsaturated esters with carbonyls and trimethylsilane to give good yields of β-siloxy esters (**19**, Scheme 14).

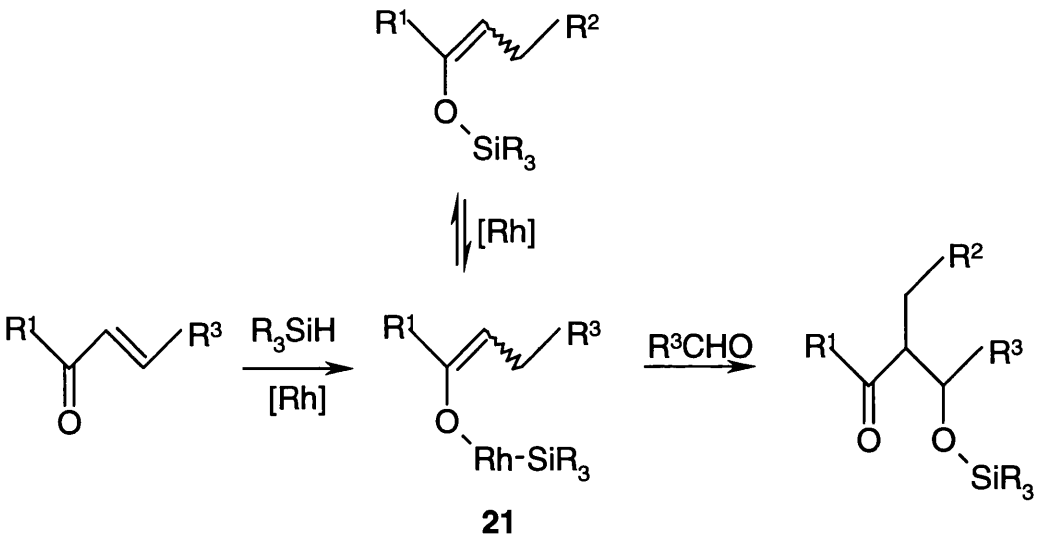


Scheme 14

Since the hydrosilylation of the α, β-unsaturated ester was known to give the silyl ketene acetal (**20**), Revis and Hilty[37] investigated whether the β-siloxy ester proceeded through the formation of the silyl ketene acetal, as reported by Matsuda.[36] They reported that in this one-pot three component reaction at ambient temperature,

this was not the case. This constituted the first hydrosilylative condensation method of preparing β-siloxy esters.

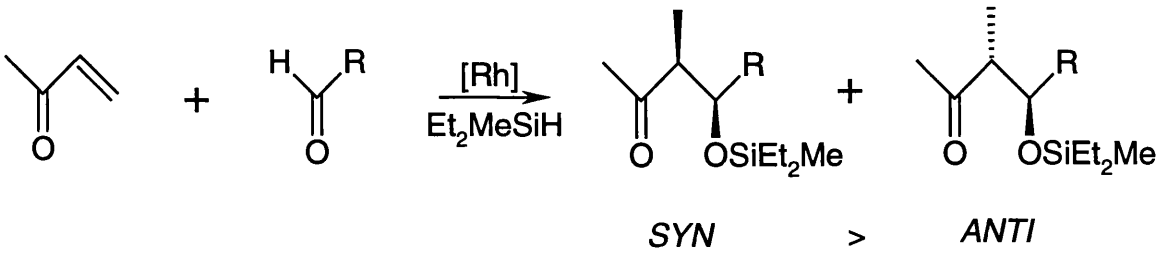
In 1990, Matsuda *et al.*[38] proposed an oxygen-bound rhodium enolate (**21**) as a plausible intermediate for the subsequent aldol condensation. This was based on the work of Heathcock[39] who had isolated such an intermediate and demonstrated its reaction with benzaldehyde to afford aldol products. It is through this intermediate that the two different reactions, *viz* the hydrosilylation of α, β-unsaturated carbonyl compounds to give silyl enol ethers and the formation of β-siloxy carbonyls from silyl enol ethers, can be formally amalgamated (Scheme 15). No direct evidence for the existence of the intermediate was obtained.



Scheme 15

Matsuda *et al.*[38] began to define the generality of this aldol type reaction (Scheme 16). They confirmed the observations by Revis and Hilty[37] that the appreciable amounts of silyl enol ether isolated along with the desired β-siloxy carbonyls were the result of a competitive reaction in the 3-component coupling and

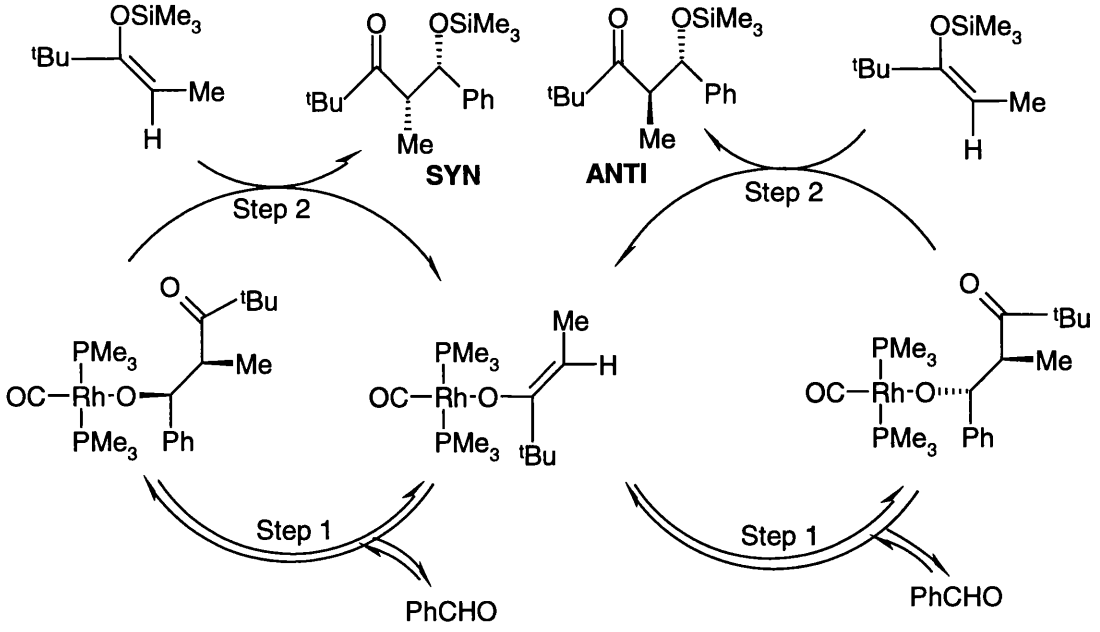
not, in fact, an intermediate precursor. *Syn* selectivity was observed throughout this rhodium catalysed direct coupling of an α, β-unsaturated ketone, an aldehyde and a trialkylsilane.



R=Ph, [Rh]=$Rh_4(CO)_{12}$ (0.5%)
R=alkyl requires [Rh]=$Rh_4(CO)_{12}$ (0.5%)+$MePh_2P$

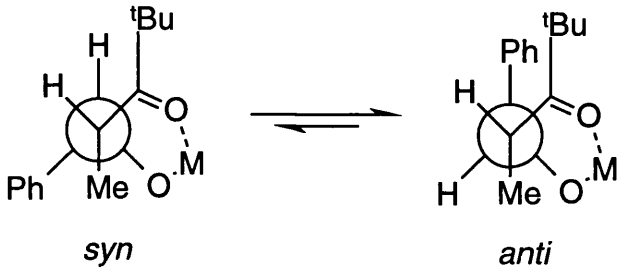
Scheme 16

Heathcock[39] rationalised this *syn*-selectivity during his investigation of oxygen bound Rhodium enolates and their applications in catalytic aldol chemistry (Scheme 17).



Scheme 17

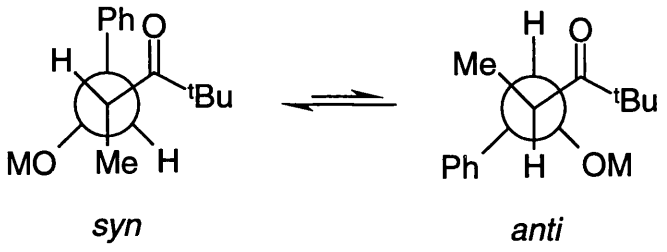
Thus, the aldol addition step (Step 1) is fast and reversible, allowing *syn:anti* equilibration, with the syn aldolate as the thermodynamic isomer. This preference for the *syn* isomer contrasts with the situation in main-group aldolates, where kinetically derived *syn*-aldolates normally equilibrate to the *anti*-diastereoisomer under thermodynamic conditions.[40, 41] Heathcock[39] proposed that this difference could be rationalised by consideration of a chelated versus non-chelated aldolate structure. With zinc and lithium ketolates,[40] the thermodynamic preference for the *anti* diastereoisomer may be understood in terms of the chelated conformations (Scheme 18), where there are more gauche interactions in the *syn* diastereoisomer than there are in the *anti* diastereoisomer.



M=Zn, Li

Scheme 18

For the non-chelated aldolates (Scheme 19), the expected conformations of the *syn* and *anti*-diastereoisomers are those with the fewest gauche interactions (two in each case). It is therefore not surprising that there is not a pronounced preference for either diastereoisomer. Furthermore, because of the very large size of OM in the case of rhodium aldolates, the gauche interactions of this group may be dominant.

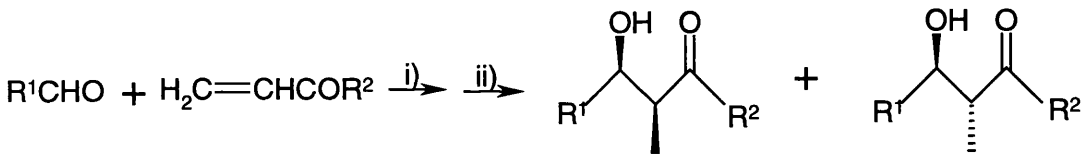


syn *anti*

M=Rh

Scheme 19

The chemistry has been further extended recently by the work of Kiyooka[42] *et al.* (Scheme 20). They reported the first example of an aldol reaction through palladium catalysed hydrosilylation, with *anti*-selectivity being observed.



SYN < *ANTI*

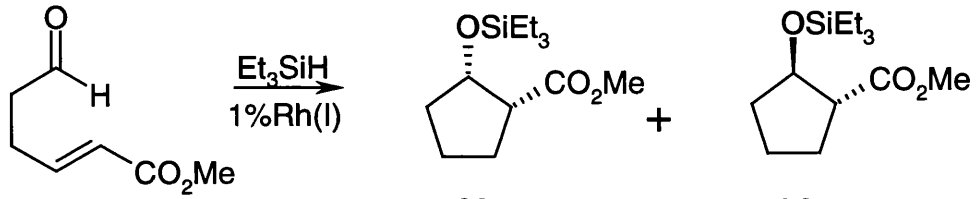
i) $Pd(PPh_3)_4$, Cl_3SiH, RT, 45h

ii) H_3^+O

Scheme 20

1.4.2 Application of existing methodology

Whitehead[33] applied this methodology to the novel intramolecular cyclisation of methyl 6-oxo-2-hexenoate (**22**) to afford the substituted cyclopentanols as the *cis* (**23**) and *trans* (**24**) diastereoisomers (Scheme 21) in good yield and with moderate selectivity.



22 **23** **24**

1%mol $RhCl(PPh_3)_3$	40°C	3	:	1	Yield 77%
1%mol $RhCl(PPh_3)_3$	80°C	2	:	1	
10%mol $RhCl(PPh_3)_3$	80°C	1	:	2	Yield 70%

Scheme 21

The ester functionality was chosen since, on reduction it provided the key 4-hydroxymethyl substituent (**7**) common to a number of five membered carbocyclic nucleosides.

A similar yield and selectivity was observed when the neutral Wilkinson's catalyst was replaced with cationic rhodium catalyst $[Rh(diphos)(NBD)]^+[ClO_4]^-$. No reaction was observed in the absence of rhodium.

Whitehead[33] also investigated the effect of temperature on the *cis* selectivity, with results being summarised in Table 1. All reactions used 1 mol% Wilkinson's catalyst in toluene and were analysed after 4 hours by ^1H NMR.

Temperature °C	*Cis:Trans*
25	no reaction
40	3:1
60	3:1
80	2:1
110	3:2

Table 1

1.4.3 Mechanism

It is plausible that the mechanism of intramolecular cyclisation follows a similar mechanistic pathway to that proposed by Matsuda[38] and Heathcock[39] for the Rh(I) catalysed intermolecular coupling of an α, β-unsaturated ketone, an aldehyde and a trialkylsilane, in that the O-bound rhodium enolate is the key intermediate (**26**, Scheme 22). The initial steps of the tentative Rh(I) catalytic cycle proposed for tandem hydrosilylation intramolecular condensation cyclisation reactions (Scheme 22) are based on the hydrosilylation mechanism proposed by Ojima (Scheme 8).[24]

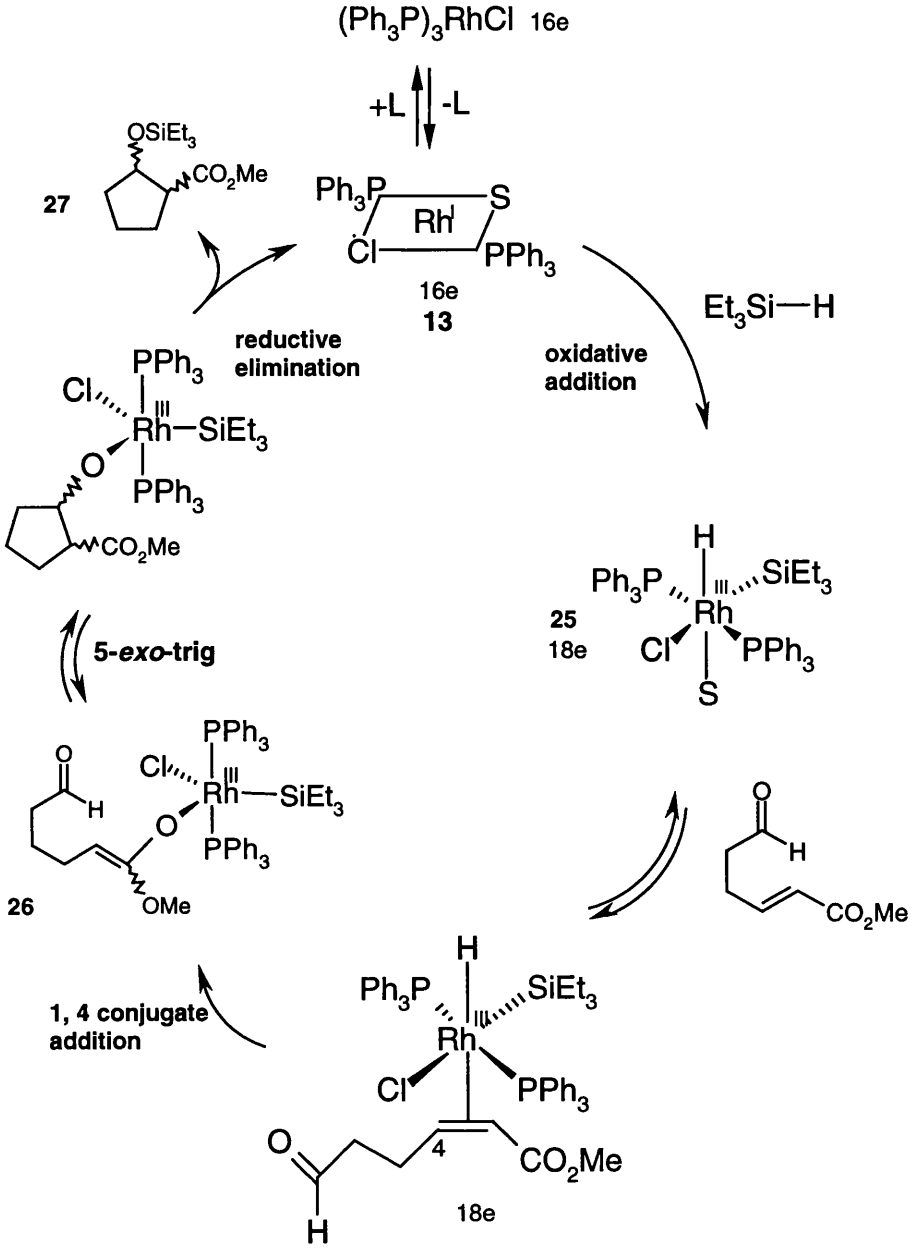
The four main steps in the catalytic cycle are believed to be as follows:

- As the oxidative addition of Rh(I) to the aldehyde is slow, the catalyst adds preferentially to the silane, to give the hydridosilylrhodium species (**25**).

- 1,4-conjugate addition of the hydridosilylrhodium(III) species to the α, β-unsaturated ester to generate a rhodium ketene acetal (**26**).

- Intramolecular addition of the rhodium ketene acetal to the aldehyde.

- Reductive elimination to regenerate the Rh(I) catalyst and yield the silyl protected cyclopentanol (**27**) as a mixture of *cis* and *trans* isomers.

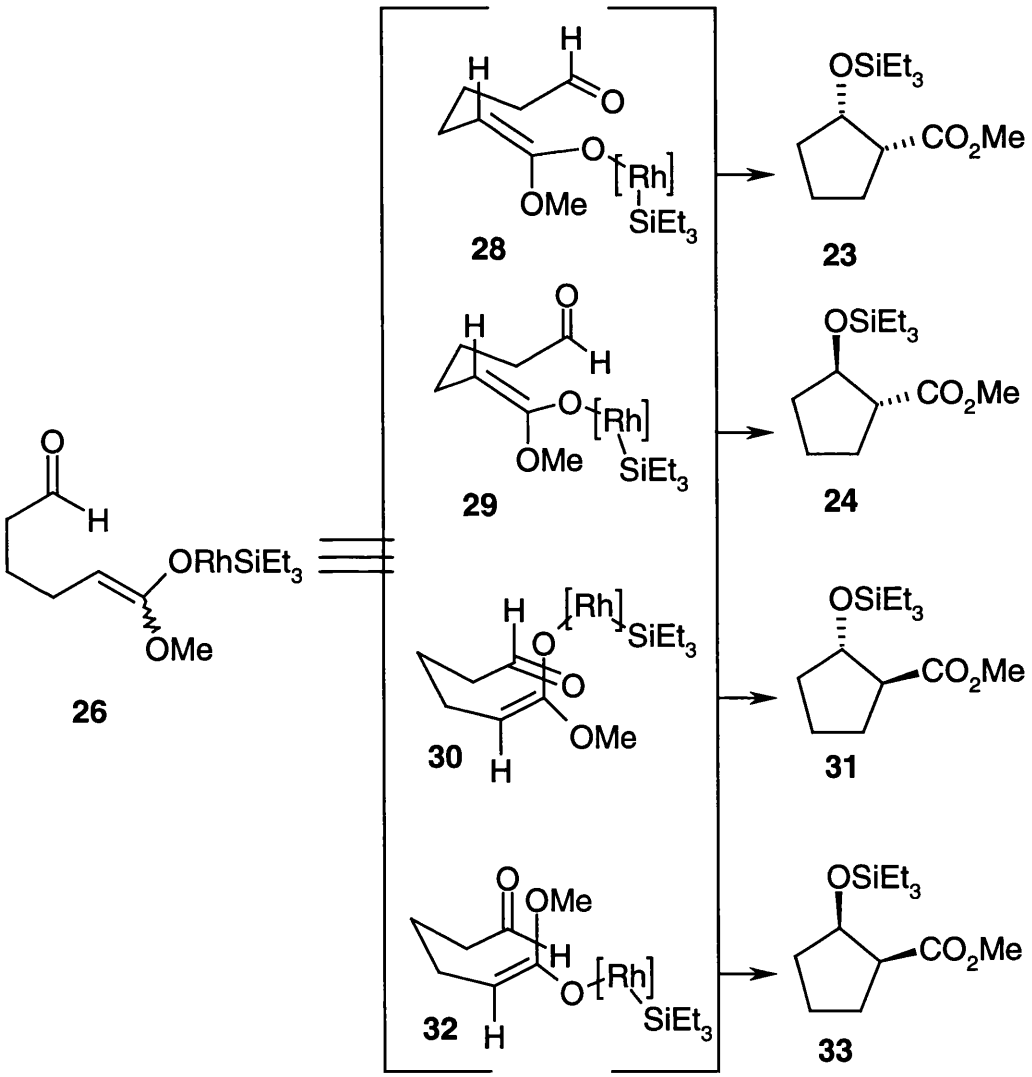


Scheme 22

1.4.4 Stereochemistry

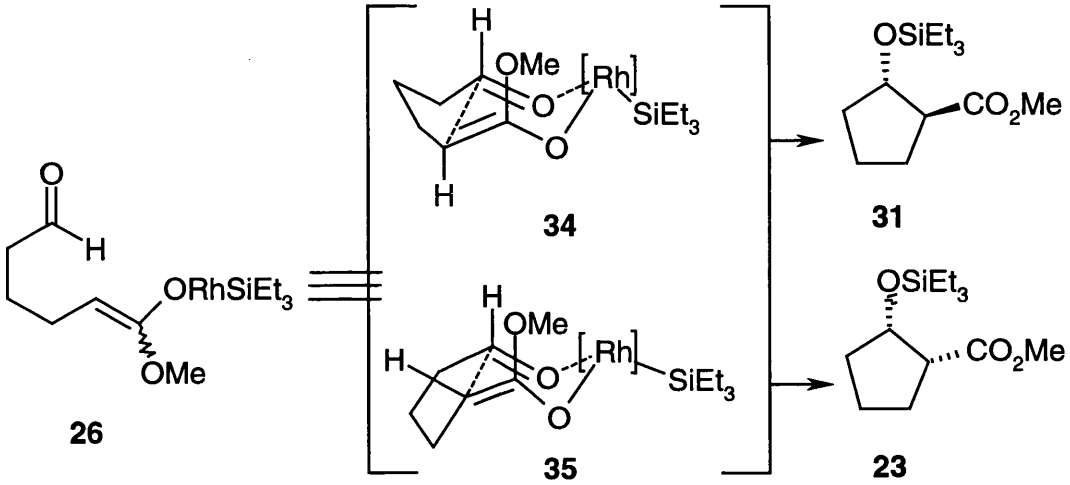
Whitehead[33] invoked two types of transition state to explain the observed selectivity based on a chelated versus a non-chelated Rh enolate. In an 'open'

transition state the (*E*), (*Z*)-regiochemistry of the rhodium ketene acetal (**26**) should not have a bearing on the stereochemical outcome. On the basis of the model shown in Scheme 23, the conformation of the intermediate rhodium ketene acetal appears to be the most important controlling factor. Of the four possible isomers, (**23**) and (**33**) are indistinguishable from one another, although (**28**) having the most favoured conformation gives rise to the *cis*-substituted product (**23**) as the major isomer. The *trans* isomers (**24**) and (**31**) are indistinguishable from one another, with conformation (**29**) leading to the *trans*-substituted product (**24**) as the observed minor isomer. The reaction was conducted with 1%mol Wilkinson's catalyst.



Scheme 23

At higher concentrations (10%mol), Rh(III) may act as a Lewis acid, helping to facilitate the formation of a 6, 5 chelate. The predominant formation of (*E*)-ketene acetal (**34**) would lead to the *trans*-substituted product (**31**) whereas the (*Z*)-ketene acetal (**35**) would give *cis*-substituted product (**23**) via the favoured chair transition states as shown in Scheme 24.



Scheme 24

Thus, at 80°C and with 10%mol of Wilkinson's catalyst, the observed *trans* selectivity most probably arose through the predominant formation of (*E*)-ketene acetal (**34**) in a closed transition state.

The reason for the reduction in *cis* selectivity as the temperature was increased is not clear. It may be due to either a combination of a change in transition state or (*Z*)/(*E*) ketene acetal ratio or, alternatively, simply because the *cis* diastereoisomer equilibrates at higher temperatures.

1.5 Project Objectives

The aim of the present work was to define the scope of the tandem hydrosilylation intramolecular cyclisation chemistry as a general method for the synthesis of substituted carbocycles.

In particular:

- to confirm the reproducibilty of the preliminary results obtained by Whitehead[33]

- Defining the conditions which give a highly stereocontrolled synthesis of protected cyclopentanols in good yields under catalytic conditions.

- To investigate the effect of substrate substitution patterns on the selectivity.

- To conduct a survey of alternative functional groups which can be incorporated into the substrate.

- To establish the feasibility of generating larger ring sizes using this methodology.

- To investigate the use of asymmetric catalyst systems to probe the levels of enantioselectivity attainable on achiral substrates.

CHAPTER TWO

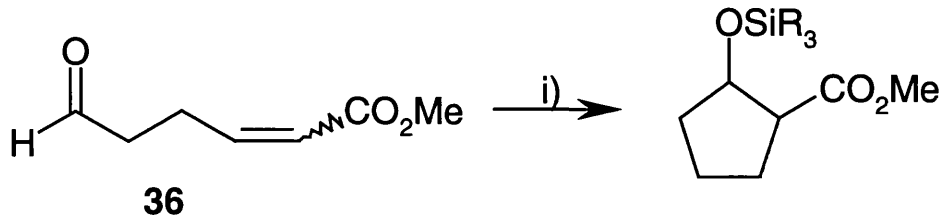
RESULTS AND DISCUSSION

2.1 Rh(I) catalysed tandem hydrosilylation cyclisation of (*E*)-Methyloxohexenoate

2.1.1 Introduction

In determining the scope and generality of the tandem hydrosilylation cyclisation chemistry as a means to substituted cyclopentanols, initial work sought to define the experimental conditions which gave optimum yields and stereochemical control.

Methyl-6-oxo-2-hexenoate (**36**), chosen as the model substrate, was subjected to a range of experimental conditions, encompassing a survey of silanes and various Rh(I) catalyst systems at a range of temperatures (Scheme 25). Work was also begun on addressing some of the mechanistic queries.



36

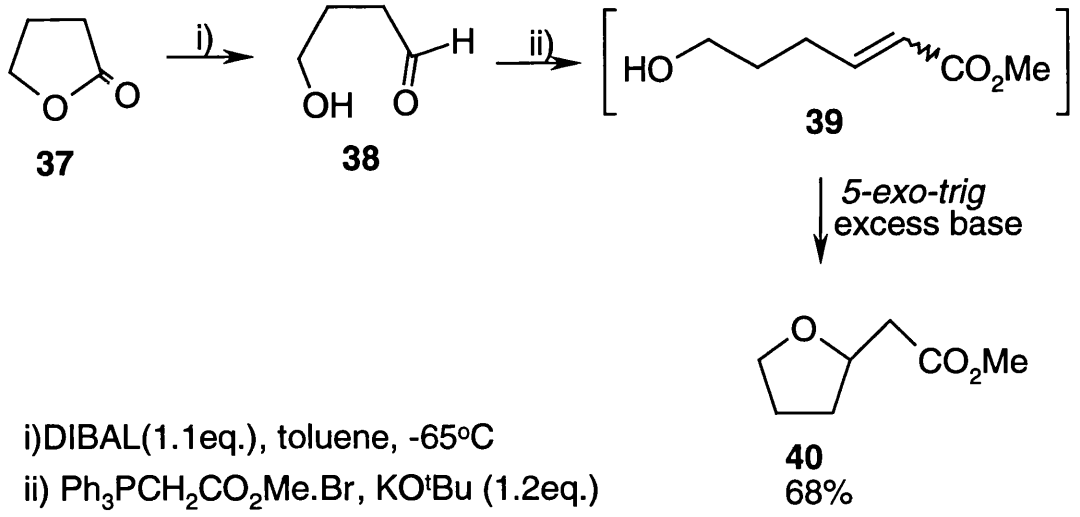
i) Rh(I), R_3SiH, toluene, heat
R=alkyl, phenyl, H

Scheme 25

2.1.2 Preparation of (*E*)-Methyl-6-hydroxy-2-hexenoate (28)

Commercially available γ-butyrolactone (**37**) was reduced, using DIBAL, to 4-

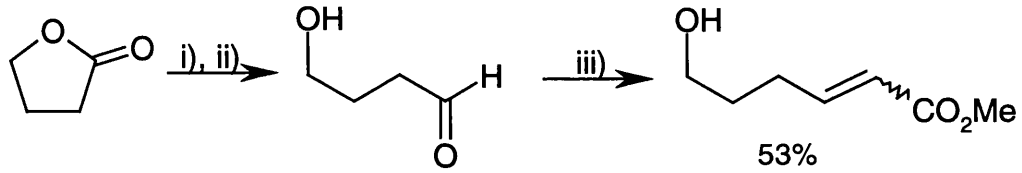
hydroxybutanal (**38**). Due to its volatility, the hemiacetal was not isolated but subjected to *in-situ* Wittig olefination. When the olefination was conducted using the phosphonium salt, carbomethoxymethyl triphenylphosphonium bromide and excess base, the major product was the tetrahydrofuran ring (**40**), in a yield of 68%. The product having initially formed, had further reacted in the presence of excess base and undergone the favorable 5-*exo-trig* cyclisation[43] (Scheme 26). Proton assignment was achieved with the aid of COSY spectroscopy.



Scheme 26

The tetrahydrofuran ring was subjected to a variety of bases at a range of temperatures, with the aim of regenerating the desired product (**39**). This proved to be unsuccessful.

Modifying the experimental conditions with the phosphonium salt now present in excess resulted in the isolation of the methyl hydroxy α, β-unsaturated ester (**39**, Scheme 27) in 53% yield, with only 1.8% of the cyclised product (**40**) detected. The *trans:cis* isomers of the enone were separated by flash chromatography in the ratio of 85:15.



37 38 39

i) DIBAL(1.1eq), toluene. -70^{0}C

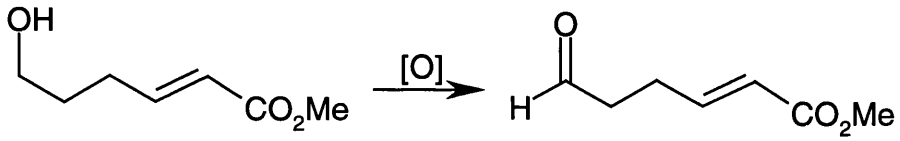
ii) MeOH (3eq), -70^{0}C

iii)$Ph_3PCH_2CO_2MeBr$, ^{n}BuLi

Scheme 27

However, substitution of the phosphonium salt base combination for the ylide[44] itself eliminated the need for base and hence the risk of cyclisation. Moreover, under these conditions, the *trans:cis* ratio was increased slightly to 92:8.

2.1.3 Preparation of (*E*)-Methyl-6-Oxo-2-hexenoate (22)



41 22

Scheme 28

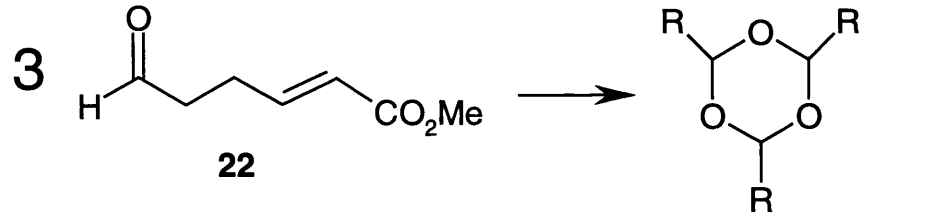
It has been reported[33] that if the oxidation of the hydroxy enone (**41**) is carried out under Swern[45] conditions as opposed to using the oxidant PCC[46], a 10% drop in yield (Table 2) is observed for the intramolecular hydroacylation of the model *trans* pentenal ester (**22**, Scheme 12, Section 1.4.1) to the methyl oxycyclopentanecarboxylate.

OXIDATION CONDITIONS	YIELD from (22)
pyridine sulphur trioxide/DMSO/base	61.8%
PCC	69.2%

Table 2

This drop in yield may reflect possible poisoning of the Rh catalyst by trace contaminants arising from DMSO methodology. This observation dictated that, where substrates pertaining to this thesis were prepared through oxidation, Swern conditions were avoided if at all possible.

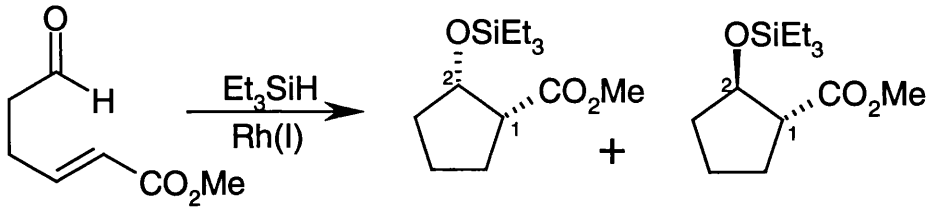
The *trans* isomer of the methyl hydroxy hexenoate (**41**) was accordingly oxidised using PCC to give the aldehyde (**22**) albeit in low 40% yield (Scheme 28). A competing side reaction was trimerisation of the aldehyde to generate the trioxane[47] (**42**, Scheme 29) as the major contaminant.



Scheme 29

Buffering the reaction with sodium acetate modified the slightly acidic nature of the reagent and increased the yield to 63%, at the expense of the trioxane. The predilection of the aldehyde to trimerize and its consequently short shelf-life meant that having been synthesised, it was used immediately.

2.1.4 Rh(I) catalysed cyclisation of (*E*)-methyloxohexenoate



22 **23** **24**

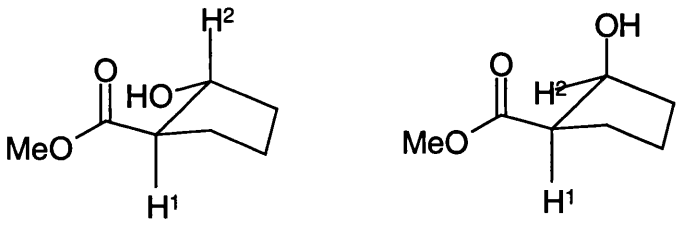
Scheme 30

To a solution of Wilkinson's catalyst in toluene was added the substrate (**22**) and excess triethylsilane at ambient temperature (Scheme 30). The solution was then heated until consumption of the starting material, as monitored by tlc, was complete. Whitehead's[33] results on using 1% mol $RhCl(PPh_3)_3$ at 50°C and 10% mol $RhCl(PPh_3)_3$ at 100°C were verified (Section 1.4), as shown in Table 3, although diastereoselectivity differed to a minor extent.

%mol $RhCl(PPh_3)_3$	YIELD %	*CIS:TRANS*
1	81	3 : 1
10	64	1 : 1.5

Table 3

The assignment of the *cis* and *trans* isomers of methyl 2-carboxycyclopentanol silyl ethers was conducted on the basis of Mohrle's[48] ^1H NMR work on methyl 2-carboxycyclopentanol carboxylate (**43**).



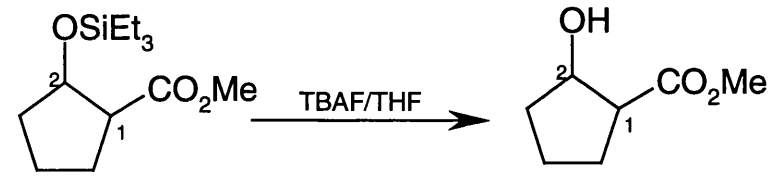
43

Mohrle established two criteria for assigning the configurations of the isomers:

- In the *cis* isomer of the cyclopentanol, the chemical shift of the H^1 proton is at a lower field than in the *trans* isomer. A similar difference in chemical shift is observed for the H^2 proton.

- The band width of the C_1 and C_2 protons is smaller for the *cis* isomer than for the *trans* isomer.

That Mohrle's criteria remain applicable to the silyl oxy substituted cyclopentyl system despite the replacement of the hydroxy group with a silyl ether was verified by a combination of COSY and NOESY spectroscopy (See Appendixes). Further proof supporting this as a valid assignment was provided upon the TBAF cleavage of the triethylsilyl oxy group, generating the known compound, methyl 2-hydroxycyclopentanecarboxylate (**43**). This did not cause any change in the *cis:trans* ratio of the diastereoisomers (Scheme 31).



cis:trans
3:1

27

cis:trans
3:1
69%

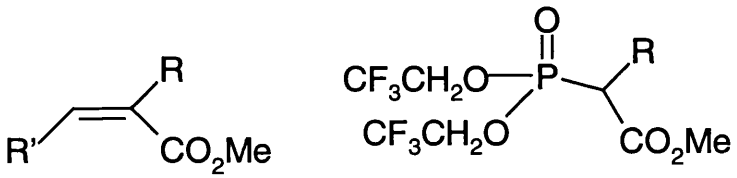
43

Scheme 31

2.2 Rh(I) catalysed tandem hydrosilylation cyclisation of (Z)-Methyloxohexenoate

2.2.1 Introduction

In 1983 Still and Gennan[49] reported that it was possible to prepare unsaturated esters from a variety of aromatic, saturated and unsaturated aliphatic aldehydes (**44**, Scheme 32) with high (*Z*) selectivity. His methodology, based on a modified Horner-Emmons reagent, involved the electrophilic bis(trifluoroethyl)phosphonoester (**45**) and a strongly dissociated base system, such as potassium bis(trimethylsilyl)amide/18-crown-6.[50]



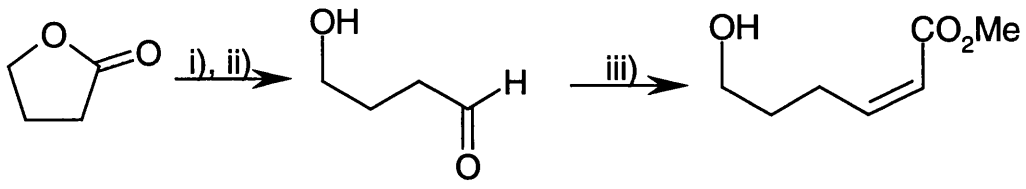
44 **45**

R=H, Me

Scheme 32

It was thought to employ this methodology in the stereoselective synthesis of (*Z*)-methyl-6-hydroxy-2-hexenoate (**46**) from 4-hydroxybutanal (**38**, Scheme 33).

2.2.2 Preparation of (Z)-Methyl-6-hydroxy-2-hexenoate



37 **38** **46**

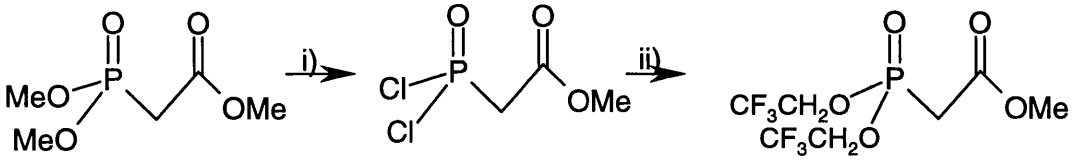
i) DIBAL(1.1eq), toluene. -70^{0}C

ii) MeOH (3eq), -70^{0}C

iii)bis(trifluoroethyl)phosphonoester, KN(TMS)$_2$/18-C-6

Scheme 33

The phosphonoester (**47**) was prepared in a two step synthesis[31] from trimethylphosphonoacetate and trifluoroethanol in 51% overall yield (Scheme 34).



47

i) PCl_5, heat

ii) trifluoroethanol, benzene, $^iPR_2NEt$

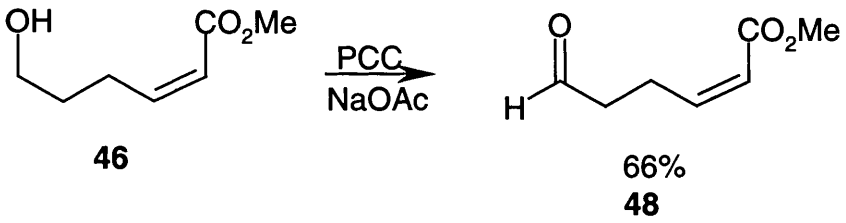
Scheme 34

On application of Still's[49] chemistry to the 4-hydroxybutanal (**38**), only the cyclised product (**40**) was isolated. It was immediately apparent that it was the use of the strongly dissociated base system KN(TMS)$_2$/18-crown-6 that was catalysing the 5-*exo-trig* cyclisation. As the (Z)-selectivity can only be obtained where elimination of the initial adduct is faster than the adduct equilibration, the use of

minimally complexing counterions is essential in facilitating elimination, thus maintaining high (*Z*) stereoselection. It was therefore concluded that this chemistry was incompatible with our chosen substrate due to its predilection to cyclise under basic conditions.

As a practical alternative, the (*E, Z*) methylhydroxyhexenoate (**39**) was synthesized by the standard methodology ($Ph_3PCH_2CO_2Me$, BuLi, Scheme 26) and the (*Z*) isomer was isolated from the predominantly *trans* mixture (85:15) by flash chromatography. This reaction was repeated several times until there was a sufficiently useful quantity of the desired (*Z*) isomer. This approach, whilst time consuming, was ultimately successful.

2.2.3 Preparation of (Z)-Methyl-6-oxo-2-hexenoate



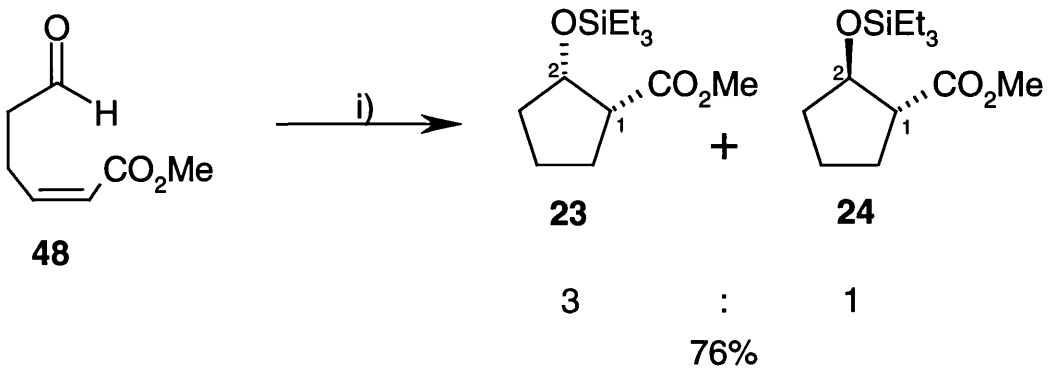
46 66% **48**

Scheme 35

The preparation of the (*Z*)-oxohexenoate followed the PCC[46] synthesis established for the (*E*)-diastereoisomer, generating the aldehyde in 66% yield (Scheme 35).

2.2.4 Rh(I) catalysed cyclisation of (Z)-methyloxohexenoate

That both the *E* and *Z* isomers of methyl-6-oxo-2-hexenoate, under the same reaction conditions, gave the same diastereoisomer ratio of *cis:trans* 3:1 (Scheme 36) allowed us to conclude that the geometry of the double bond is not a controlling factor in influencing the subsequent transition state adopted for the cyclisation.



i) 1%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, 50°C

Scheme 36

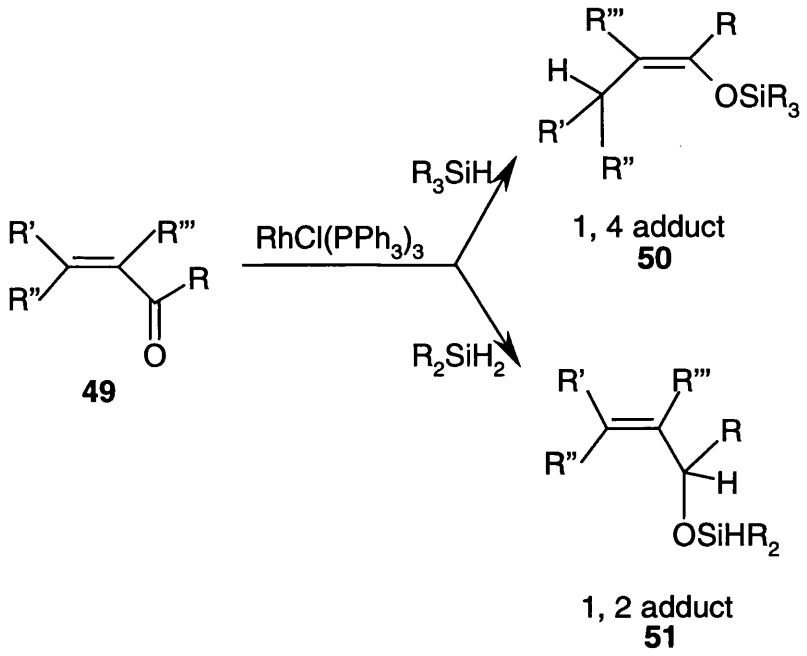
This could be synthetically useful in broadening the applicability of the chemistry to a variety of substituted olefins: there would be no need to separate the geometrical stereoisomers before applying the cyclisation methodology to the system of interest.

2.3 The role of the silane in Rh(I) catalysed tandem hydrosilylation intramolecular cyclisation reactions

2.3.1 Introduction

In defining the conditions which give a stereocontrolled synthesis of protected cyclopentanols, an investigation was conducted into the role of the silane in this methodology.

Ojima[51] *et al.* determined that in the hydrosilylation of α, β-unsaturated carbonyl compounds (**49**), regioselectivity depended markedly on the nature of the hydrosilane used (Scheme 37).



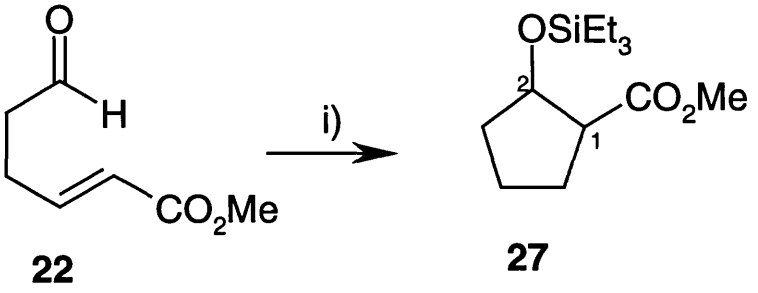
Scheme 37

In general, monohydrosilanes afforded silyl enol ethers (**50**, 1, 4 adducts) while dihydrosilanes gave silyl ethers (**51**, 1, 2 adducts). In particular, phenyl groups and hydrogens on silicon accelerated the 1, 2 addition whilst alkyl groups on silicon increased the ratio of the 1,4 addition. Chlorosilanes and di- and triethoxysilanes gave low yields of the 1,4 adduct, overreduction being a serious side reaction. Other factors favouring (**51**) over (**50**) include high concentrations of the hydrosilane, lower reaction temperatures and steric hindrance at the C_2 and C_3 position of the substrate.

In asymmetric hydrosilylation, the nature of the R groups on R_3SiH had little influence on absolute stereocontrol and only the rate of catalysis was influenced.

2.3.2 Experimental Results

The silane screen was conducted under the conditions shown in Scheme 38, with the results tabulated in Table 4.



22 **27**

i) 1%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, 50°C

Scheme 38

SILANE	YIELD %	*CIS:TRANS* (27)
Et_3SiH [a]	81	3.0 :1 .0
Me_2PhSiH [b]	62	2.4 : 1.0
$MePh_2SiH$ [c]	49	2.8 : 1.0
Ph_3SiH [d]	42	1.5 : 1.0
Ph_2SiH_2 [e]	-	-

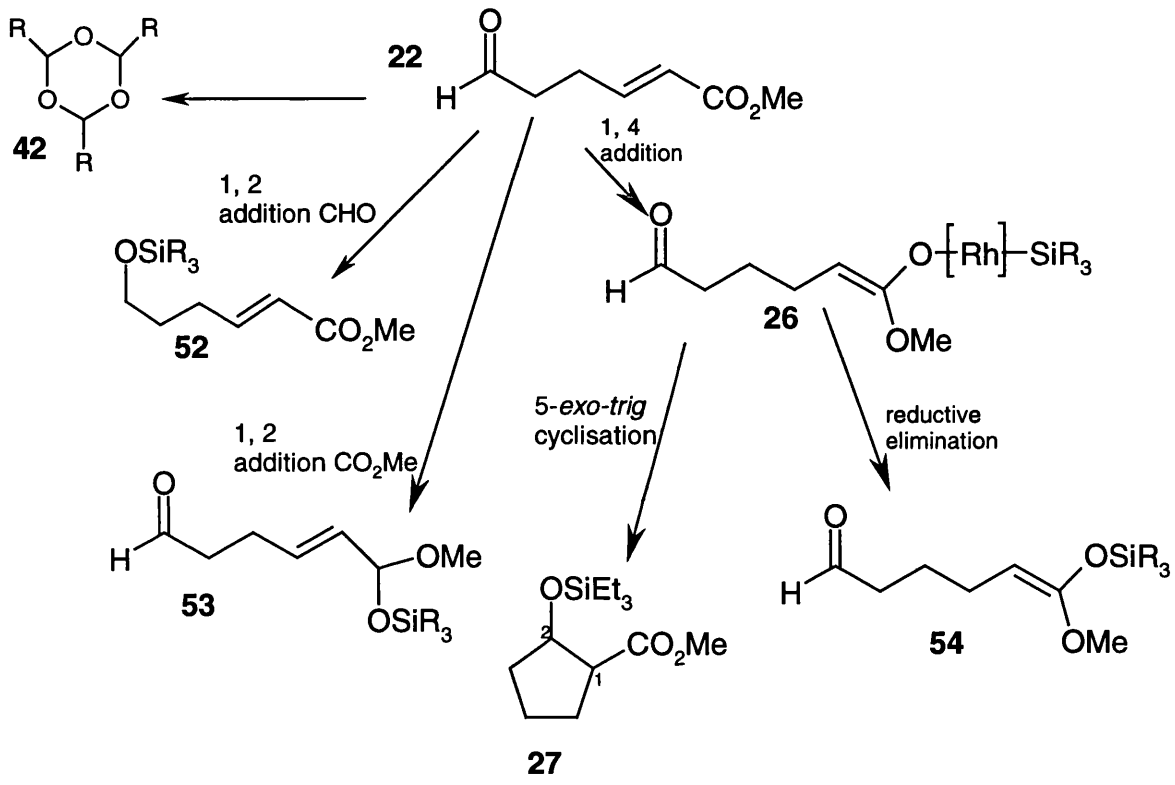
Proton assignments are on the basis of a combination of NOESY, COSY and C-H one bond correlation, which are reproduced in the appendices.

Entry a - e : see appendix

Table 4

The decreasing yield of the cyclopentanoid product (**27**) as the alkyl groups on the silane are gradually substituted for phenyl groups (entries a-d in Table 4) may be due to several factors. The competing 1, 2 addition of the silane to the aldehyde (**52**) or the ester (**53**) as accelerated by phenyl groups and hydrogen on the silane is certainly possible, although such adducts were not isolated. If the reductive elimination of the catalyst in the rhodium ketene acetal (Scheme 39) were fast in comparison to the 5-*exo-trig* cyclisation of the moiety, the silyl ester enolate (**54**) will

be favoured over the substituted cyclopentanol (**27**), (Scheme 39). However such silyl ester enolates are hydrolytically very unstable and would give the simple product of conjugate reduction on work-up. Once again, no product of this structure was isolated. Finally, steric factors of course can interfere as the bulk of the silane increases.



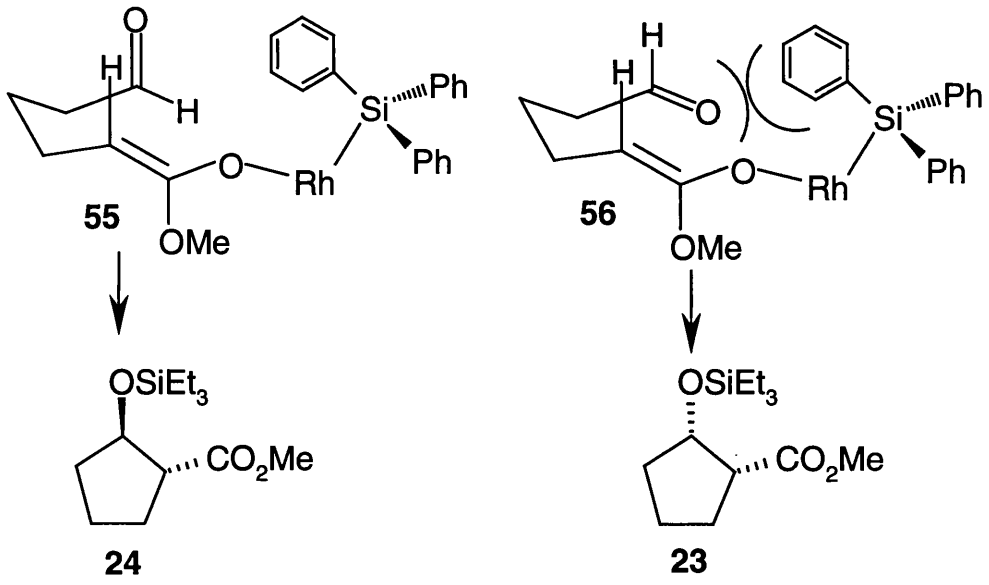
Scheme 39

When the silane used was dihydrophenylsilane (entry e, Table 4) a multiplicity of products, with complete consumption of the starting material (**22**), was formed. Attempts at isolating the components by flash chromatography were mostly unsuccessful. However, one of the components was tentatively identified as the trimerized aldehyde (**42**) through the appearance in the ^{1}H NMR spectra of a triplet peak at δ4.2, which was assigned as the acetal proton. The appearance in the mass spectrum of a *m/z* peak at 326 (50%) indicated that the silane had added to the

methyloxohexenoate (**22**) but whether by 1, 2 addition (**52, 53**) as dihydrosilanes promote or whether by 1,4 addition of the silane (**27, 54**) or by both, is not clear. Low field signals appearing at δ5.4 - δ5.8 could be interpreted as olefinic protons. The absence of a signal in the ^1H NMR spectrum corresponding to an aldehydic proton, does, however, seem to preclude the formation of (**53**) and (**54**).

As discussed previously (Section 1.4.4), it is the conformation of the rhodium ketene acetal (**26**) in the open transition state which is the most important controlling factor in determining which of the *cis* and *trans* isomers predominates. Substituents adopting an equatorial position in the transition state conformation can exert control over the relative stereochemistry of the resulting cyclopentane.

Selectivity for the *cis* isomer drops noticeably when the silane ligands are all phenyl groups (entry d, Table 4). This may be due to steric interactions between the carbonyl and R groups on the silane in the *cis* transition state (**55**) reaching such a level that the *trans* transition state, with its axial carbonyl but reduced interactions with the R groups on the silane (**56**), is not as unfavourable as on previous entries (a-d) (Scheme 40).



Scheme 40

It is only through molecular modelling that the selectivities observed for Et_3SiH, Me_2PhSiH and $MePh_2SiH$ (entries a-c) can be adequately rationalised. A correct description of a size of a substituent rests on its preferred conformational states, which are related to the interactions with both the ring to which it is bonded and neighbouring groups. Additional work is required.

2.3.3 Conclusions

- Increasing the number of phenyl substituents on the monohydrosilane results in a corresponding decrease in the yield of the cyclopentyl moiety (**27**).

- Increasing the number of phenyl substituents on the monohydrosilane results in a corresponding decrease in the *cis* stereoselectivity of the cyclopentyl moiety.

- Monohydrosilanes are more effective in promoting the desired reaction than dihydrosilanes, as expected on the basis of literature precedent concerning 1,2 versus 1,4 addition.

2.4 The role of the phosphine ligand in Rh(I) catalysed tandem hydrosilylation intramolecular cyclisation reactions

2.4.1 Introduction

By modifying the phosphine ligands attached to the rhodium, it was hoped to improve upon the original catalyst.

Larock *et al.*[52] had previously determined, through their investigation into the Rh(I) intramolecular hydroacylation of unsaturated aldehydes, that it is not possible to

prepare complexes of the type $RhClL_3$ with tertiary phosphines other than Ph_3P. Problems were encountered in isolation of the complexes owing to their increased solubility in a variety of solvents and their sensitivity toward oxygen. Consequently, the complexes were prepared *in-situ* by addition of the desired ligand to a solution of chlorobis(cyclooctene)rhodium (I) dimer (Scheme 41).

$$[RhCl(olefin)_2]_2 \quad + \quad 2nL \quad \longrightarrow \quad 2RhCl(olefin)_{3-n}L_n$$

Scheme 41

Optimum yields of cyclopentane were obtained when using 2eq of ligand per rhodium.

2.4.2 Preparation of Chlorobis(cyclooctene)rhodium (I) dimer

The cyclooctene compound $[RhCl(C_8H_{14})_2]_2$ is an important starting material for the preparation of Rhodium(I) complexes.[53]

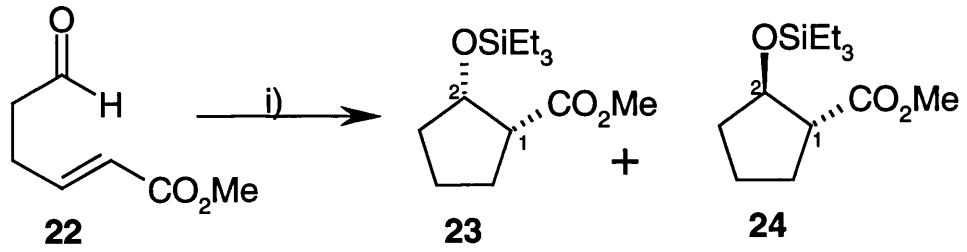
The compound was prepared[54] by dissolving rhodium (III) chloride hydrate in degassed 2-propanol, water and cyclooctene and allowing the mixture to stand at ambient temperature for 5 days before collecting the reddish-brown crystals in 68% yield (Scheme 42).

$$RhCl_3 + 2C_8H_{14} + CH_3CH(OH)CH_3 \longrightarrow \underset{\mathbf{57}}{RhCl(C_8H_{14})_2} + HCl + CH_3COCH_3$$

Scheme 42

2.4.3 Rh(I) catalysed tandem hydrosilylation cyclisation

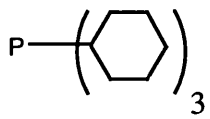
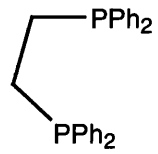
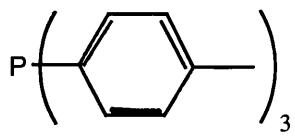
The results of the reaction of methyl-6-oxo-2-hexenoate (**22**) with chlorobis(cyclooctene)rhodium (I) dimer (Scheme 43) and a variety of phosphine ligands are tabulated below.



22 **23** **24**

i) 0.025eq. $[RhCl(C_8H_{14})_2]_2$, 0.1eq. phosphine, 2.1eq. Et_3SiH, toluene, heat

Scheme 43

PHOSPHINES	TEMP °C	YIELD%	*CIS:TRANS*
a 	95	79	2.5 : 1.0
b 	50	78	3.3 : 1.0
c 	95	27*	1.0 : 2.0

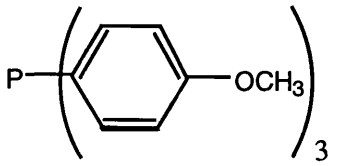
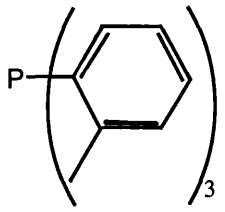
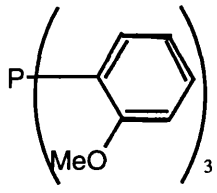
d 	50 95	61 57	1.0 : 2.0 1.0 : 1.6
e 	75 95	53 45	2.0 : 1.0 1.1 : 1.0
f 	75	51	2.0 : 1.0

Table 5

The phosphine screen yielded some interesting results, not all of which can be fully rationalised at this point in time.

All but two of the phosphines (entries b and d) showed little or no reaction at 50°C. The reaction temperature was increased in increments of 20-25°C over a period of time, as dictated by the course of the reaction. In some instances the reaction with a particular ligand was conducted at two temperatures (entries d and e) so that direct comparisons could be made with the results obtained for other phosphines.

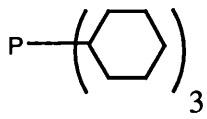
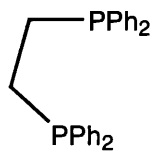
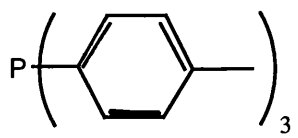
The yield seems dependent, to a certain extent, on the increased steric demands of the ligands. The greatest yield is achieved for L=tricylcohexylphosphine. This phosphine ligand has a larger Tolman's cone angle compared to the aryl ligands and as such the increased steric crowding between ligands accelerates dissociative

processes and decreases associative processes.

The exceptionally poor yield for L=tri-*p*-tolyl phosphine (entry c), which even after 3 days at 95°C still contained unreacted starting material is somewhat anomalous and suggests that some of the phosphine may have oxidised.

Trace amounts of the trimerized aldehyde (**42**) were observed for the majority of those reactions which were carried out at high temperatures for protracted periods of time. A notable exception was for the reaction involving tricyclohexylphosphine.

In most instances, the new catalyst systems compared favourably to the selectivity observed for Wilkinson's catalyst, although for a direct comparison to be valid, the reaction should be repeated with L=PPh_3. However, as time did not allow this additional experiment, the comparison, whilst flawed, is made in Table 6.

PHOSPHINES	**TEMP.°C**	***CIS:TRANS*** **$[RhCl(C_8H_{14})_2]_2$**	***CIS:TRANS*** **$RhCl(PPh_3)_3$**
a 	95	2.5 : 1.0	1.75 : 1.00
b 	50	3.3 : 1.0	3.0 : 1.0
c 	95	1.0 : 2.0	1.75 : 1.0

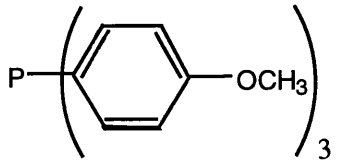
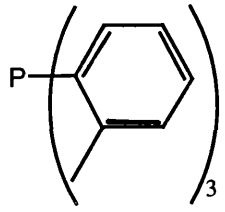
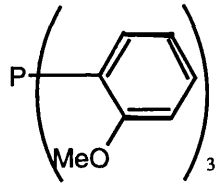
d 	50 95	1.0 : 2.0 1.0 : 1.6	3.0 : 1.0 1.75 : 1.0
e 	75 95	2.0 : 1.0 1.1 : 1.0	2.0 : 1.0 1.75 : 1.0
f 	75	1.5 : 1.0	2.0 : 1.0

Table 6

There are two notable exceptions (entries c and d) to the general trend of *cis* stereoselectivity. With both of the *p*-substituted triarylphosphines, it is the *trans* isomer that is favoured. This was an unexpected result and cannot be adequately explained at this time. One possible explanation could be the decomposition of the phosphine to the phosphine oxide and hence contamination. Further investigation is required.

2.4.4 Observations and Conclusions

- Phosphine ligands with *ortho*-substituted phenyl groups gave reduced yields of the cyclopentanoid (**27**) and required elevated temperatures for the reaction to proceed with only modest *cis* selectivity.

- Phosphine ligands with *para*-substituted phenyl groups gave *trans* selectivity (although the extremely low yields could indicate contamination with phosphine oxide)

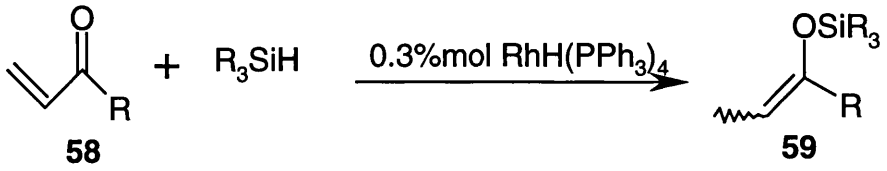
- Diastereoselectivity decreased with increasing temperature

- The most pronounced *cis* selectivity was achieved using DIPHOS as the phosphine ligand. That the use of a bidentate ligand was successful is promising for future work investigating asymmetric catalysis with such bidentate chiral phosphine ligands as BINAP and CHIRAPHOS.

2.5 Investigation of alternative catalyst systems in Rh(I) catalysed tandem hydrosilylation cyclisations

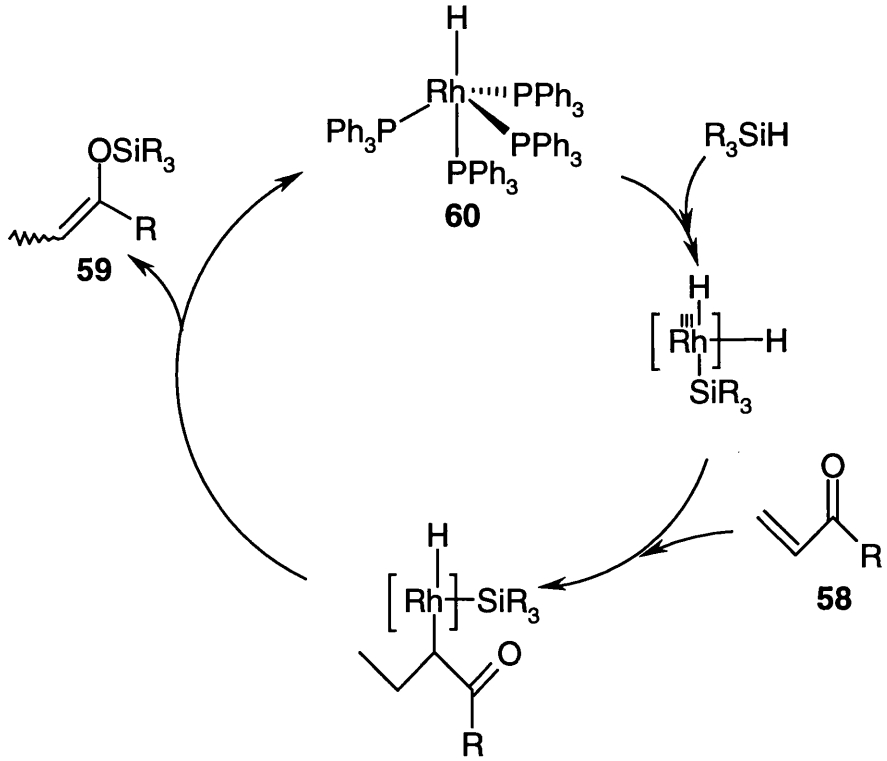
2.5.1 Introduction

In 1993, Chan and Zheng[55] reported that hydrido-tetrakis(triphenylphosphine)rhodium (I) acted as an effective catalyst for the reactions of α, β-unsaturated carbonyl compounds (**58**) with silanes (Scheme 44).



Scheme 44

The mechanism they proposed for this reaction is shown in Scheme 45. The catalyst has been shown to adopt a tetrahedral arrangement[56] of the phosphine ligands about the metal atom with the hydride ligand situated on the C_3 axis[1] (**60**).



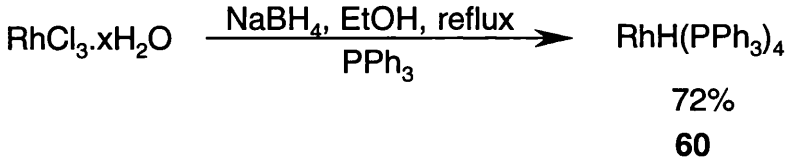
Scheme 45

In comparison with Wilkinson's catalyst[51], hydrido-

tetrakis(triphenylphosphine)rhodium (I) offers the dual advantages[55] of being a more active catalyst[57] as well as an increased regioselectivity for 1, 4-hydrosilylation.

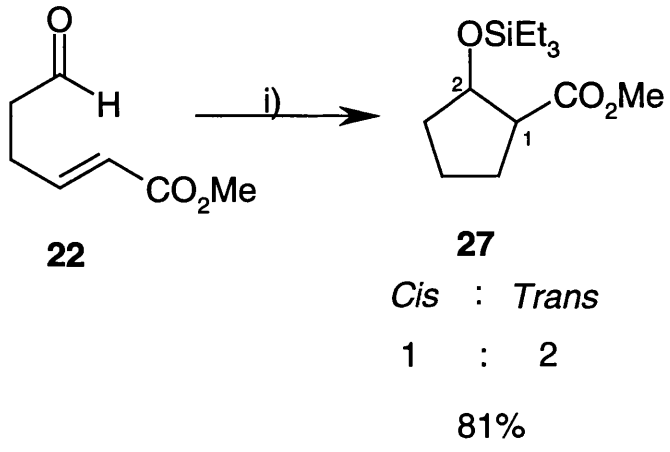
2.5.2 Preparation of Hydridotetrakis(triphenylphosphine) rhodium(I) (60)

Rhodium (III) chloride hydrate was rapidly reduced by sodium borohydride in the presence of a large excess of triphenylphosphine to give $RhH(PPh_3)_4$ in 72% yield (Scheme 46).[58] Care was taken when handling this catalyst since it is sensitive to both air and moisture.[56]



Scheme 46

2.5.3 $RhH(PPh_3)_4$ catalysed cyclisation of (*E*)-methyl-6-oxo-2-hexenoate



i)1% $RhH(PPh_3)_4$, 2.1eq.Et_3SiH, toluene, 50°C

Scheme 47

At 50°C, the freshly prepared catalyst shows:

- *trans* selectivity
- good yield for the cyclopentyl moiety (**27**)
- greater reactivity than Wilkinson's catalyst with its reduced reaction time (total consumption of the starting material was achieved in 5 hours as opposed to the 16 hours required with the latter catalyst).

This was a positive result as we now had a methodology for the synthesis of the functionalised cyclopentane ring whereby both isomers were accessible, depending on the catalyst system employed.

After several months had elapsed, a temperature screen was conducted on the model pentenal (**22**) using $RhH(PPh_3)_4$. The results are tabulated below (Table 7).

TEMPERATURE °C	YIELD %	*CIS:TRANS*
50	65	3.0 : 1.0
70	48	2.5 : 1.0
90	55	2.3 : 1.0
110	50	1.6 : 1.0

Reaction conditions : 2.1eq Et_3SiH, 4%mol $RhH(PPh_3)_4$, toluene, heat

Table 7

As is immediately apparent from the table, the selectivity for the *cis* isomer now shown is in direct contrast to that observed when the reaction was initially performed earlier in the year.

Significant observations concerning the aged catalyst, including slower reaction times (Table 7, 16 hours), lower yields and a general lightening in the colour of the

catalyst, suggested that the catalyst had decomposed to a new species in the intermittent period between experiments.

The hydridotetrakis(triphenylphosphine)rhodium (I) catalyst certainly requires further study.

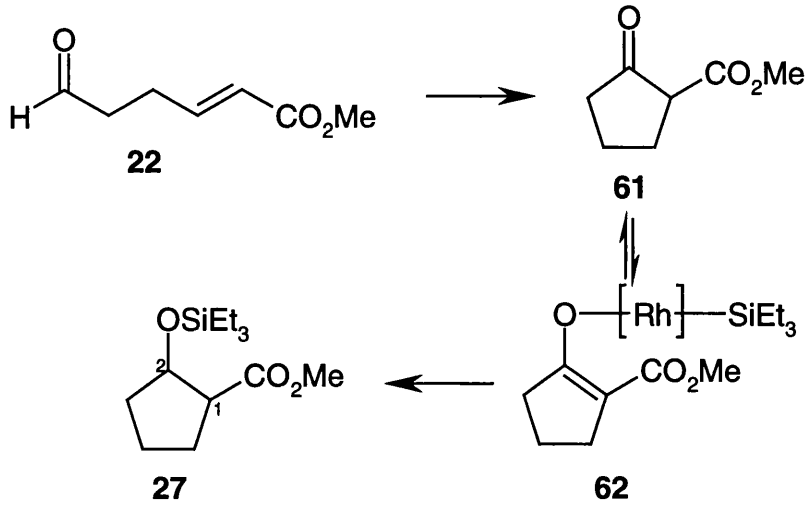
2.6 Mechanistic Investigations

2.6.1 Introduction

The key to developing a stereoselective method should depend on the ability to manipulate the factors which control the preference for the formation of one diastereoisomer over the other. In order to discover what these controlling factors are, an understanding of the mechanism of the transformation is important.

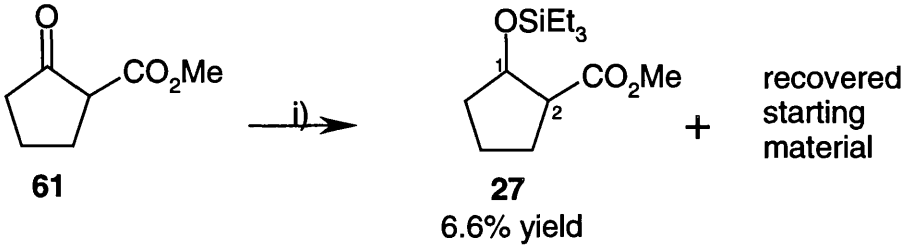
2.6.2 Verification of the mechanistic pathway

An investigation into the mechanism was conducted in order to ascertain whether the reaction was indeed hydrosilylation followed by cyclisation and not in fact hydroacylation followed by hydrosilylation (Scheme 48), with the silane in some way inhibiting the decarbonylation previously observed.



Scheme 48

To a solution of the commercially available methyl-2-oxocyclopentane carboxylate (**61**) was added 1% $RhCl(PPh_3)_3$ and Et_3SiH (Scheme 49).



61 **27**
6.6% yield

i) 1%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene
50°C

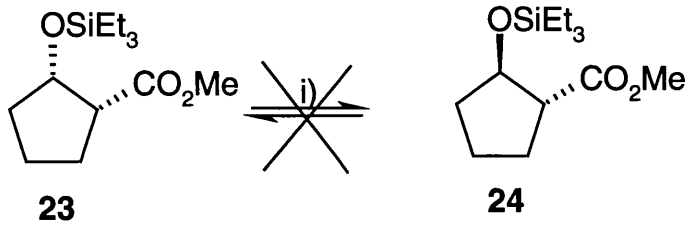
Scheme 49

Under identical conditions to those that yielded 81% of the product (**27**) from methyloxohexenoate (**22**), only 6.6% of methyl 2-triethylsilyloxycyclopentane carboxylate was recovered from this reaction (Scheme 49). This experiment provides strong presumptive evidence that the mechanism of the reaction is a novel tandem hydrosilylation cyclisation, with hydroacylation of the methyloxohexenoate followed by hydrosilylation as a minor competing pathway.

2.6.3 Investigation of the interconversion of the *cis, trans* diastereoisomers

A predominantly *cis* mixture of the diastereoisomers was subjected to conditions (10%mol $RhCl(PPh_3)_3$, silane, 100°C), which when applied to the starting material methyl-6-hydroxy-2-hexenoate (**22**), generated the *trans* isomer as the major isomer.

No change was observed in the *cis:trans* ratio of 2:1 after 21 hours at these reaction conditions (Scheme 50).



23 **24**

i) 10%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, 100°C

Scheme 50

This seems to indicate that even at elevated temperatures, the kinetic *cis* isomer does not equilibrate to the thermodynamic *trans* isomer.

2.7 Conclusions

- Alkyl monohydrosilanes promote optimum stereoselectivity and yield of the functionalised cyclopentane.

- For the silane R_3SiH, when R=alkyl is substituted for R=phenyl, there is a corresponding progressive decrease in stereoselectivity and yield.

- Dihydrosilanes promote 1, 2 addition to the carbonyl function over 1, 4 addition to the α, β-unsaturated ester, resulting in a negilible yield of the desired product.

- Increasing the reaction temperature decreases stereoselectivity.

- The mechanism proceeds through hydrosilylation followed by 5-*exo-trig* cyclisation. Intramolecular hydroacylation followed by

hydrosilylation is a minor competing pathway.

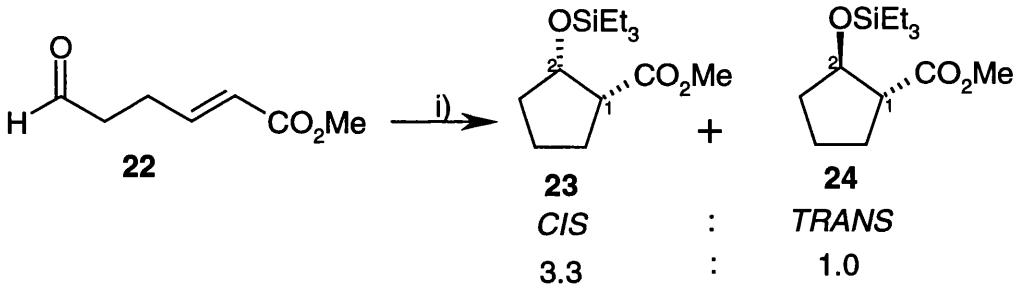
- The kinetic *cis* isomer of the cyclopentyl moiety cannot be interconverted to the thermodynamic *trans* isomer under the reaction conditions.

- The geometry of the double bond of the oxo-unsaturated ester has no influence on the stereochemical outcome of the reaction.

- Through variation of the catalyst system and temperature, either diastereoisomers can be formed as the major product.

<u>*CIS* STEREOSELECTIVITY:</u>

Optimum *cis* stereoselectivity was achieved with the catalyst system shown in Scheme 51.

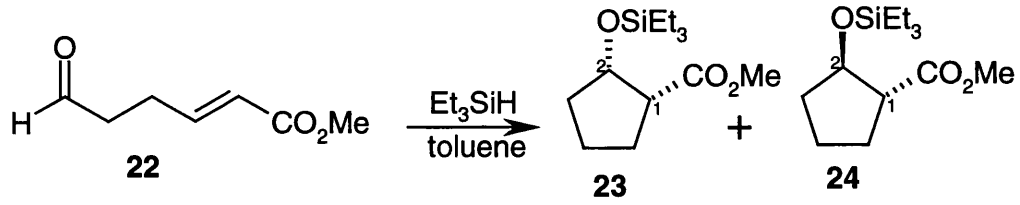


i) $[RhCl(C_8H_{14})_2]_2$, L=DIPHOS (n=2), toluene, 50°C

Scheme 51

TRANS SELECTIVITY

Trans selectivity can be achieved in several catalyst systems (Scheme 52), although their precise mode of action is not understood at this moment in time and needs to be verified:



	CIS	:	*TRANS*
$[RhCl(C_8H_{14})_2]_2$, L=tris (4-methoxyphenyl)phosphine, (n=2), 50°C	1.0	:	2.0
$[RhCl(C_8H_{14})_2]_2$, L=tri-4-tolylphosphine(n=2), 95°C	1.0	:	2.0
$RhH(PPh_3)_4$, 50°C	1.0	:	2.0
10%mol $RhCl(PPh_3)_3$, 100°C	1.0	:	1.5

Scheme 52

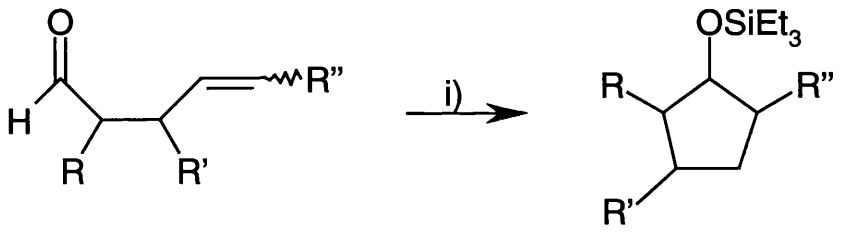
CHAPTER THREE

RESULTS AND DISCUSSION

3.1 Introduction

Having defined the scope of tandem hydrosilylation cyclisation chemistry in general terms, the investigations were extended to include additional functional groups that could also be incorporated into the substrate. If successful, a more general synthesis of cyclopentanols, offering the advantage of compatibility with a more diverse range of functionality than in the parent substrate, would be available.

The compatibility of this chemistry with Michael acceptors other than the α, β-unsaturated ester was investigated, as was the effect of further peripheral substitution around the pentenal (Scheme 53).



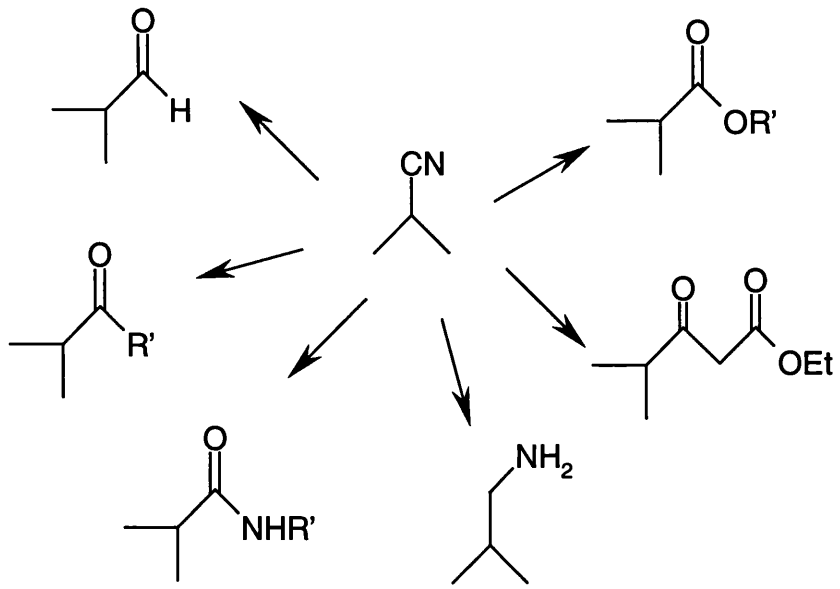
i) 1%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, heat

Scheme 53

3.2 Investigation of oxo-α, β-unsaturated nitriles

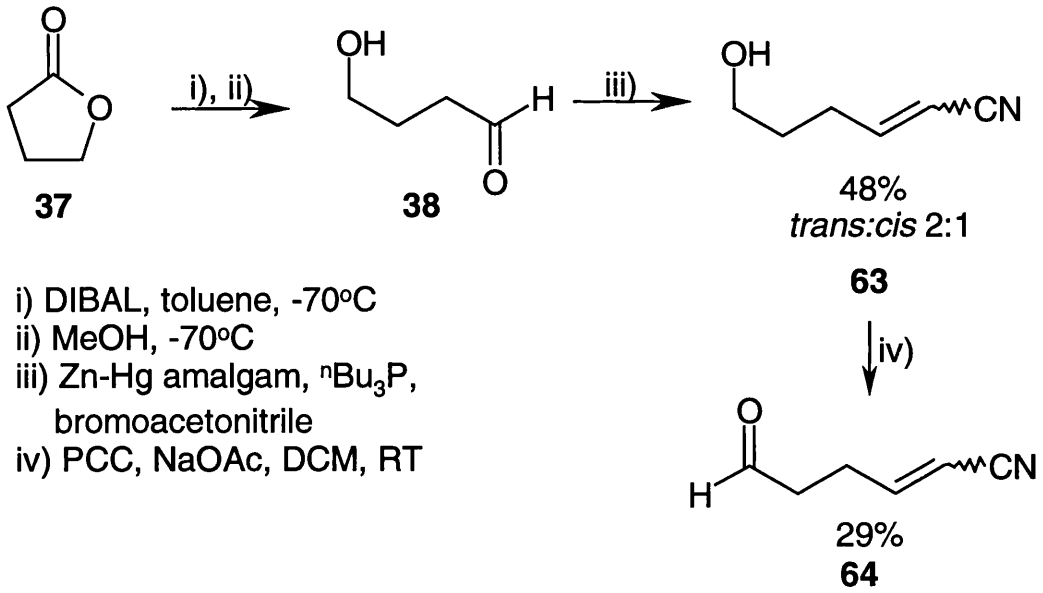
3.2.1 Introduction

It is well known that nitriles are useful intermediates in organic synthesis and are capable of undergoing many valuable transformations (Scheme 54).



Scheme 54

3.2.2 Preparation of 6-oxo-hex-2-enenitrile

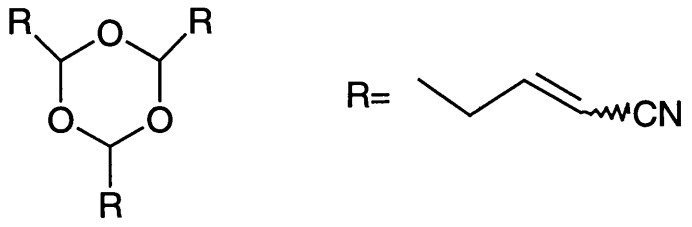


Scheme 55

Having generated 4-Hydroxybutanal (**38**) through reduction of γ-butyrolactone (**37**), it was further reacted *in-situ* with bromoacetonitrile, tri-n-butylphosphine and

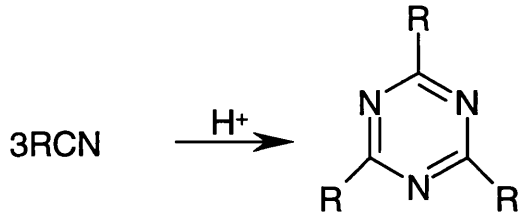
zinc-mercury amalgam to afford the hydroxy α, β-unsaturated nitrile (**63**) in 48% yield (Scheme 55).[59] Attempts to separate the *trans:cis* isomers, generated in a ratio of 2:1, using flash chromatography, were unsuccessful.

Extraction of the desired 6-oxo-unsaturated nitrile (**64**) from the gelatinous PCC[46] residue proved difficult, suggesting that the aldehyde had polymerised. Yields for the oxidation were low at 29% (Scheme 57),[60] although optimisation was not attempted at this juncture. Separation of the isomers was achieved at this point. The trioxane (**65**), resulting from trimerisation through the aldehyde function, was isolated in 8% yield. This suggests that it is the instability of the aldehyde functionality that is reducing the yield of this reaction.



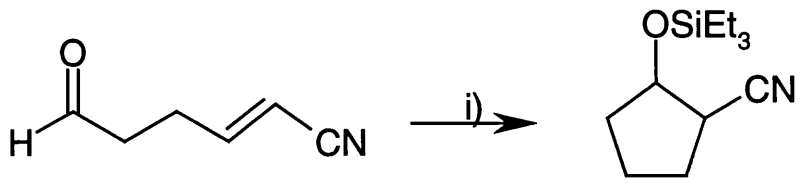
65

Whilst nitriles can be trimerised[61] with various acids, bases or other catalysts to give triazines (**66**), this reaction was not observed.



66

3.2.3 Rh(I) catalysed cyclisation of (*E*)-6-oxo-hex-2-enenitrile



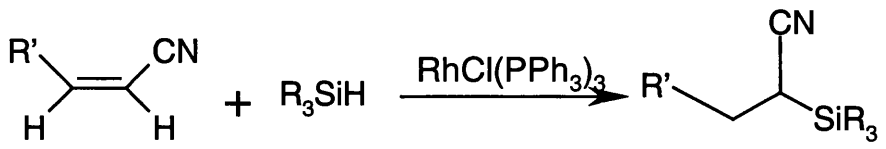
67 **10% yield**
68

i) 7.75%mol $RhCl(PPh_3)_3$, toluene, 100°C, 2.1 eq Et_3SiH

Scheme 56

Scheme 56 depicts the reaction conditions for the attempted cyclisation of (*E*)-methyl-6-oxohex-2-enenitrile (**67**). After 4 hours at 100°C, unreacted starting material was the main component of the crude reaction mixture. Although it was clear that the aldehyde was trimerizing under these conditions in significant amounts, only a trace of the desired product was detected at this point. The reaction was left for a further 14 hours under the same conditions. The ^1H NMR of the crude reaction mixture at this stage confirmed it to be a multicomponent reaction.

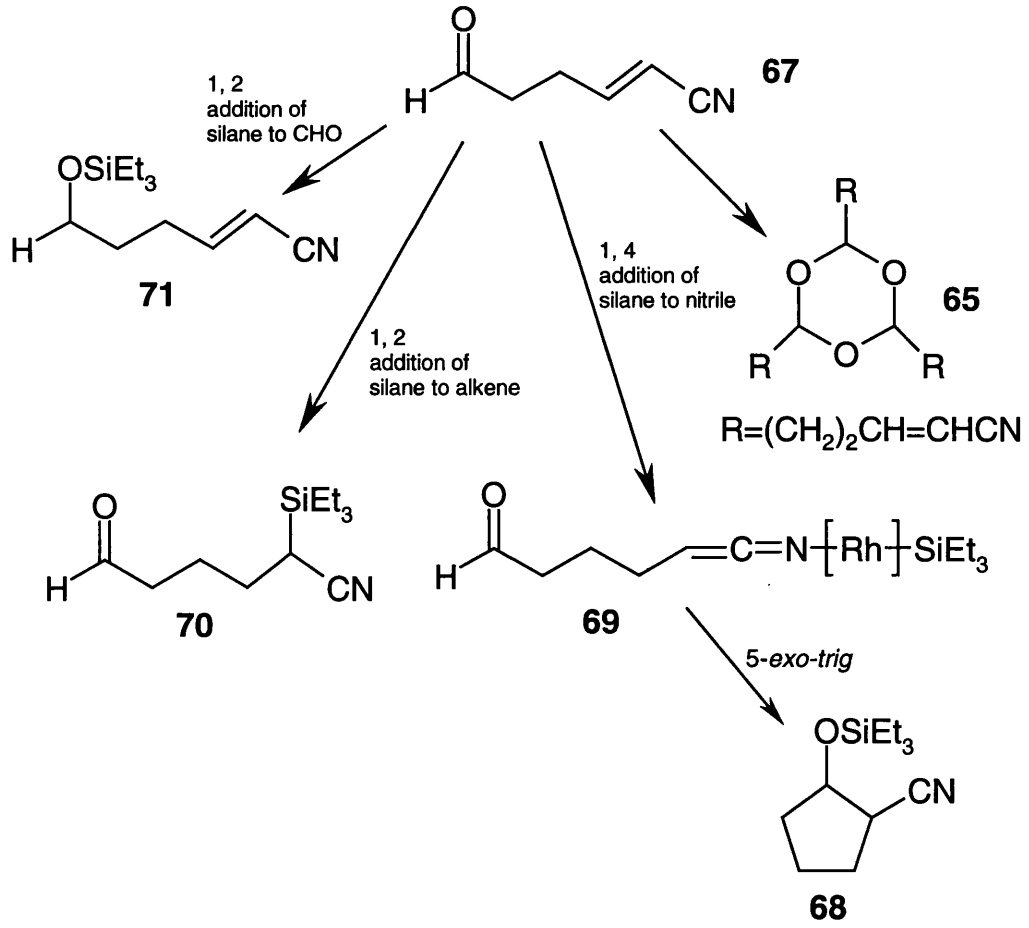
Ojima and Kumagai[62] conducted a series of experiments on the hydrosilylation of α, β-unsaturated nitriles and concluded that the use of monohydrosilanes afforded the addition of product exclusively across the double bond (Scheme 57). This is in direct contrast to the regioselectivity observed for unsaturated carbonyl compounds, where monohydrosilanes promote formation of silyl ester enolates (Section 2.3).[51]



R'=H, Me, Ph

Scheme 57

Scheme 58 depicts all of the possible products following the reaction of 6-oxo-hex-2-enitrile with Wilkinson's catalyst and triethylsilane at 100°C.



Scheme 58

Whilst purification of the crude mixture by flash chromatography proved difficult, it was possible to isolate the trimerized aldehyde as the major product (54%yield). The trioxane was identified using ^{1}H NMR, with its defining peaks for the acetal proton at δ4.2. The high reaction temperature was in all probability a contributing factor to the predominance of the trioxane and should be taken into consideration when redesigning the experiment.

The appearance of two peaks at δ4.5 (dt) and δ4.3 (dt) in the crude ^{1}H NMR spectrum was interpreted as the characteristic silyloxy *cis* and *trans* protons (in the approximate ratio of 1:1), leading to the conclusion that there had been some product formation (**67,** 10% yield). The presence in the EI mass spectra of a *m/z* peak at 226 further supported the ^{1}H NMR evidence that there had been addition of the silyl group, although these data may also indicate the formation of compounds (**68**), (**70**) and (**71**): they all possess the same molecular weight.

The trace presence of a low field signal in the crude ^{1}H NMR spectra corresponding to an aldehyde proton indicates unreacted starting material and / or the formation of **67**. The IR spectrum of the crude mixture has similarities to that of the precursor methyl-6-hydroxy-2-hexenenitrile (**63**).

3.2.4 Conclusions

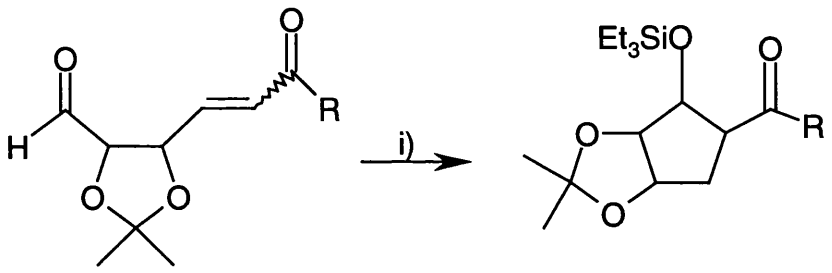
These preliminary results therefore indicate that the formation of a nitrile functionalised cyclopentyl moiety (**68**) will not be straightforward due to the tendency of the starting material, (*E*)-6-oxo-2-hexenitrile (**67**) to undergo trimerisation to form the trioxane. Further complications arise from the Rh(I) catalysed 1, 2-addition of the silane to the carbon-carbon double bond of the α, β-unsaturated nitrile unit as a competing pathway. Despite these apparent problems, the cyclisation to form the desired product (**67**), whilst a minor pathway, did occur. This may be amenable to further optimisation.

3.3 Carbohydrate derived 4, 5-disubstituted substrates in the Rh(I) catalysed tandem hydrosilylation cyclisation

3.3.1 Introduction

The construction of carbocycles from carbohydrates has always generated significant interest.[63] The highly oxygenated carbocyclic products possess considerable synthetic utility because of their application to the total synthesis of biologically important molecules such as enzyme regulators,[64] the Corey lactone, related prostaglandin intermediates[65] and carbocyclic ribose derivatives.[66]

The pentenal **72,** accessible from a carbohydrate, was chosen to investigate whether tandem hydrosilylation cyclisation chemistry was compatible with increased peripheral substitution around the substrate. If successful, this would result in the increased functionality of the cyclopentyl ring (Scheme 59).

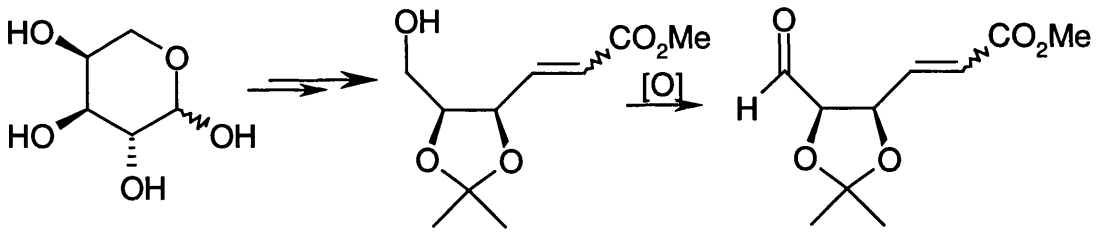


72 **73**

i) 1% $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, heat

Scheme 59

3.3.2 Preparation of Methyl oxo isopropylidenedioxy hexenoate

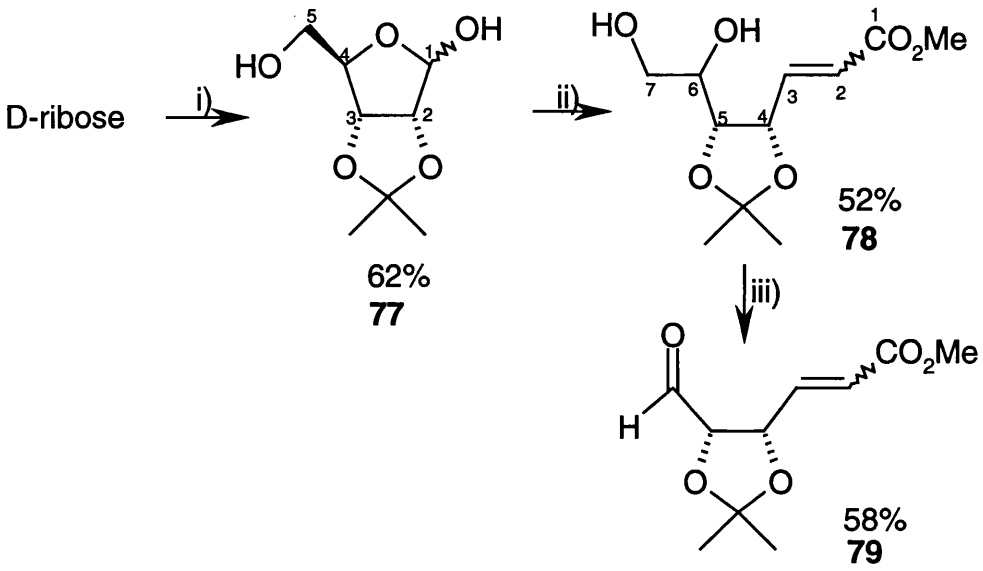


L-Arabinose **74** | yield 25% **75** | **76**

Scheme 60

In the initial attempt to synthesise methyl oxo isopropylidene hexenoate (**76**, Scheme 60), L-Arabinose (**74**) was transformed into the methyl hydroxy isopropylidene hexenoate [67] in a total yield of 25%. In trying to avoid Swern[68] conditions for the oxidation of **75** (as previously discussed, Section 2.1.3) alternative oxidants were sought. Despite a wide variety of oxidants tested (PCC, PDC, [69] Dess-Martin periodinane, [70] TPAP and NMO [71]), it was not possible to isolate the aldehyde **76** in a preparatively useful yield. An alternative strategy was therefore devised.

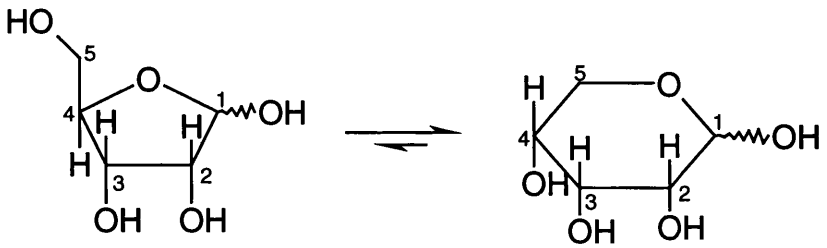
The first step in the synthetic strategy outlined in Scheme 61, [72] is the acetonation of D-ribose. There has been much research conducted on the numerous approaches to the protection of carbohydrates as isopropylidene derivatives.[73, 74] Carbohydrates vary dramatically in their properties, as is demonstrated amongst the four aldopentoses (arabinose, lyxose, ribose and xylose): the differing stereochemistries dictate the precise acetonation conditions, with varying degrees of success.



i) *p*TSA, 2-methoxypropane, O^{0}C
ii) $Ph_3P{=}CHCO_2Me$, DCM, 18hr
iii)$NaIO_4$, $MeOH/H_2O$

Scheme 61

D-ribose reacts mainly via the pyranose form (**81**, Scheme 62), with the furanoid ring being the minor tautomer (**80**).



furanoid
D-ribose

80

pyranoid
D-ribose

81

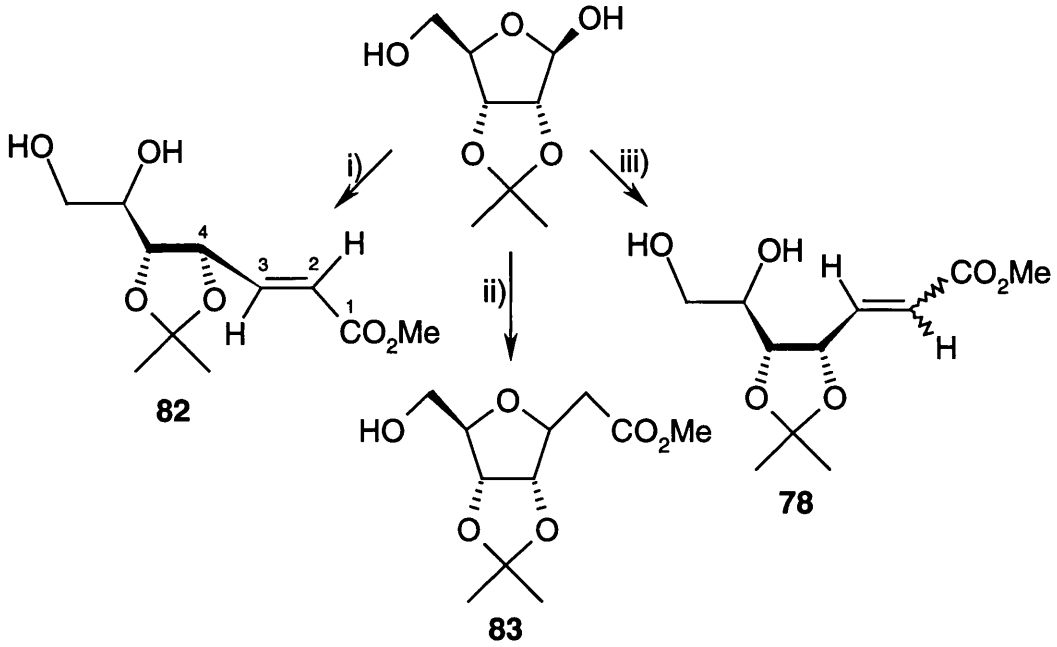
Scheme 62

Acetonation of D-ribose can be problematic due to the many possible side-products.[75, 76] The established, most favoured mode of initial attack of 2, 2-dimethoxypropane is at 1° hydroxymethyl groups. However, as this is not possible in the pyranoid form (**81**), reaction takes place at *cis*-disposed hydroxyl groups, of which there are 3 such groups in D-ribose. The carbohydrate reacts to give the pyranoid 3, 4 acetal and the 2, 3 acetal. After acetonation, the 2, 3 acetal then tautomerises to the more stable furanoid ring. A subsequent 1, 5 acetal bridge can be formed in β-D-ribofuranose to give the 1, 5 : 2, 3 diacetal. In addition, if the acid catalyst is not fully neutralised prior to work-up, the yield can further be affected by loss of product through its conversion to the enol ether.

D-ribose was reacted with 2, 2-dimethoxypropane and *p*-toluenesulphonic acid in acetone at ambient temperature over 3 days to give the isopropylidene derivative (**77**) in a yield of 42%. On reacting D-ribose with 2-methoxypropane, *p*-toluenesulphonic acid in DMF at 0°C over 3 hours, a 20% increase in yield to 62% was observed (Scheme 61). In both reactions, however, the presence of numerous methyl peaks in the ^{1}H NMR spectrum in addition to the main isopropylidene methyl peaks at ~δ1.3, indicated various side-product formation, as typical of D-ribose chemistry. Mass spectrometry indicated the formation of the diacetal ($M+H^+$, 20%).

It was the group of Moffatt *et al.*[77] who first examined the reaction of D-ribose with phosphorus ylides in terms of the stereochemical outcome and formation of acyclic products.

As a point of interest, Herrera and Gonzalez[78] later derived the C-4 epimer (**82**) of the Wittig product, identified through its different physical properties, via the Knoevenagel-Doebner reaction of 2, 3-*O*-isopropylidene-D-ribofuranose. Their results are summarised in Scheme 63.



i) Methyl hydrogen malonate, pyridine, piperidine, 85°C
ii)$Ph_3P{=}CHCO_2Me$, refluxing CH_3CN
iii)$Ph_3P{=}CHCO_2Me$, DCM, RT

Scheme 63

In the course of this research, 2, 3-*O*-isopropylidene-D-ribofuranose (**77**) was reacted with carbomethoxymethylene triphenylphosphorane in DCM at ambient temperature on two occasions. In both instances the reaction proceeded to completion to give **78** (Scheme 61) in a yield of 52% but, on initial inspection, with the anomalous result of the *cis* diastereoisomer being the major isomer (*cis:trans* 7:3).

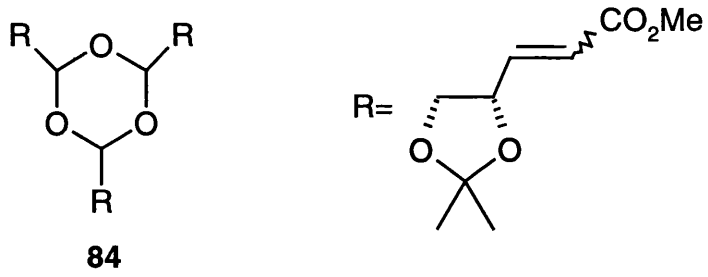
This reversal in stereochemistry from the normally favoured *trans* geometry from a stabilised ylide has been observed with other carbohydrate lactols. In general, lactols of *ribo* configuration react with stabilised ylides to afford an olefin mixture containing predominantly *Z* olefin. The C4 hydroxyl group of the hydroxy-aldehyde (formed on the opening of the lactol hemiacetal), significantly influences the stereochemical outcome of the Wittig reaction through the formation of an intramolecular hydrogen bond to the oxygen atom at C1.[79]

The tendency of the product to undergo *5-exo-trig* cyclisation to the acyclic

product during purification by flash column chromatography, dictated that this step was conducted with all haste. The propensity of the 6-hydroxy 2-hexenoate functionality to cyclise has been a characteristic exhibited throughout this research.

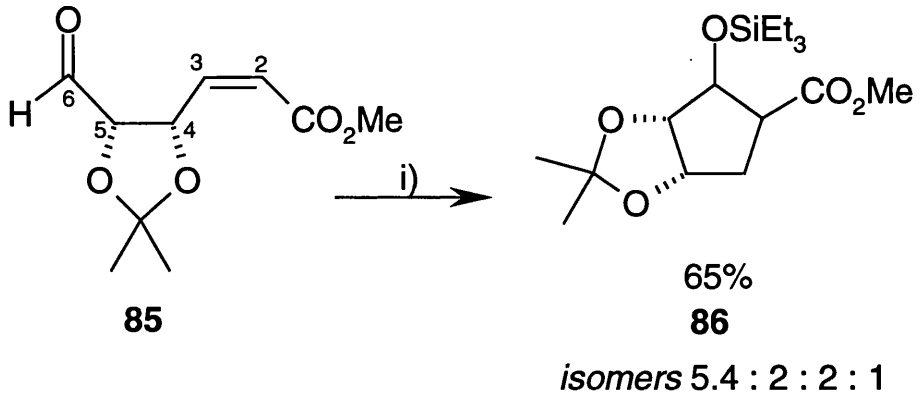
Sodium periodate is frequently employed to effect oxidative cleavage of diols.[80] In this instance, diol **78** was subjected to an aqueous (4%v/v):DCM:$NaIO_4$ system. The aldehyde **79** (Scheme 61) was isolated in a yield of 58% as separate isomers.

Due to the instability of the aldehyde (the trioxane (**84**, Scheme 64) was isolated from the aldehyde after just 24 hours storage at ambient temperature), it was immediately subjected to the tandem hydrosilylation cyclisation conditions being investigated in this project.



Scheme 64

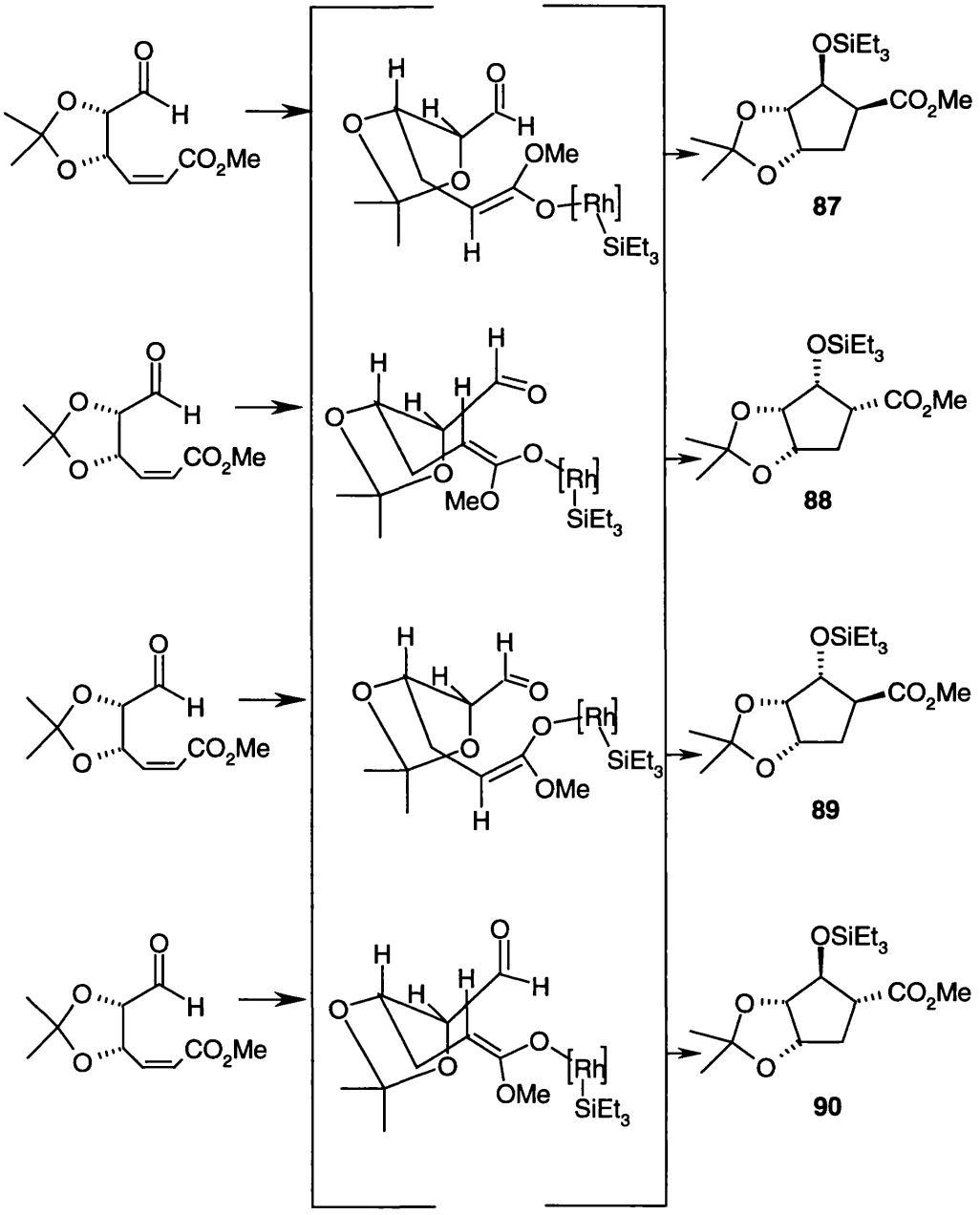
3.3.3 Rh (I) catalysed tandem hydrosilylation cyclisations



i) 1%mol $RhCl(PPh_3)_3$, 2.1eq. Et_3SiH, toluene, 50°C, 3 days

Scheme 65

After subjecting (*Z*)-methyl-6-oxo-4, 5-*O*-isopropylidene-hex-2-enonoate (**85**) to the reaction conditions shown in Scheme 65 for 3 days, there remained only a trace of starting material. The cyclisation had proceeded, with the cyclopentyl moiety being produced in a yield of 65%. The crude ^{1}H NMR spectra was used to determine the ratio of the four diastereoisomers as 5.4 : 2 : 2 : 1.



Scheme 66

With all of the 4 possible diastereoisomers being present, proton assignment and subsequent determination of the stereochemistry by experimental means alone, was extremely difficult in the time available. The identity of the isomers and their relative predominance was tentatively deduced from an examination of their transition states (Scheme 66). On the basis of which diastereoisomer had the most favourable conformation with substituents occupying the more favourable positions in the transition state, the identities of the isomers were proposed as the following: **88** (5.4) : **89** (2) : **90** (2) : **87** (1).

Purification by flash column chromatography, whilst bringing limited success in separating the diastereoisomers, resulted in the cleavage of the silyl group to yield the hydroxy group.

The cyclisation of (*Z*)-methyl-6-oxo-4,5-*O*-isopropylidene-hex-2-enonoate (**85**) was repeated under identical conditions, except that the triethylsilane was ommited. After 16 hours at 50°C, mostly starting material was recovered with a trace of product being detected. From this observation, it can be deduced that the main reaction pathway is tandem hydrosilylation cyclisation, with hydroacylation of the methyloxohexenoate as a minor competing pathway.

3.3.4 Conclusions

- Tandem hydrosilylation cyclisation chemistry is compatible with substrates derived from carbohydrates and proceeds in moderate yield under mild reaction conditions.

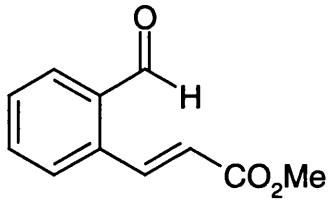
- *O*-Substitution in the 4, 5 position of the pentenal has resulted in moderate diastereoselectivity.

- Tandem hydrosilylation cyclisation is the major reaction pathway, with hydroacylation as a minor competing reaction pathway.

3.4 4, 5-Phenyl substituted substrates in Rh(I) catalysed tandem hydrosilylation cyclisations

3.4.1 Introduction

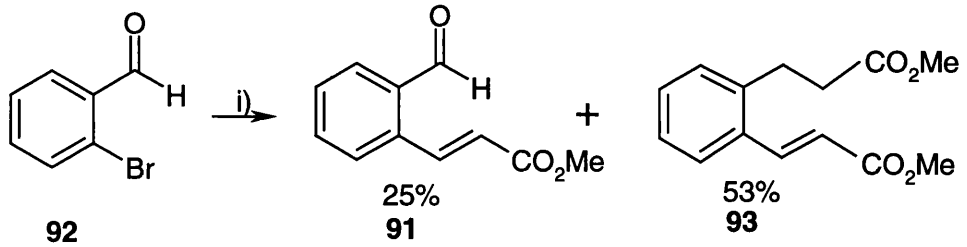
The tandem hydrosilylation cyclisation reaction with the 4, 5-isopropylidene subsitituted substrate was difficult to push to completion. After 3 days at 50°C, starting material, albeit in a small amount, still remained. It was rationalised that in replacing the isopropylidene group with a phenyl group as in (**91**), the two ends of the substrate would be conformationally restricted and hence ideally placed through entropic arguments for the ring to form quickly. It remained to be seen whether the aromatic substitution would adversely affect the selectivity.



91

3.4.2 Preparation of Methyl 3-(2'-formylphenyl) propenoate (8891)

The synthetic route employed was based on an interesting paper on the Heck reaction. Thus in 1992, Rodrigo *et al.* [81] determined that the formation of the doubly substituted product (**93**, Scheme 67) was favoured, at the expense of the conventional Heck product (**91**), simply by running the reaction in concentrated solution in the presence of excess methyl acrylate.

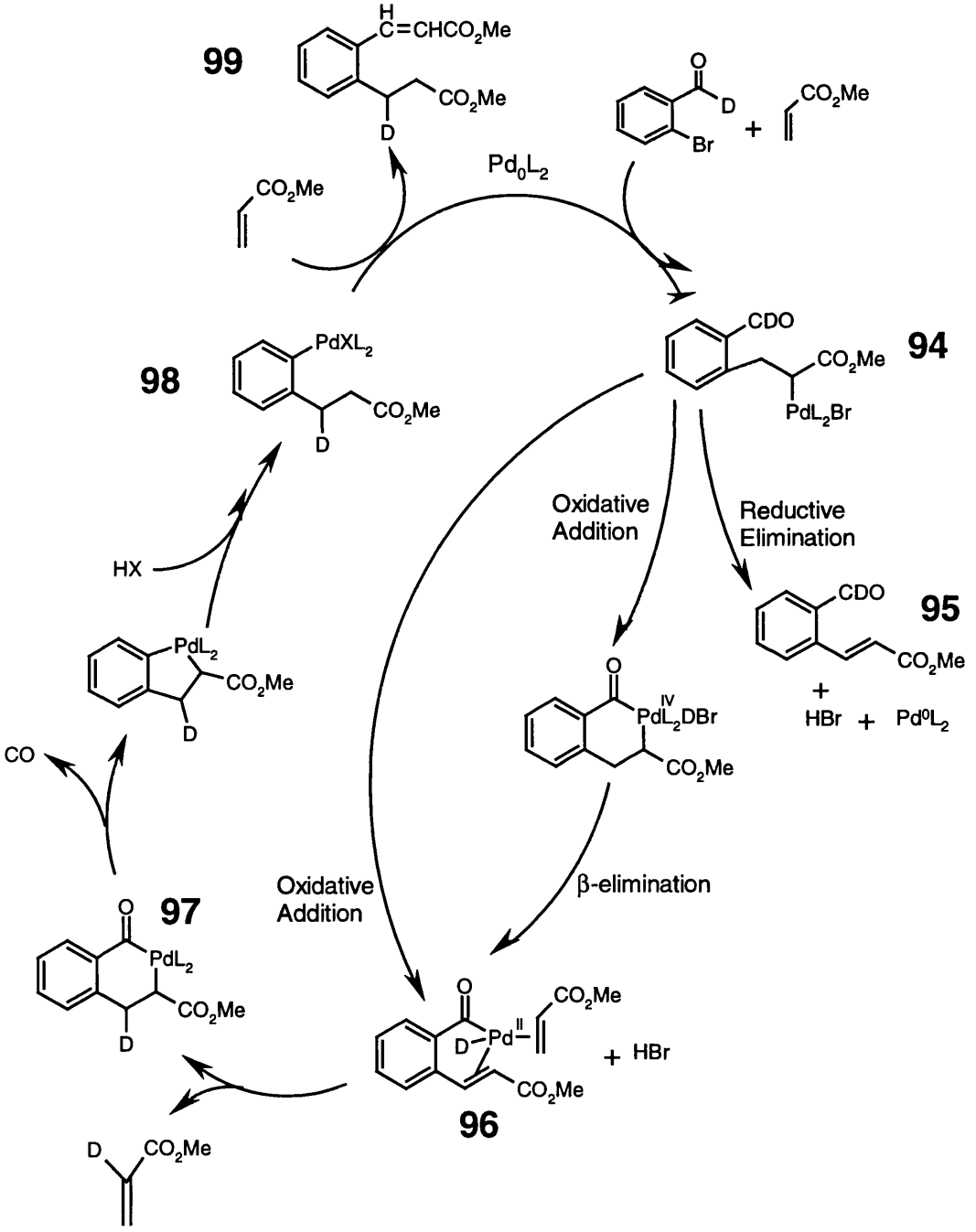


92 **91** **93**

i) excess $H_2C{=}CHCO_2Me$, $Pd(OAc)_2$, K_2CO_3

Scheme 67

Having employed deuterium-labelled substrates, Rodrigo *et al.* [81] were able to propose the catalytic cycle outlined in Scheme 68.



Scheme 68

The four main steps in the catalytic cycle are as follows:

- reductive elimination to regenerate the palladium (0) catalyst and yield the conventional Heck product **95**.

- The proximity of the formyl group in **94** presents this intermediate with an alternative pathway besides that of reductive elimination:

  (i) The palladium (0) species generated in the conventional step is delivered directly to the proximate C-H(D) bond of the formyl group (**94**) for oxidative addition.

  (ii) Alternatively, oxidative addition of the Pd(II) of **94** to the C-H(D) bond, provides the Pd(IV) species, which then undergoes β-elimination, returning to Pd(II) in **96**.

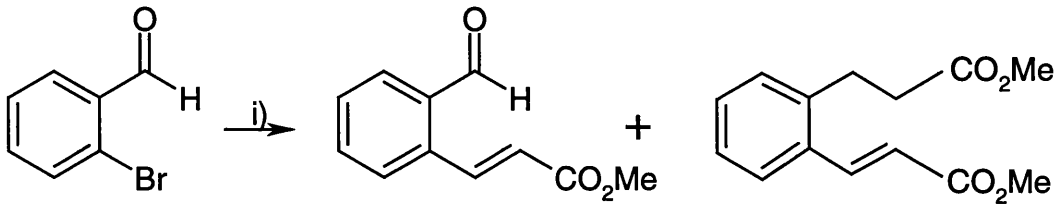
- The decomposition of **97** with loss of carbon monoxide leads to the deuterated intermediate **98**.

- This intermediate **98** then undergoes a simple Heck reaction with more methyl acrylate to provide the doubly substituted product **99**.

The lack of aromatic deuteration requires that the transfer of deuterium take place before the decarbonylation step. Rodrigo *et al.* [81] also proved the inability of the conventional Heck product (**95**) to re-enter the cycle and transform into the doubly substituted material, thus rationalising that this was due to the difficulty of reversing the reductive elimination step **97** to **98** in the presence of the excess of potassium carbonate used.

In the application of these discoveries to this project, it was successfully rationalised that the optimum yield of the desired Heck product could therefore be

achieved using moderate amounts of methyl acrylate and more dilute solutions.



69%
91

8.5%
93

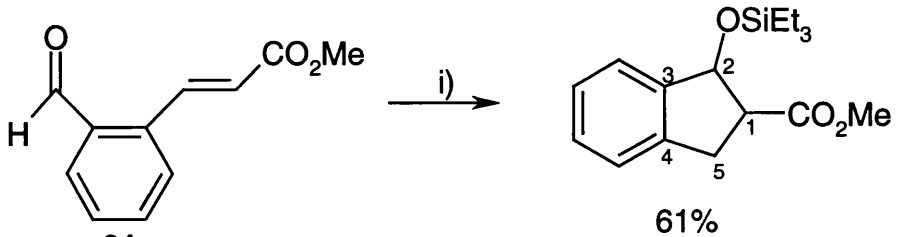
92

i) excess $H_2C=CHCO_2Me$
$Pd(OAc)_2$, K_2CO_3

Scheme 69

On the first attempt, the desired product (**91**) was isolated in 46% yield as the *trans* isomer (69% when adjusted for recovered starting material) with the doubly substituted product (**93**) as a minor but persistent contaminant (Scheme 69). All attempts to remove **93** through standard purification techniques were unsuccessful, a result also noted by Rodrigo *et al.* [81]. It was only through protecting the aldehyde as the dimethyl acetal functionality, using trimethylorthoformate, that it became possible to separate the impurity from the acetal through preparative tlc, although multiple elutions were required. The aldehyde was then regenerated from the acetal using hydrochloric acid in a 83% yield.

3.4.3 Rh(I) catalysed tandem hydrosilylation cyclisations



91

61%
100

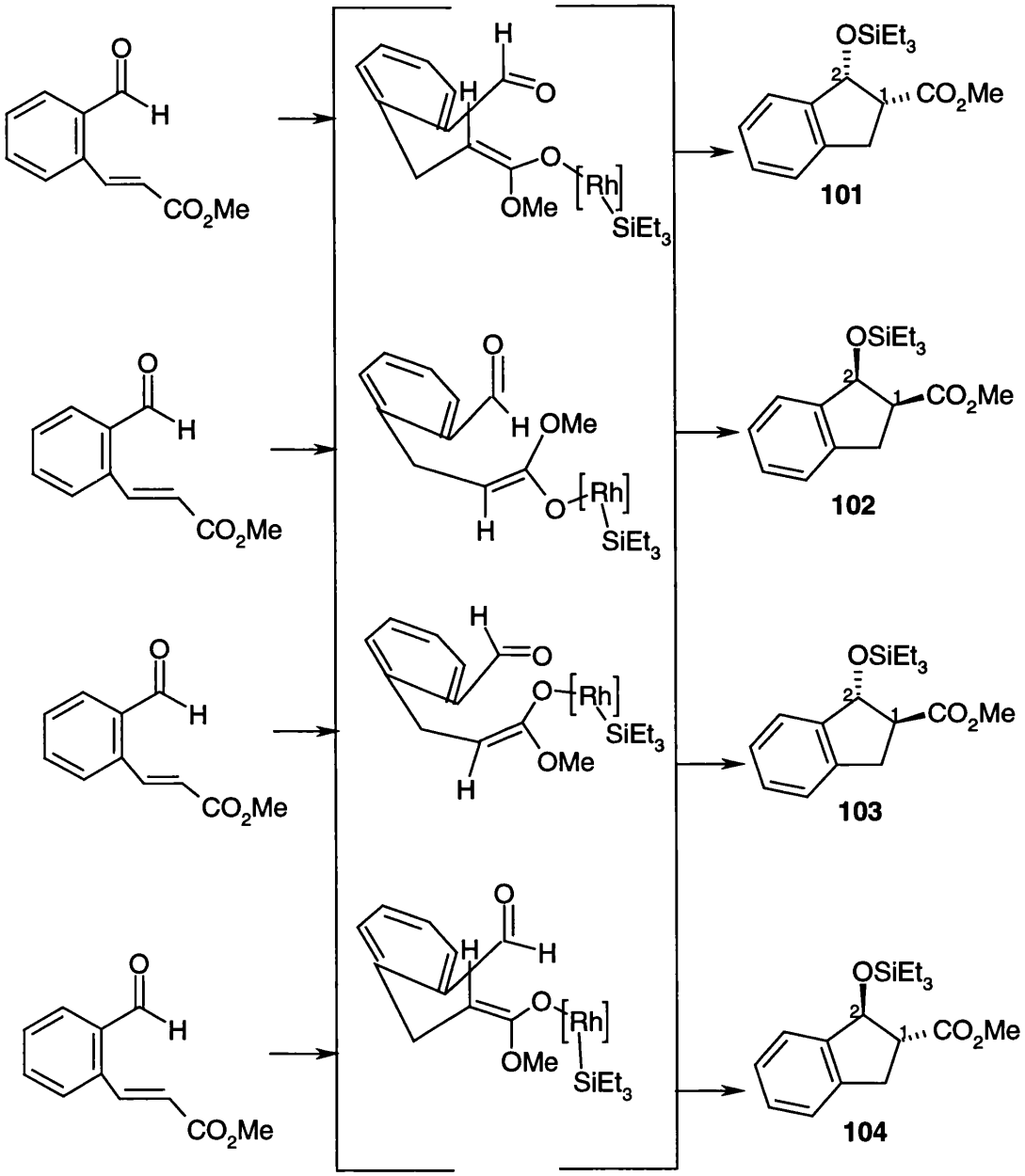
i) 4%mol $RhCl(PPh_3)_3$, Et_3SiH, toluene, 70°C, 16hr

Scheme 70

The methyl 3-(2'-formylphenyl) propenoate (**91**, Scheme 70) was reacted with 4% mol of Wilkinson's catalyst and triethylsilane at 50°C. Close monitoring by tlc indicated no reaction at this temperature after 3 hours. Having increased the temperature to 70°C, all starting material was consumed within 16 hours, as indicated by the absence of the aldehyde peak at 10.3ppm on the ^{1}H NMR spectrum. Whilst it was apparent from tlc and the ^{1}H NMR spectrum that there was more than one product formed during the course of the reaction, the desired product **100** formed the main component, with a yield of 61%.

The appearance of two peaks at δ4.7 (d, J 5.4Hz) and δ4.85 (d, J 4.9Hz) in the ^{1}H NMR spectrum was interpreted as the characteristic C<u>H</u>(OSiEt$_3$) proton, with the *cis* and *trans* isomers being formed in the approximate ratio of 1:1.5. All attempts to separate the isomers and hence identify the major isomer by experimental means, were unsuccessful.

Through careful consideration of the transition states (Scheme 71), the *cis* isomer (**101**, **102**) is tentatively proposed as the major isomer with the *trans* isomer (**103**, **104**) as the minor component. The phenyl substituent forces the substrate to adopt much the same conformation, regardless of the geometry of the rhodiun ketene acetal. The overall effect is to reduce diastereoselectivity.


O
H
CO2Me
H
H
O
O
Rh
OMe
SiEt3
OSiEt3
2
1
CO2Me
101
H OMe
102
103
104

Scheme 71

3.4.4 Conclusions

- Tandem hydrosilylation cyclisation chemistry is compatible with the aromatic pentenal and proceeds in moderate yield under mild reaction conditions.

- Whilst the phenyl group does indeed accelerate the closure of the substrate to form the cyclopentyl moiety, it is at the expense of diastereoselectivity.

CHAPTER FOUR

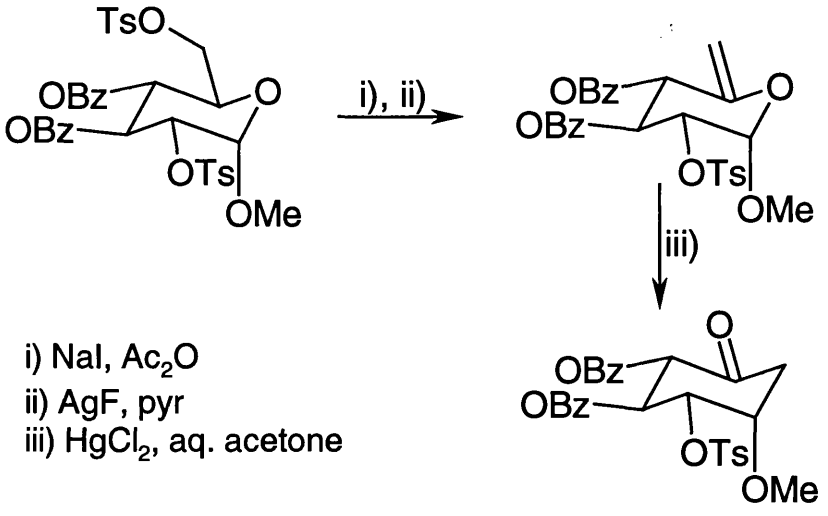
RESULTS AND DISCUSSION

4.1 Introduction

Following the reasonable success in generating cyclopentyl derivatives with some stereocontrol using the novel tandem hydrosilylation cyclisation chemistry, an investigation was conducted to see if this methodology was applicable to the synthesis of larger ring sizes.

4.1.1 Existing methodology for the synthesis of cyclohexanones from carbohydrate precursors

Ring opening followed by intramolecular ring closure of carbohydrates offers access to highly functionalised carbocyclic compounds. One such route, known as the Ferrier reaction,[82] provides a chiral cyclohexanone synthesis with the transformation of the enol ether into a cyclohexanone derivative by heating in aqueous acetone with mercury (II) salts (Scheme 72). [83]

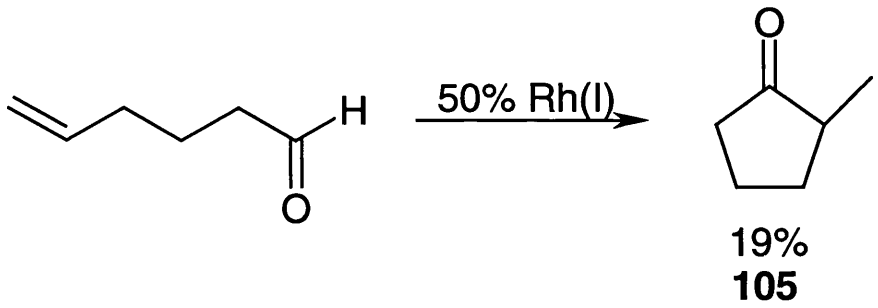


Scheme 72

This carbohydrate-into-deoxyinosose conversion has been shown to have general applicability[84] in the cyclitol area and value in the synthesis of inosamines and other compounds of interest in the areas of aminoglycoside antibiotics[85] and pseudo-oligosaccharides.[86] An apparent disadvantage to this methodology, however, is the pivotal role of mercury chloride, rendering it unattractive for large scale chemistry.

4.1.2 Preparation of cyclohexanones via Rhodium catalysed intramolecular hydroacylation

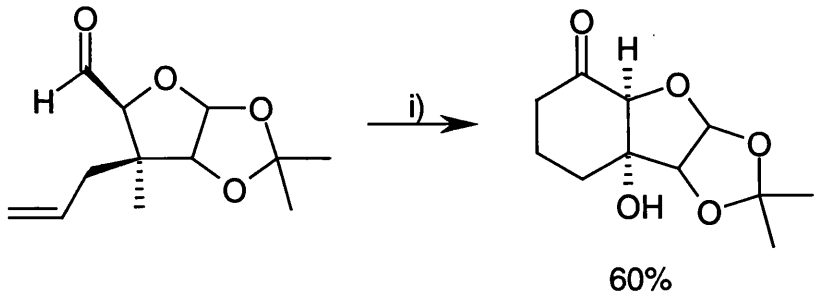
In an attempt to complement existing methodology, Larock *et al.*[27] first investigated whether 5,6-unsaturated aldehydes could be cyclised to cyclohexanones.



Scheme 73

No cyclohexanone was observed but the alternative product 2-methylcyclopentanone (**105**, Scheme 73) was isolated in 19% yield. The poor yield was attributed to the extensive decarbonylation which occurred and the consequential poisoning of the catalyst.

The first and as yet, only hydroacylation of a hexenal to form a cyclohexanone was reported by Gable and Benz (Scheme 74).[87]



i) $[RhCl(PPh_3)_2]_2$, CH_2Cl_2, 70°C

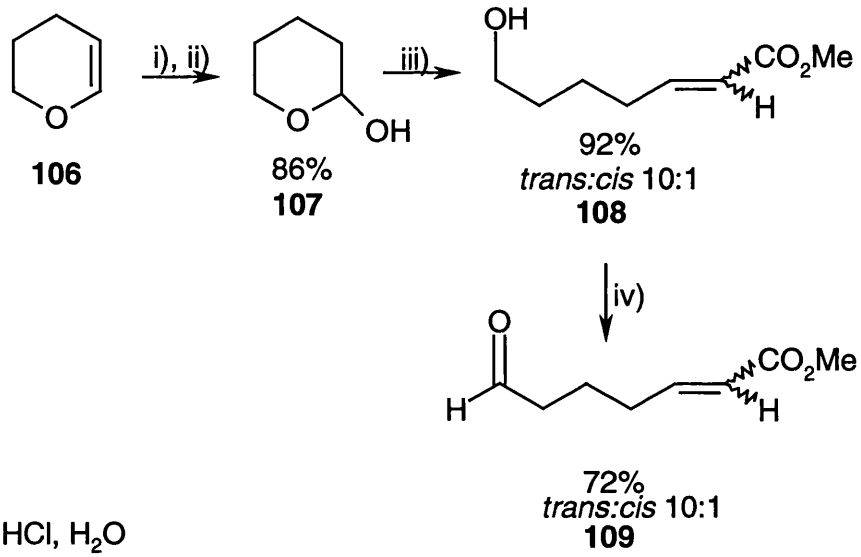
Scheme 74

One possible explanation for the success of the reaction is that the formation of the alternative fused 5,5,5 tricyclic product may be inhibited by ring strain.

4.2 Experimental

4.2.1 Preparation of Methyl-7-oxo-2-heptenoate (115)

The preparation of an appropriate precursor was therefore carried out, as shown in Scheme 75.



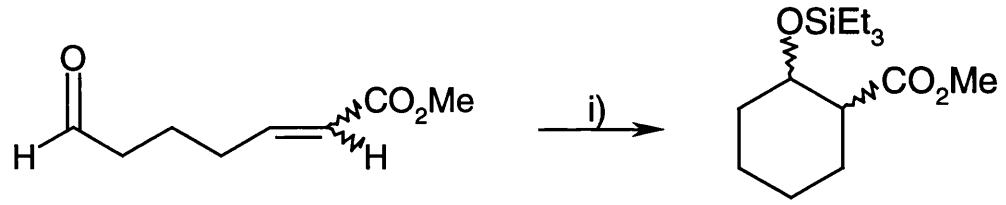
i) HCl, H_2O
ii) Et_2O, 16hrs, liquid liquid extraction
iiii) $Ph_3P{=}CHCO_2Me$, $(CH_2Cl)_2$, 60°C
iv) PCC, DCM

Scheme 75

1-tetrahydropyran (**107**) was synthesised from 3, 4-dihydropyran (**106**) in 86% yield (Scheme 75).[88] Reaction of 1-hydroxypyran with the Wittig reagent carbomethoxymethylene triphenylphosphorane[89] yielded the desired 7-hydroxy-α,β-hept-2-enoate in 92% yield (**108**). Attempts at separating the isomers, generated in the ratio *trans:cis* 10:1,were unsuccessful.

The oxidation of the hydroxy group to the aldehyde, using Corey's reagent PCC,[46] proceeded cleanly in under 3 hours with a yield of 72% (**109**). On increasing the reaction time, only trace amounts of aldol addition products were detected by ^{1}H NMR and mass spectroscopy.

4.2.2 Reaction of Methyl-7-oxo-2-heptenoate under Rh(I) catalysed tandem hydrosilylation cyclisation conditions



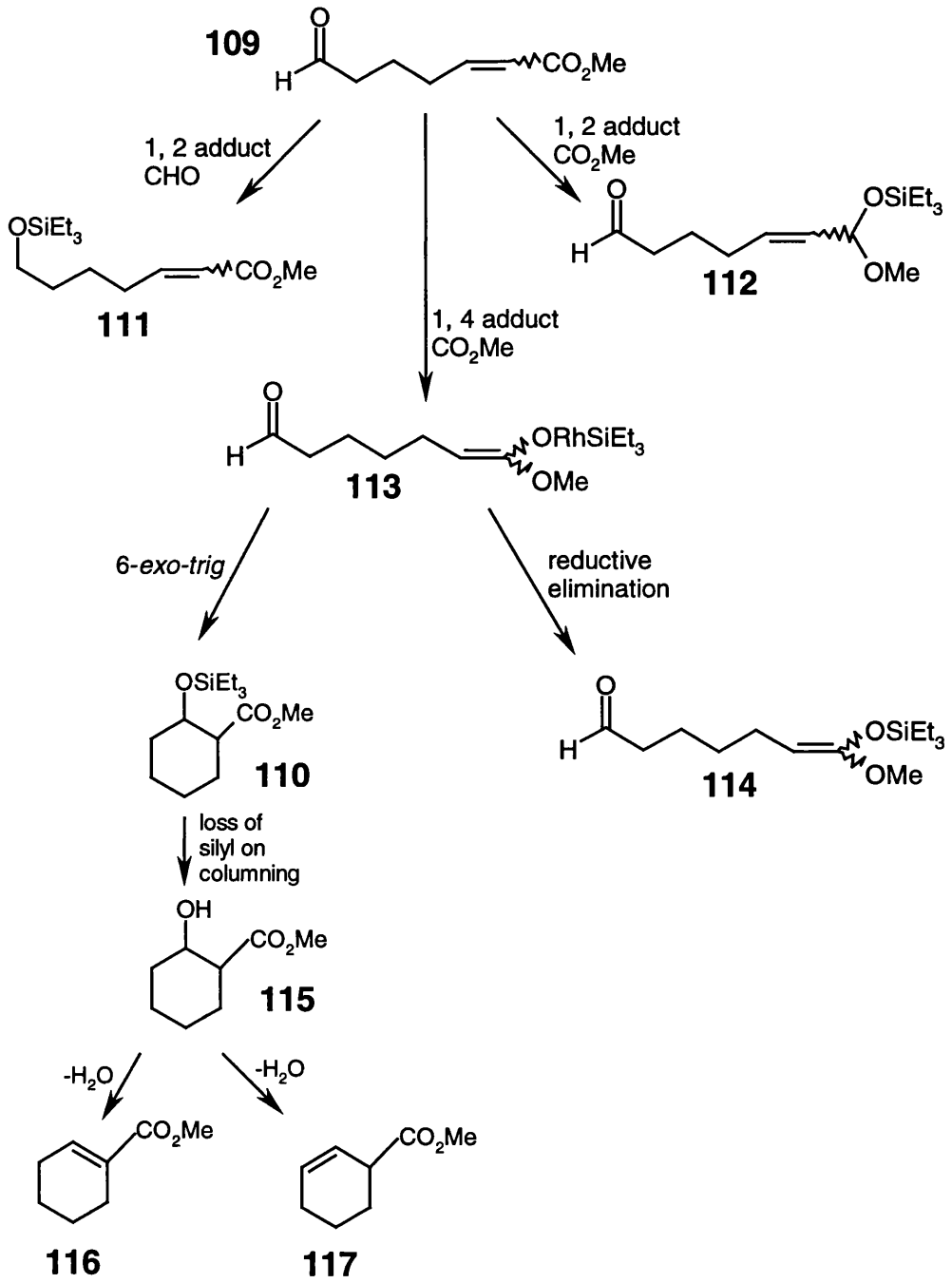
109 **110**

i) 1% $(PPh_3)_3RhCl$, 2.1eq. Et_3SiH, toluene, heat

Scheme 76

After 16 hours at 50°C under the conditions shown in Scheme 76, there had been no consumption of starting material (**109**), either through formation of the desired substituted cyclohexanol ring (**110**) or through oligomerisation of the aldehyde. This is in direct contrast to the previous transformations observed under the same reaction conditions, for the evidently more reactive analogue methyl oxo hexenoate (**22**). It was only after 36 hours at 70°C that all of the methyl oxo heptenoate was consumed. The crude ^{1}H NMR of the reaction mixture showed multiple products. Purification by

preparative tlc isolated two distinct products in low yield.

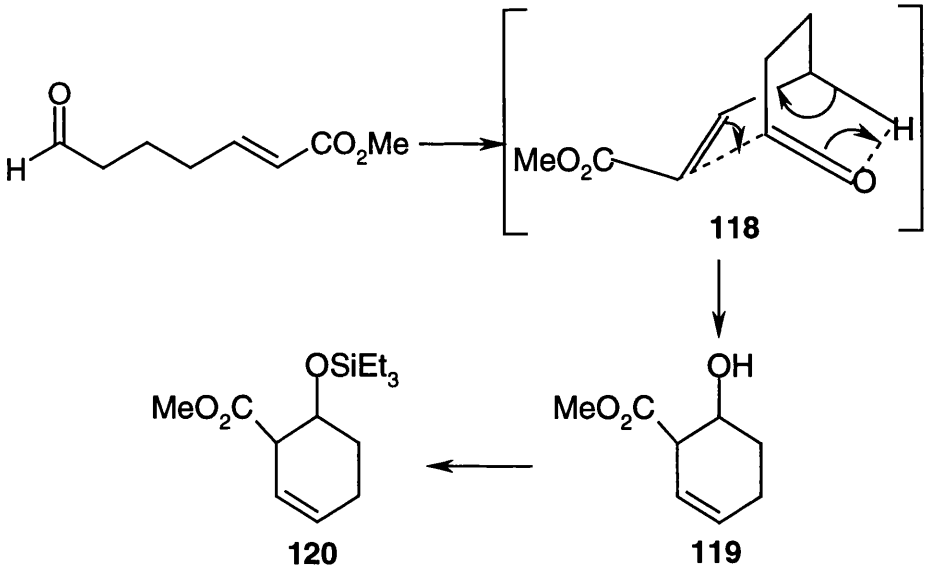


Scheme 77

Scheme 77 shows all of the possible products that could result from this reaction, with the hydrosilane adding in either a 1, 2 fashion to the aldehyde group (**111**) or to the ester group (**112**). After the 1, 4 addition to give the rhodium ketene acetal (**113**), reductive elimination of the catalyst yields the silyl ester enolate (**114**) whilst 6-*exo-trig* cyclisation would give the desired product **110**.

There were no low field peaks in the ^1H NMR spectrum corresponding to an aldehyde proton, thus precluding the formation of (**112**) and (**114**). The appearance of a *m/z* peak at 273 (40%) in the EI^+ mass spectrum confirmed that it could be one of the products (**110**) and / or (**111**) with the ^1H NMR confirming the addition of the silane.

A relatively major component of the crude mixture possessed distinctive low field signals (δ6.2(d), δ5.0(dt), δ4.4(q)), quite different to the signals of the starting materials unsaturated protons (**109**: *trans* isomer : δ6.9(dt), δ5.8 (d); *cis* isomer : δ6.2 (dt), δ5.8 (d)). A COSY spectra showed coupling between the protons of the unknown product at δ6.2(d) and δ4.4(q) and again at δ6.2(d) and δ5.0(dt), indicating the presence of isomers. It was postulated that these distinctive low field chemical shifts might be indicative of unsaturated protons. The molecules **116**, **117** (Scheme 77) and **120** (Scheme 78) were subsequently proposed, as was **111**.



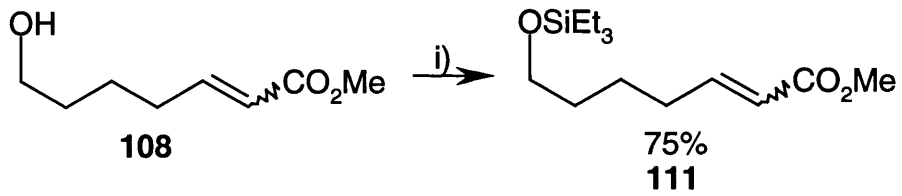
Scheme 78

Scheme 78 indicates that the unsaturated product (**120**) could be formed by an intramolecular carbonyl-ene reaction, with **118** as the proposed transition state adopted by methyl-7-oxo-2-heptenoate.[90] Comparison with the known spectra of the compounds **116**[91] and **117**[92] eliminated them from the search to explain the appearance of the low field signals at δ6.2, δ5.0 and δ4.4.

4.3 Interpretation of results

The compounds (**110**) and (**111**) were synthesised by alternative routes so that their ^{1}H NMR spectra could be directly compared with the unidentified products isolated following the reaction of methyl-oxo-heptenoate with Wilkinson's catalyst and triethylsilane.

4.3.1 Preparation of 7-Triethylsilyloxyhept-2-enoate

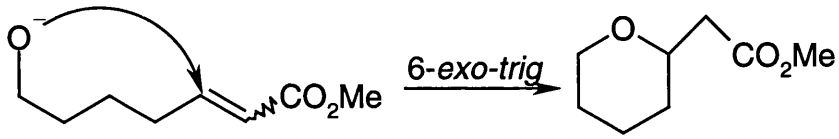


108 **75%** **111**

i) imidazole, Et_3SiCl, DMF, 3 days

Scheme 79

Triethylsilyl chloride was chosen as the silylating agent[93] for 7-hydroxyhept-2-enoate (**108**, Scheme 79). The reaction proved difficult to force to completion, with starting material remaining even after prolonged reaction times. This may have been due to the choice of base: a stronger base system eg. triethylamine/4-dimethylaminopyridine[94] or neat pyridine[95] would have introduced the unacceptable risk of 6-*exo-trig* cyclisation (Scheme 80).



121

Scheme 80

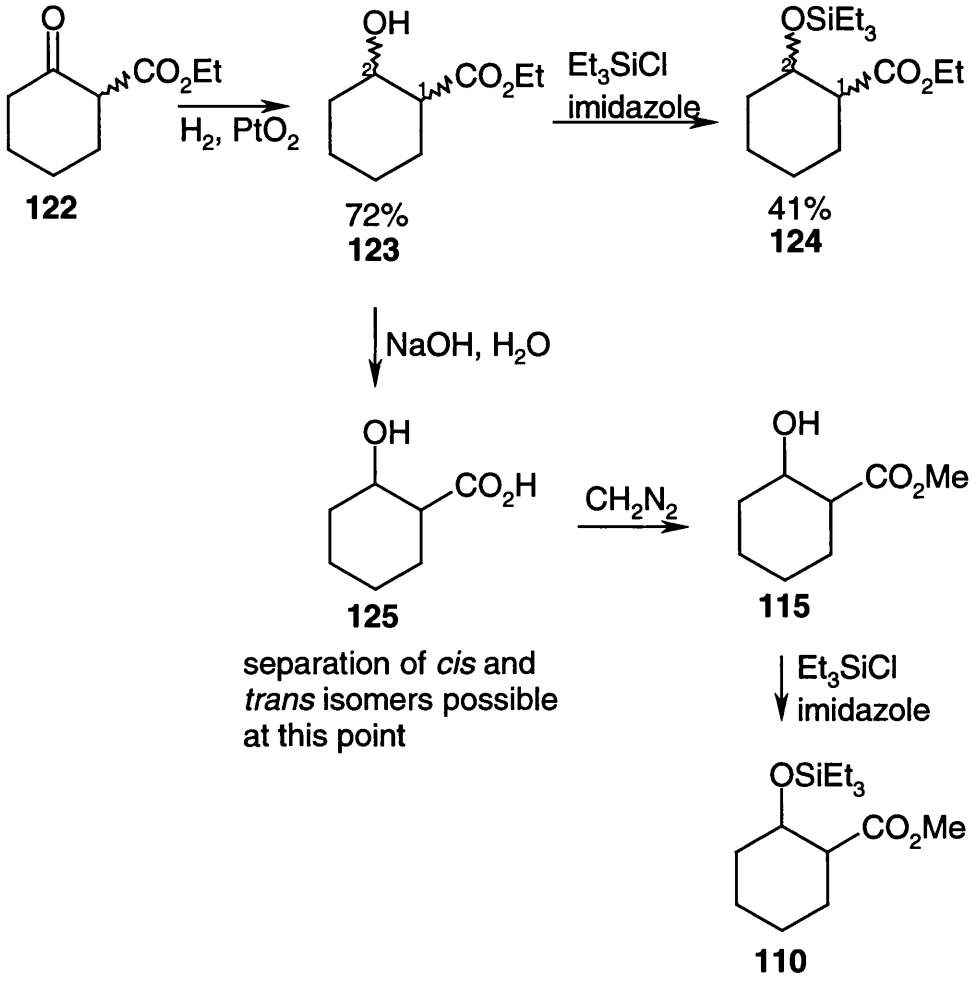
Using the reaction conditions detailed in Scheme 79, the silylated product **111** was isolated, along with recovered starting material (**108**), in a 51% yield and an adjusted yield of 75% based on recovered starting material.

As expected, there was little change in the ^{1}H NMR spectrum upon silylating the hydroxy group; there were no chemical shifts corresponding to the low field signals δ6.2, δ5.0 and δ4.4, observed for the unidentified products. This indicates that 1, 2 additon of the silane to the aldehyde had not occurred.

4.3.2 Preparation of Ethyl-2-triethylsilyloxycyclohexanecarboxylate

A direct comparison with the unidentified products isolated on the reaction of methyl-7-hydroxy-2-heptenoate with Wilkinson's catalyst and triethylsilane, required the synthesis of **110**. One possible strategy to this compound involved the reduction of the readily available ethyl cyclohexanonecarboxylate (**122**) to give **123**, saponification to give the acid **125**,[96] re-esterification with diazomethane[97] to generate the methyl ester **115** and silylation to give the desired product **110** (Scheme 81).

It was deemed that a simpler approach would be the synthesis of ethyl-7-oxo-2-heptenoate and its subsequent reaction with Wilkinson's catalyst and triethylsilane and to compare the product obtained with **124**, whose generation from **122** via hydrogenation and silylation are shown in Scheme 81.

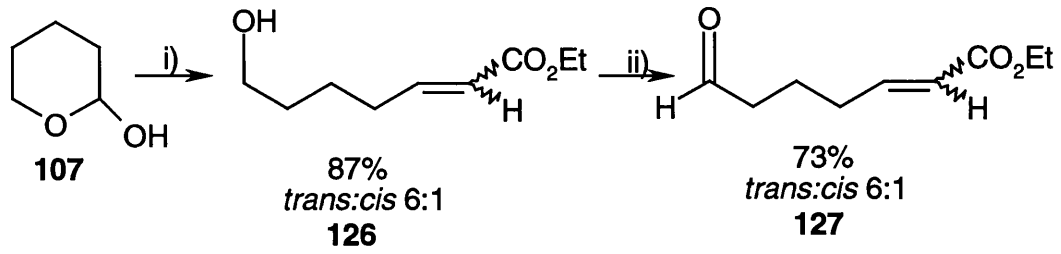


Scheme 81

Freshly distilled 2-carboethoxycyclohexanone was hydrogenated in its own volume of absolute EtOH with 3.5% PtO_2 to give the product (**123**) in 72% yield (Scheme 81). Lower catalyst concentrations and more dilute reaction solutions were found to adversely affect the product yield.

The hydroxy functional group was silylated with triethylsilylchloride and imidazole in DMF to give the product (**124**) in 41% yield. Unfortunately, in both compounds **123** and **124**, the two distinctive proton peaks for H^1 and H^2 both coincided with other peaks: H^1 was superimposed on the OCH_2CH_3 peak and H^2 was superimposed on the $(CH_2)_2$ peak.

4.3.3 Preparation of Ethyl-7-oxo-2-heptenoate



i) $Ph_3P{=}CHCO_2Et$, $(CH_2Cl)_2$, 60°C, 16 hr
ii) PCC, DCM

Scheme 82

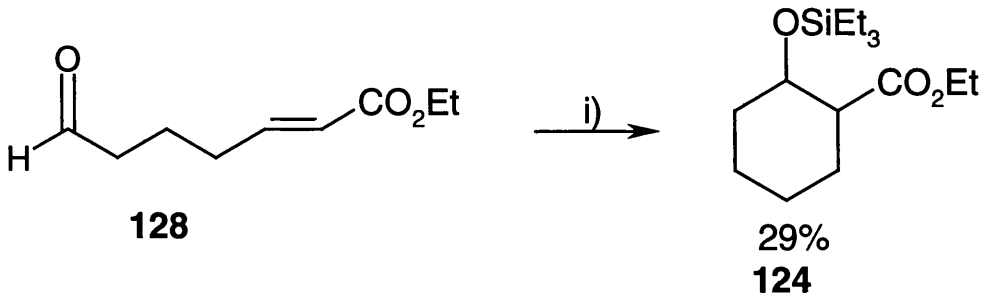
Reaction of 1-tetrahydropyran (**107**) with the Wittig reagent carboethoxymethylene triphenylphosphorane in dichloroethane (Scheme 82) generated the desired ethyl-7-hydroxy α, β-hept-2-enoate (**126**) in 87% yield. This result compares favourably with that reported by Thompson *et al*,[98] who isolated the product **126** in 70% yield, having refluxed 1-tetrahydropyran with the Wittig reagent in acetonitrile for 48 hours. Attempts at separating the isomers at this point, generated in the ratio *trans:cis* 6:1, were unsuccessful.

The oxidation of the hydroxy group to the aldehyde (**127**), using Corey's reagent PCC,[46] proceeded cleanly in under 2.5 hours with a yield of 73% (Scheme 82). Purification by flash column chromatography enabled the isomers to be separated.

4.3.4 Reaction of (*E*)-Ethyl-7-oxo-2-heptenoate under Rh(I) catalysed tandem hydrosilylation cyclisation conditions

(*E*)-Ethyl-7-oxo-2-heptenoate (**128**) was reacted with Wilkinson's catalyst and excess triethylsilane for 16 hours at 70°C (Scheme 83). The crude ^1H NMR spectrum showed the reaction mixture to be multi-component. The desired product, identified through comparison with the ^1H NMR spectrum obtained for **124** synthesised from

ethyl cyclohexanonecarboxylate, was isolated in a yield of 29% as a mixture of *cis* and *trans* diastereoisomers.



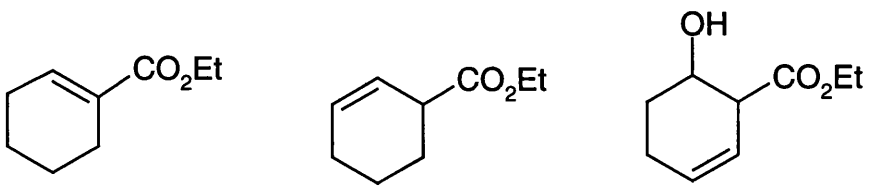
128 **124** 29%

i) 3% $(PPh_3)_3RhCl$, 2.1eq. Et_3SiH, toluene, 70°C

Scheme 83

As previously mentioned, the two distinctive proton peaks for H^1 and H^2 in compound **124** both coincided with other peaks: H^1 was superimposed on the OCH_2CH_3 peak and H^2 was superimposed on the $(CH_2)_2$ peak. Consequently, the diastereoisomer ratio could not be deduced from the spectrum.

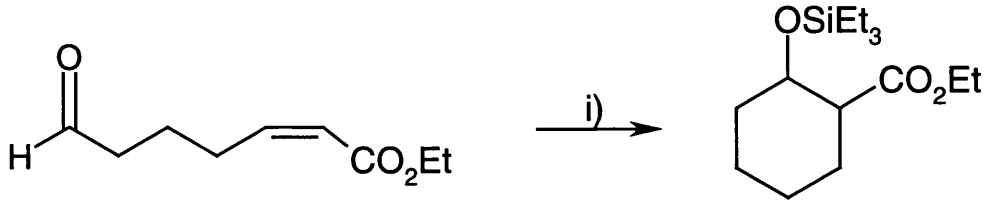
As was seen for the analogous reaction with the methyl ester, an unidentified component with additional low field signals at δ6.2, δ5.0 and δ4.4 was also isolated. As was proposed for the unidentified component found on reacting methyl-7-oxo-2-heptenoate under tandem hydrosilylation cyclisation conditions, the analogous compounds **129**, **130** (from loss of the silyl group and subsequent dehydration) and **131** (carbonyl-ene reaction of starting material **128**) were proposed.



129 **130** **131**

As yet, literature searches for NMR data on these compounds **129**, **130** and **131**, have proved unsuccessful. However, since **129** contains one olefinic proton in conjugation, it is reasonable to eliminate it as a possible product of this reaction.

4.3.5 Reaction of (Z)-Ethyl-7-oxo-2-heptenoate under Rh(I) catalysed tandem hydrosilylation cyclisation conditions



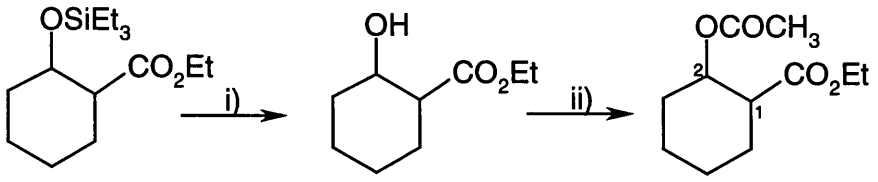
132 → **19%** **124**

i) 3% $(PPh_3)_3RhCl$, 2.1eq. Et_3SiH, toluene, heat

Scheme 84

(*Z*)-Ethyl-7-oxo-2-heptenoate (**132**) was also reacted with Wilkinson's catalyst and excess triethylsilane for 16 hours at 70°C (Scheme 84). The crude ^1H NMR spectrum showed the reaction mixture to be multi-component. The (*Z*)-isomer proved to be less reactive than the (*E*)-isomer (**128**) under the same experimental conditions, with a small amount of unreacted starting material apparent in the spectrum. The desired product, identified through comparison with the ^1H NMR spectrum obtained for **124** synthesised from ethyl cyclohexanonecarboxylate, was produced in a yield of 19%. Again, the two distinctive proton peaks for H^1 and H^2 were coincident with other peaks and so the diastereoisomer ratio could not be deduced from the spectrum. Consequently, it was not possible to determine if the selectivity was dependent upon the geometry of the double bond in the starting material.

It is proposed that the diastereoisomer ratio for **124** may be determined by desilylating the triethylsilyloxy group and acetylating (Scheme 85), in order to shift the defining H^2 proton from under the OCH_2CH_3 proton peak.

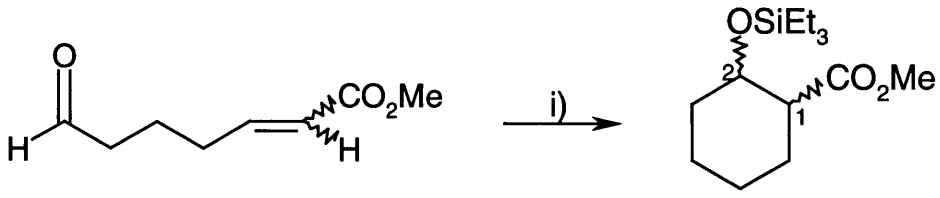


124 **123** **133**

i)TBAF
ii) Ac_2O, pyridine, DMAP

Scheme 85

By comparison of the ^1H NMR spectrum for the products obtained following the reaction of methyl-7-oxo-2-heptenoate with Wilkinson's catalyst and triethylsilane at 70°C, with the spectra for **124** synthesised from ethyl cyclohexanonecarboxylate, the following conclusions were reached. Tandem hydrosilylation cyclisation had occurred, although the yield was low at 15% (Scheme 86). The 'unsaturated' compound was predominant in the multi-component mixture. As for the ethyl ester analogue **124**, the characteristic *cis*, *trans* H^2 proton came under the OCH_3 chemical shift and so a reliable measurement of the diastereoisomer ratio could not be ascertained.



109 15% **110**

i) 1% $(PPh_3)_3RhCl$, 2.1eq. Et_3SiH, toluene, heat

Scheme 86

4.4 Conclusions

- 1, 2 substituted cyclohexanols can be prepared via the novel tandem hydrosilylation cyclisation reaction, in albeit low yield. The as yet unknown predominant 'unsaturated' compound needs to be identified. Work could then begin on inhibiting the competing side reaction resulting in the optimisation of the cyclohexanol yield.

- As the characteristic *cis, trans* H^2 proton resides under the ester chemical shift in the ^1H NMR spectrum, the triethylsilyloxy group would have to be converted to an $OCOCH_3$ group before the selectivity of this reaction can be investigated.

CHAPTER FIVE: FUTURE WORK

5.1 Introduction

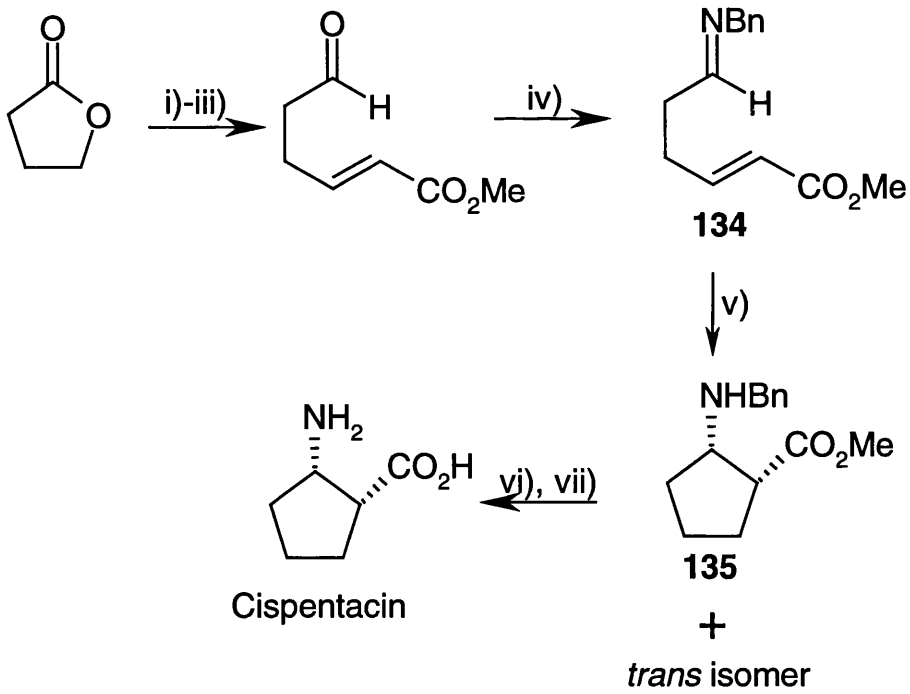
The initial study has proved to be most promising, showing that there is considerable potential in this approach to generate functionalised cyclopentanols and possibly larger rings.

The scope of tandem hydrosilylation cyclisation chemistry has, to some extent, been defined through investigations into differing reaction conditions eg. silanes, temperature and catalytic systems. Further work in this area, however, is warranted. In particular our understanding of those systems showing *trans* selectivity [catalyst=$RhH(PPh_3)_4$, $RhCl(C_8H_{14})_2]_2$, L=tris-4-tolylphosphine, tris-4-methoxyphenylphosphine] is limited. Once an understanding of those factors affecting selectivity has been gained, asymmetric catalyst systems could be used in order to probe the levels of enantioselectivity attainable on achiral substrates.

Future work should also focus on developing the preliminary investigations into alternative Michael acceptors such as α, β-unsaturated ketones, nitriles, nitro and sulphonyl derivatives. Work should also be commenced on exploring the compatibility of this methodology with alternative electrophilic acceptor groups including imines, epoxides and alkenes. These investigations should lead to a more general synthesis of cyclopentyls, offering the advantage of compatibility with a diverse range of functionality in the parent substrate. Alternatively, the incorporation of heteroatoms into the substrate chain may also provide access to a range of substituted pyrrolidines, tetrahydrofurans or albeit less likely, tetrahydrothiophenes. The possibility of tandem cascade reactions as a means to fused carbocycles also warrants investigation. These aspects are discussed further in Section 5.2.

5.2. Alternative electrophilic acceptors

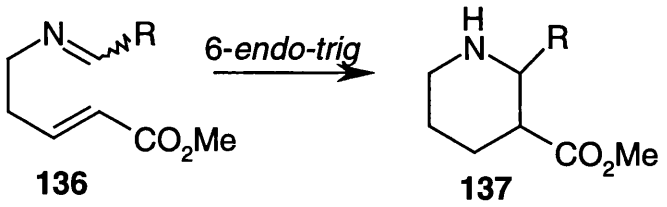
The aldehyde functionality can, in principle, be replaced by a range of electrophilic functionalities such as imines, nitriles, epoxides and alkenes. For example, cyclisation of the imine (**134**) may provide an efficient seven step synthesis of the potent antifungal agent Cispentacin (Scheme 87).[99] Hydrogenation of the cyclic-β-amino ester (**135**) followed by acid hydrolysis of the ester gives the racemic Cispentacin. The use of a chiral phosphine ligand may provide an attractive asymmetric synthesis of Cispentacin. Since substitution in the 2 and 3 position is easily introduced into the substrate, isosteres of Cispentacin would then be readily accessible.



i) DIBAL ii) $Ph_3P{=}CHCO_2Me$ iii) PCC iv) $BnNH_2$, PPTS
v) Rh(I), Et_3SiH vi) H_2, Pd/C vii) H^+

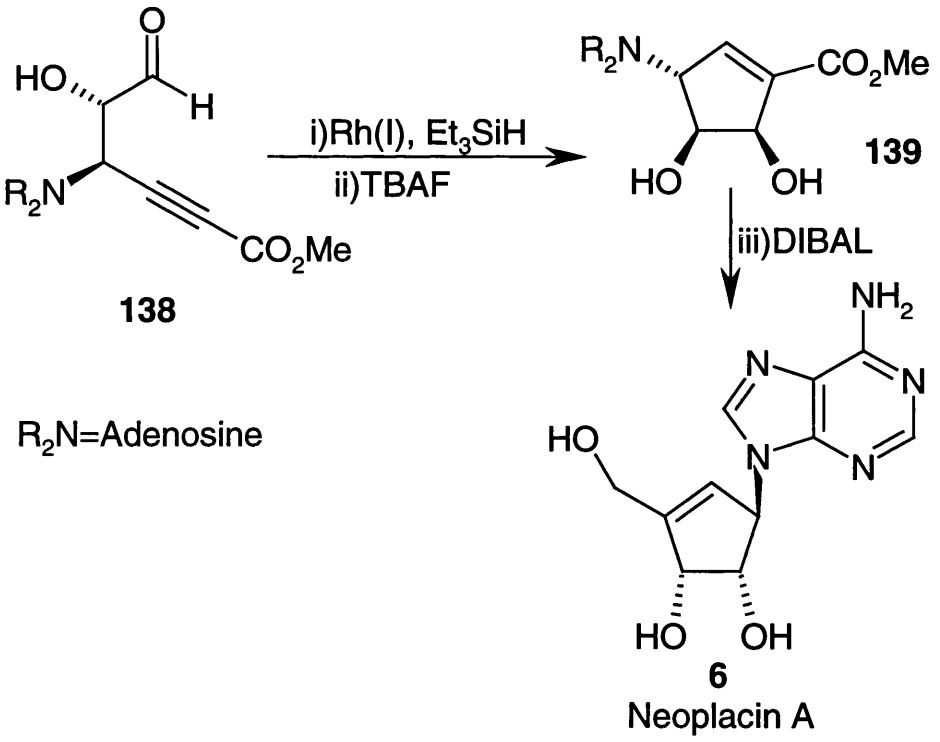
Scheme 87

Substituted piperidines (**137**) may be accessed by a 6-*endo-trig* cyclisation of the imine (**136**, Scheme 88).



Scheme 88

5.3 Alternative Michael Acceptors

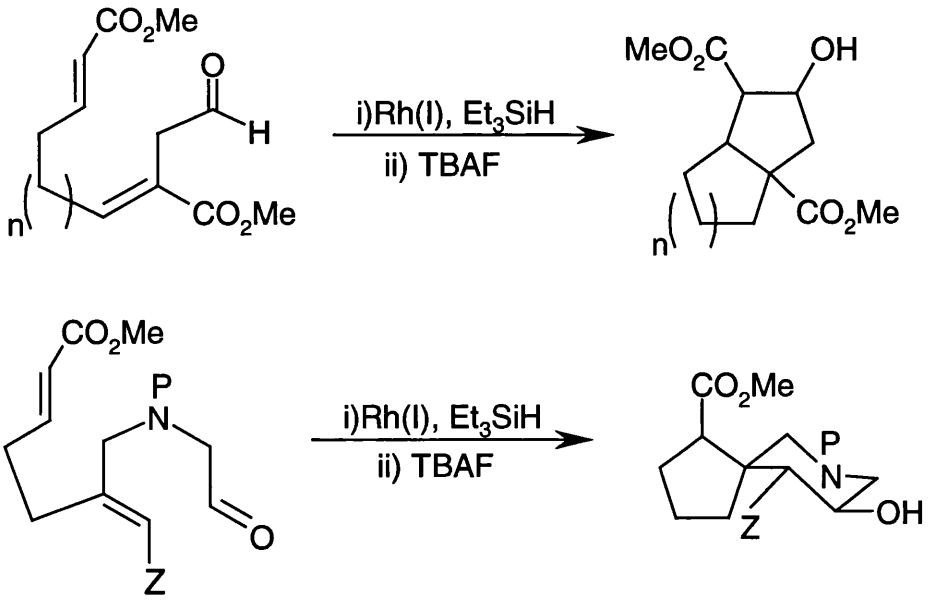


Scheme 89

Work needs to continue on investigating alternative Michael acceptors to the α, β-unsaturated ester. For example, the methyl-4-pentyl ester (**138**) may cyclise to give the corresponding substituted cyclopentanol (**139**). This methodology, if successful, could then be extended to the synthesis of the carbocyclic nucleoside antibiotic, Neoplacin A[7] (**6**, Scheme 89), which has recently received considerable attention due to its potent anti-cancer activity.

5.4 Cascade methodology

An investigation may be conducted as to whether this methodology might be applied to fused carbocyclic synthesis via a cascade cyclisation (Scheme 90).

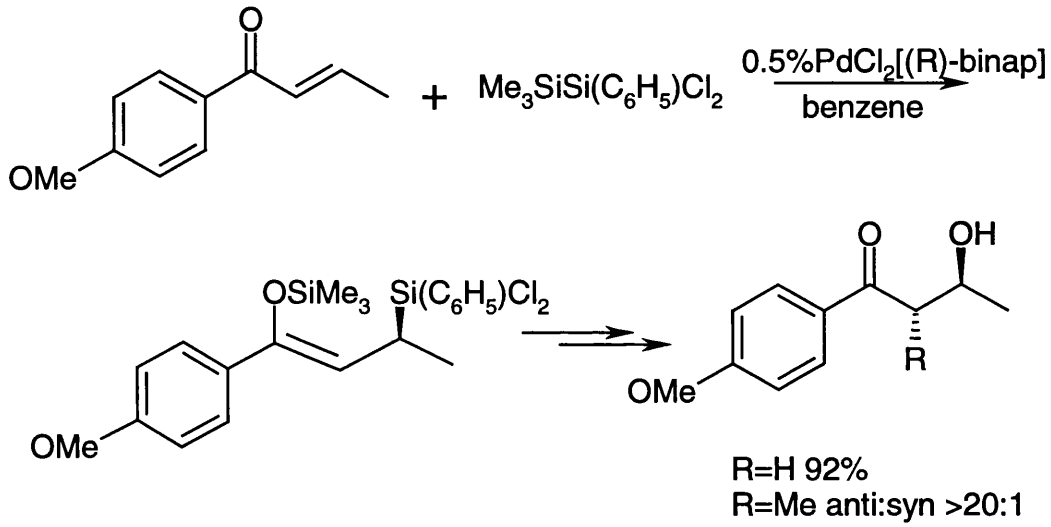


Z= eg. SO_2Ph
P=protecting group

Scheme 90

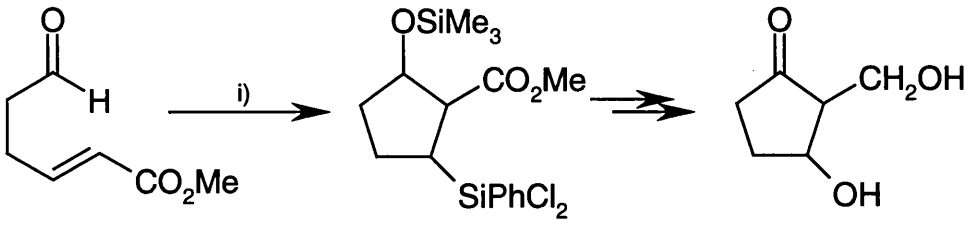
5.5 Disilanes

Certain disilanes react with olefinic substrates.[100] An (R)-BINAP complex brings about enantioselective 1,4-disilylation of α, β-unsaturated ketones with chlorinated disilanes. The resulting enol silyl ethers, produced in 74-92% ee, can be converted to β-hydroxy ketones or α-substituted β-hydroxy ketones using lithium enolates. The diastereoselectivity in the enolate alkylation is greater than 20:1 (Scheme 91).[101]



Scheme 91

The applicability of this strategy to transition metal catalysed tandem hydrosilylation cyclisation should be explored due to its potential to access β-hydroxy cyclopentanoids (Scheme 92). If this approach proved successful, it would form a complementary reaction to existing β-hydroxy cyclopentanone syntheses, which range from the catalytic decompositon of 1, 3-epiperoxycyclopentane[102] to the reduction of 2, 3-epoxycyclopentanone.[103]



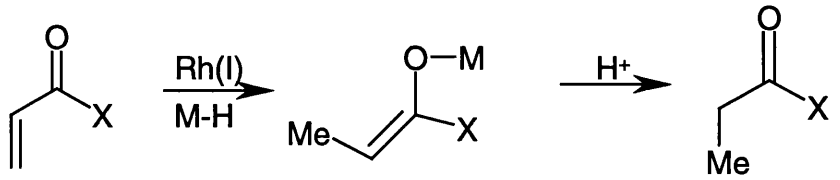
β-hydroxy cyclopentanone

i) $Me_3SiSi(C_6H_5)Cl_2$, benzene, 0.5%$PdCl_2$[(R)-binap]

Scheme 92

5.6 Tandem Hydroboration Cyclisation

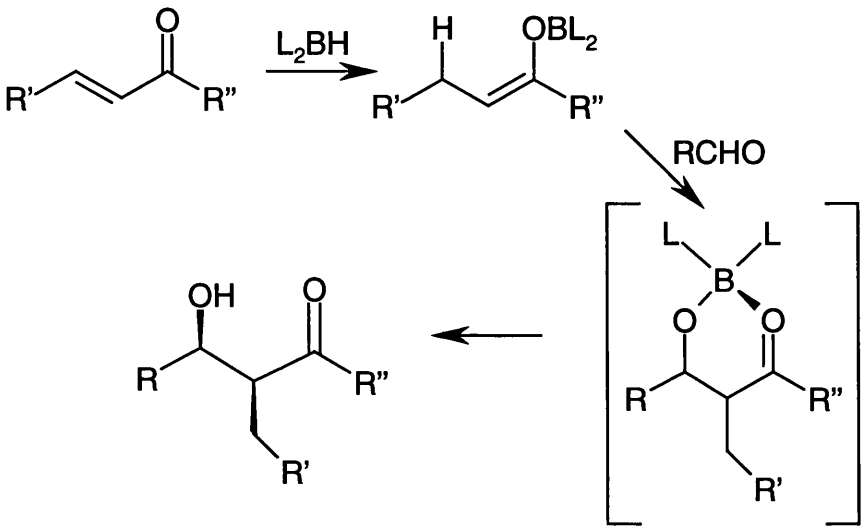
In 1990, Evans and Fu[104] reported that Rh(I) complexes, in addition to catalysing the 1, 4-addition of silicon hydrides to enones, will also catalyse hydroboration (Scheme 93). This mild method for conjugate reduction is compatible with a wide variety of functional groups and is amenable to large-scale reactions.



M=SiR_3, $B(OR)_2$
X=R, OR, NR_2
(X=R does not require catalyst)

Scheme 93

In 1991, Boldrini *et al.*[105] reported a new protocol for regio- and stereocontrolled aldol reactions through the conjugate addition of dialkylboranes to α, β-unsaturated ketones (Scheme 94). In the case of boron enolates, the short B-O bond length (1.36-1.47Å) and the acceptor properties of the trico-ordinated boron atom favour the formation of tightly closed transition-state structures (**140**) where steric effects among substituents are magnified and stereocontrol is enhanced. The 1, 4 addition of dialkylboranes to β-substituted (*E*)-α, β-unsaturated ketones affords configurationally pure (*Z*)-(vinyloxy)boranes, with the following reaction with aldehydes giving virtually pure *syn* aldols (Scheme 94).



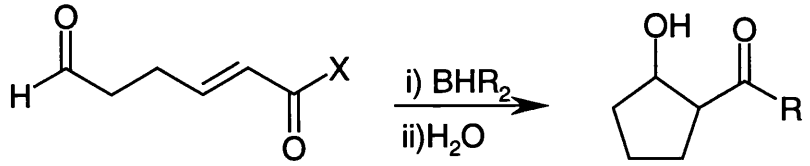
140

Scheme 94

Cyclic enones do not undergo conjugate addition, while (*Z*)-β-substituted or β, β-disubstituted α, β-unsaturated ketones still react in a 1, 4-fashion, but with a slower rate

and a lower degree of chemoselectivity with respect to β-substituted (*E*)-α, β-unsaturated ketones. A mixture of *E* and *Z* enolates is obtained upon reacting α, β-disubstituted α, β-unsaturated ketones with dicyclohexylborane.

Whilst this methodology certainly has some limitations, the very high level of diastereoselectivity (>95% *syn* purity of the resulting aldol) and chemoselectivity exhibited for β-substituted (*E*)-α, β-unsaturated ketones suggest it would be a complementary reaction to tandem hydrosilylation cyclisation (Scheme 95).

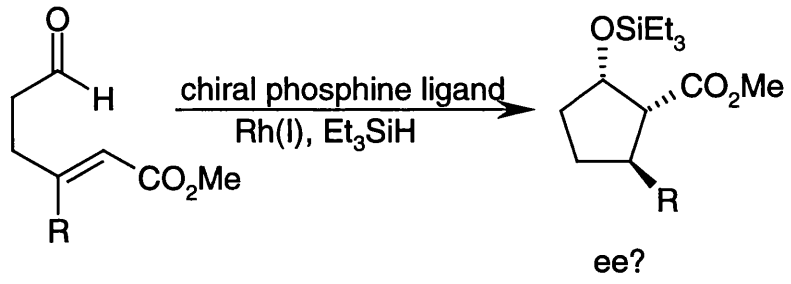


X=alkyl-catalyst not required
(X=OR, NR'_2 - requires Rh(I))

Scheme 95

5.7 Asymmetric Catalysis

A number of asymmetric catalyst systems have been successfully employed in intramolecular hydroacylation chemistry to afford enantiomerically enriched cyclopentanones.[106-110] In particular, the BINAP ligand has proved to be the most effective in exerting very high enantiocontrol. Work should be commenced on screening a number of chiral catalysts to probe their effectiveness in the tandem hydrosilylation cyclisation chemistry. If this approach is successful, then substituted 4-pentenals can be investigated in order to establish a method of producing cyclopentanes with three contiguous chiral centers from a readily available achiral substrate (Scheme 96).

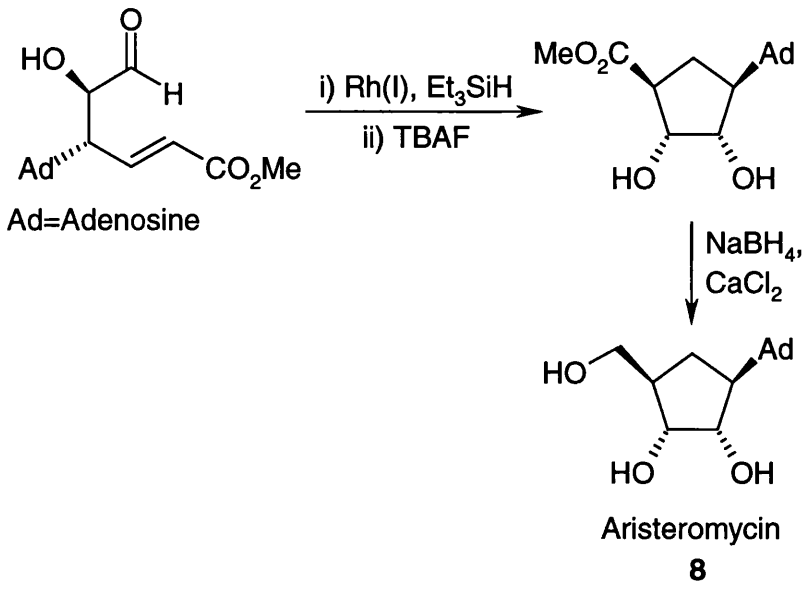


Scheme 96

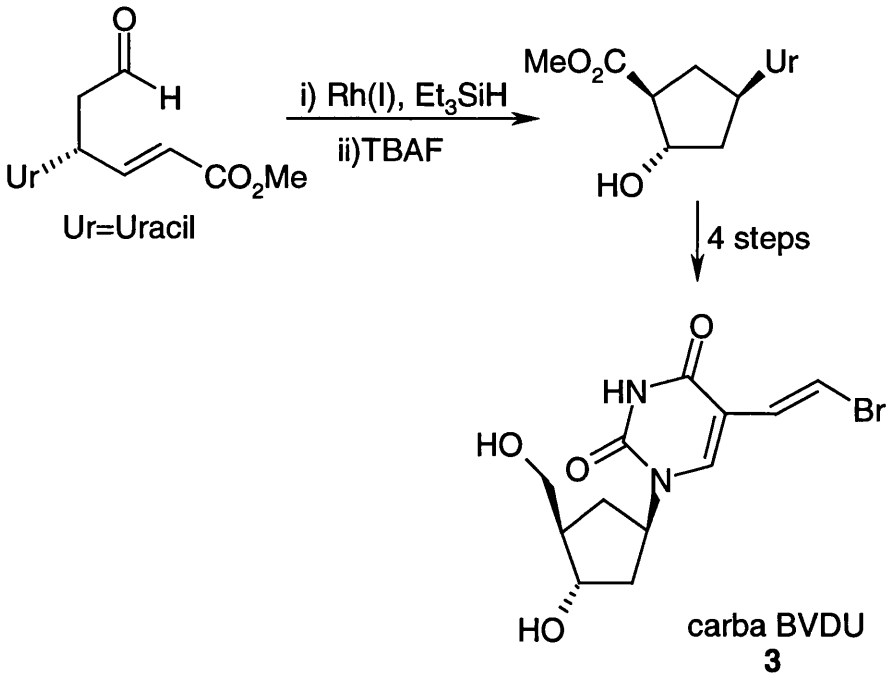
5.8 Synthesis of Carbocyclic Nucleosides

This novel tandem hydrosilylation cyclisation chemistry could provide an efficient synthetic route to a wide range of carbocyclic nucleosides from simple readily available starting materials e.g. Aristeromycin[111] (**8**) from D-ribonolactone and the highly potent antiherpes agent, the carbocyclic analogue of 5-(2-bromovinyl)-2'-deoxyuridine (carba BVDU) (**3**) from (R)-α-amino-γ-butyrolactone[112] (Scheme 97). In both cases, the appropriate catalyst system would give the required *trans* selectivity between the methyl ester and the adjacent hydroxyl group.

Aristeromycin Synthesis



Carba BVDU Synthesis



Scheme 97

CHAPTER SIX : EXPERIMENTAL

6.1 General Experimental Procedure

Melting points were determined using a Reichert stage melting apparatus and are uncorrected.

Infrared spectra were recorded as thin films, nujol mulls or in CCl_4 solution on a Perkin–Elmer 1605 FT-IR spectrometer.. Major features of each spectrum are reported. The following abbreviations are used : w = weak, m = medium, s = strong.

Proton NMR spectra were recorded at 300MHz on a Bruker AC300 spectrometer and at 400MHz on a Varian VXR400 spectrometer. Chemical shifts (δH) are quoted in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants are recorded in Hertz and are recorded to the nearest 0.1 Hertz.

Carbon-13 NMR spectra were recorded at 75.5MHz on a Bruker AC300 spectrometer and at 100.6MHz on a Varian VXR400 spectrometer. Chemical shifts (δC) are quoted in parts per million (ppm) and are referenced to the residual solvent peak.

Low resolution mass spectra were recorded using a VG 305 and a VG ZAB SE mass spectrometer. Only molecular ions, fragments from molecular ions and major peaks are reported.

High resolution mass spectra were recorded using a VG7070b mass spectrometer by the School of Pharmacy Mass Spectrometry Service.

Thin layer chromatography was performed on aluminium-backed plates (Merk Kieselgel 60 F_{254}, 2mm). Components were visualised by the quenching of u.v. fluorescence (λ_{max} 254nm) and by staining with alkaline potassium permanganate or 10% w/v ammonium molybdate in 2M sulphuric acid, followed by heat. Retention factors are quoted to the nearest 0.01.

Flash chromatography was carried out using BDH silica 40-63μm.

Anhydrous dichloromethane and acetonitrile were obtained by stirring over calcium hydride followed by distillation under nitrogen. Anhydrous tetrahydrofuran and

anhydrous diethylether were obtained by distillation from sodium / benzophenone ketyl under nitrogen. Anhydrous toluene was obtained by distillation from sodium under nitrogen. Petroleum ether 40-60°C was distilled before use. Solvents were evaporated on a Buchi R110 Rotavapor.

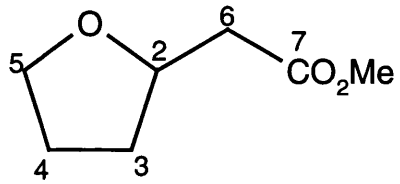
All reactions were performed using oven dried glassware under a positive pressure of nitrogen unless otherwise stated.

6.2 Experimental Results

CHAPTER TWO

Section 2.1

2.1.2 Tetrahydrofuran-2-yl acetic acid methyl ester (40)



40

The reducing agent DIBAL (1.5M solution in toluene, 1.1eq., 25.7ml) was added in a dropwise fashion to a stirred solution of γ-butyrolactone (1.0eq., 3.00g, 34.85 mmol) in anhydrous toluene (50ml) at –65°C to –70°C. The resulting solution was stirred at -65°C for a total of 2.5 hours. Prior to addition of the reaction mixture, potassium butoxide (4.84g, 43.13mmol, 1.2eq., 97%) and carbomethoxymethyl triphenylphosphonium bromide (17.37g, 41.83 mmol, 1.2eq.) were suspended in anhydrous THF(100ml) and stirred at 0°C for 30 minutes. The reducing agent was quenched with anhydrous MeOH (5ml, 3eq.) and then the 4-hydroxybutanal (**40**) solution was added to the suspension. The resulting mixture was heated to reflux for 2.5 hours. The gelatinous mixture was cooled to 40°C, 2M NH_4Cl (75ml) was added and the resulting solution was stirred at ambient temperature for 1 hour. The biphasic mixture was separated and the lower aqueous phase was extracted with EtOAc (2x50ml). The organic extracts were combined, washed with water (2x50ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting pale green oil was triturated with isopropyl ether (30ml) and the resulting white crystalline precipitate of $Ph_3P=O$ was removed by filtration. The filtrate was concentrated under reduced pressure to yield 8.95g of crude material. The oil was purified by flash column chromatography, eluting with 25% EtOAc/P.E.40-60°C to give the tetrahydrofuran **40** in 68% yield.

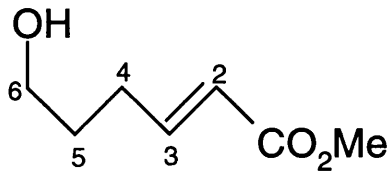
R_f 0.82 (100% EtOAc).

δH (400 MHz, $CDCl_3$)[43]: 4.24 (1H, q, J 6.8, H^2), 3.90-3.85 (1H, m, H^5), 3.78-3.72 (1H, m, H^5), 3.69 (3H, s, OCH_3), 2.62-2.56 (1H, m, H^6), 2.51-2.45 (1H, m, H^6), 2.04-2.13 (1H, m, H^3), 1.94-1.84 (2H, m, $H^4{}_2$), 1.59-1.52 (1H, m, H^3);

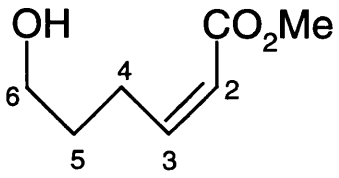
m/z (EI^+, 70eV): 143 ($M-H^+$, 10%), 71 ($M-CH_2CO_2CH_3$, 100%);

2.1.2 Methyl-(*E*)-6-hydroxy-hex-2-enoate (41)[44]

2.2.2 Methyl-(*Z*)-6-hydroxy-hex-2-enoate (46)



41



46

METHOD A:

The reducing agent DIBAL (1.5M solution in toluene, 1.1eq., 27.4ml) was added in a dropwise fashion to a stirred solution of γ-butyrolactone (1.0eq., 3.20g, 34.85 mmol) in anhydrous toluene (50ml) at –65°C to –70°C. The resulting solution was stirred at –65°C for a total of 2 hours. The reducing agent was quenched with anhydrous MeOH (7.5ml, 5eq.) before the addition of carbomethoxymethylene triphenylphosphorane (13.67g, 40.88 mmol, 1.2eq.). The resulting solution was heated to 80°C for 16 hours. The heat was removed and the solution was concentrated under reduced pressure. Isopropyl ether (25ml) was added and the resulting white crystalline precipitate of $Ph_3P=O$ was removed by filtration and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography,

eluting with 30% EtOAc/P.E. 40-60°C to yield the methylhydroxy unsaturated ester as separate diastereoisomers (**41**) and (**46**) in the ratio *E:Z* 92:8 and the combined yield of 53%.

METHOD B:

The reducing agent DIBAL (1.5M solution in toluene, 1.1eq., 2.14ml) was added in a dropwise fashion to a stirred solution of γ-butyrolactone (1.0eq.,0.25g, 2.90mmol) in anhydrous toluene (10ml) at –65°C to –70°C. The resulting solution was stirred at –65°C for a total of 2.5 hours. Prior to addition of the reaction mixture, butyllithium (1.21ml, 0.9eq, 2.11M solution in hexanes) and carbomethoxymethyl triphenylphosphonium bromide (1.21g, 2.90mmol, 1.0eq.) were suspended in anhydrous THF(100ml) and stirred at 0°C for 30 minutes. The reducing agent was quenched with anhydrous MeOH (0.8ml, 3eq.) and then the 4-hydroxybutanal (**40**) solution was added to the suspension. The resulting mixture was heated to reflux for 2.5 hours. The gelatinous mixture was cooled to 40°C, 2M NH_4Cl (75ml) was added and the resulting solution was stirred at ambient temperature for 1 hour. The biphasic mixture was separated and the lower aqueous phase was extracted with EtOAc (2x50ml). The organic extracts were combined, washed with water (2x50ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting pale green oil was triturated with isopropyl ether (30ml) and the resulting white crystalline precipitate of $Ph_3P=O$ was removed by filtration. The filtrate was concentrated under reduced pressure to yield 9.14g of crude material. The oil was purified by flash column chromatography, eluting with 30% EtOAc/P.E.40-60°C to yield the methylhydroxy unsaturated ester as separate diastereoisomers (**38**) and (**43**) in the ratio *E:Z* 85:15 and the combined yield of 58%.

2.1.2 Methyl-(*E*)-6-hydroxy-hex-2-enoate (41)[44]

R_f 0.62 (40% EtOAc/P.E.40-60°C);

δH (400MHz, $CDCl_3$): 6.97 (1H, dt, J 15.6, 7.0, ^3H), 5.85 (1H, d, J 15.6, H^2), 3.72 (3H, s, OCH_3), 3.69-3.66 (2H, m, $H^6{}_2$), 2.34-2.28 (2H, m, $H^4{}_2$), 1.76-1.69 (2H, m, $H^5{}_2$);

m/z (EI^+, 70eV): 127 (M-OH, 15%), 113 (M-OCH_3, 85%), 94 (100%).

2.2.2 Methyl-(*Z*)-6-hydroxy-hex-2-enoate (46)

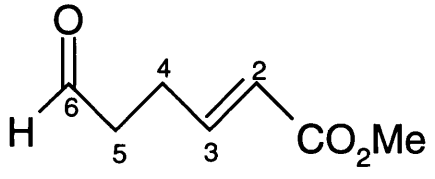
R_f 0.35 (3:2 EtOAc/ P.E.40-60°C);

δH (400MHz, $CDCl_3$): 6.21 (1H, dt, J 11.5, 8.3, H^3), 5.85 (1H, d, J 11.5, ^2H), 3.70 (3H, s, OCH_3), 3.61-3.58 (2H, m, $H^6{}_2$), 2.74-2.68 (2H, m, $H^4{}_2$), 1.74-1.66 (2H, m, $H^5{}_2$);

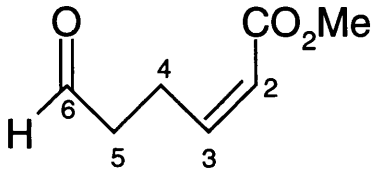
m/z (EI^+, 70eV): 127 (M-OH, 15%), 113 (M-OCH_3, 85%), 94% (100%).

2.1.3 Methyl-(*E*)-6-oxo-2-hexenoate (22)[44]

2.2.3 Methyl-(*Z*)-6-oxo-2-hexenoate (48)



22



48

A solution of methyl-(*E*)-6-hydroxy-2-hexenoate (**41**, 0.2g, 1.39mmol) in anhydrous DCM (5ml) was added in one portion to a stirred suspension of the oxidising agent pyridinium chlorochromate (PCC, 0.449g, 2.08mmol, 1.5eq., 98%) and the buffering agent sodium acetate (0.034g, 0.41mmol, 0.3eq.) in anhydrous DCM (2ml). The resulting black solution was stirred, with careful monitoring by tlc, for 3 hours. The reaction solution was poured into diethylether (10ml) and the black

gum was extracted with additional diethylether (3x10ml) until the gum had transformed into a granular solid. The combined organic extracts were passed through a short pad of florisil® and concentrated under reduced pressure to give the crude product. The oil was purified by flash column chromatography, eluting with 10% EtOAc/P.E.40-60°C to give the (*E*)-product in 63% yield. The trimerized aldehyde 2, 4, 6 trioxane (**42**) was isolated in 2% yield as a colourless oil.

The same process was repeated for the (*Z*)-isomer, giving the methyl-(*Z*)-hexenoate (**48**) in a 66% yield.

2.1.3 Methyl-(*E*)-6-oxo-2-hexenoate (22)[44]

R_f 0.46 (50% EtOAc/P.E.40-60°C);

δH (400MHz, $CDCl_3$): 9.77 (1H, s, CHO), 6.92 (1H, dt, J 15.6, 6.6, H^3), 5.83 (1H, d, J 15.6, H^2), 3.70 (3H, s, OCH_3), 2.61 (2H, t, J 7.3, $H^5{}_2$), 2.54-2.47 (2H, m, $H^4{}_2$);

m/z (EI^+, 70eV): 142 (M^+, 15%), 127 (M^+-CH_3, 50%), 111 (M^+-OCH_3, 55%), 54 (100%).

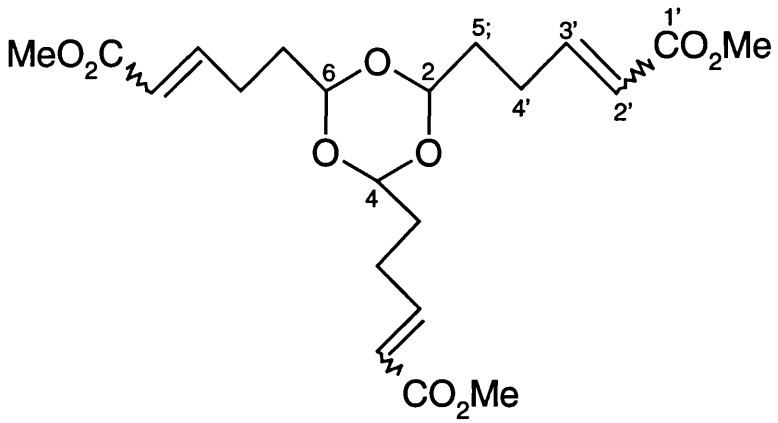
2.2.3 Methyl-(*Z*)-6-oxo-2-hexenoate (48)

R_f 0.49 (50% EtOAc/P.E.40-60°C);

δH(400MHz, $CDCl_3$): 9.76 (1H, s, CHO), 6.23 (1H, dt, J 11.5, 5.7, H^3), 5.80 (1H, d, J 11.5, H^2), 3.68 (3H, s, OCH_3), 2.96-2.90 (2H, m, $H^5{}_2$), 2.62-2.58 (2H, m, $H^4{}_2$);

m/z (EI^+, 70eV): 142 (M^+, 20%), 127 (M^+-CH_3, 45%), 111 (M+-OCH_3).

2.1.3 2, 4, 6-trimethyl-2'-hexenoate-1, 3, 5-trioxane (42)



42

The trioxane (**42**) was isolated as a contaminant in the preceding synthesis of methyl-6-oxo-2-hexenoate.

2.1.3 Trioxane:*Trans* isomer

δH (400MHz, $CDCl_3$): 6.91 (3H, dt, J 15.6, 6.3, $H^{3'}{}_3$), 5.81 (3H, d, J 15.6, $H^{2'}{}_3$), 4.06 (3H, t, J 6.43, $H^2{}_3$), 3.68 (9H, s, OCH_3), 2.49-2.41 (6H, m, $CH^{4'}$, $CH^{5'}$), 2.27-2.21 (3H, m, $CH^{4'}$), 1.80-1.75 (3H, m, $CH^{5'}$);

δC (100.6MHz, $CDCl_3$): 172.16 (C=O), 147.82 (C<u>H</u>=CHCO$_2$Me), 121.78 (CH=C<u>H</u>CO$_2$Me), 63.71 (C-2), 51.50 (OCH_3), 32.33 (CH_2), 26.96 (CH_2).

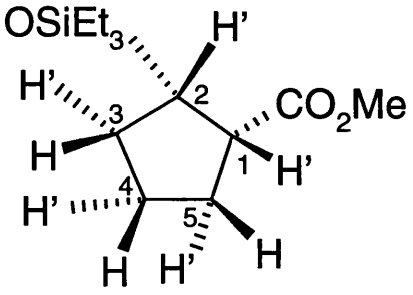
2.1.3 Trioxane:*Cis* isomer

δH (400MHz, $CDCl_3$): 6.91 (3H, dt, J 11.3, 6.3, $H^{3'}{}_3$), 6.43 (3H, d, J 11.3, $H^{2'}{}_3$), 4.06 (3H, t, J 6.43, $H^2{}_3$), 3.68 (9H, s, OCH_3), 2.49-2.41 (6H, m, $CH^{4'}$, $CH^{5'}$), 2.27-2.21 (3H, m, $CH^{4'}$,), 1.80-1.75 (3H, m, $CH^{5'}$);

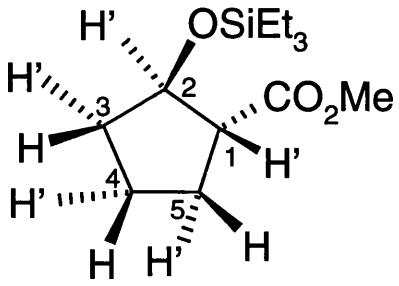
δC (100.6MHz, $CDCl_3$): 166.87 (C=O), 146.83 (C<u>H</u>=CHCO$_2$Me), 121.57 (CH=C<u>H</u>CO$_2$Me), 63.71 (C-2), 51.46 (OCH_3), 28.60 (CH_2), 27.15 (CH_2).

m/z (FAB$^+$, 70eV) 285 (100%), 307 (65%).

2.1.4 Methyl-2-Triethylsilyloxycyclopentanecarboxylate



23



24

Method A: With Wilkinson's catalyst $Rh(PPh_3)_3Cl$ (8)

Triethylsilane (2.1eq., 0.288ml, 0.21g, 1.80mmol) was added to a stirred solution of (*E*)-methyl-6-oxo-2-hexenoate (**22**, 0.122g, 0.86mmol) and tris(triphenylphosphine) rhodium (I) chloride (1%mol, 7.9mg, 0.011mmol) in anhydrous, degassed toluene (3ml) at ambient temperature. The resulting solution was then heated for 16 hours at 50°C. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material. The oil was purified by preparative tlc, eluting with 10% EtOAc/P.E.40-60°C to give the desired product as a mixture of diastereoisomers (**23**, **24**) in a combined yield of 81% yield, *cis:trans* 3:1.

ν_{max} (thin film/cm^{-1}) 2955, 2912, 2877 (C-H), 1732 (C=O), 1062, 1010 (C-O);

m/z (FAB+, 70eV) M+H measured 259.1710 actual 259.1729.

2.1.4 Methyl-2-Triethylsilyloxycyclopentanecarboxylate : *Cis* isomer (23)

δH(400MHz, $CDCl_3$): 4.43-4.40 (1H, m, $H^{2'}$), 3.59 (3H, s, OCH_3), 2.71-2.65 (1H, m, $H^{1'}$), 2.25-2.07 (1H, m, H^{5}), 1.86-1.83 (1H, m, H^{4}), 1.77-1.65 (2H, m, $H^{3'}$, $H^{5'}$), 1.65-

1.64 (1H, m, H^3), 1.54-1.46 (1H, m, $H^{4'}$), 0.8 (9H, t, J 7.98, $C\underline{H}_3CH_2$), 0.51 (6H, q, J 7.98, $CH_3C\underline{H}_2$);

δC(100.6MHz, $CDCl_3$): 172.27 (C=O), 74.29 (C-2), 50.57 (OCH_3), 50.45 (C-1), 34.47 (C-3), 23.78 (C-5), 21.73 (C-4), 5.74 ($\underline{C}H_3CH_2$), 3.78 ($CH_3\underline{C}H_2$).

2.1.4 Methyl-2-Triethylsilyloxycyclopentanecarboxylate : *Trans* isomer (24)

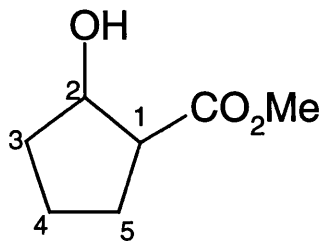
δH(400MHz, $CDCl_3$): 4.36-4.27 (1H, m, $H^{2'}$), 3.60 (3H, s, OCH_3), 2.71-2.65 (1H, m, H^1), 2.02-1.91 (1H, m, H^5), 1.86-1.83 (1H, m, H^3), 1.77-1.65 (1H, m, $H^{5'}$), 1.65-1.64 (1H, m, $H^{3'}$), 1.54-1.46 (1H, m, H^4), 1.37-1.26 (1H, m, $H^{4'}$), 0.87 (9H, t, J 8.3, $C\underline{H}_3CH_2$), 0.51 (6H, q, J 8.3, $CH_3C\underline{H}_2$);

δC (100.6MHz, $CDCl_3$): 174.64 (C=O), 78.28 (C-2), 53.12 (C-1), 51.11 (OCH_3), 35.49 (C-3), 28.13 (C-5), 22.73 (C-4), 5.63 ($\underline{C}H_3CH_2$), 3.62 ($CH3\underline{C}H_2$).

APPENDIX 1: COSY

APPENDIX 2: NOESY

2.1.4 Methyl 2-Hydroxycyclopentanecarboxylate (43)



43

Tetrabutylammonium fluoride (9.8ml of a 1.0M solution in tetrahydrofuran, 9.8mmol) was added to a stirred solution of methyl 2-triethylsilyloxycyclopentanecarboxylate (**23**, **24**, 1.14g, 4.4mmol) in tetrahydrofuran (10ml) at ambient temperature. The resulting solution was stirred at ambient

temperature for 1 hour, then diluted with water (25ml) and the resulting solution was extracted with DCM (3x10ml). The combined organic extracts were washed with water (3x10ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a green oil. The crude oil was purified by flash column chromatography, eluting with 40% EtOAc/P.E.40-60°C, to give the product (**43**) as a mixture of diastereoisomers, with retention of stereochemistry, in the yield of 69%.

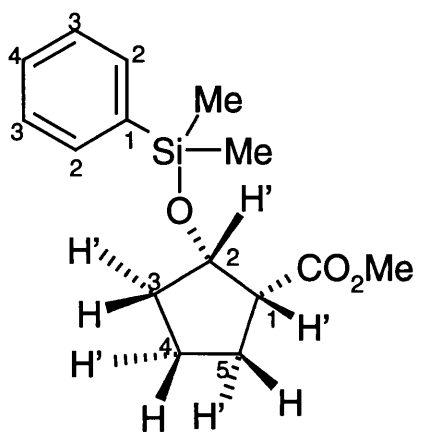
***CIS* ISOMER**[113]:

δH (300MHz, $CDCl_3$): 4.44 (1H, m, H^2), 3.73 (3H, s, OCH_3), 3.03 (1H, br, OH), 2.70 (1H, m, H^1), 2.52-1.54 (6H, m, $H^3{}_2$, $H^4{}_2$, $H^5{}_2$).

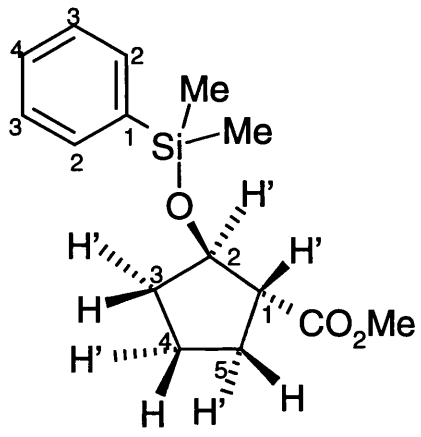
***TRANS* ISOMER**[113]:

δH (300MHz, $CDCl_3$): 4.38 (1H, m, H^2), 3.71 (3H, s, OCH_3), 2.67 (1H, m, H^1), 2.31 (1H, br, OH), 2.55-1.51 (6H, m, $H^3{}_2$, $H^4{}_2$, $H^5{}_2$).

2.3.2 Methyl 2-Dimethylphenylsilyloxycyclopentanecarboxylate



141



142

The synthesis of methyl-2-dimethylphenylsilyloxycyclopentanecarboxylate followed the exact procedure as that used in the synthesis of methyl-2-triethylsilyloxycyclopentanecarboxylate (**23**, **24**), except triethylsilane (2.1eq.) was substituted by dimethylphenylsilane (2.1eq.). The product was produced as a mixture of diastereoisomers, in the combined yield of 62%, *cis:trans* 2.4:1.0.

ν_{max} (thin film/cm^{-1}) 2953, 2933, 2863 (C-H), 1730 (C=O), 1059, 1013(C-O);
m/z (70eV, FAB+) M+H: Measured 279.1426 Actual 279.1416.

***CIS* ISOMER (141)**:

δH(400MHz, $CDCl_3$): 7.50-7.47 (2H, m, phenyl H), 7.31-7.27 (3H, m, phenyl H), 4.46-4.41 (1H, m, $H^{2'}$), 3.54 (3H, s, OCH_3), 2.72-2.69 (1H, m, $H^{1'}$), 2.15-2.10 (1H, m, H^5), 1.85-1.81 (1H, m, H^4), 1.70-1.66 (1H, m, $H^{5'}$), 1.64-1.55 (2H, m, H^3, $H^{3'}$), 1.55-1.43 (1H, m, $H^{4'}$), 0.29 (3H, s, CH_3), 0.26 (3H, s, CH_3);

δC (100.6MHz, $CDCl_3$): 174.60 (C=O), 139.55 (C-1 phenyl), 134.80 (C-2 phenyl), 130.90 (C-3 phenyl), 129.12 (C-4 phenyl), 76.98 (C-2), 52.66 (OCH_3), 52.33 (C-1), 36.58 (C-3), 26.41 (C-5), 23.48 (C-4), 0.22 (CH_3), 0.01(CH_3).

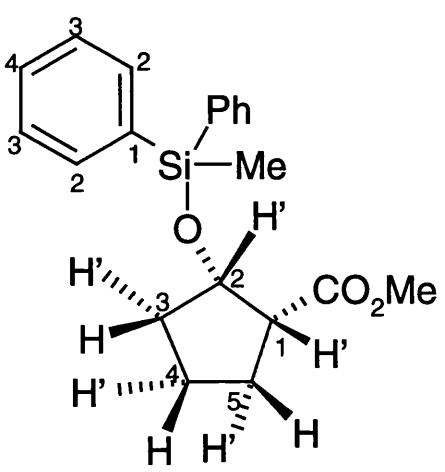
***TRANS* ISOMER (142)**:

δH(400MHz, $CDCl_3$): 7.50-7.47 (2H, m, phenyl H), 7.31-7.27 (3H, m, phenyl H), 4.35-4.33 (1H, m, $H^{2'}$), 3.53 (3H, s, OCH_3), 2.70-2.64 (1H, m, $H^{1'}$), 2.01-1.94 (1H, m, H^5), 1.75-1.65 (1H, m, $H^{3'}$), 1.64-1.58 (2H, m, $H^{5'}$, H^4), 1.57-1.54 (2H, m, $H^{4'}$, H^3), 0.29 (3H, s, CH_3), 0.28 (3H, s, CH_3);

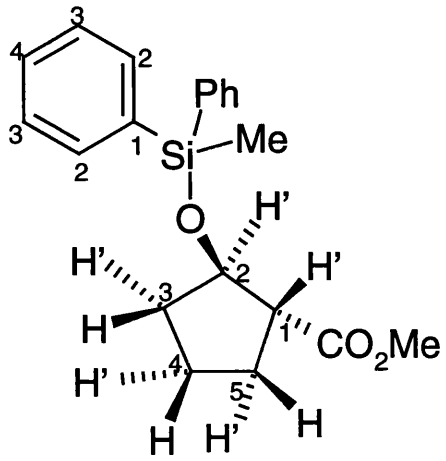
δC (100.6MHz, $CDCl_3$): 177.14 (C=O), 139.37 (C-1 phenyl), 134.84 (C-2 phenyl), 130.82 (C-3 phenyl), 129.08 (C-4 phenyl), 78.71 (C-2), 54.30 (C-1), 52.93 (OCH_3), 36.66 (C-3), 29.47 (C-5), 24.10 (C-4), 0.03 (CH_3), -0.07 (CH_3).

APPENDIX 3: COSY
APPENDIX 4: NOESY

2.3.2 Methyl 2-Methyldiphenylsilyloxycyclopentanecarboxylate



143



144

The synthesis of methyl 2-methyldiphenylsilyloxycyclopentanecarboxylate followed the exact procedure as that used in the synthesis of methyl 2-triethylsilyloxycyclopentanecarboxylate (**23**, **24**), except triethylsilane (2.1eq.) was substituted by methyldiphenylsilane (2.1eq.). The product was produced as a mixture of diastereoisomers, in the combined yield of 49%, *cis:trans* 2.8:1.0.

ν_{max} (thin film/cm^{-1}): 2945, 2934, 2856 (C-H), 1733 (C=O), 1056, 1009(C-O);

m/z (FAB^+, 70eV): M+Na Measured 363.1402, Actual 363.1392.

***CIS* ISOMER (143)**:

δH (400MHz, $CDCl_3$): 7.51-7.45 (4H, m, phenyl), 7.31-7.26 (6H, m, phenyl), 4.53-4.49 (1H, m, $H^{2'}$), 3.47 (3H, s, OCH_3), 2.68-2.73 (1H, m, $H^{1'}$), 2.22-2.16 (1H, m, H^5), 1.87-1.82 (1H, m, H^4), 1.75-1.56 (1H, m, $H^{5'}$), 1.55-1.51 (2H, m, H^3, $H^{3'}$), 1.46-1.43 (1H, m, $H^{4'}$), 0.55 (3H, s, CH_3);

δC (100.6MHz, $CDCl_3$): 175.88 (C=O), 138.93 (C-1, phenyl), 137.00 (C-2 phenyl), 132.42 (C-3 phenyl), 130.42 (C-4 phenyl), 78.74 (C-2), 54.00 (OCH_3), 53.66 (C-1), 37.74 (C-3), 27.73 (C-5), 24.71 (C-4), -0.06 (CH_3).

***TRANS* ISOMER (144)**:

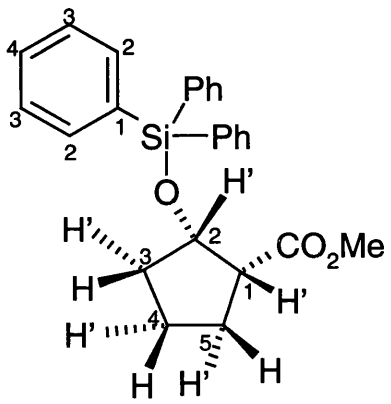
δH (400MHz, $CDCl_3$): 7.51-7.45 (4H, m, phenyl), 7.31-7.26 (6H, m, phenyl), 4.48-4.43 (1H, m, $H^{2'}$), 3.49 (3H, s, OCH_3), 2.68-2.73 (1H, m, $H^{1'}$), 2.09-1.89 (1H, m, $H^{5'}$), 1.75-1.56 (2H, m, H^5, $H^{4'}$), 1.55-1.51 (2H, m, H^3, $H^{3'}$), 1.56-1.54 (1H, m, H^4), 0.57 (3H, s, CH_3);

δC (100.6MHz, $CDCl_3$): 178.32 (C=O), 139.03 (C-1 phenyl), 136.97 (C-2 phenyl), 132.37 (C-3 phenyl), 130.43 (C-4 phenyl), 80.36 (C-2), 54.00 (OCH_3), 55.69 (C-1), 38.02 (C-3), 30.79 (C-5), 25.48 (C-4), 0.01 (CH_3).

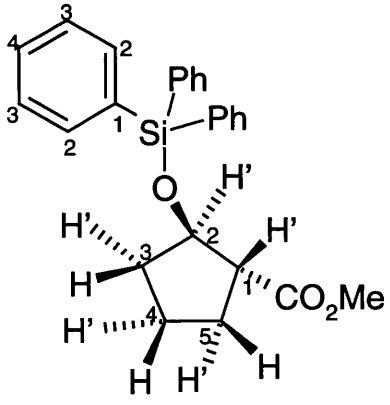
APPENDIX 5 : COSY

APPENDIX 6 : NOESY

2.3.2 Methyl-2-Triphenylsilyloxycyclopentanecarboxylate



145



146

The synthesis of methyl-2-triphenylsilyloxycyclopentanecarboxylate followed the exact procedure as that used in the synthesis of methyl-2-triethylsilyloxycyclopentanecarboxylate (**23**, **24**), except triethylsilane (2.1eq.) was

substituted by triphenylsilane (2.1eq.). The product was produced as a mixture of diastereoisomers, in the combined yield of 42%, *cis:trans* 1.5:1.0.

ν_{max} (thin film/cm^{-1}): 2956 (C-H), 1738 (C=O), 1115s, 1057 (C-O);

m/z (FAB^+, 70eV): M+Na Measured 425.1535, Actual 425.1549.

***CIS* ISOMER (145)**:

δH (400MHz, $CDCl_3$): 7.65-7.53 (5H, m, phenyl), 7.46-7.30 (10H, m, phenyl), 4.67-4.65 (1H, m, $H^{2'}$), 3.46 (3H, s, OCH_3), 2.79-2.73 (1H, m, $H^{1'}$), 2.32-2.23 (1H, m, H^5), 1.95-1.83 (1H, m, H^4), 1.81-1.65 (2H, m, $H^{5'}$, H^3), 1.64-1.48 (2H, m, $H^{4'}$, $H^{3'}$);

δC (100.6MHz, $CDCl_3$): 172.23 (C=O), 134.45 (C-2 phenyl), 13.49 (C-1 phenyl), 128.91 (C-3 phenyl), 126.90 (C-4 phenyl), 75.70 (C-2), 50.28 (OCH_3), 50.28 (C-1), 33.86 (C-3), 24.35 (C-5), 20.95 (C-4).

***TRANS* ISOMER (146)**:

δH (400MHz, $CDCl_3$): 7.65-7.53 (5H, m, phenyl), 7.46-7.30 (10H, m, phenyl), 4.64-4.60 (1H, m, $H^{2'}$), 3.47 (3H, s, OCH_3), 2.81-2.79 (1H, m, $H^{1'}$), 2.00-1.97 (1H, m, H^5), 1.81-1.65 (5H, m, $H^{5'}$, $H^{4'}$, H^4, $H^{3'}$, H^3);

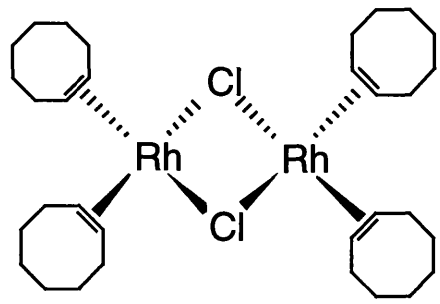
δC (100.6MHz, $CDCl_3$): 174.50 (C=O), 134.45 (C-2 phenyl), 133.49 (C-1 phenyl), 128.91 (C-3 phenyl), 126.90 (C-4 phenyl), 77.09 (C-2), 50.49 (OCH_3), 52.08 (C-1), 34.40 (C-3), 27.13 (C-5), 21.92 (C-4).

APPENDIX 7 : COSY

APPENDIX 8 : NOESY

Section 2.4

2.4.2 Chlorobis(cyclooctene) rhodium(I) dimer (57)[54]

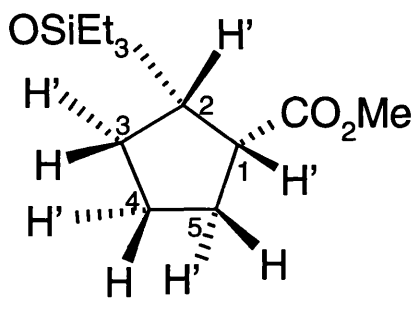


57

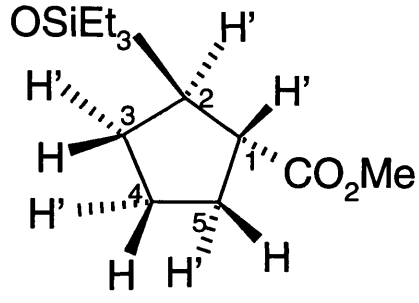
In a 50ml 3-necked round bottomed flask, rhodium (III) chloride hydrate (475mg, 2.27mmol) was dissolved in an oxygen-free mixture of 2-propanol (9.50ml) and water (2.38ml). Cyclooctene (6eq., 1.43ml, 10.98mmol) was added. The deep red solution was stirred for 15 minutes under N_2. The flask was then closed and allowed to stand at ambient temperature for 5 days. The resulting reddish-brown crystals were filtered under N_2, washed with degassed EtOH and dried under vacuum. The yield was 68%.

Mpt 188°C (lit. 190°C);

2.4.3 Methyl-2-Triphenylsilyloxycyclopentanecarboxylate



23



24

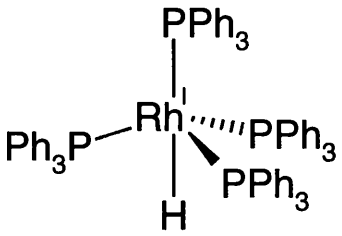
2.4.3 Method B: With chloro(biscyclooctene)rhodium(I) dimer (57)

Triethylsilane (2.1eq., 0.066ml, 0.41mmol) was added to a stirred solution of (*E*)-methyl-6-oxo-2-hexenoate (**22**, 28mg, 0.20mmol), chloro(biscyclooctene)rhodium(I) dimer (0.025eq., 3.5mg, 0.005mmol) and the phosphine of interest (0.1eq.) in

anhydrous, degassed toluene (2ml) at ambient temperature. The resulting solution was heated, with the reaction being monitored by tlc. See Section 2.4 for details.

Section 2.5

2.5.2 Hydridotetrakis(triphenylphosphine)rhodium (I) (60)[58]



60

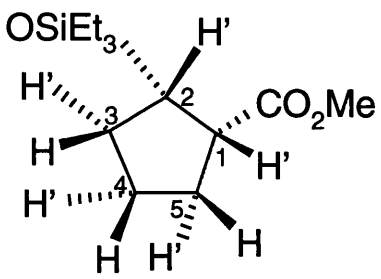
Rhodium trichloride hydrate (130mg, 0.62mmol) was dissolved in warm degassed EtOH (10ml) and sodium borohydride (100mg, 2.64mmol, 5eq.) was dissolved separately in warm degassed EtOH (10ml). The solutions were then added rapidly and successively to a vigorously stirred solution of triphenylphosphine (1.31g, 4.99mmol, 10eq.) in boiling degassed EtOH (40ml). The mixture was heated under reflux for 5 minutes to ensure complete reaction, then cooled to 30°C, filtered and the precipitate washed with water, ethanol and ^{n}hexane to give the product as orange-brown microcrystals in 72% yield.

Mpt : 161°C (lit 162-163°C);

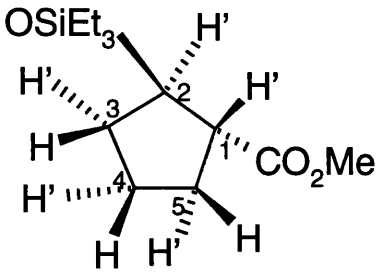
ν_{max} (thin film/cm^{-1}): 2147 (Rh-H), 1582 (C=C);

m/z (FAB^{+}, 70eV): 627 ($Rh(PPh_3)_2$, 5%), 557(35%), 411(80%), 369(65%).

2.5.3 Methyl-2-triethylsilyloxycyclopentanecarboxylate



23



24

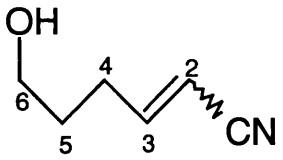
Method C: With hydridotetrakis(triphenylphosphine)rhodium (I) catalyst $RhH(PPh_3)_4$ (60)

Triethylsilane (2.1eq., 0.053ml, 0.33mmol) was added to a stirred solution of methyl-6-oxo-2-hexenoate (**22**, 0.16mmol, 22.5mg) and hydridotetrakis(triphenylphosphine)rhodium (I) catalyst (**60**, 1%mol, 1.8mg, 0.0016mmol) in anhydrous, degassed toluene (3ml) at ambient temperature. The resulting solution was then heated for 16 hours at 50°C. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil® rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material. The oil was purified by preparative tlc, eluting with 10% EtOAc/P.E.40-60°C to give the desired product as a mixture of diastereoisomers, in a combined yield of 81%, *cis:trans* 3:1.

CHAPTER THREE

Section 3.2

3.2.2 (*E, Z*) 6-Hydroxy-2-hexenenitrile



63

The reducing agent DIBAL (1.5M solution in toluene, 1.1eq., 13.63ml) was added in a dropwise fashion to a stirred solution of γ-butyrolactone (1.0eq., 1.6g, 18.59mmol) in anhydrous toluene (20ml) at –65°C to –70°C. The resulting solution was stirred at -65°C for a total of 2.5 hours. The reducing agent was quenched with anhydrous MeOH (5eq., 3.75ml). The aldehyde was then added to Zn-Hg amalgam (1.1eq., 1.34g), tri(^{n}butyl)phosphine (1.1eq., 5.25ml, 21.07mmol) and bromoacetonitrile (1.1eq., 1.48ml, 21.25mmol). The solution was heated to 100°C and monitored by tlc. After 19 hours the heat was removed and the grey precipitate removed by passing the solution through a pad of celite® and rinsing with EtOAc. The combined organic extracts were concentrated under reduced pressure to yield an orange oil. The crude material was purified by flash column chromatography, eluting with 5% EtOAc/P.E.40-60°C to give the product as (*trans:cis*, 2:1) non-separable diastereoisomers in the yield of 48%.

***TRANS* ISOMER**[59b]:

R_f 0.46 (100% EtOAc);

δH (400MHz, $CDCl_3$) 6.73 (1H, dt, J 16.3, 7.0, H^3), 5.35 (1H, d, J 16.3, H^2), 3.69-3.64 (2H, m, $H^6{}_2$), 2.33 (2H, q, J 7.2, $H^4{}_2$), 1.76-1.66 (2H, m, $H^5{}_2$);

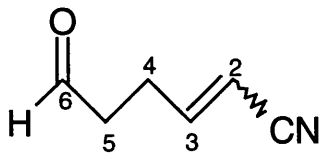
m/z (EI^+, 70eV) 94 (M^+-OH, 45%), 66 (M^+-$(CH_2)_2OH$, 100%).

***CIS* ISOMER**[59b]:

R_f 0.43 (100% EtOAc);

δH (400MHz, $CDCl_3$) 6.51 (1H, dt, J 10.9, 7.7, H^3), 5.35 (1H, d, J 10.9, H^2), 3.69-3.64 (2H, m, $H^6{}_2$), 2.54-2.48 (2H, m, $H^4{}_2$), 1.76-1.66 (2H, m, $H^5{}_2$);

3.2.2 (*E, Z*) 6-Oxo-2-hexenenitrile



64

A solution of (*E, Z*) 6-hydroxy-2-hexenenitrile (0.20g, 1.80mmol) in anhydrous dichloromethane (3ml) was added, in one portion, to a stirred suspension of pyridinium chlorochromate (1.5eq., 0.582g, 2.70mmol) and sodium acetate (0.3eq., 0.044g, 0.54mmol) in anhydrous dichloromethane (2ml). The resulting black solution was stirred at ambient temperature for 3 hours. The reaction solution was poured into diethylether (10ml) and the black gum was extracted with additional diethylether (3x10ml) until the black gum had transformed into a grannular solid. The combined organic extracts were passed through a short pad of florisil® and concentrated under reduced pressure to give the crude product. The oil was purified by flash chromatography, eluting with 10%EtOAc/P.E.40-60°C to give the product in 29% yield, as a non-separable mixture of isomers.

***TRANS* ISOMER**[60]:

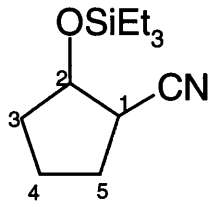
δH (300MHz, $CDCl_3$) 9.82 (1H, s, CHO), 6.72 (1H, dt, J 16.1, 6.8, H^3), 5.44 (1H, d, J 16.1, H^2), 2.76-2.28 (4H, m, $H^4{}_2$, $H^5{}_2$);

m/z (EI+, 70eV) 108 ($M\text{-}H^+$, 25%), 80 (M-CHO, 100%).

***CIS* ISOMER**[60]:

δH (300MHz, $CDCl_3$) 9.82 (1H, s, CHO), 6.53 (1H, dt, J 11.0, 6.9, H^3), 5.38 (1H, d, J 11.0, H^2), 2.76-2.28 (4H, m, $H^4{}_2$, $H^5{}_2$);

3.2.3 2-Triethylsilyloxycyclopentanecarbonitrile



68

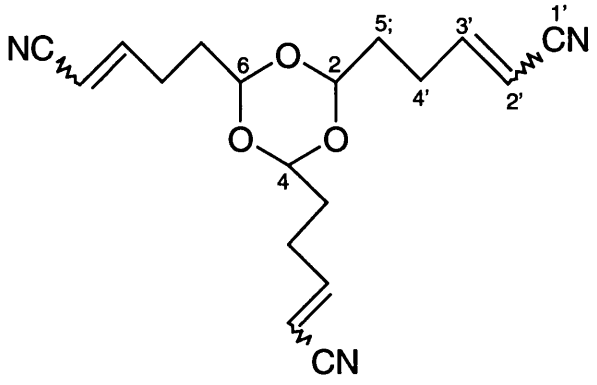
Triethylsilane (2.1eq., 0.271ml, 1.70mmol) was added to a stirred solution of (*E*) 6-Oxo-2-hexenenitrile (**64**, 88mg, 0.81mmol) and tris(triphenylphosphine) rhodium (I) chloride (7.75%mol, 58mg, 0.063mmol) in anhydrous,degassed toluene (3ml) at ambient temperature. The resulting solution was then heated for 18 hours at 100°C. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material as a multi-component mixture. The oil was purified by flash column chromatography, eluting with 30% EtOAc/P.E.40-60°C to give the trioxane (54%), recovered starting material (6%) and the desired product as a mixture of diastereoisomers (**68**, 1:1, 10% yield).

ν_{max} (thin film/cm^{-1}) 2955, 2912, (C-H), 2240 (C=N), 1059 (C-O);

m/z (FAB+, 70eV) 226 (M+H, 10%), 201 (15%), 154 (80%).

δH(400MHz, $CDCl_3$): 4.54-4.32, 4.29-4.01 (1H, m, $H^{2'}$), 2.73-2.71 (1H, m, $H^{1'}$), 2.44-2.28 (2H, m, CH_2), 1.85-1.61 (4H, m, CH_2), 0.87 (9H, t, J 8.0, $C\underline{H}_3CH_2$), 0.50 (6H, q, J 8.0, $CH_3C\underline{H}_2$);

3.2.2 2, 4, 6-nitrile-2'-hexenoate-1, 3, 5-trioxane (65)



65

The trioxane was isolated in a 54% yield upon the reaction of (*E, Z*)-6-Oxo-2-hexenenitrile (**64**) with 7.75mol%(triphenylphosphine) rhodium (I) chloride and triethylsilane at 100°C as well as in the oxidation of **63** to **64** (8% yield).

***TRANS* ISOMER**:

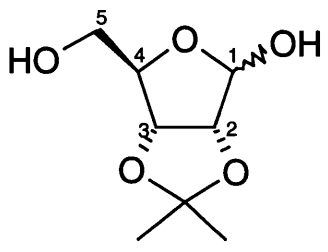
δH (400MHz, $CDCl_3$): 6.69 (3H, dt, J 15.8, 6.8, $H^{3'}{}_3$), 5.36 (3H, d, J 15.8, $H^{2'}{}_3$), 4.08 (3H, t, J 6.43, $H^2{}_3$), 2.72-2.24 (7H, m, $CH^{4'}$, $CH^{5'}$), 1.88-1.48 (5H, m, $CH^{4'}$, $CH^{5'}$).

***CIS* ISOMER**:

δH (400MHz, $CDCl_3$): 6.47 (3H, dt, J 11.2, 2.9, $H^{3'}{}_3$), 5.37 (3H, d, J 11.2, $H^{2'}{}_3$), 4.07 (3H, t, J 6.43, $H^2{}_3$), 2.72-2.24 (7H, m, $CH^{4'}$, $CH^{5'}$), 1.88-1.48 (5H, m, $CH^{4'}$, $CH^{5'}$).

Section 3.3

3.3.2 2, 3-*O*-isopropylidenedioxy-D-ribose[72]

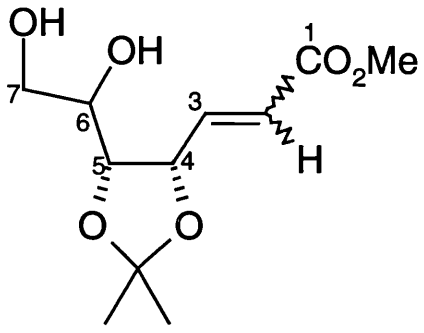


77

To a solution of D-ribose (3.05g, 20.32mmol) in anhydrous N, N dimethylformamide (15ml) and dessicant (Drierite), was added, at 0°C, 2-methoxypropene (1eq., 3.89ml, 40.62mmolbpt. 34-36°C) followed by a catalytic amount of *p*-toluenesulphonic acid. After 1hr at 0°C, an additional stoichiometric amount of reagent was added and stirring was continued for 2 hours at 0°C. Sodium carbonate (~3g) was added to achieve a neutral pH. The neutralisation with base prior to work-up was included to minimise the undesirable formation of enol ethers via the acid-catalysed loss of one molecule of alcohol from the acetal. The mixture was then stirred at ambient temperature for a further hour. The solids were filtered off and the filtrate was condensed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 30%EtOAc/P.E. 40-60°C, to give the protected carbohydrate in 62% yield.

δH(300MHz, DMSO): 6.23 (1H, d, J 4.2, OH), 5.12 (1H, d, J 0.5, H^1), 4.58 (1H, t, J 5.4, OH), 4.49 (1H, dd, J 3.4, H^3), 4.42 (1H, d, J 6.0, H^2), 3.8-3.3 (3H, m, H^4, $H^5{}_2$), 1.33 (3H, s, CH_3), 1.23 (3H, s, CH_3);
m/z (FAB+, 70eV) 173 (M-OH, 100%).

3.3.2 Methyl-2, 3-dideoxy-4, 5-O-isopropylidenedioxy-D-ribo-hept-2-enonate[72]



78

To a solution of 2, 3 isopropylidene D-ribose (1.795g, 9.44mmol) in anhydrous DCM (15ml), was added carbomethoxymethylene triphenylphosphorane (3.47g,

10.38mmol, 1.1eq.). The resulting clear solution was stirred at ambient temperature for 18 hours. The reaction mixture was concentrated under reduced pressure and then eluted with Et_2O. The resulting white precipitate was removed by filtration and the solvent was subsequently removed on the rotary evaporator. The crude product was purified by flash column chromatography, eluting with 40% EtOAc/P.E.40-60°C, gradually increasing to 50% EtOAc/P.E.40-60°C to give the product in the yield 52%, as a non-separable mixture of diastereoisomers, in the ratio 7:3 *cis:trans*.

***CIS* ISOMER:**

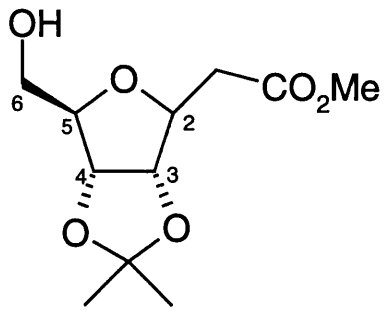
δH(300MHz, $CDCl_3$) 6.32 (1H, dd, J 11.6, 8.4, H^3), 6.06 (1H, dd, J 11.6, 8.4, H^2), 5.57 (1H, ddd, J 8.1, 6.5, H^4), 4.35 (1H, ddd, J 8.1, 6.5, H^5), 3.78 (3H, s, OCH_3), 3.76-3.52 (3H, m, H^6, $H^7{}_2$), 1.52, 1.40 (6H, 2s, Me_2C).

***TRANS* ISOMER:**

δH(300MHz, $CDCl_3$) 7.10 (1H, dd, J 15.5, 5.0, H^3), 6.15 (1H, dd, J 15.5, 5.0, H^2), 4.87 (1H, ddd, J 6.4, 5.0, H^4), 4.18-4.15 (1H, m, H^5), 3.75 (3H, s, OCH_3), 3.91-3.55 (3H, m, H^6, $H^7{}_2$), 1.47, 1.36 (6H, 2s, Me_2C).

m/z (FAB+, 70eV) 245 (M+, 15%), 229 (MH-OH, 100%).

3.3.2 Methyl 2-(3, 4-isopropylidenedioxy-D-ribofuranose) carboxylate



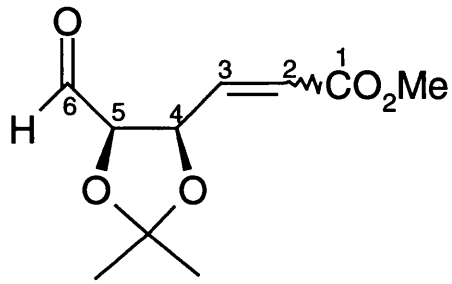
83

The substituted furan was isolated during the flash column chromatography purification of 2, 3-dideoxy-4, 5-isopropylidene-D-ribo-hept-2-enoate. The conjecture was made that, with furan having been absent from the crude mixture prior to

purification, the product had cyclised on the column. This supposition was supported by a corresponding decrease in the amount of product retrieved from the column.

δH(300MHz, $CDCl_3$) : 1.36 (3H, s, Me), 1.56 (3H, s, Me), 2.47 (2H, d, J 6.1, $C\underline{H}_2CO_2Me$), 3.48 (3H, s, OCH_3), 3.72-4.76 (6H, m, H^2, H^3, H^4, H^5, $H^6{}_2$).

3.3.2 Methyl-(4R, 5S)-6-Oxo-4, 5-isopropylidenedioxy-2-hexenoate[72]



79

Methyl-2, 3-dideoxy-4, 5-O-isopropylidene-D-*ribo*-hept-2-enoate (0.576g, 2.35mmol) was dissolved in dichloromethane (35ml) and the vessel was placed in a water bath at 25°C. Sodium periodate (2.0eq., 1.005g, 4.70mmol) was added with vigorous stirring, followed by the minimum volume of water required to effect solution (4ml). The reaction was left stirring at ambient temperature for 16 hours. Sufficient $MgSO_4$ was then added to the reaction to absorb the water, with the suspension being stirred for 15 minutes. The reaction mixture was filtered and the cake washed with DCM. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography, eluting with 60%Et_2O/P.E. 40-60°C%, to give the product, as separate isomers (*cis:trans* 7:3) in a combined yield of 58% yield.

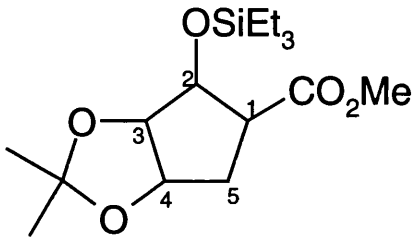
***CIS* ISOMER:**

ν_{max} (thin film/cm^{-1}) 1723 (C=O aldehyde), 1650 (C=O ester);

δH (300MHz, $CDCl_3$) 9.49 (1H, d, J 2.9, CHO), 6.26 (1H, dd, J 11.5, 6.8, H^3), 6.02 (1H, dd, J 11.5, 6.8, H^2), 5.99-5.79 (2H, m, $H^4{}_2$), 4.85-4.78 (2H, m, $H^5{}_2$), 3.76 (3H, s, OCH_3), 1.62 (3H, s, CH_3), 1.48 (3H, s, CH_3);

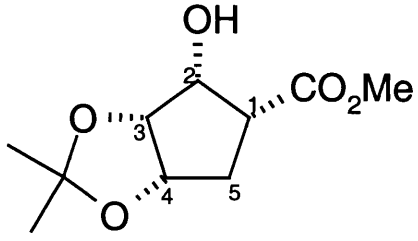
m/z (FAB$^+$, 70eV) 215 (MH+, 25%), 154 (80%), 135 (100%).

3.3.3 Methyl-2-Triethylsilyloxy-3, 4-isopropylidenedioxy cyclopentane carboxylate



86

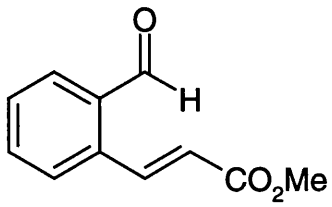
Triethylsilane (2.1eq., 81.4µl, 0.51mmol) was added to a stirred solution of methyl-(*Z*)-4, 5-isopropylidene-6-oxo-2-hexenoate (**85**, 52mg, 0.24mmol) and tris(triphenylphosphine) rhodium (I) chloride (1%mol, 2.25mg, 0.0024mmol) in anhydrous, degassed toluene (5ml) at ambient temperature. The resulting solution was then heated for 20 hours at 50°C. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material as a mixture of the 4 diastereoisomers in the ratio 5.4:2:2:1 (**88**:**89**:**90**:**87**, Section 3.3.3), along with a trace of recovered starting material. The oil was purified by flash column chromatography, eluting with 10% EtOAc/P.E.40-60°C to give **88** (1, 2, 3, 4 *cis*) separately, with the other 3 diastereoisomers as a non-separable mixture, in a combined yield of 65%. In the process of columning the crude mixture, the silyl group was cleaved to give the hydroxy group.



δH (300MHz, $CDCl_3$): 4.69-4.74 (1H, m, H^2), 4.55-4.61 (1H, m, H^1), 4.38-4.42 (1H, m, H^3), 3.74 (3H, s, OCH_3), 2.75-2.89 (1H, m, H^5), 2.26-2.31 (2H, m, $H^4{}_2$), 1.43 (3H, s, Me), 1.30 (3H, s, Me).

Section 3.4

3.4.2 Methyl 3-(2'-Formylphenyl) propenoate



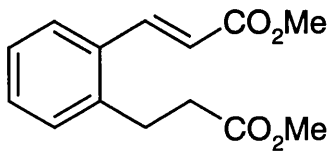
91

Tetrabutylammonium bromide (0.05eq., 0.562g, 1.74mmol), potassium carbonate (0.5eq., 0.803g, 5.81mmol), palladium (II) acetate (2%mol, 0.156g, 0.69mmol) and methyl acrylate (1.0eq., 3.14ml, 34.87mmol) were stirred for 5 minutes under nitrogen, forming a dark orange solution. To the resulting solution was added *o*-bromobenzaldehyde (0.2eq., 0.813ml, 6.96mmol) in degassed DMF (4ml). The reaction was stirred at 65°C-70°C for 16 hours. The mixture was diluted with EtOAc and passed through a thin pad of celite. The filtrate was diluted with water and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was composed of product:starting material 2:1, with the doubly substituted product (**93**) present in 8.5%. Purification by flash column chromatography enabled *o*-bromobenzaldehyde to be removed from the crude mixture, with the desired aldehyde being isolated in 69% yield (when adjusted for recovered starting material). However, all attempts at isolating methyl 3-[2'-(2-carbomethoxyethyl)phenyl]-2-propenoate (**93**) from the desired product **91** via standard purification techniques were unsuccessful.

ν_{max} [81](neat/cm^{-1}) 1728 (C=O), 1699 (CHO), 1621 (C=C).

δH(300MHz, $CDCl_3$) 10.31 (1H, s, CHO), 8.55 (1H, d, J 15.9, alkene H), 7.91-7.56 (4H, m, phenyl H), 6.40 (1H, d, J 15.9, alkene H), 3.85 (3H, s, OCH_3).

3.4.2 Methyl 3-[2'-(2-Carbomethoxyethyl)phenyl]-2-propenoate



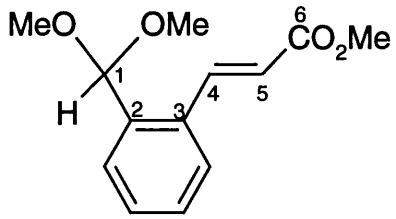
93

The above product was identified as a minor (8.5%) but persistant contaminant in the Heck synthesis of methyl 3-(2'-formylphenyl) propenoate.

ν_{max} [81] (neat/cm^{-1}) 1733 (C=O), 1712 (C=O), 1630 (C=C).

δH(300MHz, $CDCl_3$) 8.00 (1H, d, J 15.8, alkene H), 7.58-7.23 (4H, m, phenyl H), 6.39 (1H, d, J 15.8, alkene H), 3.83 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.11 (2H, t, J 7.8, $C\underline{H}_2CO_2Me$), 2.60 (2H, t, J 7.8, $C\underline{H}_2CH_2CO_2Me$).

3.4.2 Methyl 3-(2'-dimethyl acetal formylphenyl) propenoate (147) [81]



147

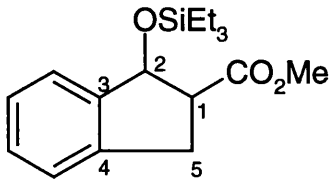
The aldehyde (0.329g, **91**, 1.73mmol), contaminated with the doubly substituted product **93**, was dissolved up in anhydrous MeOH (15ml) and trimethylorthoformate (5ml). The resulting solution was refluxed for 12 hours with Dowex (50W-x8, mesh 50-100, strongly acidic, 0.1g). The reaction mixture was filtered and concentrated under reduced pressure to obtain a viscous oil. The oil was subjected to preparative tlc on silica (multiple elutions, 10%EtOAc/P.E.40-60°C) to obtain the dimethyl acetal of the aldehyde (**147**, 83% yield) and the impurity as separate components.

ν_{max}^{81} (neat/cm^{-1}) 1722 (C=O), 1635 (C=C), 1195, 1172, 1113, 1052 (C-O)

δH(300MHz, $CDCl_3$): 8.17 (1H, d, J 15.9, alkene H), 7.65-7.59 (2H, m, phenyl H), 7.44-7.35 (2H, m, phenyl H), 6.37 (1H, d, J 15.9, alkene H), 5.59 (1H, s, H^1), 3.83 (3H, s, $COOC\underline{H}_3$), 3.56 (6H, s, $2xOCH_3$).

The aldehyde **91** was regenerated after a solution (THF, 10ml) of the dimethyl acetal (0.292g) was stirred in 2M HCl (5ml) for 4 hours and subsequently subjected to the appropriate work-up and purification.

3.4.3 Methyl 2-Triethylsilyloxy-3, 4-phenyl cyclopentanecarboxylate



100

Triethylsilane (0.404ml, 2.53mmol2.1eq.,) was added to a stirred solution of methyl 3-(2'-formylphenyl) propenoate (**91**, 0.229g, 1.20mmol) and Wilkinson's catalyst (4%mol., 48mg, 0.052mmol) in degassed, anhydrous toluene (7ml). The reaction mixture was heated to 50°C and followed by tlc. After 5 hours at this temperature there appeared to be little change by tlc. The reaction temperature was consequently increased to 70°C and the mixture stirred for a further 16 hours. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad

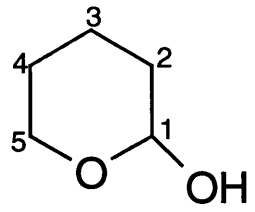
of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material, which was purified by flash column chromatography, eluting with 12% EtOAc/P.E.40-60°C. The desired product was isolated in a yield of 61% as a 1.5:1 *cis:trans* mixture of diastereoisomers.

δH(300MHz, $CDCl_3$): 7.65-7.24 (4H, m, phenyl), 4.86 (0.6H, d, J 4.9, H^2 cis), 4.76 (0.4H, d, J 5.4, H^2 *trans*), 3.71 (3H, s, OCH_3), 3.09-3.04 (1H, m, H^1), 2.74 (2H, d, J 7.2, $^5H_2$), 0.93 (9H, t, J 7.9, $OSi(CH_2CH_3)_3$), 0.55 (6H, q, J 7.9, $OSi(CH_2CH_3)_3$).

CHAPTER FOUR

Section 4.2

4.2.1 1-Hydroxy pyran[88]



107

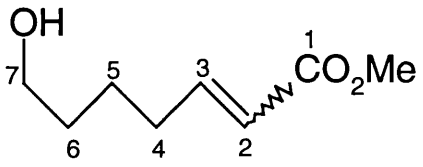
In a 250ml 3-necked flask, equipped with a large stirrer bar, were mixed, in the following order, water (75ml), concentrated hydrochloric acid (6.25ml) and 3, 4 dihydropyran (25.0g, 0.297mol). The mixture was stirred until the solution was homogenous and then stirred for a further 20 minutes. After the addition of a few drops of phenol-phthalein indicator to the mixture, the acid was neutralized with 20% NaOH, adding just enough alkali so that the faint pink colour persisted. The solution was then transferred to a continuous liquid-liquid extractor and extracted with diethylether (250ml) for 16 hours. Having removed the diethylether under reduced

pressure, the mobile oil was then distilled, with the forerun being discarded. The product distilled as a clear, colourless oil at 62-66°C/9-10mmHg in a yield of 86%.

δH(300MHz, $CDCl_3$) 4.90-4.86 (1H, m, H^1), 4.04-3.97 (1H, m, H^5), 3.56-3.49 (2H, m, OH, H^5), 1.87-1.75 (2H, m, $H^2{}_2$), 1.61-1.45 (4H, m, $H^3{}_2$, $H^4{}_2$);

m/z(EI$^+$, 70eV) 101 ($M-H^+$, 20%), 85 (M-OH, 30%), 56 (M-OCHOH, 100%).

4.2.1 (*E, Z*) Methyl-7-hydroxy-2-heptenoate[89]



108

To a solution of 1-hydroxypyran (4.0g, 39.17mmol) in dichloroethane (55ml) was added carbomethoxymethylene triphenylphosphorane (1.0eq., 13.1g, 39.18mmol). The resulting clear solution was stirred at 60°C for 16 hours. The solution was concentrated under reduced pressure and subsequently diluted with diethylether. The resulting white crystalline precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 15%EtOAc/P.E.40-60°C to give the product as the isomers *trans:cis* 10:1 with a combined yield of 92%. Attempts to separate the isomers by flash chromatography were unsuccessful at this point.

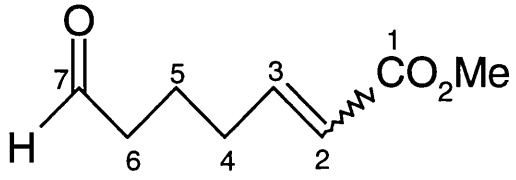
***TRANS* ISOMER**:

R_f 0.42 (100% EtOAc/P.E.40-60°C);

δH (400MHz, $CDCl_3$) 6.94 (1H, dt, J 15.6, 7.0, H^3), 5.80 (1H, d, J 15.6, H^2), 3.69 (3H, s, OCH_3), 3.62 (2H, t, J 5.7, $H^7{}_2$), 2.21 (2H, q, J 7.0, $H^4{}_2$), 1.61-1.48 (4H, m, $H^6{}_2$, $H^5{}_2$);

m/z (FAB$^+$, 70eV) 159 (MH$^+$, 100%).

4.2.1 (*E*, *Z*)-Methyl-7-oxo-2-hexenoate



109

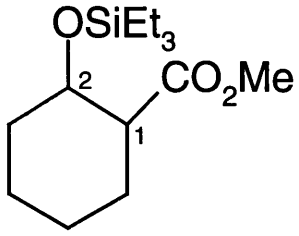
Pyridinium chlorochromate (0.85g, 3.94mmol) was added to a 3-necked flask equipped with an addition funnel and containing 4A molecular sieves. The solids were dissolved in anhydrous DCM (5ml). A solution of methyl-7-hydroxy-2-hexenoate (0.291g, 1.84mmol) in anhydrous DCM (5ml) was added dropwise over 5 minutes. The resulting dark brown solution was stirred at ambient temperature for 3 hours. The reaction solution was poured into diethylether (10ml) and the black gum was extracted with additional diethylether (3x10ml) until the gum had transformed into a granular solid. The combined organic extracts were passed through a short pad of florisil® and concentrated under reduced pressure to give the crude product. The oil was purified by flash column chromatography, eluting with 10% EtOAc/P.E.40-60°C to give the product in 72% yield as a mixture of diastereoisomers, *trans:cis* 10:1

***TRANS* ISOMER**[89]**:**

δH (400MHz, $CDCl_3$) 9.77 (1H, t, J 1.3, CHO), 6.91 (1H, dt, J 15.7, 7.0, H^3), 5.84 (1H, d, J 15.7, H^2), 3.72 (3H, s, OCH_3), 2.48 (2H, td, J 7.3, 1.3, $H^6{}_2$), 2.24 (2H, q, J 7.3, $H^4{}_2$), 1.78 (2H, q, J 7.3, $H^5{}_2$);

m/z (EI$^+$, 70eV) 125 (M-OCH_3, 95%), 113 (M-CH_2CHO, 60%).

4.2.2 Methyl 2-Triethylsilyloxycylcohexanecarboxylate



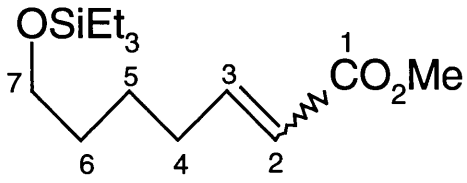
110

Triethylsilane (0.129ml, 0.81mmol, 2.1eq.) was added at ambient temperature to a stirred solution of ethyl-7-oxo-2-heptenoate and Wilkinson's catalyst (1%mol, 3.56mg, 0.0038mmol) in degassed, anhydrous toluene. The resulting solution was heated to 70°C for 16 hours. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material. The oil was purified by flash column chromatography, eluting with 12% EtOAc/P.E.40-60°C to give the desired product in a 15% yield as a mixture of diastereoisomers.

δH (300MHz, $CDCl_3$): 3.84-3.78, 3.76-3.64 (1H, m, H^2), 3.68 (3H, s, OCH_3), 2.37-2.28 (2H, m, H^1, H^3), 2.10-2.02 (1H, m, H^3), 1.92-1.83 (1H, m, CH), 1.64-1.57 (2H, m, CH_2), 1.42-1.19 (3H, m, CH_2), 0.93 (9H, t, J 7.9, $OSi(CH_2C\underline{H}_3)_3$), 0.68 (6H, q, J 7.9, $OSi(C\underline{H}_2CH_3)_3$).

m/z (EI^+, 70eV) 273 (35%, MH+), 243 (50%), 183 (70%), 136 (100%).

4.3.1(*E, Z*) Methyl-7-triethylsilyloxy-2-heptenoate



111

The alcohol (0.250g, 1.60mmol) was dissolved up in anhydrous DMF (4ml), imidazole (0.327g, 4.80mmol, 3eq.) and triethylchlorosilane (0.322ml, 1.92mmol, 1.2eq.). The reaction mixture was stirred at ambient temperature for 16 hours. Under these conditions, the reaction proved difficult to force to completion: the reaction was quenched at this point at the expense of product yield as the desired compound was only needed for identification purposes. The reaction mixture was dissolved up in DCM (20ml), washed with 1M HCl (2x10ml), H_2O (5x10ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% EtOAc/P.E.40-60°C, separated unreacted starting material (80mg) from contaminated product. The silylether was distilled (175°C, 0.5mmHg reduced pressure) from the excess silane, as a mixture of diastereoisomers *trans:cis* 10:1, with an adjusted yield of 75% .

***TRANS* ISOMER**

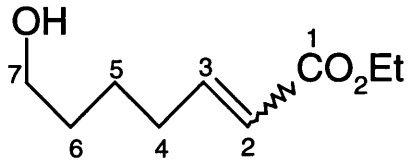
ν_{max} (thin film/cm^{-1}) 2951, 2879 (C-H), 1727 (C=O), 1657 (C=C), 1099, 1023 (s, C-O);

m/z (FAB+, 70eV) M+H Measured 273.1872 Actual 273.1886

δH (300MHz, $CDCl_3$) 6.99 (1H, dt, J 15.6, 7.0, H^3), 5.84 (1H, d, J 15.6, H^2), 3.75 (3H, s, OCH_3), 3.63 (2H, t, J 5.97, $H^7{}_2$), 2.28-2.21 (2H, m, CH_2), 1.59-1.52 (4H, m, $(CH_2)_2$), 0.97 (9H, t, J 7.9, $OSi(CH_2C\underline{H}_3)_3$), 0.61 (6H, q, J 7.9, $OSi(C\underline{H}_2CH_3)_3$).

δC (100.6MHz, $CDCl_3$) 167.11 (C=O), 149.44 (C-3), 120.96 (C-2), 62.38 (OCH_3), 51.36 (C-7), 32.22 (C-6), 31.97 (C-4), 24.37 (C-5), 6.76 ($OSi(CH_2\underline{C}H_3)_3$), 4.37 ($OSi(\underline{C}H_2CH_3)_3$).

4.3.3 (*E, Z*) Ethyl-7-hydroxy-2-heptenoate[89]



126

To a solution of 1-hydroxypyran (2.0g, 19.58mmol) in dichloroethane (28ml) was added carboethoxymethylene triphenylphosphorane (1.0eq., 6.82g, 19.58mmol). The resulting clear solution was stirred at 60°C for 16 hours. The solution was concentrated under reduced pressure and subsequently diluted with diethylether. The resulting white crystalline precipitate was filtered off and the filtrate concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with 20%EtOAc/P.E.40-60°C, gradually increasing polarity to 25%EtOAc/P.E.40-60°C. The product, a colourless oil, was isolated as a mixture of diastereoisomers in the ratio *trans*:*cis* 6:1 in the combined yield of 87%.

***TRANS* ISOMER**[114]:

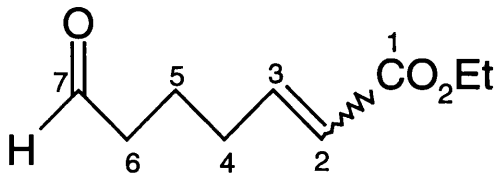
δH (400MHz, $CDCl_3$) 6.95 (1H, dt, J 15.7, 6.9, H^3), 5.82 (1H, dt, J 15.7, 1.5, H^2), 4.17 (2H, q, J 7.2, $OC\underline{H}_2CH_3$), 3.64 (2H, br t, J 4.5, $H^7{}_2$), 2.26-2.20 (2H, m, $H^4{}_2$), 1.63-1.50 (4H, m, $H^6{}_2$, $H^5{}_2$), 1.27 (3H, t, J 7.2, $OCH_2C\underline{H}_3$);

m/z (FAB^+, 70eV) 173 (MH^+, 80%), 127 (M-OEt, 100%).

***CIS* ISOMER**[114]:

δH (400MHz, $CDCl_3$) 6.23-6.21 (1H, m, H^3), 5.79-5.75 (1H, m, H^2), 4.17 (2H, q, J 7.1, $OC\underline{H}_2CH_3$), 3.64 (2H, br t, J 4.5, $H^7{}_2$), 2.68-2.66 (2H, m, $H^4{}_2$), 1.63-1.50 (4H, m, $H^6{}_2$, $H^5{}_2$), 1.29-1.26 (3H, t, J 7.1, $OCH_2C\underline{H}_3$);

4.3.3 (*E, Z*)-Ethyl-7-oxo-2-hexenoate



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Pyridinium chlorochromate (1.347g, 6.25mmol) was added to a 3-necked flask equipped with an addition funnel and containing 4A molecular sieves. The solids were dissolved in anhydrous DCM (10ml). A solution of methyl-7-hydroxy-2-hexenoate (0.538g, 3.12mmol) in anhydrous DCM (5ml) was added dropwise over 5 minutes. The resulting dark brown solution was stirred at ambient temperature for 2.5 hours. The reaction solution was poured into diethylether (10ml) and the black gum was extracted with additional diethylether (3x10ml) until the gum had transformed into a grannular solid. The combined organic extracts were passed through a short pad of florisil® and concentrated under reduced pressure to give the crude product. The oil was purified by flash column chromatography, eluting with 10% EtOAc/P.E.40-60°C to give the product in 73% yield as separate isomers *cis:trans* 1:6.

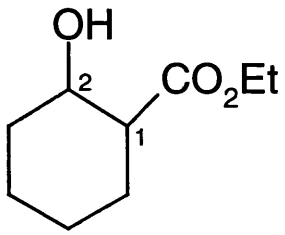
***TRANS* ISOMER:**

δH (400MHz, $CDCl_3$) 9.75 (1H, t, J 1.4, CHO6.89 (1H, dt, J 15.6, 6.9, H^3), 5.80 (1H, dt, J 15.6, 1.6, H^2), 4.18-4.12 (2H, m, $OC\underline{H}_2CH_3$), 2.46 (2H, t, J 7.3, $H^6{}_2$), 2.22 (2H, m, $H^4{}_2$), 1.78 (2H, q, J 7.3, $H^5{}_2$), 1.25 (3H, t, J 7.2, $OCH_2C\underline{H}_3$).

***CIS* ISOMER:**

δH (300MHz, $CDCl_3$) 9.78 (1H, t, J 1.3, CHO), 6.18 (1H, dt, J 11.5, 5.7, H^3), 5.80 (1H, dt, J 11.5, 1.5, H^2), 4.16 (2H, q, J 7.1, $OC\underline{H}_2CH_3$), 2.73-2.65 (2H, m, $H^6{}_2$), 2.49 (2H, dt, J 7.4, 5.7, $H^4{}_2$), 1.79 (2H, q, J 7.4, $H^5{}_2$), 1.28 (3H, t, J 7.1, $OCH_2C\underline{H}_3$).

4.3.2 Ethyl-2-hydroxycyclohexanecarboxylate[96]



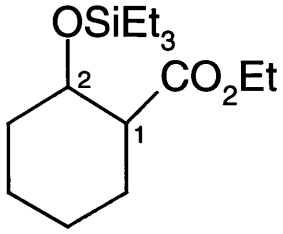
123

Freshly distilled ethyl cyclohexanonecarboxylate (3.6ml, 22.50mmol) was hydrogenated with Adam's catalyst (0.13g, 0.57mmol, 3.5%) in its own volume of absolute EtOH (3.6ml,) at ambient temperature and 5 atmospheres pressure. After 16 hrs, the reaction solution had ceased to take up any further H_2 and the catalyst was removed by filtration. The solvent was removed under reduced pressure. The crude oil was distilled through a Vigreux column (bp117-118°C/17mmHg) to give the product in 72% yield as a mixture of diastereoisomers.

ν_{max}[115] (thin film/cm^{-1}): 3410 (br, OH), 1716 (C=O ester), 1236 (C-O).

δH (300MHz, $CDCl_3$): 6.98 (1H, br, OH), 4.23-4.15 (3H, m, H^2, $O\underline{CH}_2CH_3$), 2.36-2.13 (5H, m, $(CH_2)_2$, H^1), 1.90-1.57 (4H, m, $(CH_2)_2$), 1.27 (3H, t, J 7.1, $OCH_2\underline{CH}_3$).

4.3.4 Ethyl 2-Triethylsilyloxycylcohexanecarboxylate



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METHOD A:

Ethyl 2-hydroxycyclohexanecarboxylate (0.4g, 2.32mmol) was dissolved up in anhydrous DMF (5ml) with imidazole (0.474g, 6.97mmol, 3eq.) and triethylchlorosilane (0.468ml, 2.79mmol, 1.2eq.). The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was dissolved up in DCM (20ml), washed with 1M HCl (2x10ml), H_2O (5x10ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% EtOAc/P.E.40-60°C followed by a Kugelrohr distillation gave the product in a 41% yield as a mixture of diastereoisomers.

METHOD B:

Triethylsilane (0.394ml, 2.47mmol, 2.1eq.) was added at ambient temperature to a stirred solution of (*E*)-ethyl-7-oxo-2-heptenoate (0.20g, 1.18mmol) and Wilkinson's catalyst (3%mol, 32.6mg, 0.035mmol) in degassed, anhydrous toluene. The resulting solution was heated to 70°C for 16 hours. ^{n}Hexane was added to the cooled solution, which was then passed through a short pad of florisil®, rinsing with 30% EtOAc/P.E.40-60°C. The combined organic extracts were concentrated under reduced pressure to give the crude material. The oil was purified by preparative tlc, eluting with 10% EtOAc/P.E.40-60°C to give the desired product in a 29% yield as a mixture of diastereoisomers.

δH (300MHz, $CDCl_3$): 4.17-4.12 (3H, m, 2H, $OC\underline{H}_2CH_3$), 2.29-2.13 (5H, m, $(CH_2)_2$, H^1), 1.64-1.61 (2H, m, CH_2), 1.57-1.52 (2H, m, CH_2), 1.25 (3H, t, J 7.1, $OCH_2C\underline{H}_3$), 0.96 (9H, t, J 7.9, $OSi(CH_2C\underline{H}_3)_3$), 0.68 (6H, q, J 7.9, $OSi(C\underline{H}_2CH_3)_3$).

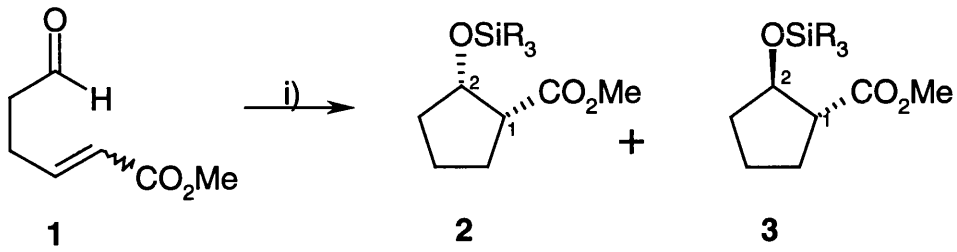
δC (100.6MHz, $CDCl_3$): 167.88 (C=O), 68.27 (C-2), 59.57 ($O\underline{C}H_2CH_3$), 48.42 (C-1), 32.10 (C-6), 25.35 (C-3), 22.72 (C-4), 22.30 (C-5), 14.47 ($OCH_2\underline{C}H_3$), 6.70 ($OSi(CH_2\underline{C}H_3)_3$), 5.53 ($OSi(\underline{C}H_2CH_3)_3$).

CHAPTER SEVEN: SUMMARY

Work has begun on defining the scope of the tandem hydrosilylation cyclisation chemistry as a general method for the synthesis of substituted carbocycles.

CHAPTER TWO

Part I



1 2 3

i) catalytic Rh(I), excess R_3SiH, toluene, heat

Scheme 1

In defining the conditions which give a stereocontrolled synthesis of substituted cyclopentanols (Scheme 1), a survey of silanes and various catalyst systems at a range of temperatures was conducted.

Table 1 shows the most promising results achieved to date.

CATALYST	YIELD %	*CIS : TRANS*
1% $RhH(PPh_3)_4$	81	1 : 2
0.025eq $[Rh(C_8H_{14})_2]_2$ 0.5eq DIPHOS	78	3.3 : 1.0

Table 1

Both isomers are accessible under catalytic conditions in good yield.

Part II

Investigations into the mechanism have revealed the following:

- The mechanism proceeds through hydrosilylation followed by 5-*exo-trig* cyclisation. Intramolecular hydroacylation followed by hydrosilylation is a minor competing pathway.

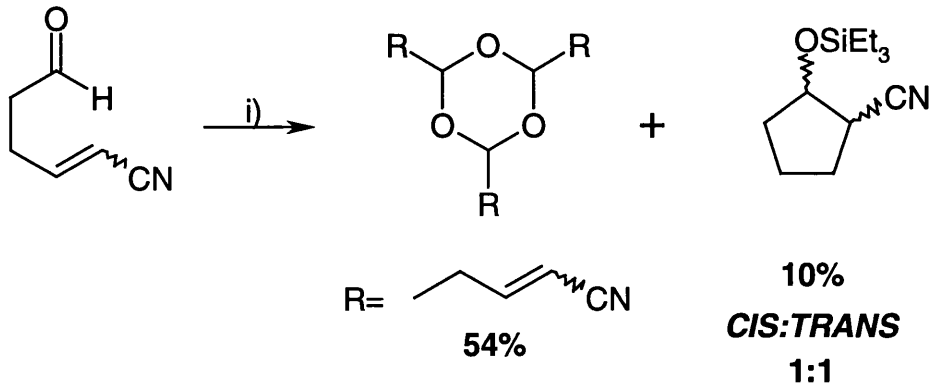
- The kinetic *cis* isomer (**2**) of the cyclopentyl moiety cannot be converted to the thermodynamic *trans* isomer (**3**) under the reaction conditions.

- The geometry of the double bond of the oxo-unsaturated ester (**1**) has no influence on the stereochemical outcome of the reaction

CHAPTER THREE

Investigations were extended to include alternative functional groups which could be incorporated into the substrate. Results were promising, allowing a more general synthesis of cyclopentanols. This affords the advantage of compatibility with a range of functionality in the parent substrate.

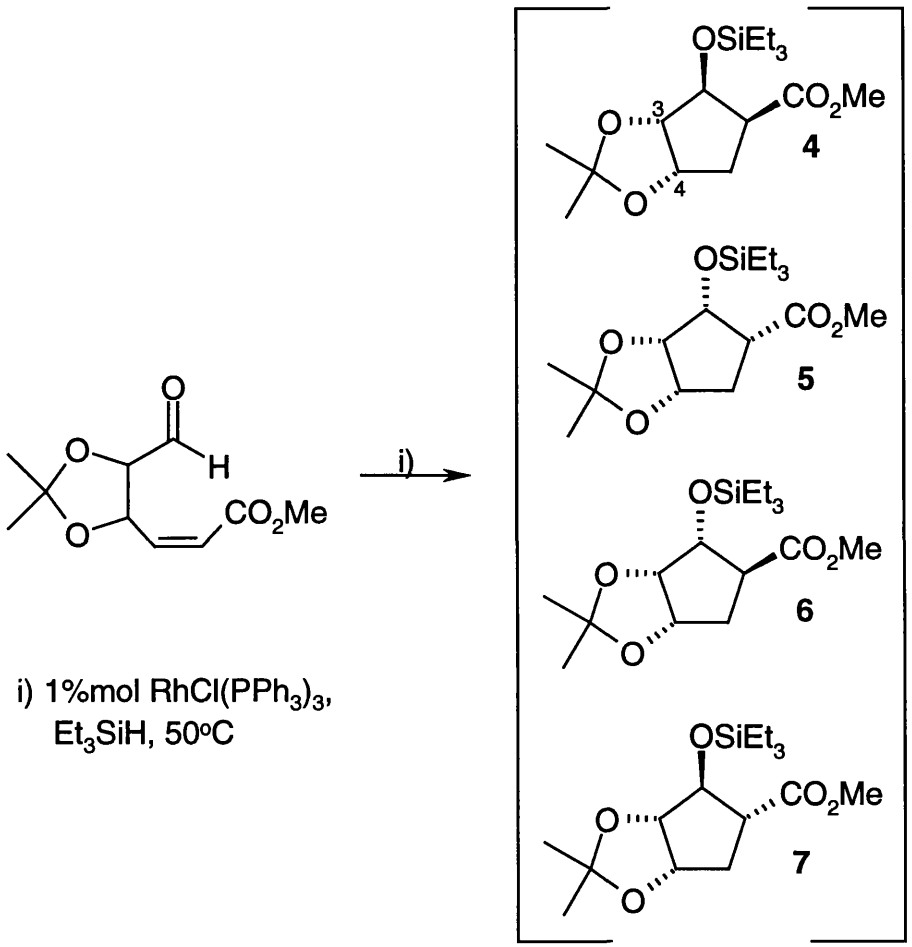
Alternative Michael Acceptors: Replacement of the ester functionality with a nitrile resulted in a dramatic decrease in both yield and selectivity (Scheme 2).



i) 7.75%mol $RhCl(PPh_3)_3$, Et_3SiH, toluene, 100°C

Scheme 2

4, 5 Substrate Substitution, Part I: 4, 5 substitution of the pentenal with isopropylidene resulted in all four of the possible diastereoisomers being produced in moderate yield and selectivity (Scheme 3).

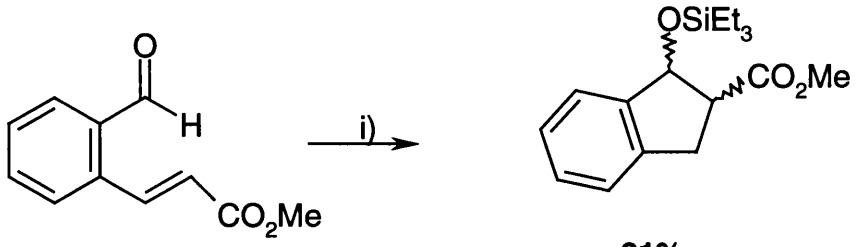


TOTAL YIELD
65%
5 : 6 : 7 : 4
5.4 : 2 : 2 : 1

Scheme 3

• Tandem hydrosilylation cyclisation was confirmed as the major reacting pathway.

4, 5 Substrate Substitution, Part II: The benzannulated substrate produced the substituted cyclopentanol in moderate yield but with poor selectivity (Scheme 4).



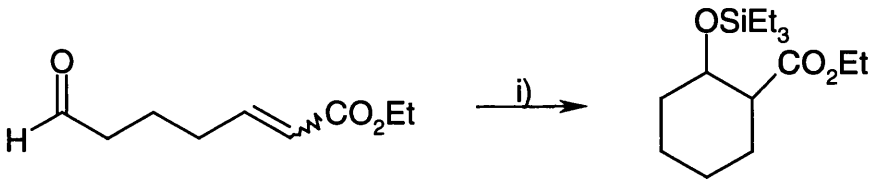
61%
CIS:TRANS
1.5 : 1

i) 4% mol $RhCl(PPh_3)_3$, Et_3SiH, 70°C, 16hr

Scheme 4

CHAPTER FOUR

This methodology was shown to be applicable to the synthesis of a substituted cyclohexanol from a 7-oxo-2-heptenoate substrate (Scheme 5).



19%-29%

i) 3%mol $RhCl(PPh_3)_3$, Et_3SiH, toluene, 70°C, 16hr

Scheme 5

CONCLUSION: This novel methodology provides a simple route from lactols to highly functionalised cyclopentanols and cyclohexanols in moderate yield and selectivity.

CHAPTER EIGHT

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Appendix

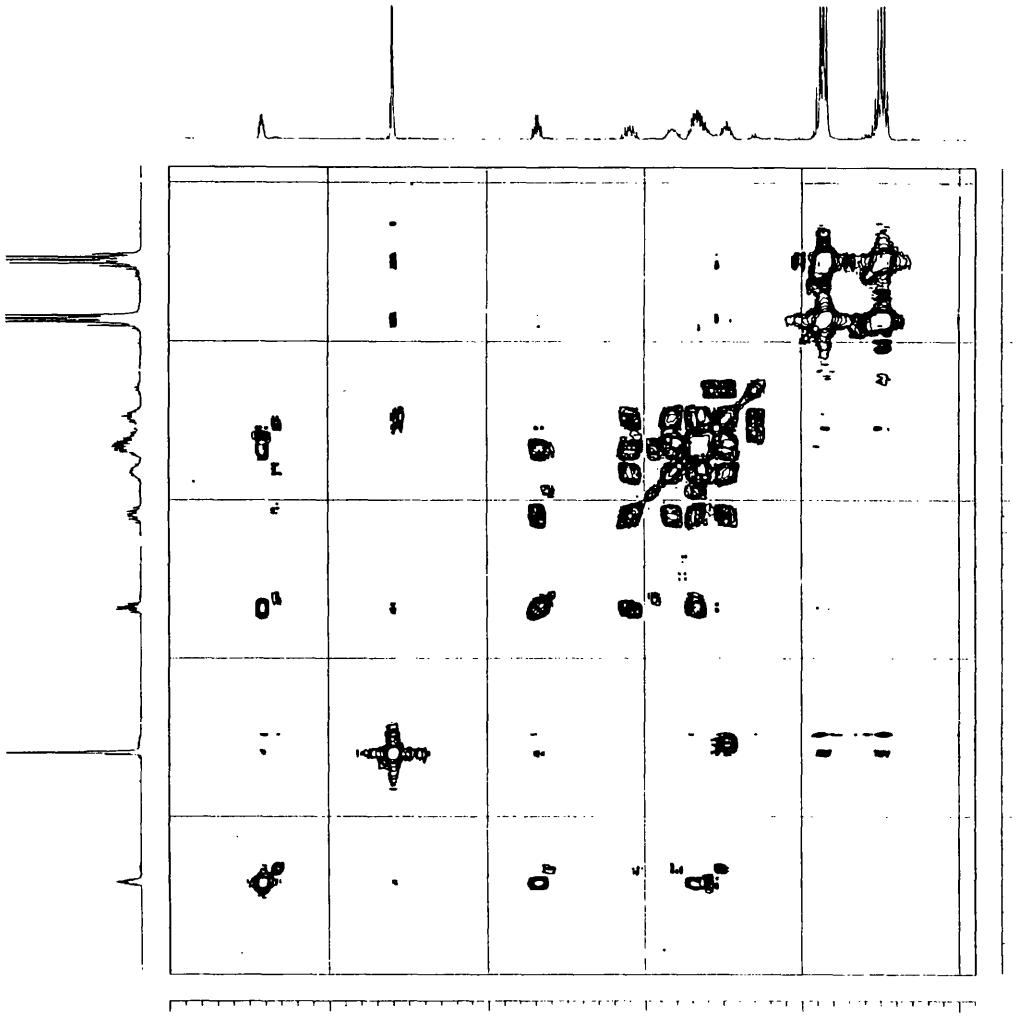
This appendix details lectures attended as partial fulfilment of the requirements for the award of the degree of Master of Science of the University of London.

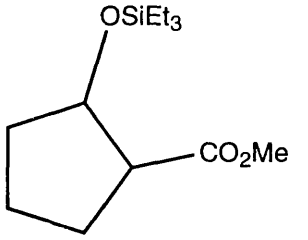
Postgraduate Lectures attended:

CPG15	Peptide Chemistry	Passed
CPG16	General Analytical and Synthetic Techniques	Passed
CPG20	Cyclic Organic Chemistry	Passed

External Symposium attended:

Astra-Loughborough Organic Synthesis Symposium	November 1998





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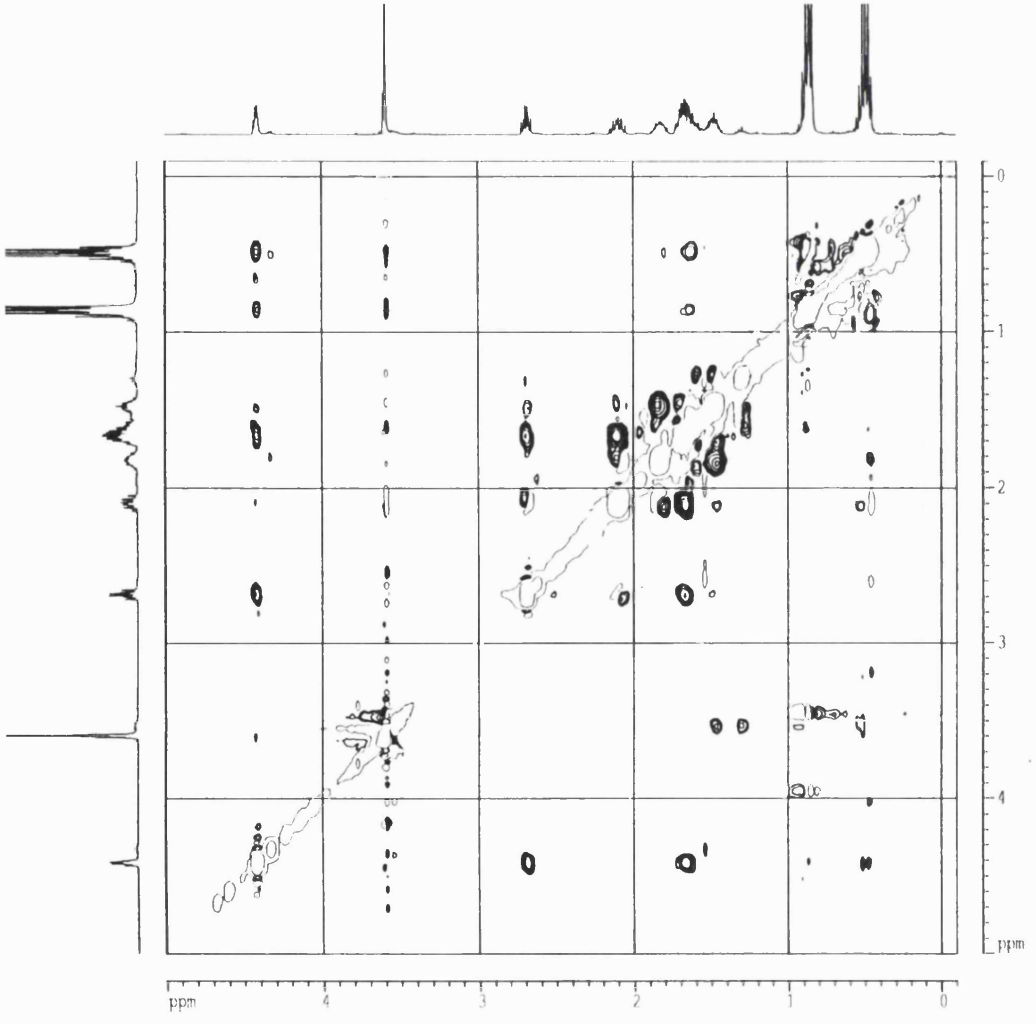

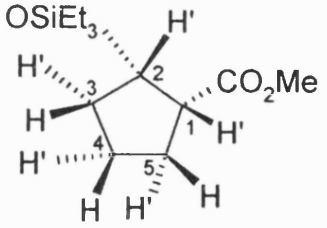

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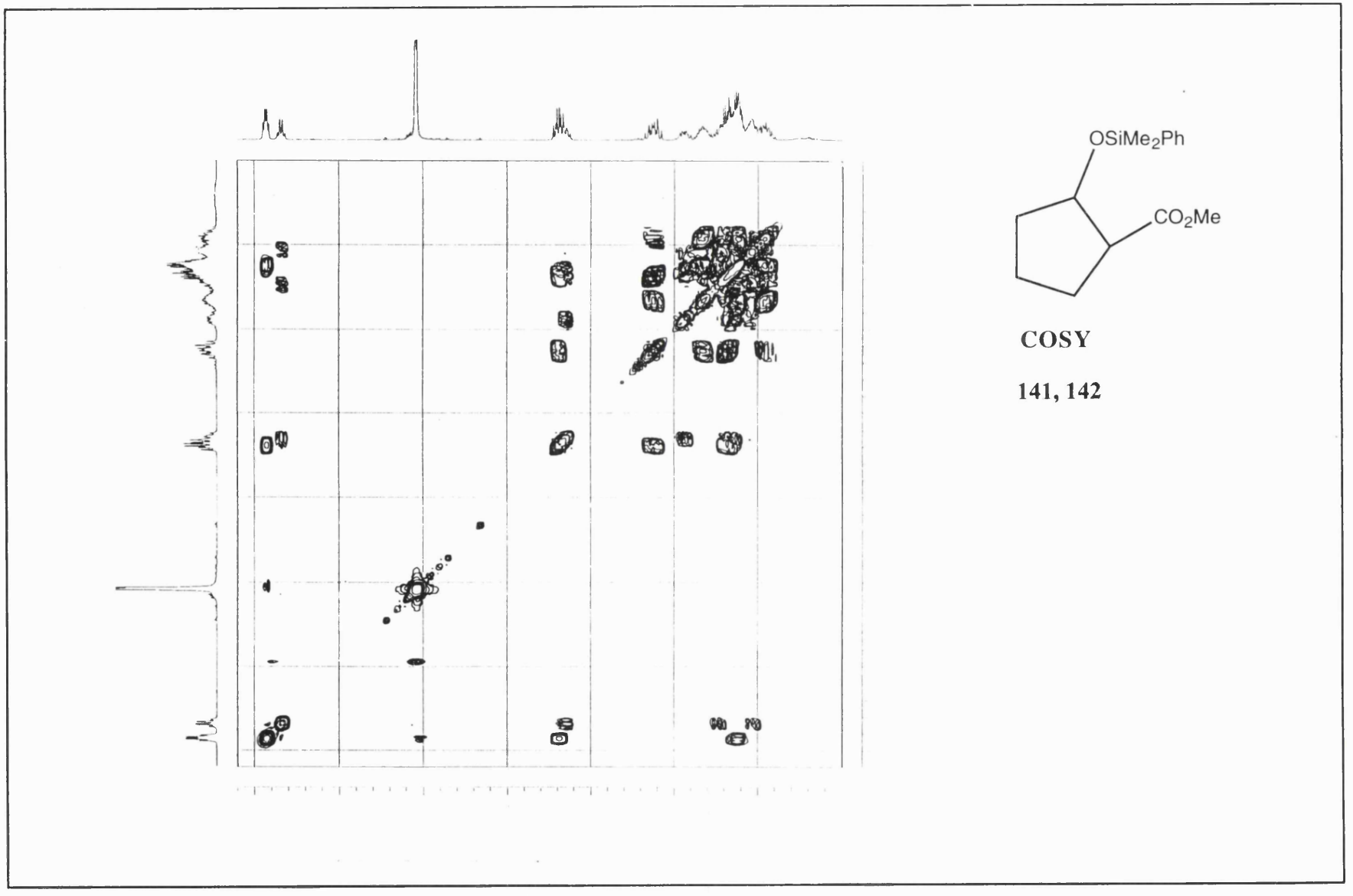

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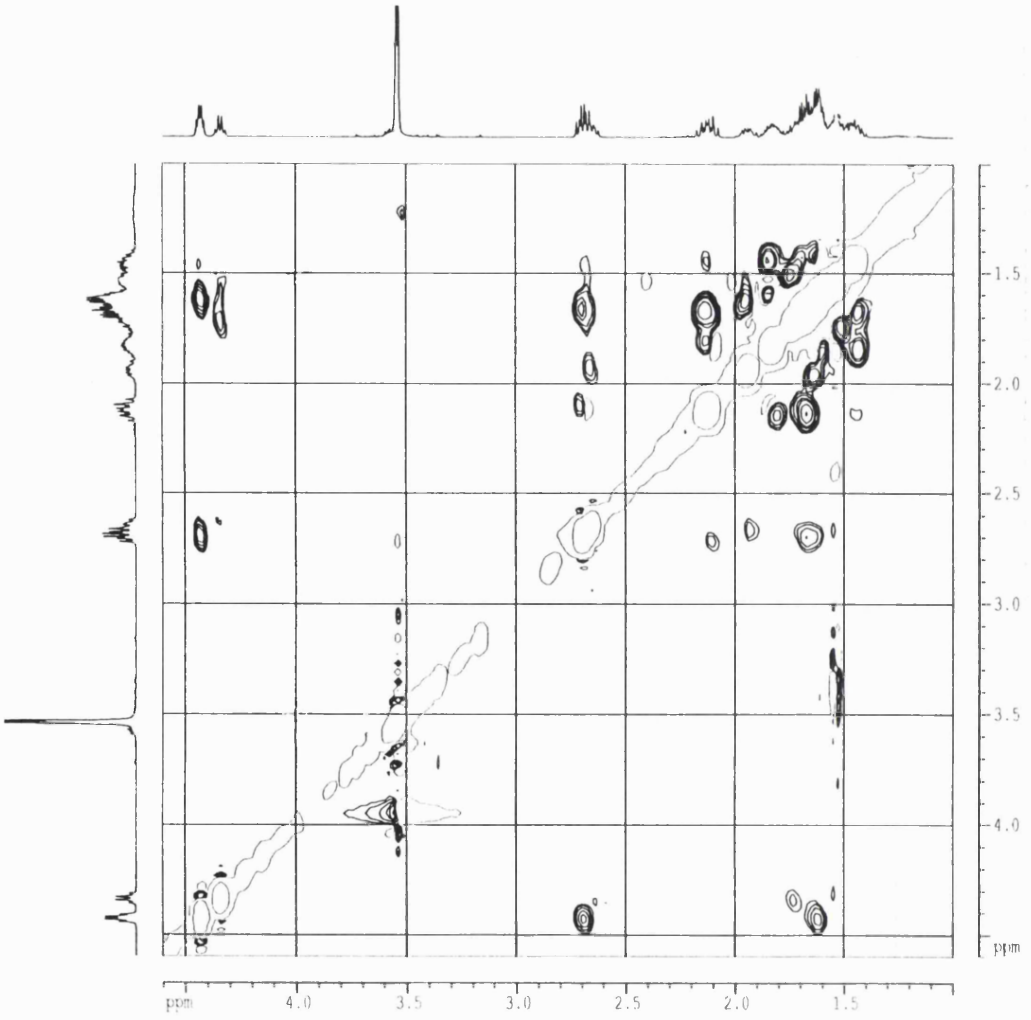

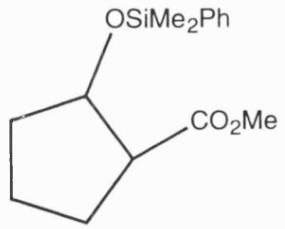

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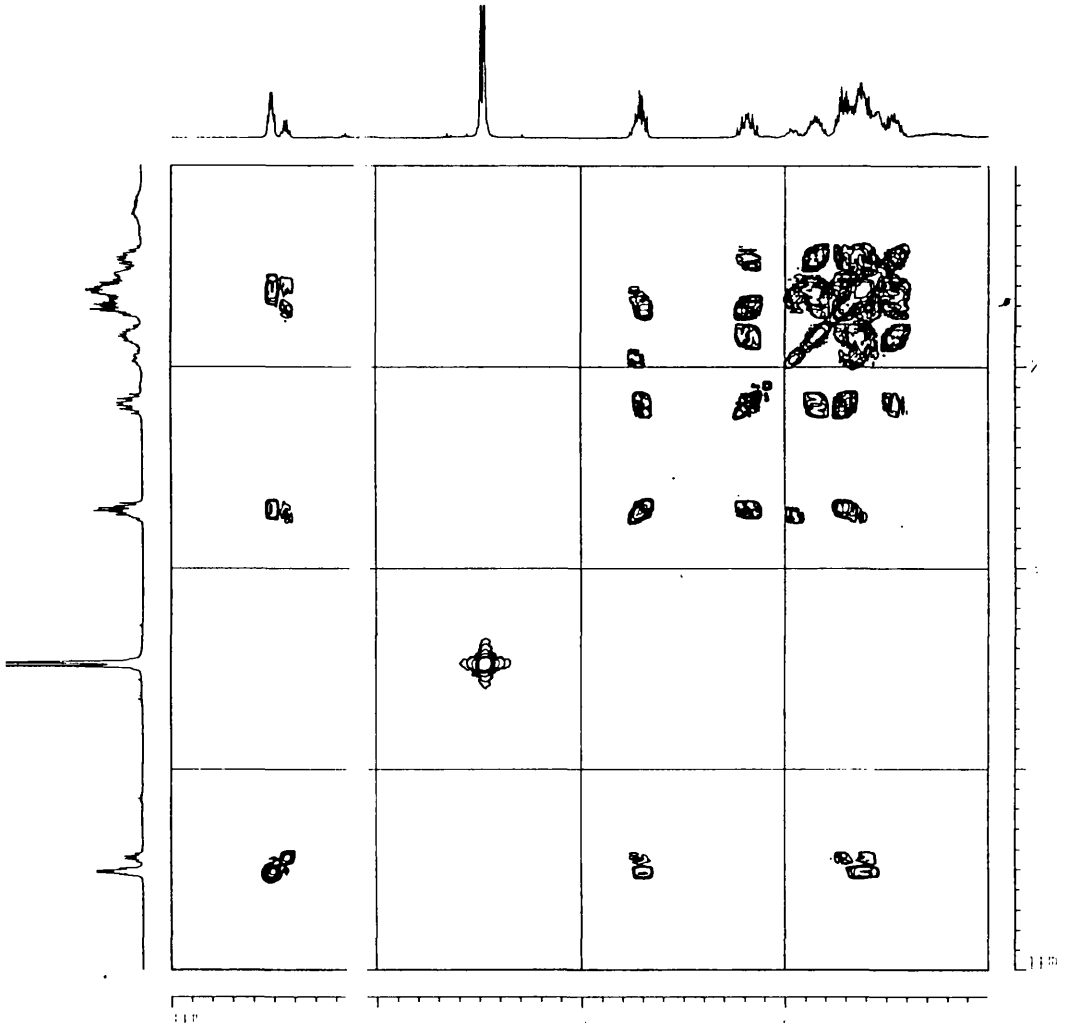

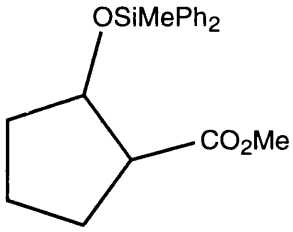

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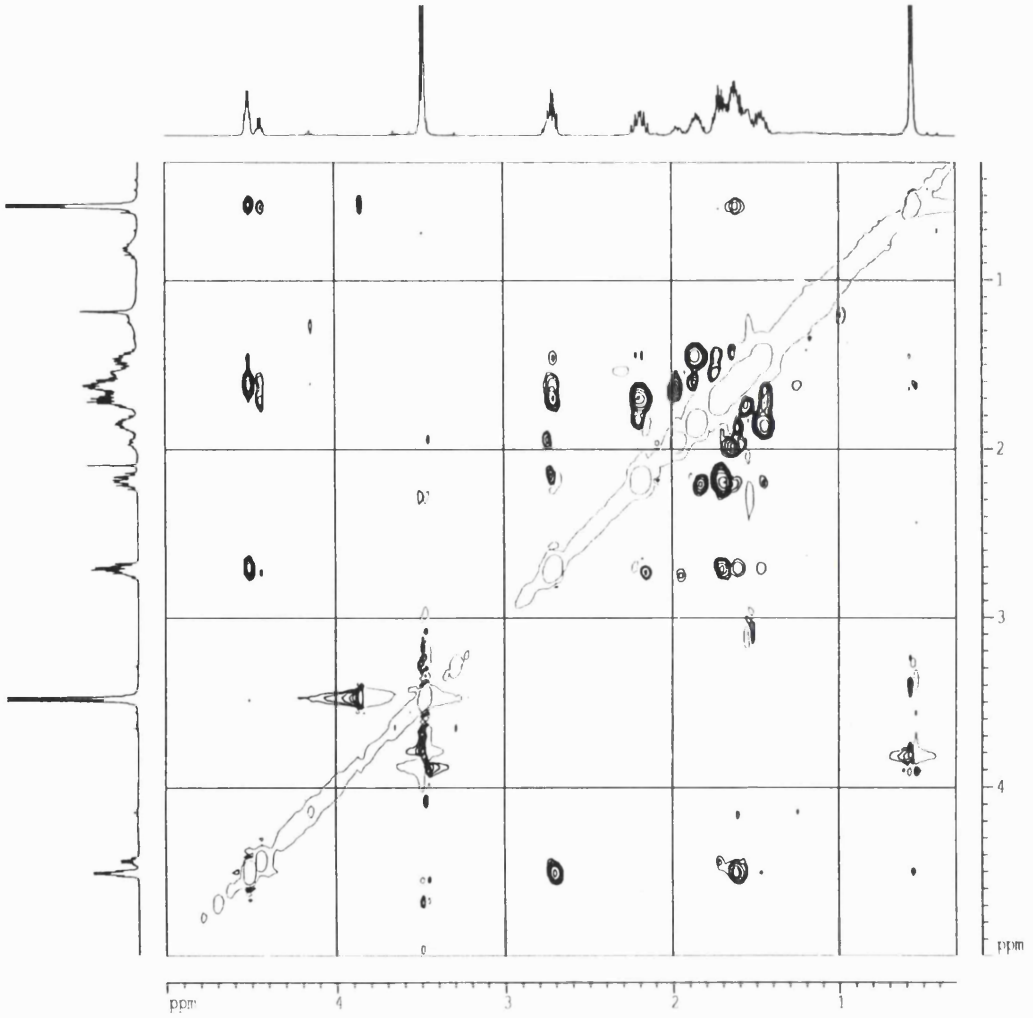

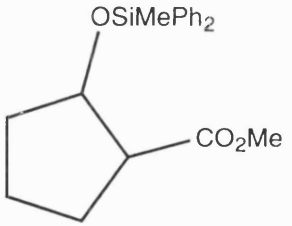

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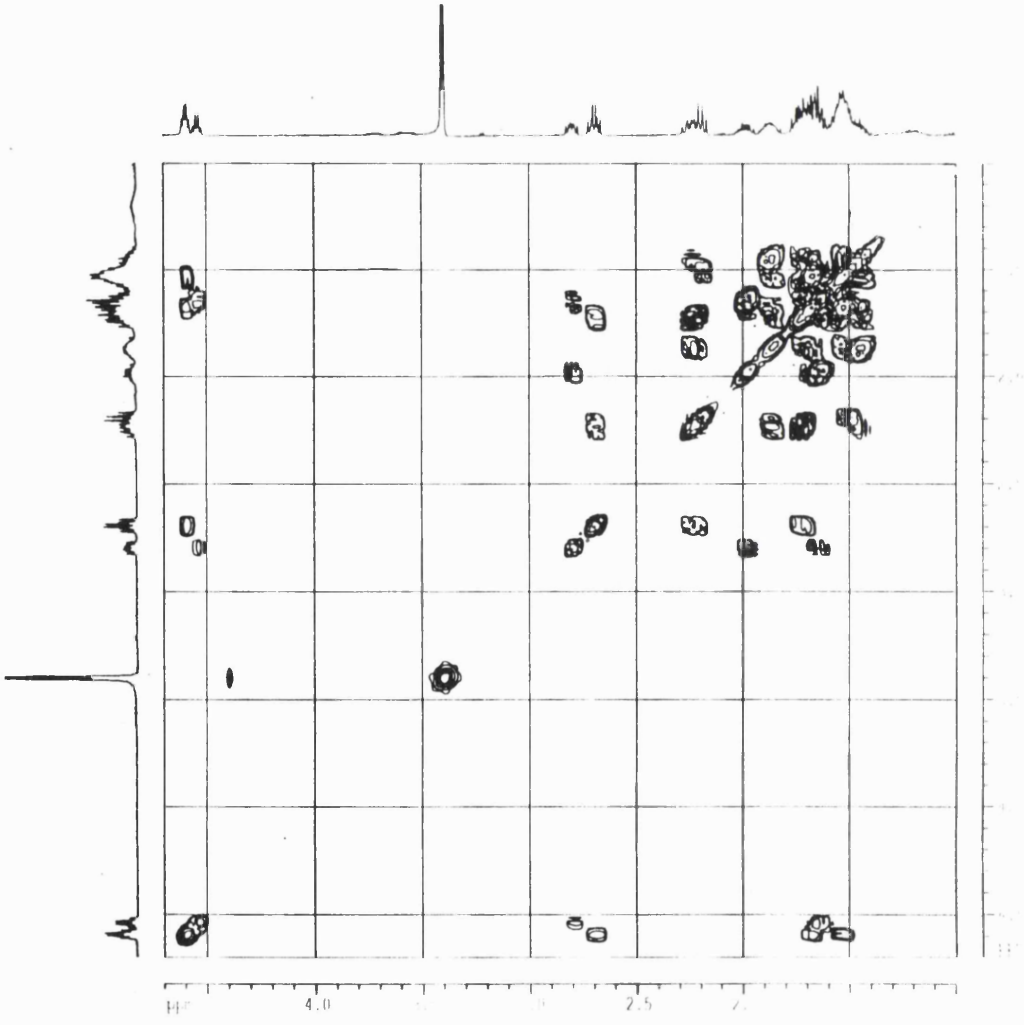

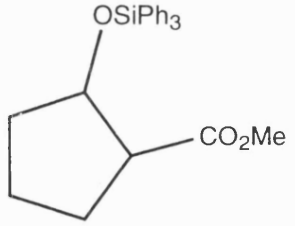

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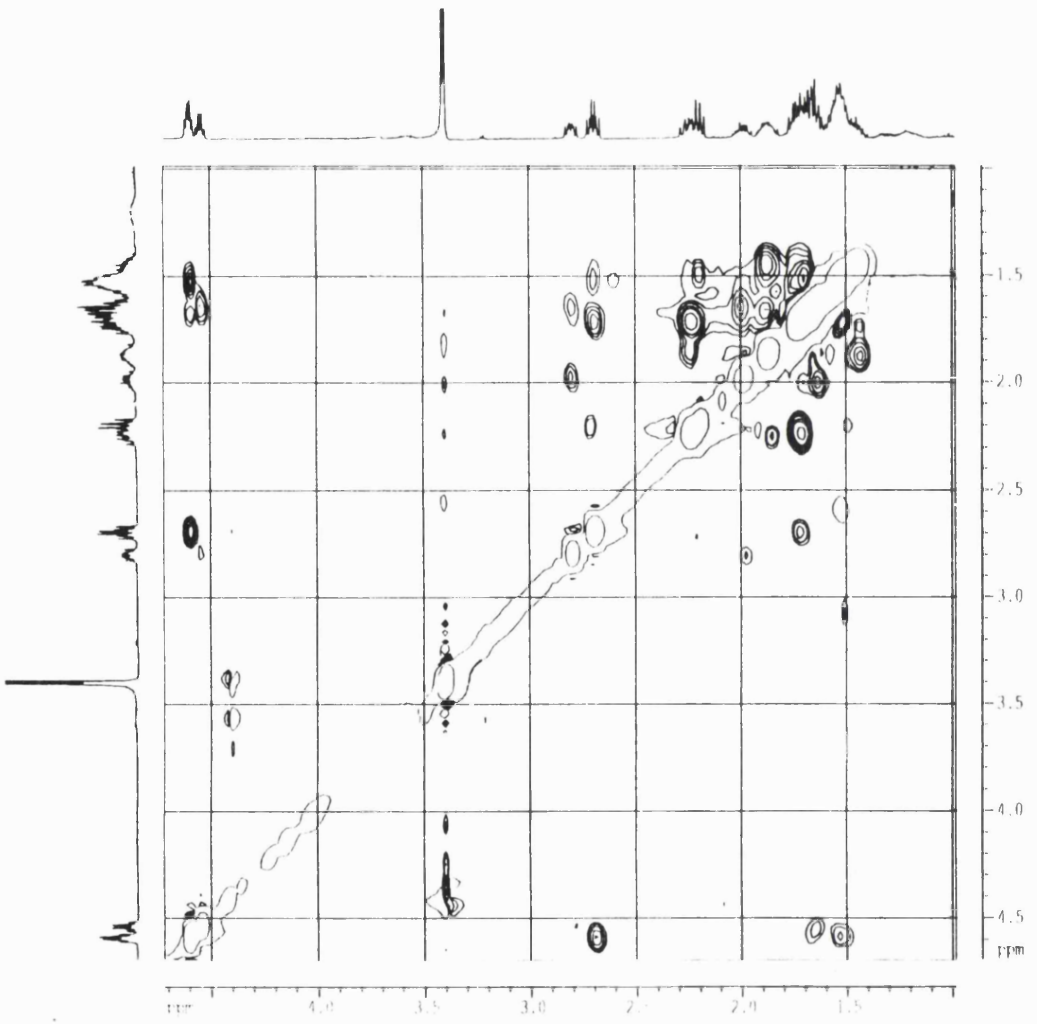

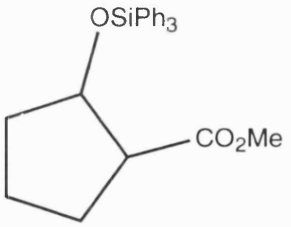

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