Novel rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction

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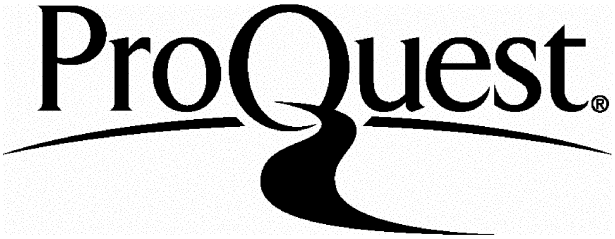

A mis padres y a mi hermana

Abstract

This thesis focuses on the study of the scope and generality of a novel atom efficient intramolecular transition metal catalysed tandem reductive-aldol cyclisation as a general stereoselective route for the preparation of carbocyclic rings from 6-oxo-2-hexenoates and related homologues. The thesis is divided into three major sections.

The introductory review is divided into two sections. The first of these presents a general overview covering the significance of biologically active carbocyclic nucleosides and their previous asymmetric synthesis, with special attention devoted to asymmetric methods for the construction of the carbocyclic moiety. In a second section, some recent developments in the intermolecular reductive aldol reaction and related transformations for the preparation of carbocycles are described.

The second chapter opens with a preliminary study on the optimisation of the hydrosilylation-intramolecular aldol reaction conditions that lead to the best yields and levels of stereocontrol. The results of screening a series of silanes and rhodium catalysts was effectuated and revealed several features of interest. Subsequent sections then describe the synthesis of the cyclisation precursors, comprising the development of a simple atom efficient route to 5,5-disubstituted-6-oxo-2-hexenoates. The scope of our novel methodology was then investigated, with special emphasis in the influence of the substitution pattern on reactivity and selectivity as well as in the tolerance of heteroatomic substituents. The feasibility of larger ring sizes was also assessed, as was the possibility of replacing the aldehyde functionality in the substrate by alternative electrophiles. The related hydroboration-intramolecular aldol reaction was then investigated and a variety of alternative catalysts containing a transition metal other than rhodium were evaluated. This section is followed by some mechanistic investigations and a detailed discussion on the mechanism and the stereochemical outcome of this transformation. Finally, the generality of the method was evaluated in the synthesis of the carbocyclic moiety of two biologically active carbocyclic nucleosides.

The concluding section provides a formal description of the experimental results and procedures together with appropriate references.

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Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
acac	Acetylacetonate
An	Anisole
APCI	Atmospheric pressure chemical ionisation
aq	Aqueous
atm	Atmospheres
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphtyl
Bn	Benzyl
BnBr	Benzyl bromide
BnCl	Benzyl chloride
BnOH	Benzyl alcohol
b.p.	Boiling point
br	Broad
Bu	Butyl
BuOH	Butanol
cat.	Catalytic
CBz	Benzyloxycarbonyl
Chiraphos	(2*S*, 3*S*)-Bis(diphenylphosphino)butane
CI	Chemical ionisation
COD	1,5-Cyclooctadiene
con	Concentrated
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Doublet or days as appropriate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane

DCM	Dichloromethane
dd	Double doublet
ddd	Double doublet doublet
d.e.	Diastereoisomeric excess
DIBAL	Di-*iso*-butylaluminium hydride
DIPEA	Di-*iso*-propylethylamine
Diphos	1,2-Bis(diphenylphosphino)ethane
DMAP	4-(Dimethylamino)pyridine
DMF	*N,N*-Dimethyl formamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dpm	Dipivaloylmethane
dppb	1,4-Bis(diphenylphosphino)butane
dq	Doublet quartets
dt	Doublet triplets
Duphos	1,2-Bis(2,5-dimethylphospholano)benzene
e.e.	Enantiomeric excess
EI	Electronic impact
Eq	Equation
equiv	Molar equivalent
e.r.	Enantiomeric ratio
ES	Electrospray
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast atom bombardment
g	Grams
G.C.	Gas chromatography
h	Hour(s)
hυ	Light
Hz	Hertz

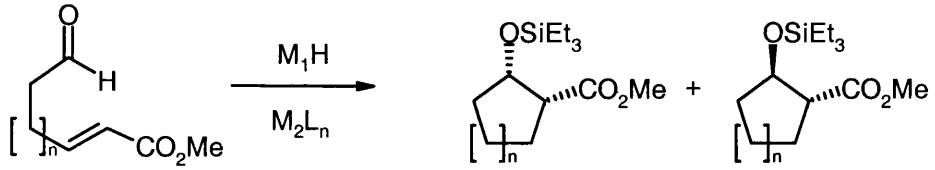
i	*iso*
IR	Infrared
J	Coupling constant
L	Unspecified ligand
LDA	Lithium di-*iso*-propylamide
Lit	Literature value
m	Multiplet
m-CPBA	*meta*-Chloro-perbenzoic acid
Me	Methyl
MeOH	Methanol
mg	Milligram(s)
min	Minutes
mL	Millilitre(s)
mm Hg	Millimetres of mercury
m.p.	Melting point
mol	Moles
mmol	Millimoles
MS	Molecular sieves
n	*neo*
NMO	*N*-Methylmorfoline *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhäuser effect
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PMP	*p*-Methoxyphenyl
p	*para*
P	Protecting group
PE	Petroleum ether
Ph	Phenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridine
q	Quartet
R	Unspecified carbon substituent

Rf	Retention factor
r.t.	Room temperature
s	Singlet
S	Solvent
t	Triplet or *tert* as appropriate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
t.l.c.	Thin layer chromatography
Tol	Tolyl
TPAP	Tetrapropylammonium perruthenate
Tr	Triphenylmethyl
Ts	*para*-Toluenesulfonyl
TsOH	*para*-Toluenesulfonic acid
UV	Ultraviolet
W	Unspecified group
Z	Unspecified group

Chapter I Introduction

I Preface

The present thesis is concerned with a study of the scope and generality of a novel atom efficient transition metal mediated tandem hydrometallation-intramolecular aldol reaction as a general stereoselective method for the construction of functionalised carbocyclic rings from 6-oxo-2-hexenoates and related homologues (Scheme 1).



M_1 = main group metal
M_2 = transition metal
L = ancillary ligand

Scheme 1

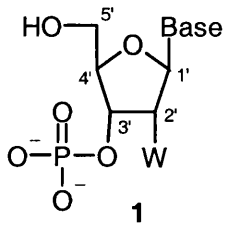
Within this framework, application of the methodology developed towards construction of the cyclopentanoid core of biologically active carbocyclic nucleosides was considered to be an especially important objective.

In consequence, this introductory review will comprise two distinct overviews, one concerned with the approaches taken in previous asymmetric syntheses of carbocyclic nucleosides, with special emphasis on asymmetric methods for the construction of the carbocyclic moiety, and the second with recent developments in the intermolecular reductive aldol reaction and related applications for carbocyclic ring formation.

I.1 Carbocyclic nucleosides

I.1.1 Structure

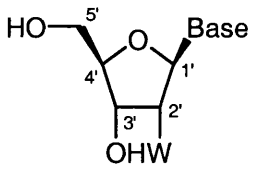
The past two decades have witnessed great advances in research on the nucleic acids and their components, both in synthetic organic chemistry and in related fields. Nucleic acids occur in every living cell; they direct the synthesis of proteins and are responsible for the transfer of genetic information. Like proteins they are polymers of high molecular weight but their repeating unit is a mononucleotide rather than an amino acid. A nucleotide **1** consists of a nitrogen-containing base and a 5-carbon sugar with one or more phosphate groups (Figure 1).



Ribose W=OH
2-Deoxyribose W=H

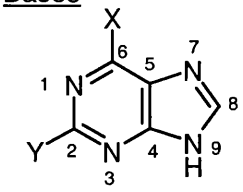
Figure 1

The nucleosides **2** are carbohydrate derivatives in which the purine and pyrimidine bases are linked to the sugar in a β-*N*-glycosyl bond (Figure 2). It is said to be β if the base is *cis* to the 4'-hydroxymethyl group and α if it is *trans* to this function. In the naturally occurring nucleosides the sugar is either D-ribose or 2-deoxy-D-ribose.

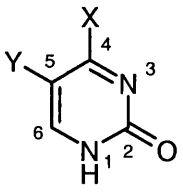


Ribose W=OH
2-Deoxyribose W=H

Bases



Purines

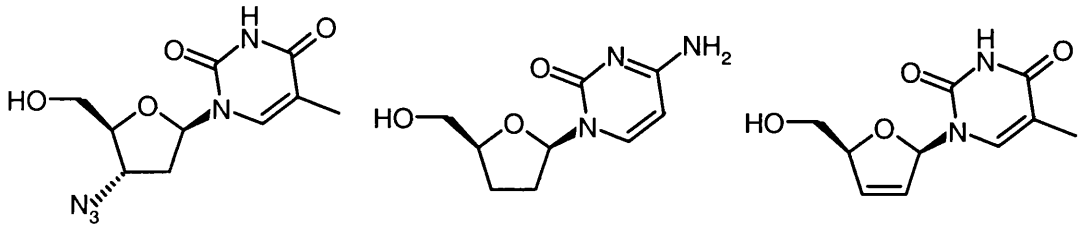


Pyrimidines

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

Figure 2

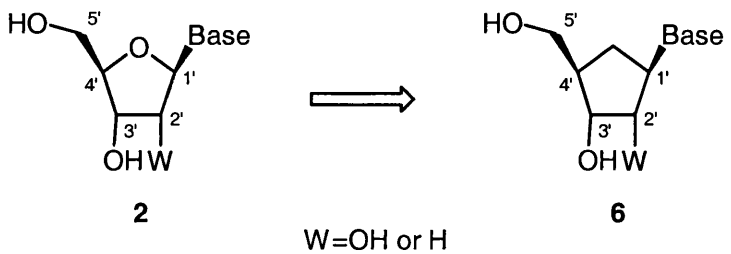
The potential value of nucleosides as anti-viral, fungicidal and anti-cancer agents[1] has stimulated the search not only for more effective methods of nucleoside synthesis, but also in particular, the synthesis of nucleoside analogues.[2],[3] Among them, AZT (3'-azido-2',3'-dideoxythymidine) **3**, ddC (2',3'-dideoxycytidine) **4** and d4T (2',3'-didehydro-2',3'-dideoxythymidine) **5** are three nucleosides approved by the Food and Drug Administration (FDA) for the treatment of the human immunodeficiency virus (HIV) as reverse transcriptase inhibitors (Figure 3).



3 **4** **5**

Figure 3

However, the clinical application of these nucleosides is greatly limited because they are also substrates for phosphorilases, enzymes which cleave the *N*-glycosidic bond between the heterocyclic moiety and the sugar.[4] In order to avoid these enzymatic degradations and to improve the antiviral properties of nucleosides, a large number of modifications have been carried out on both the sugar and the heterocycle. The replacement of the furanose oxygen atom by a methylene group leads to carbocyclic nucleoside analogues of type **6** (Scheme 2). The direct result of this isosteric replacement is that the carbocyclic nucleoside possesses enhanced activity, increased enzymatic resistance,[5] better metabolic stability[6] and a decrease in the toxicity.[7] Furthermore, the comparatively higher lipophilicity of the carbocyclic nucleoside is potentially beneficial for increasing oral efficiency and cell wall penetration.

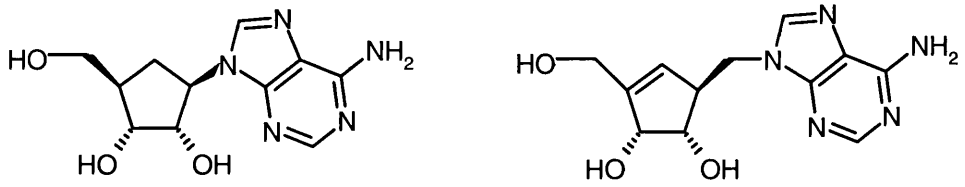


2 **6**

W=OH or H

Scheme 2

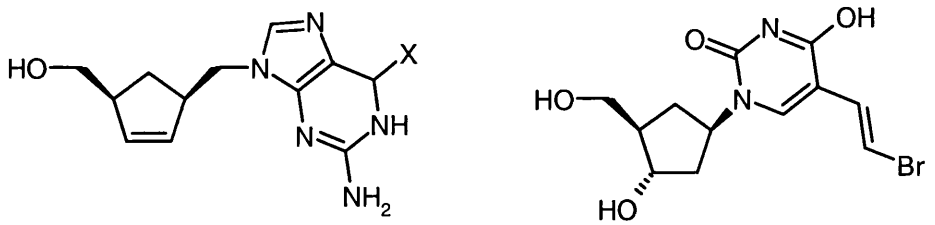
Since the first racemic synthesis of the carbocyclic analogue of adenosine by Shealy[8] and Clayton in 1966 and the subsequent isolation of its (-)-enantiomer, the antifungal antibiotic aristeromycin[9] **7** from *Streptomyces citricolor,* interest in this class of compounds has grown rapidly. More recently, another natural product neplanocin A[10] **8**, was isolated from *Actinoplanacea ampullariella* and has also been shown to exhibit selective antitumor activity (Figure 4).



7 **8**

Figure 4

Subsequently, other synthetic carbocyclic nucleosides with important therapeutic properties were discovered. Particularly, carbovir[11] (*C*-2',3'-didehydro-2',3'-dideoxyguanosine) **9** and the structurally related abacavir (1592U89) **10**, emerged as potent and selective anti-HIV agents, the causative agent for the Acquired Immunodeficiency Syndrome (AIDS), while the carbocyclic analogue of BVDU[12] (5-bromovinyl-2'-deoxyuridine) **11** has been shown to be a highly potent and selective anti-HSV-1 (Herpes Simplex Virus) and anti-VZV (Varicella Zoster Virus) agent (Figure 5).



9 X=O

11

10 X= NH

Figure 5

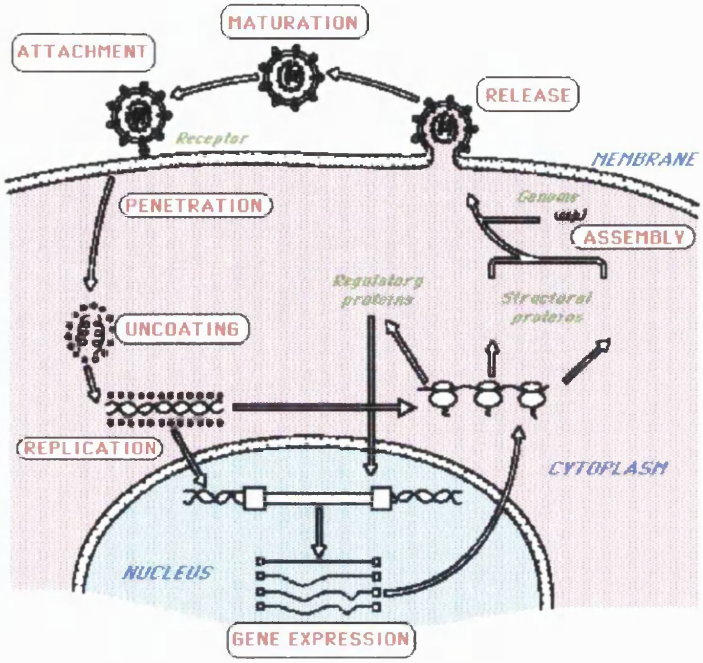
Although promising new antiviral agents have been discovered, the search for potent inhibitors of a variety of viral infective agents continues.[13] There is a need for new inhibitors of HIV, HSV types 1 and 2, HCMV (Human CytoMegalo Virus), VZV, EBV (Epstein-Barr Virus) and HBV (Hepatitis B Virus). Furthermore, owing to their potential use as therapeutic agents, there is an intense search for efficient synthetic approaches to carbocyclic nucleosides analogues, and most importantly, for their enantioselective synthesis.

I.1.2 Mode of action

Viruses have long been recognised as the cause of a wide variety of infections in animals and humans, ranging from the common cold to Acquired Immunodeficiency Virus (AIDS).[14] A virus may be considered to be an organism consisting of a nucleic acid core (the genome) surrounded by a protein-containing coat. It reproduces exclusively within the infected host cell, which supplies the energy and building materials for the production of a new viral particle.

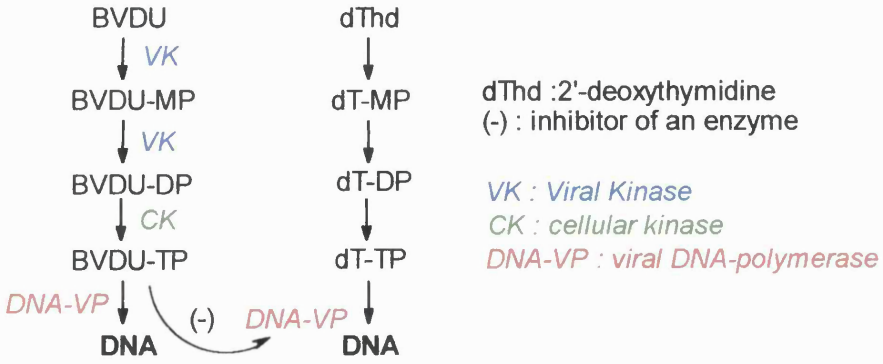
Despite intensive efforts to discover drugs that may be of value in the treatment of human viral infections, such infections have been singularly resistant to chemotherapy. The intracellular and intimate relationship between viral and host functions makes it difficult to destroy a virus without irreparable damage of the host cell. An understanding of the viral replicative cycle[15] can give us some insight into possible areas of selective chemical interference that lead to successful chemotherapy (Scheme 3):

i. **Adsorption** of the virion to the cellular membrane by specific receptors of the host cell.
ii. **Penetration** and **uncoating**.
iii. **Expression of the genome and synthesis of proteins**. Viral nucleic acid is replicated within the host cell resulting in synthesis of viral proteins. Some of these proteins are enzymes for viral replication; others are the building blocks for the capsid.
iv. **Assembling** of the new virion from the replicated viral DNA and the newly synthesised coat proteins.
v. **Release of the virus** by lysis of the host cell or budding.



Scheme 3

The main targets for the carbocyclic nucleoside analogues in anti-viral chemotherapy are the intracellular elements of replication of the genome and the synthesis of the proteins. The selectivity of these compounds depends on their preferential activation (phosphorylation) by a viral enzyme. For example, *C*-BVDU **11** is mono and diphosphorylated by viral kinases into *C*-BVDU-DP. After triphosphorylation by means of a cellular enzyme, *C*-BVDU-TP inhibits viral DNA-polymerases through the replication step of the virus. It acts as a competitive inhibitor of the natural substrate dTTP (Scheme 4).



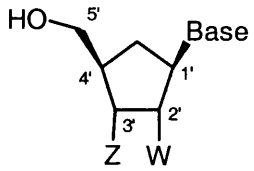
Scheme 4

I.2 Existing stereoselective methodology for the synthesis of *C*-nucleosides

I.2.1 Introduction

Without exception, all syntheses of carbocyclic nucleosides, both in racemic and enantiomerically pure form, have been carried out by prior formation of a functionalised cyclopentane followed either by coupling of a purine or pyrimidine heterocycle or an appropriate precursor. The functionalised cyclopentane, by analogy with the β-D-nucleosides, must have certain structural features that will direct the design of the precursor **12** (Figure 6). It must have:

i. A hydroxymethyl group or derivative in the 4' position.
ii. A group that could react with a precursor of the heterocycle in the 1' position.



12

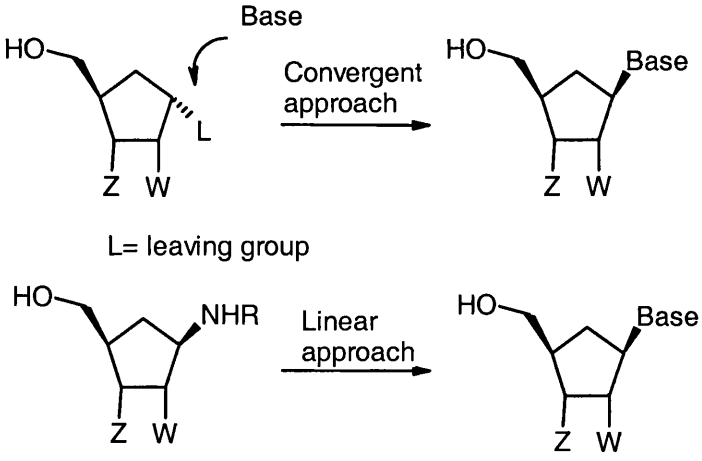
Figure 6

The preparation of carbocyclic nucleosides requires the following two crucial elements, both of which will be discussed briefly, *viz.*,

i. The construction or introduction of the heterocyclic base in a highly regio- and stereoselective manner.
ii. The stereocontrolled synthesis of the carbocyclic unit containing appropriate functional groups.

I.2.2 Coupling procedures of the heterocyclic moiety

In general, there are two fundamental approaches for the introduction of a purine or a pyrimidine base onto the carbocycle (Scheme 5):



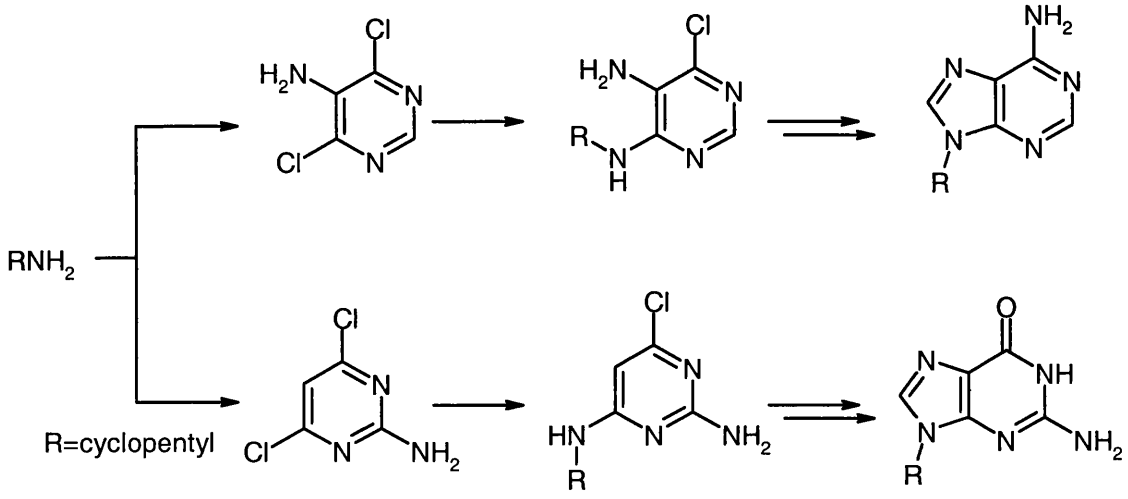
Scheme 5

In the **convergent approach** the intact heterocyclic base is directly attached to an appropriately functionalised carbocyclic ring by nucleophilic substitution. Direct coupling can then be accomplished by several methods:

i. Nucleophilic displacement of a halide ion or activated α hydroxyl group such as mesylate, tosylate or triflate.[16]
ii. Ring opening of an epoxide[17] or cyclic sulfate.[18]
iii. By a Mitsunobu coupling with a cycloalkanol.[19]
iv. Michael addition to an activated cyclopentene.[20]
v. Palladium (0) catalysed displacement of an allylic ester or carbonate.[21]

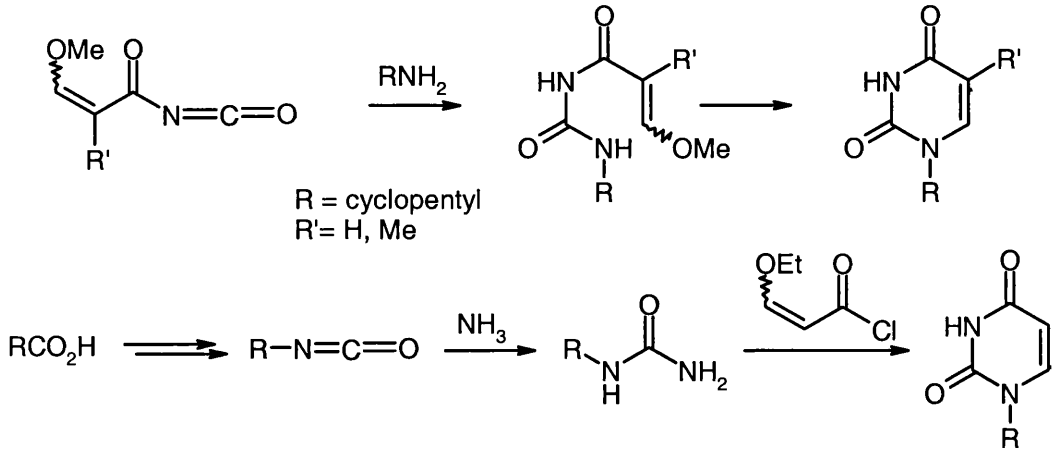
Direct coupling of the heterocyclic moiety provides a more convergent and highly useful strategy for the synthesis of carbocyclic nucleosides, but introduces the problem of regioselectivity with respect to attack by the base. With purines, attachment at the N9, N7, N3 nitrogens is possible as is often observed.

In the **linear approach** the heterocyclic base is synthesised from a cyclopentanoid possessing a 1'-β-amino function, in which this amino group then becomes the N9 of a purine moiety or the N1 of a pyrimidine. Alternatively, a 1'-β-acidic function may be used *via* the Curtius Schmidt reaction to introduce this functionality. Purines are generally constructed *via* a Traube type synthesis which provides access to both adenosine[22] and guanosine[23] derivatives from 5-amino-4,6-dichloropyrimidine or 2-amino-4,6-dichloropyrimidine respectively (Scheme 6).



Scheme 6

On the other hand, pyrimidines can be prepared by the method reported by Shaw and Warrener,[24] which involves reaction of the appropriate isocyanate with the cyclopentylamine (Scheme 7). Alternatively, pyrimidines can be synthesised from the apropriate carboxylic acid *via* a Curtius degradation.[25] The isocyanate is then reacted with ammonia to produce the urea derivative from which the base is constructed.

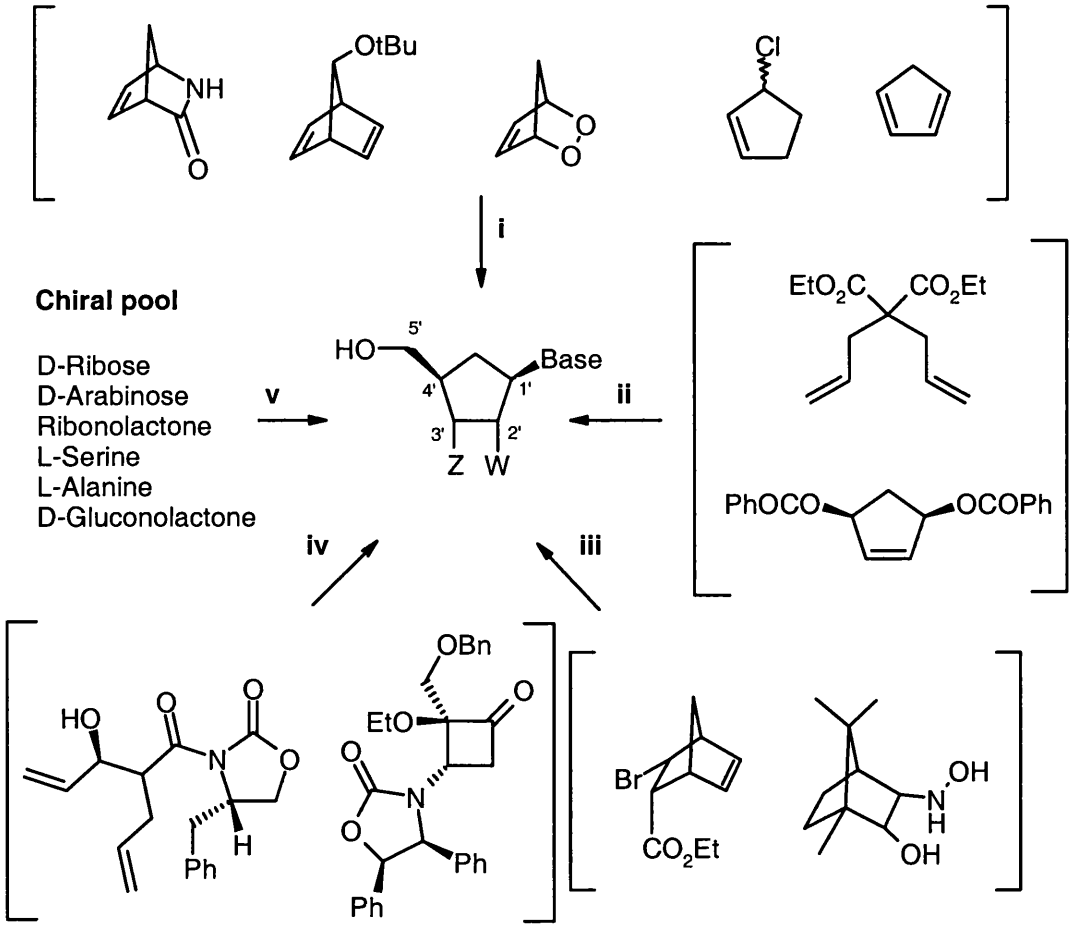


Scheme 7

I.2.3 Existing stereoselective syntheses of functionalised cyclopentanes

The majority of the literature approaches to ribofuranosyl carbocyclic analogues rely on the use of cyclopentadiene as the source of the carbocyclic "sugar". Using cyclopentadiene as starting material is highly advantageous since the five-membered

carbocyclic ring is already intact and also because it is a very inexpensive starting material. In particular, Diels-Alder methodology has received considerable attention as a consequence of the fixed configuration at *C*-1' and *C*-4' in the resultant rigid bicyclic systems providing the necessary cisoid stereochemistry for the 1' and 4' substituents of the β-D-nucleoside. However, in order to accomplish an enantioselective synthesis, introduction of chirality into the carbocyclic ring is also necessary and this aspect constitutes the main synthetic challenge. Various strategies have been developed to synthesise the carbocyclic subunit of this class of compounds in an enantiomerically pure form. They can be classified into five main groups (Scheme 8):



Scheme 8

i. Enantioselective approaches based on enzymatic or chemical resolution.

ii. Catalytic asymmetric desymmetrizations.

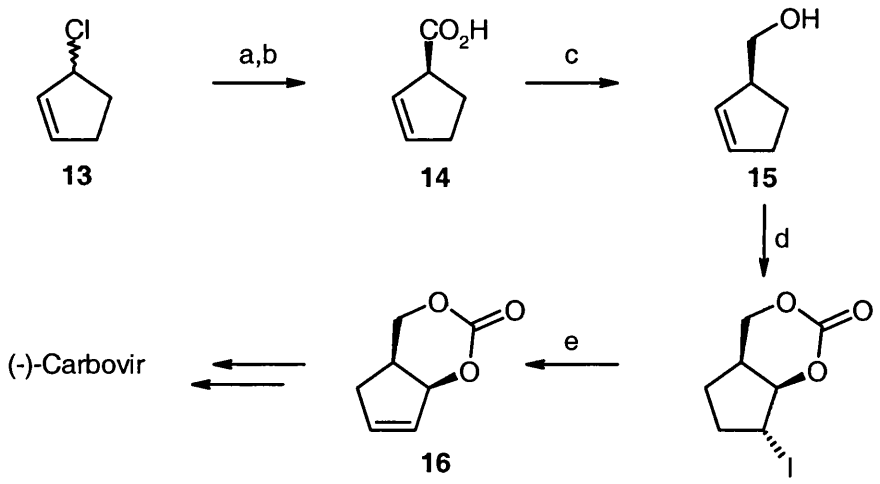
iii. Enantioselective synthesis through asymmetric synthetic methods.

iv. Auxiliary based asymmetric reactions.

v. Synthesis from the chiral pool of carbohydrates and aminoacids.

I.2.3.1 Enantioselective approaches based on enzymatic or chemical resolution

Both enzymatic resolution of *meso* intermediates and racemic mixtures as well as chemical resolution by preparation of diastereomeric salts or chromatographically separable diastereomers have been used in the enantioselective synthesis of carbocyclic nucleosides. Scheffold[26] has described a synthesis of (-)-carbovir *via* the cyclic carbonate **16** starting from 1-chloro-2-cyclopentene **13** (Scheme 9). After formation of the corresponding carboxylic acid, crystallisation of the α-phenylethylamine salt of acid **14** gave, after reduction, the alcohol **15** (98% e.e.). Iodocarbonation followed by elimination of the iodide provided the cyclic carbonate **16**, which was converted to (-)-carbovir through a palladium catalysed substitution with 2-amino-6-chloropurine and subsequent hydrolysis.

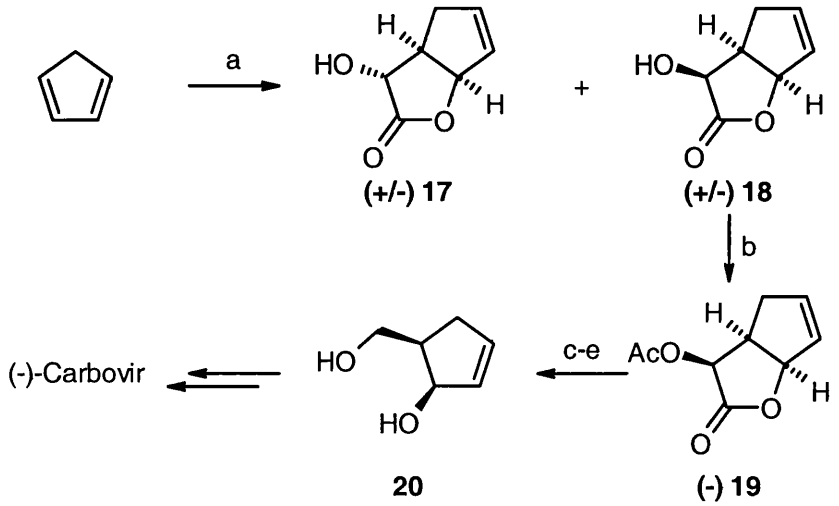


a) Mg, then CO_2, 85%. b) (-)-α-phenylethylamine; recrystallisation, 16% overall of (-)-enantiomer. c) $LiAlH_4$, Et_2O, 64%. d) BuLi, then CO_2, then I_2, THF, 53%. g) DBU, CO_2, toluene, 90°C, 63%.

Scheme 9

The bicyclic lactones **17** and **18**, products of the Prins reaction between cyclopentadiene and glyoxalic acid, have also been used in enantioselective approaches to aristeromycin and carbovir (Scheme 10).[27] Thus, diastereomeric lactones **17** and **18** were firstly separated by chromatography. The major isomer **18** was resolved enzymatically by esterification with vinyl acetate and *Pseudomonas flourescens* lipase to afford acetate **19** (95% e.e.). Reduction of the lactone, oxidative

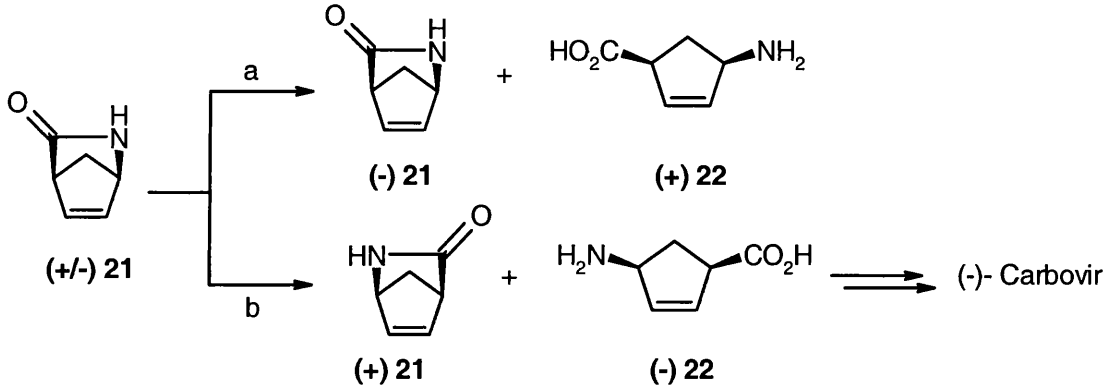
cleavage of the resultant triol and further reduction afforded diol **20**, which was converted into the corresponding carbocyclic nucleoside after several steps.



a) Glyoxalic acid, H_2O, 4d, 65%. b) Vinyl acetate, *Pseudomonas flourescens* lipase, 40% conversion, 95% e.e. c) $LiAlH_4$, THF. d) $NaIO_4$, Et_2O-H_2O. e) $NaBH_4$, MeOH, 50% 3 steps.

Scheme 10

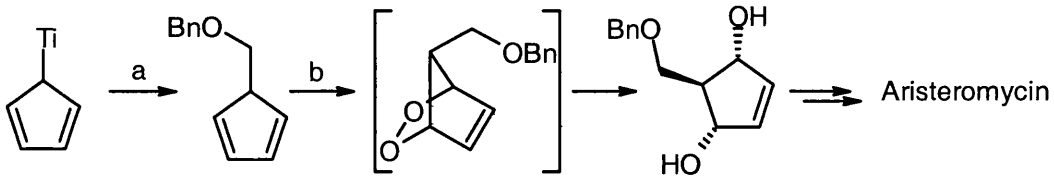
As we have mentioned, rigid bicyclic systems obtained by Diels-Alder approaches have been widely used in the synthesis of carbocyclic nucleosides. For example, the bicyclic lactam **21** has been identified as a key building block to aminocyclopentyl precursors (Scheme 11).[28] It is readily prepared from cyclopentadiene and tosylcyanide followed by aqueous hydrolysis. Kinetic resolution of lactam **21** by two different enzymatic systems then lead to either enantiomer and the enantiomeric ring opened amino acid **22**.[29]



a) *Pseudomonas flourescens*. b) *Aureobacterium.*

Scheme 11

Hetero Diels-Alder cycloadditions with singlet oxygen and cyclopentadiene derivatives have also been reported (Scheme 12).[30] Cleavage of the [O-O] bicyclic system **23** affords 2-cyclopenten-1,4-diol **24** which after a series of chemical steps leads to the carbocyclic nucleoside aristeromycin. 2-Cyclopenten-1,4-diol has proven to be a key precursor of a series of carbocyclic nucleosides.[17],[31] The corresponding monoacetate can be obtained in enantiomerically enriched form by enzymatic resolution.



23 **24**

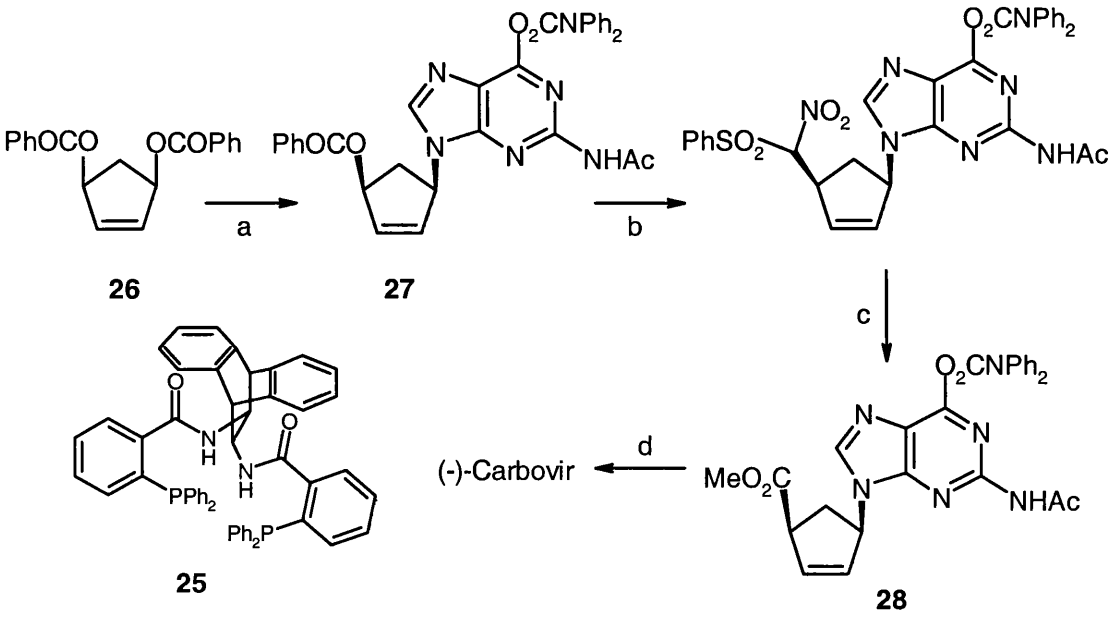
a) $BnOCH_2Cl$. b) $^1O_2$, hυ.

Scheme 12

Finally, several approaches rely on the use of a norbornadiene derivative as a key synthon to carbocyclic nucleosides.[32] The advantage is the ready availability of the starting materials in large quantities. However, the necessity of cleaving the bicyclic ring and the requirement to remove one carbon from the cleavage product increases the overall number of steps through this approach.

I.2.3.2 Catalytic asymmetric desymmetrizations

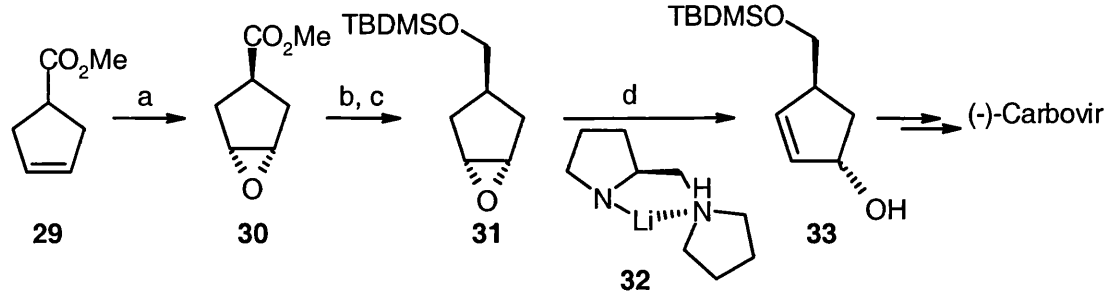
Recently, Trost has reported an outstanding approach to (-)-carbovir in four steps *via* a highly imaginative palladium-catalysed asymmetric desymmetrization of a *meso*-diester with a nucleophilic base using the chiral ligand **25**.[33] Thus, the *meso*-dibenzoate **26** was reacted with the heterocyclic base in the presence of $(\eta^3\text{-}C_3H_5PdCl)_2$ and ligand **25** to afford the desired product **27** (>98% e.e.). Treatment of **27** with phenylsulfonylnitromethane under Pd(0)-catalysed conditions gave, after chemoselective oxidative cleavage, the ester **28**. Subsequent reduction followed by an aqueous ammonia work-up afforded (-)-carbovir (Scheme 13).



a) (η^3-$C_3H_5PdCl)_2$, ligand, base, THF/DMSO, 0°C, 8h, 59%. b) Phenylsulfonylnitromethane, Et_3N, THF, 1.5 mol% Pd(0) cat., PPh_3, rt, 99%. c) Tetrabutylammonium-oxone, $MeOH/CH_2Cl_2$, 71%. d) $Ca(BH_4)_2$, THF, then aq ammonia, 61%.

Scheme 13

Another example of asymmetric desymmetrization has been reported by Asami (Scheme 14).[34] The ester **29**, available from dimethyl malonate and 1,4-dichloro-*cis*-butene, was converted into epoxide **30**, followed by reduction of the ester and protection of the resulting alcohol as a silyl ether. The *meso*-epoxide **31** was desymmetrised upon exposure to chiral lithium amide **32**, affording allylic alcohol **33** in 83% e.e. Mitsonobu coupling of 2-amino-6-chloropurine led to (-)-carbovir after removal of the silyl ether and subsequent hydrolysis.

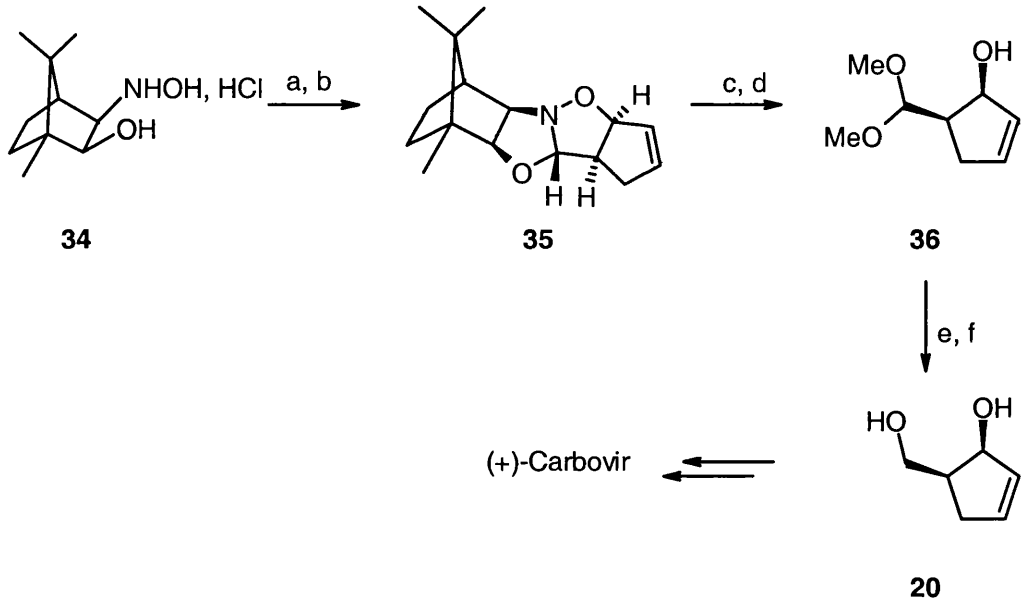


a) *m*-CPBA, C_6H_{12}, 91%, 79% *trans*, 21% *cis*. b) $LiAlH_4$, 76%. c) *t*-$BuMe_2SiCl$, imidazole, DMF, 100%. d) 1.5 equiv **31**, THF, DBU, 25°C, 74%, 83% e.e.

Scheme 14

I.2.3.3 Enantioselective synthesis through asymmetric synthetic methods

More recently, asymmetric synthetic methods such as asymmetric cycloadditions have been employed for the enantioselective synthesis of carbocyclic nucleosides. Langlois has reported a concise approach to (+)-carbovir based on an asymmetric cycloaddition (Scheme 15).[35] The bicyclic hydroxylamine hydrochloride **34** was synthesised from borneol in several steps. Reaction with trimethylorthoformate gave an oxazoline *N*-oxide, which was subsequently reacted with cyclopentadiene to afford the cycloadduct **35** as the only product. After oxidation of the nitrogen atom and treatment with acidic methanol, acetal **36** was readily converted into diol **20** and subsequently into (+)-carbovir by the well-established route.

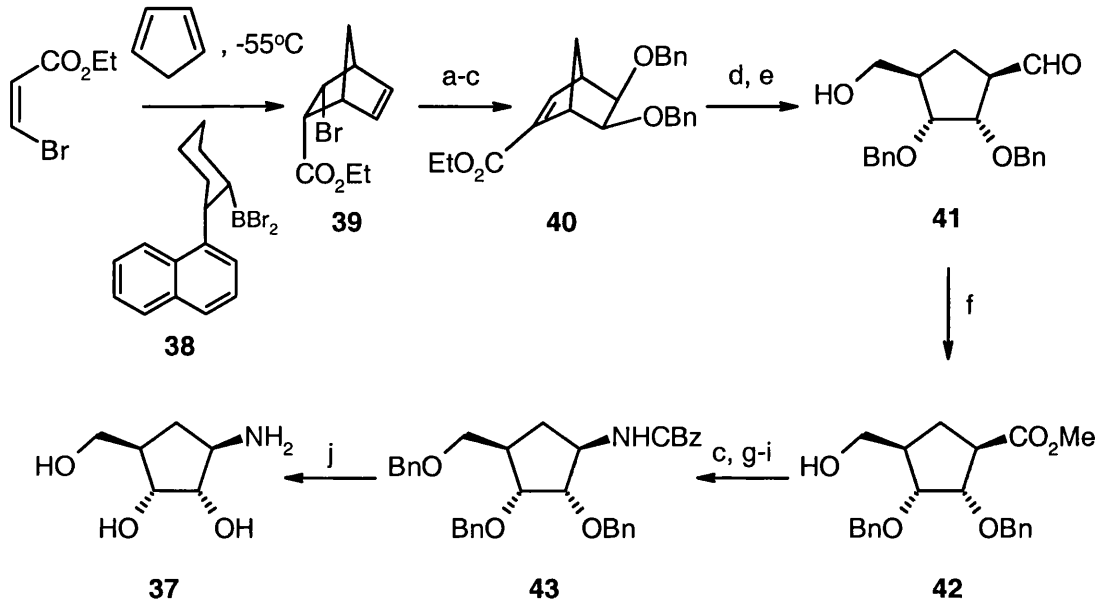


a) $HC(OMe)_3$, CH_2Cl_2, $CaCO_3$, 40°C. b) Cyclopentadiene, CH_2Cl_2, 40°C, 24h. c) *m*-CPBA, 0°C, 3h. d) CSA, MeOH, 20°C, 4h, 65%. e) CSA, CH_3CN, H_2O. f) $NaBH_4$, 0°C, 60% overall.

Scheme 15

Leahy recently accomplished the synthesis of the versatile ribo-carbocyclic nucleoside precursor **37** by Hawkins' asymmetric Diels-Alder reaction between cyclopentadiene and ethyl 3-bromoacrylate using the chiral Lewis acid **38**, and obtained the adduct **39** with high enantioselectivity (95.4% e.e.).[36] Dihydroxylation of **39** with osmium tetroxide from the least hindered face of the bicyclic system and elimination of the bromide gave the corresponding diol which was protected as the corresponding bisbenzyl ether **40**. Ozonolytic cleavage of the bicyclic system **40** followed by reductive workup and periodate oxidation generated aldehyde **41**, which

was immediately oxidased to ester **42** with bromine in methanol. After protection of the primary alcohol as a benzyl ether, ester **42** was converted into the corresponding acyl azide, which after Curtius rearrangement yielded the fully protected cyclopentane **43**. Final deprotection provided the cyclopentylamine carbocyclic precursor **37** (Scheme 16).



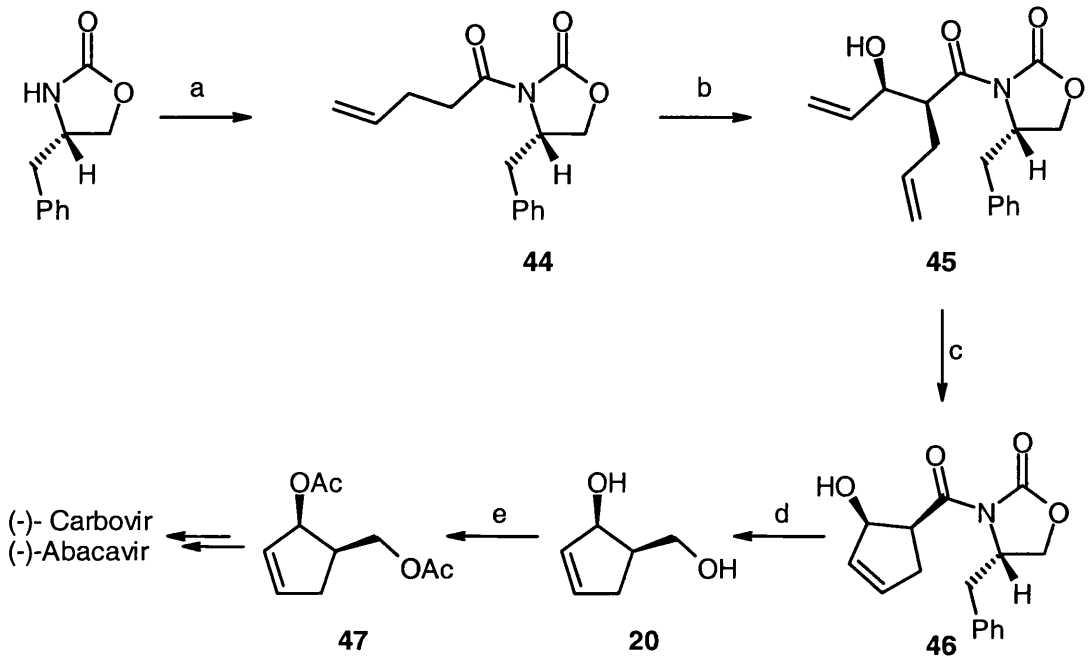
a) OsO_4, NMO, 74%. b) DBU, 97%. c) BnBr, Ag_2O, 3Å sieves, 80%. d) O_3, $LiBH_4$. e) $NaIO_4$. f) Br_2, $NaHCO_3$, MeOH, 66% 3 steps. g) NH_2NH_2. h) N_2O_4. i) PhH, BnOH, heat, 67% 3 steps. j) Na, NH_3, 61%.

Scheme 16

I.2.3.4 Auxiliary based asymmetric reactions

Crimmins has recently reported an original approach to (-)-carbovir and its structurally related analogue (-)-abacavir which does not rely on cyclopentadiene as the initial starting material (Scheme 17).[37] The strategy relied on an auxiliary mediated asymmetric aldol addition to establish the absolute and relative configuration in combination with ring-closing metathesis to construct the pseudosugar ring. Thus, condensation of lithiated (*S*)-4-benzyl-2-oxazolidinone with the mixed anhydride of 4-pentenoic acid and pivalic acid provided **44**. Evans' dialkyl boron triflate protocol for asymmetric aldol condensation with acrolein gave the *syn* aldol adduct **45** in >99% d.e. Ring closing metathesis in the presence of Grubbs catalyst afforded **46** which was reduced with lithium borohydride to remove the

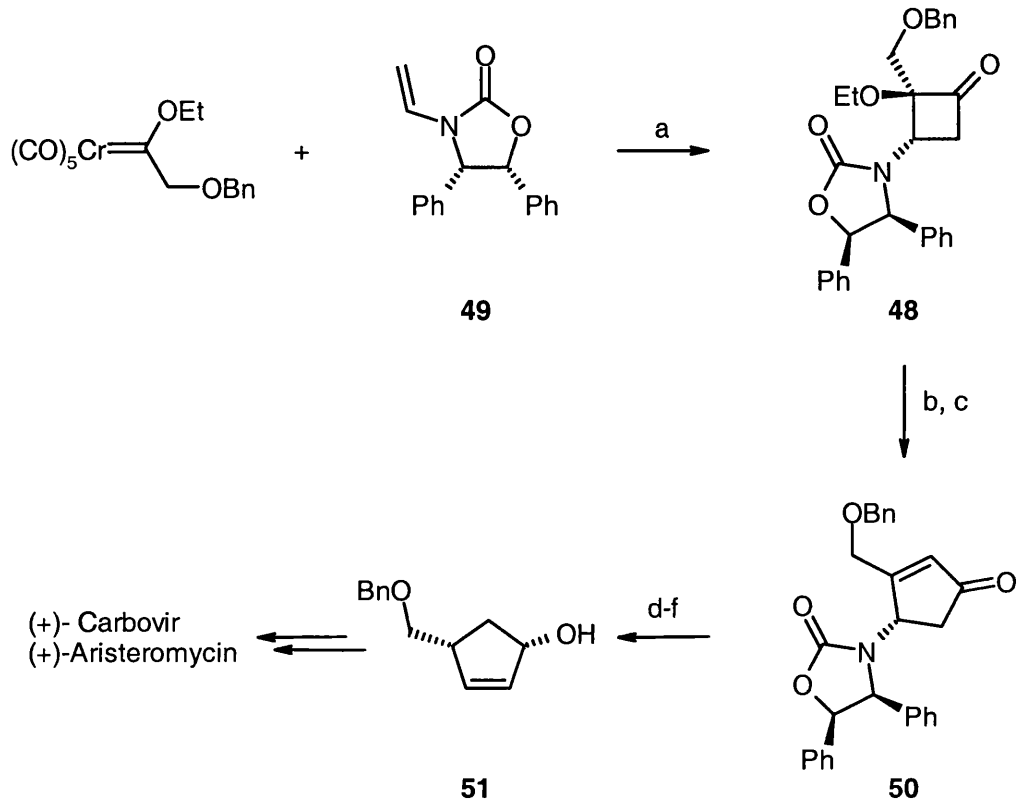
chiral auxiliary. The diol **20** (>99.6% e.e.) was diacetylated to give **47** which underwent a palladium catalysed coupling with the corresponding purine to afford, after hydrolysis, (-)-carbovir and (-)-abacavir. This approach will be discussed in further detail in Chapter 2, Section 6.



a) *n*-BuLi, CH_2=CH$(CH_2)_2CO_2COCMe_3$, THF, -78°C, 99%. b) Bu_2BOTf, Et_3N, CH_2Cl_2, CH_2=CHCHO, -78°C, 82%. c) $Cl_2(Cy_3P)_2Ru$=CHPh, CH_2Cl_2, 97%. d) $LiBH_4$, MeOH, THF, 78%. e) Ac_2O, Et_3N, CH_2Cl_2, DMAP, 90%.

Scheme 17

Very recently, Hegedus has reported a novel one-pot ring-expansion reaction of cyclobutanone **48** for the synthesis of (+)-aristeromycin and (+)-carbovir (Scheme 18).[38] Thus, cyclobutanone **48** was obtained as a single diastereomer by photolysis of the chromium carbene complex with carbamate **49**. Ring expansion followed by elimination of ethanol led to cyclopentenone **50**. The enone was reduced by hydrogenation and after the oxazolidinone elimination step, a single enantiomer of the corresponding cyclopentenone was obtained which was reduced to the allylic alcohol **51**. The synthesis of the desired *C*-nucleosides was accomplished by Trost palladium-catalysed coupling of the heterocyclic base from the corresponding allylic carbonate.



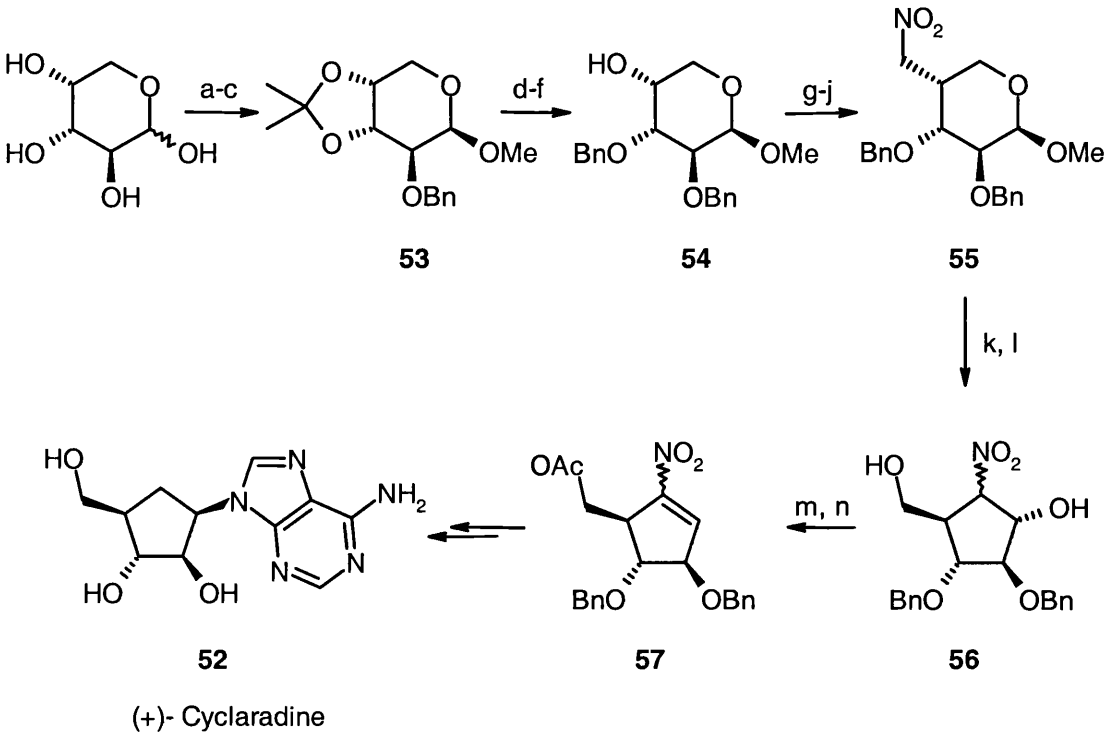
a) hυ, CH_2Cl_2, 76%. b) $Me_3S(O)I$, NaH, $Sc(OTf)_3$, DMF. c) Li_2CO_3, 74% 2 steps. d) H_2 (80 psi), [Rh(COD)dppb]BF_4, DMF, 77%. e) LDA, THF, 0°C. f) DIBAL, THF, 0°C, 50% 2 steps.

Scheme 18

I.2.3.5 Synthesis from the chiral pool of carbohydrates and aminoacids

Several recent syntheses of carbocyclic nucleosides utilise substrates from the "chiral pool" of natural carbohydrates (D-glucose,[20] D-ribose,[39],[40] D-erythrose,[41] γ-lactone-D-ribonic acid,[42] and D-arabinose[20]) and amino acids.[43],[44] Although the synthesis of aminocyclopentyl precursors from homochiral natural products has proven less efficient than Diels-Alder approaches, there are a few interesting examples that rely on elegant strategies for the construction of the carbocyclic ring. Yoshikawa has completed the synthesis of (+)-cyclaradine **52** from the natural sugar D-arabinose (Scheme 19).[20] After transformation of the sugar to the corresponding methyl glycoside **53**, hydrolysis of the acetonide and selective protection of the 3'-hydroxyl gave the alcohol **54**. Oxidation of the alcohol followed by reaction with nitromethane enolate afforded **55** after dehydration and reduction of the nitro olefin. Hydrolysis of the acetal effected an interesting ring contraction *via* aldol addition of

the nitronate to the resultant aldehyde to afford the carbocyclic ring. Dehydration of alcohol **56** through the acetate gave nitro olefin **57**. Introduction of the purine was then accomplished by Michael addition, and subsequent reductive removal of the nitro group with tributyltin hydride and final deprotection gave (+)-cyclaradine **52**.

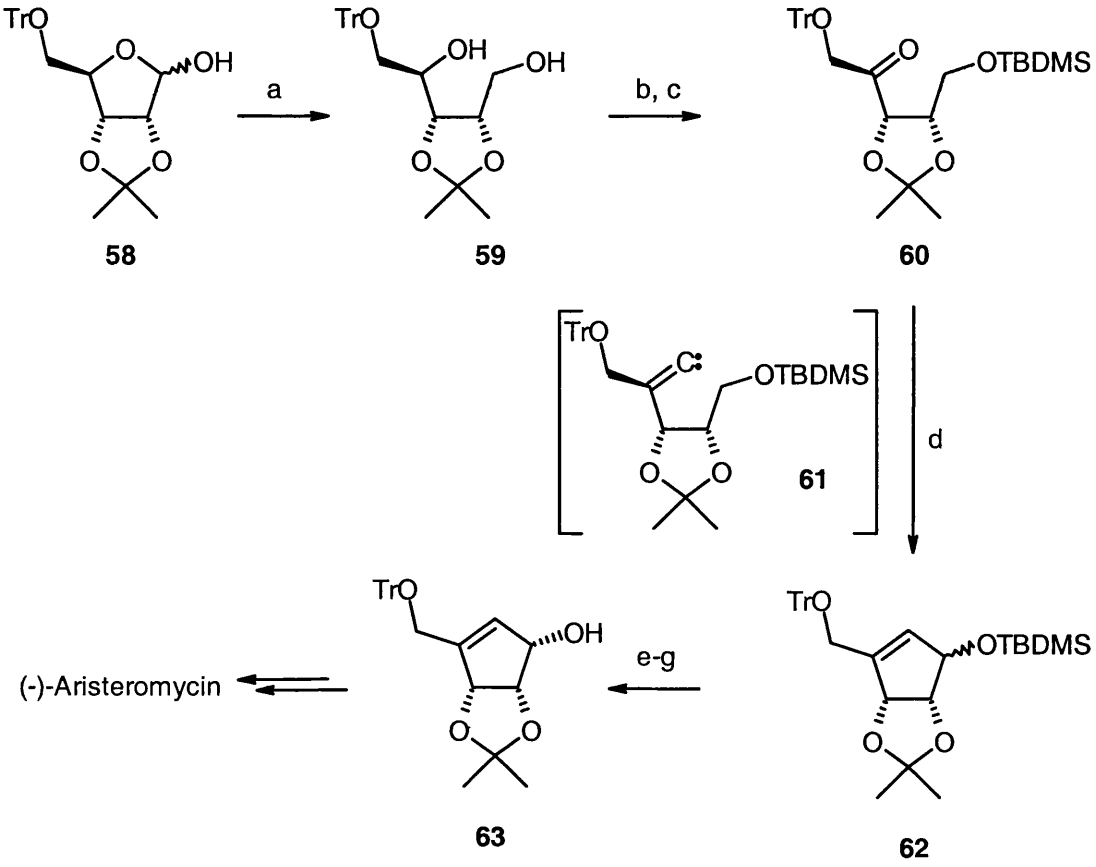


a) HCl, MeOH. b) $(MeO)_2CMe_2$, *p*-TsOH, DMF. c) BnCl, NaH, DMF, 100%. d) 80% AcOH, 50°C. e) Bu_2SnO, toluene. f) BnBr, CsF, DMF, 100%. g) $(COCl)_2$, CH_2Cl_2, Et_3N, DMSO. h) CH_3NO_2, KF, 18-Cr-6, DMF, 72%. i) *p*-TsOH, Ac_2O. j) $NaBH_4$, EtOH, 85%. k) con. HCl, CH_3CO_2H, 57%. l) CsF, DMF, 86%. m) *p*-TsOH, Ac_2O. n) Pyridine, 82%.

Scheme 19

A very interesting approach to (-)-aristeromycin using a C-H insertion reaction of methylidene carbene as the key step to close the carbocyclic ring has been reported by Ohira (Scheme 20).[40] Acetonide **58**, which was easily obtained from D-ribose, was reduced to alcohol **59**. Selective protection of the primary alcohol followed by Swern oxidation of the remaining hydroxyl group led to ketone **60**. Treatment of **60** with lithium(trimethylsilyl)diazomethane generated the vinyl carbene **61** which underwent insertion into the C-H bond adjacent to the protected hydroxyl group resulting in a diastereomeric mixture of cyclopentenes **62**. After a deprotection-oxidation-reduction sequence, the desired alcohol **63** was obtained as a single

stereoisomer. Adenine was incorporated *via* a direct Mitsonobu reaction to afford protected (-)-aristeromycin.



a) $LiAlH_4$, Et_2O, 85%. b) *t*-$BuMe_2SiCl$, imidazole, DMF, 97%. c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 89%. d) $TMSC(Li)N_2$, THF, 0°C, 55-65%. e) Bu_4NF, THF, 69%. f) PDC, CH_2Cl_2, 80%. g) $LiAlH_4$, THF, 87%.

Scheme 20

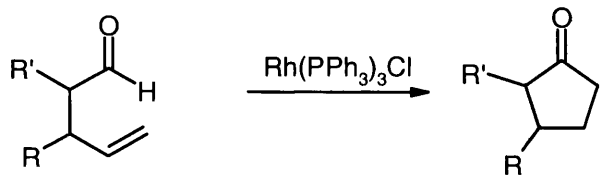
Although many varied approaches have been published for the asymmetric synthesis of carbanucleosides, there is nevertheless a need for new more atom efficient stereoselective methodologies for construction of the cyclopentanoid unit.

I.3 Intramolecular hydroacylation as a route to functionalised cyclopentanoids

Since the approach towards cyclopentanoids which was to be adopted in the present work involved a tandem hydrometallation-intramolecular aldol sequence, it is therefore appropriate to provide a brief overview of recent developments in transition metal mediated reactions for C-C bond formation which are of relevance to our own study. In the following reactions, relevant themes relating both to cyclisation methodology and the reductive aldol reaction are accordingly developed.

I.3.1 Rhodium-catalysed intramolecular hydroacylation

The rhodium-catalysed intramolecular hydroacylation of 4-alkenals, first introduced by Sakai,[45] has become a well-established method for the construction of functionalised cyclopentanones. In this study, 2,3-substituted pentenals were cyclised to the corresponding cyclopentanones using stoichiometric amounts of Wilkinson's catalyst (Scheme 21). Yields however were quite low (17-34%).

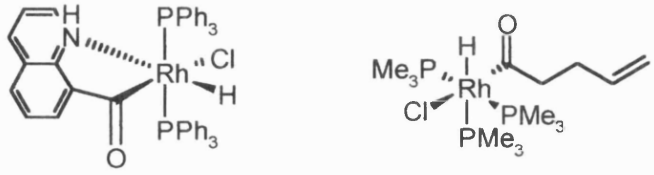


Scheme 21

Lochow and Miller[46] subsequently observed that catalytic amounts of Wilkinson's catalyst (10 mol%) could also be used for the hydroacylation of 4-pentenal units in the presence of ethylene-saturated chloroform. The yields of the corresponding cyclopentanones improved to 70%. At a later stage, Larock developed three useful catalytic systems for the rhodium-catalysed intramolecular hydroacylation of unsaturated aldehydes, consisting in the replacement of the triphenylphosphine ligands present in Wilkinson's catalyst by tri-*p*-tolylphosphine, tri-*p*-anisylphosphine or tris(*p*-dimethylaminophenyl)phosphine.[47] 4,5-Substituted cyclopentanones were then obtained in very good yields (up to 90%) with only 5-10 mol% of catalyst. More recently, Bosnich[48] has achieved excellent yields of cyclopentanones (90-

95%) using catalytic quantities (1-10 mol%) of cationic rhodium complexes with a range of bidentate phosphine ligands.

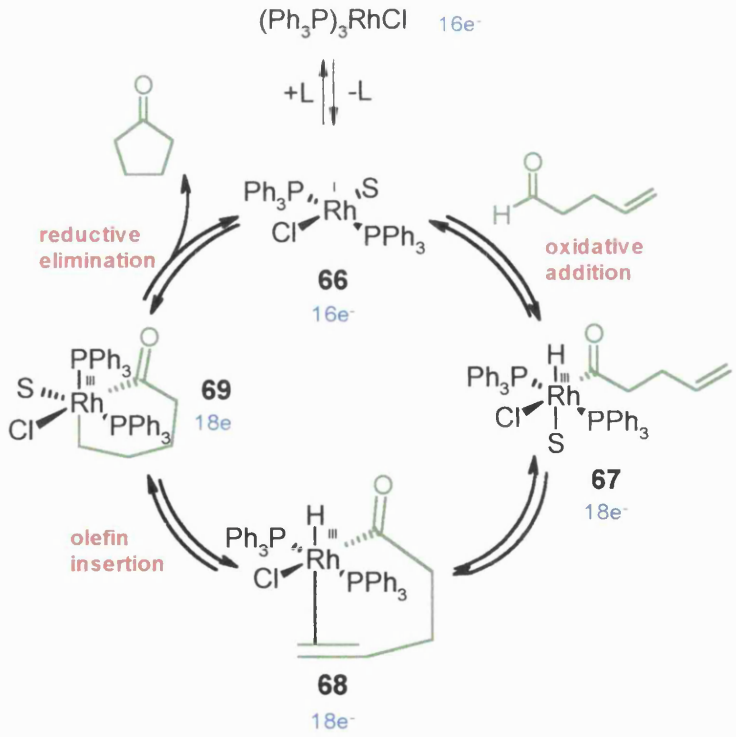
Labelling work by Miller[49] and isolation of acylrhodium (III) hydride species such as **64** by Suggs[50] and **65** by Milstein[51] (Figure 7), allowed a general mechanism and catalytic cycle for intramolecular hydroacylation to be identified.



64 **65**

Figure 7

Thus, the reaction appears to follow the pathway outlined in Scheme 22.



Scheme 22

The following steps are therefore thought to be involved:

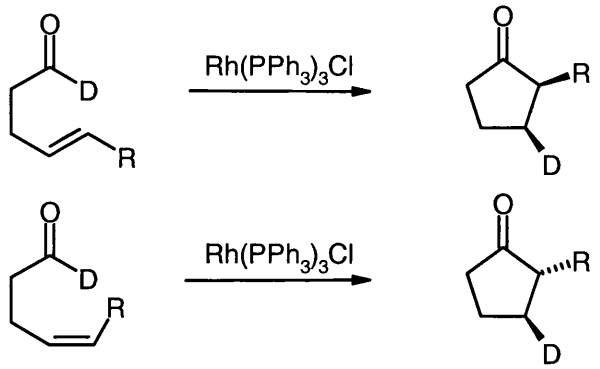
i. Oxidative addition of the aldehyde to the 16 electron rhodium catalyst **66** generates an 18 electron cordinatively saturated hydridoacylrhodium (III) species **67**.

ii. The hydride ligand in the hydridoacylrhodium (III) species exerts a strong *trans* effect[51] and thus the *trans* ligand is labilised which allows olefin coordination **68**.

iii. Following hydride insertion at the 4-position, the resulting rhodium (III) carbometallocycle **69** undergoes reductive elimination to generate the cyclopentanone and also regenerate the rhodium (I) catalyst.

By general consensus, the active catalyst is believed to be the 16 electron species $Rh(PPh_3)_2ClS$ **66**, being S a suitable co-ordinating solvent, although this species has proved too reactive and unstable to be detected.[52]

As far as stereochemistry is concerned, in a deuterium labelling experiment Miller has found that, in the case of terminal substituted alkenes, the regiochemistry of the olefin would determine the relative stereochemical outcome of the reaction (Scheme 23).[49]. Thus, a *trans*-substituted olefin led to the corresponding *syn* cyclopentanone, whereas with a *cis*-substituted olefin deuterium incorporation was observed *anti* to the substituent.

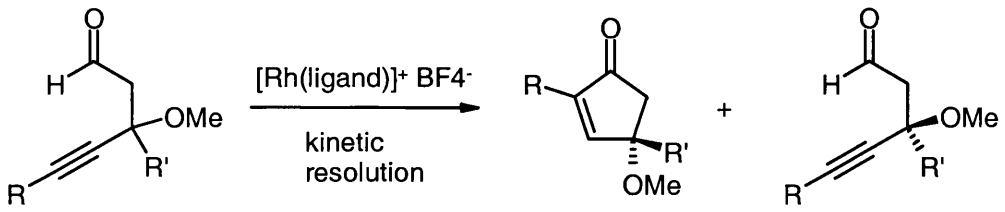


Scheme 23

Sakai[53] has also demonstrated that intramolecular rhodium-catalysed hydroacylation of 3,4-substituted-4-pentenals in the presence of stoichiometric

amounts of Wilkinson's catalyst was highly stereoselective affording only the *cis*-substituted cyclopentanones. It is also significant that this reaction can be carried out in an enantioselective way. The first example of enantioselective intramolecular hydroacylation was reported by James[54] using the chiral rhodium complex $[Rh(chiraphos)_2]Cl$ (chiraphos= 2(*S*),3(*S*)-bis(diphenylphosphino)butane), although the selectivity was rather poor (52% e.e.). Sakai[55] has replaced chiraphos by (+)-1(*S*),2(*S*)-trans-1,2-bis(diphenylphosphinomethyl)cyclohexane ((+)-DIPMC) as ligand and obtained an improved selectivity of 73% e.e. The best selectivities to date however have been obtained with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as ligand, as reported by Bosnich.[56] Interestingly, with racemic 3,4-disubstituted pentenals, chiral cationic rhodium catalysts led preferentially to the *trans* isomer whereas in the presence of neutral chiral rhodium catalysts, the *cis* isomer predominated.[57]

Very recently, Fu has reported a rhodium-catalysed intramolecular hydroacylation of 4-alkynals to generate substituted cyclopentenones in good yields.[58] He has also studied the asymmetric variant of this new reaction using a cationic rhodium catalyst in the presence of different chiral ligands, being (*R*)-Tol-BINAP the best choice in terms of yield and selectivity (Scheme 24).[59]



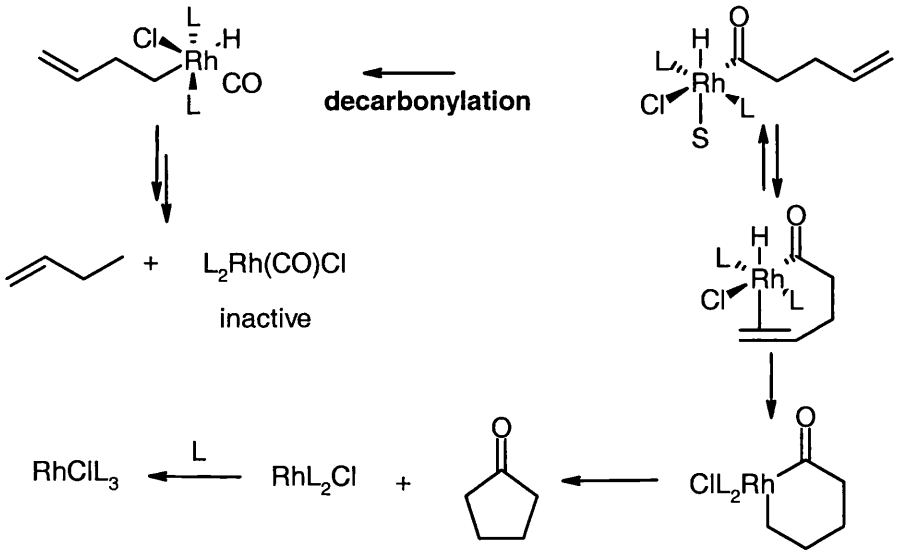
Scheme 24

I.3.2 Limitations of the rhodium (I) catalysed intramolecular hydroacylation

One of the advantages of hydroacylation as a synthetic route to cyclopentanones is the ease of preparation of the 4-pentenals, substrates which are readily available from commercial compounds. In addition, a careful choice of both substrate and catalytic system could, in principle, permit stereoselective construction of substituted cyclopentanones which could in turn serve as carbocyclic nucleoside precursors. Although intramolecular hydroacylation therefore appears as a very valuable method

for the synthesis of cyclopentanones, closer scruting reveals however a number of limitations:

- Substitution in the 2 and 5 positions tends to reduce the yield of the cyclic ketone, and disubstitution in the 2-position gives rise to ethyl ketones instead.[47]
- Large amounts of catalyst (20-50 mol%) are needed in many examples.[47]
- It is restricted to the use of an aldehyde functionality since oxidative addition to this group is the first step in the catalytic cycle.
- Heteroatomic substituents give reduced yields, in particular, amino groups are not tolerated under the reaction conditions.
- Intramolecular hydroacylation is not applicable to the synthesis of ring sizes other than five.
- Decarbonylation is a competing side reaction which renders the catalyst inactive (Scheme 25).



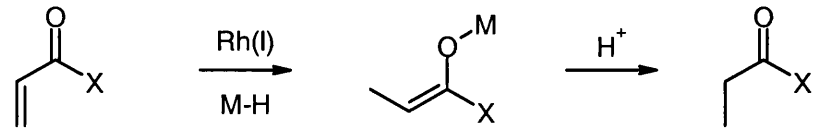
Scheme 25

As already mentioned, addition of ethene to the reaction mixture enhances the catalytic activity of the rhodium (I) catalyst as it occupies the free co-ordination site that is required for the decarbonylation process, thus increasing the yield of the cyclopentanone.[46] However, in the case of less reactive electron deficient olefins[60] or because of steric interactions of the alkene with surrounding ligands,[47],[48] co-ordination of the olefin to the acyl rhodium hydride species is slow and decarbonylation remains a serious problem.

I.4 Tandem reductive-aldol reaction for the preparation of *C*-nucleoside precursors and related transformations

I.4.1 Transition metal-catalysed intermolecular reductive-aldol processes

The regiocontrolled formation of a useful enolate anion for reactions such as aldolisation is traditionally achieved by deprotonation of an appropriate carbonyl precursor. In recent years however, increasing attention has been paid to the conjugate reduction of α,β-unsaturated carbonyl moieties, with mild transition metal mediated hydrometallation sequences replacing brutal reagent combinations such as lithium in liquid ammonia. Numerous catalytic systems have been intensively investigated for this reaction, including Rh,[61] Pt,[62] Ni[63] and Cu[64] catalysts and a wide selection of metal hydrides is also available, with boranes and silanes being especially favoured. In addition, catalytic processes involving one-pot two-step conjugate reduction-electrophilic trapping of the resulting enolate have been reported.[65] Evans and Fu[66] observed that enones which can readily adopt a *cis* conformation underwent conjugate reduction with catecholborane at room temperature (Scheme 26). Other carbonyl compounds, such as esters, imides and amides, were completely unreactive under the same reaction conditions. However, addition of 2 mol% of Wilkinson's catalyst resulted in conjugate reduction of these substrates with catecholborane under very mild conditions (-20°C, 12 h).



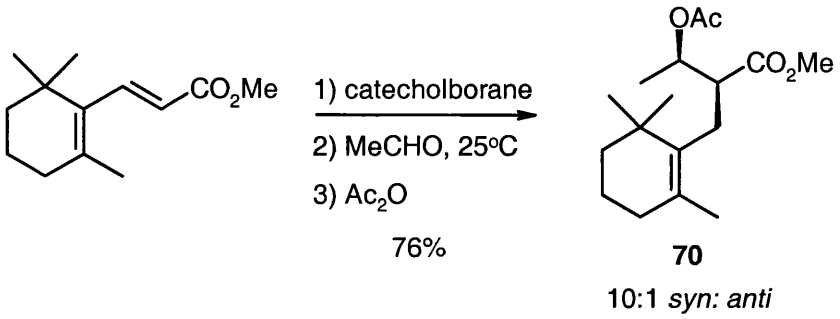
X= R, OR, NR_2

(X= R does not require catalyst)

Scheme 26

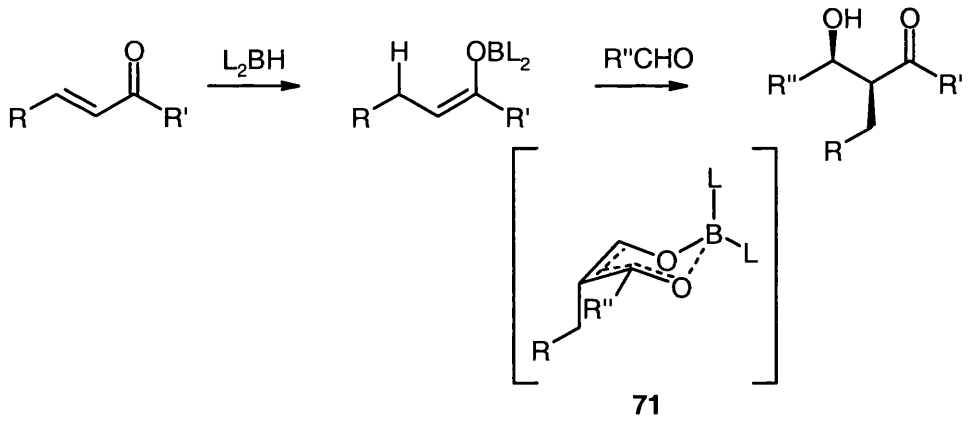
They found that this mild method for reduction of α,β-unsaturated systems was compatible with a wide variety of functional groups and was amenable to large-scale reactions. They also investigated the one pot two-step trapping of the resulting *Z* boron enolate with different electrophiles other than protons. In the case of β-ionone

for example, a subsequent aldol reaction with acetaldehyde afforded the *syn* product **70** with good selectivity (Scheme 27).



Scheme 27

One year later, Boldrini[67] reported a similar one-pot two-step procedure through the 1,4-conjugate addition of dialkylboranes to β-substituted (*E*)-enones followed by trapping of the resulting configurationally pure (*Z*)-(vinyloxy)boranes with aldehydes (Scheme 28). The overall process therefore constitutes the regio- and stereocontrolled aldol reaction of an unsymmetrical ketone with an aldehyde.

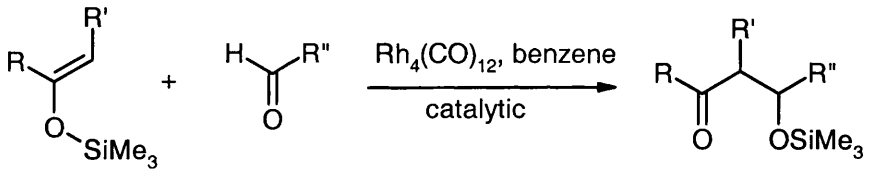


Scheme 28

In comparison with aldol reactions involving enolates of other metals, the short B-O bond length (1.36-1.46 Å) and the acceptor properties of the tricoordinated boron atom favour the formation of a tightly closed transition state structure of type **71**, where steric effects such as the equatorial preference for the aldehyde substituent are magnified resulting in enhanced stereocontrol. The chemoselectivity of the hydroboration process is highly dependant on the geometry of the double bond of the enone substrate. Thus, while (*E*)-α,β-unsaturated ketones undergo mainly 1,4-

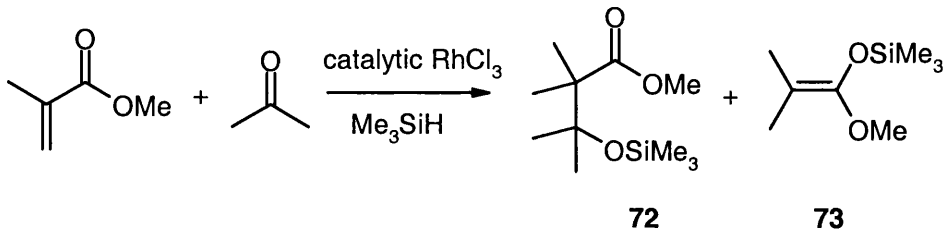
addition leading exclusively to (*Z*)-boron enolates, (*Z*)-α,β-unsaturated ketones still react in a 1,4-fashion, but with a slower rate and a lower degree of chemoselectivity.

In addition to the preceding one-pot two-step procedures for reductive-aldol reactions, catalytic systems effecting conjugate reduction-electrophilic trapping but in the presence of the electrophilic partner have also been described. Most of these transformations involve the use of aldehyde electrophiles in the catalytic reductive aldol sequence. In 1986, Matsuda[68] first reported the rhodium catalysed coupling of enol trimethylsilyl ethers with aldehydes to yield β-siloxy carbonyls (Scheme 29). Such reactions require at least two steps, namely, prior preparation and isolation of a silyl enol ether of defined geometry followed by condensation with the carbonyl compound.



Scheme 29

One year later, in 1987, Revis and Hilty[69] reported that the one pot reaction of α,β-unsaturated esters with carbonyl compounds, trimethylsilane and Rh(III) as the precatalyst gave good yields of β-siloxy esters **72** (Scheme 30).

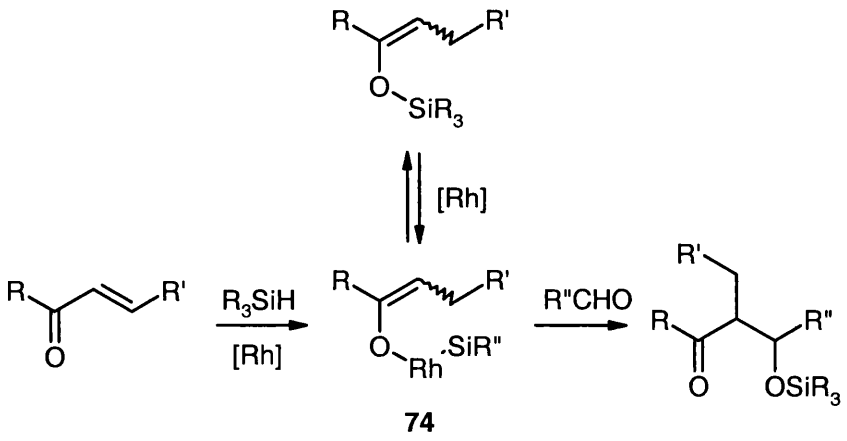


Scheme 30

Since hydrosilylation of the α,β-unsaturated ester itself was known to give the silyl ketene acetal **73**, Revis and Hilty investigated whether the β-siloxy ester product proceeded *via* intermediate formation of the silyl ketene acetal, as reported by Matsuda.[68] They observed that for this one-pot three component reaction at room

temperature this was not the case. This constitutes the first example of an intermolecular tandem hydrosilylation-aldol reaction for the synthesis of β-siloxy esters.

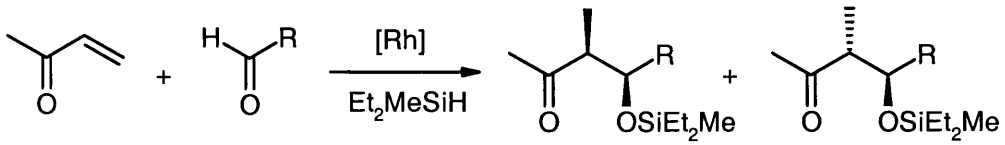
In 1990, Matsuda[70] proposed an oxygen-bound rhodium enolate **74** as a plausible intermediate for the subsequent aldol condensation. This was based on the work of Heathcock who had isolated such an intermediate and demonstrated its reaction with benzaldehyde to afford aldol products.[71] It is through this intermediate **74** that the two different reactions, 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 31).



74

Scheme 31

A second rhodium catalylic system using $Rh_4(CO)_{12}$ was also described by Matsuda[70] in 1990. He began to define the generality of this reductive-aldol type reaction in the presence of different aromatic and aliphatic aldehydes and reported that a preference for *syn* stereoselectivity was observed throughout this rhodium catalysed coupling of an enone, an aldehyde and a trialkylsilane (Scheme 32). He also found that aromatic aldehydes readily yielded the corresponding aldol adducts whereas aliphatic aldehydes required the addition of methyldiphenylphosphine as an ancillary ligand in order to obtain acceptable yields.



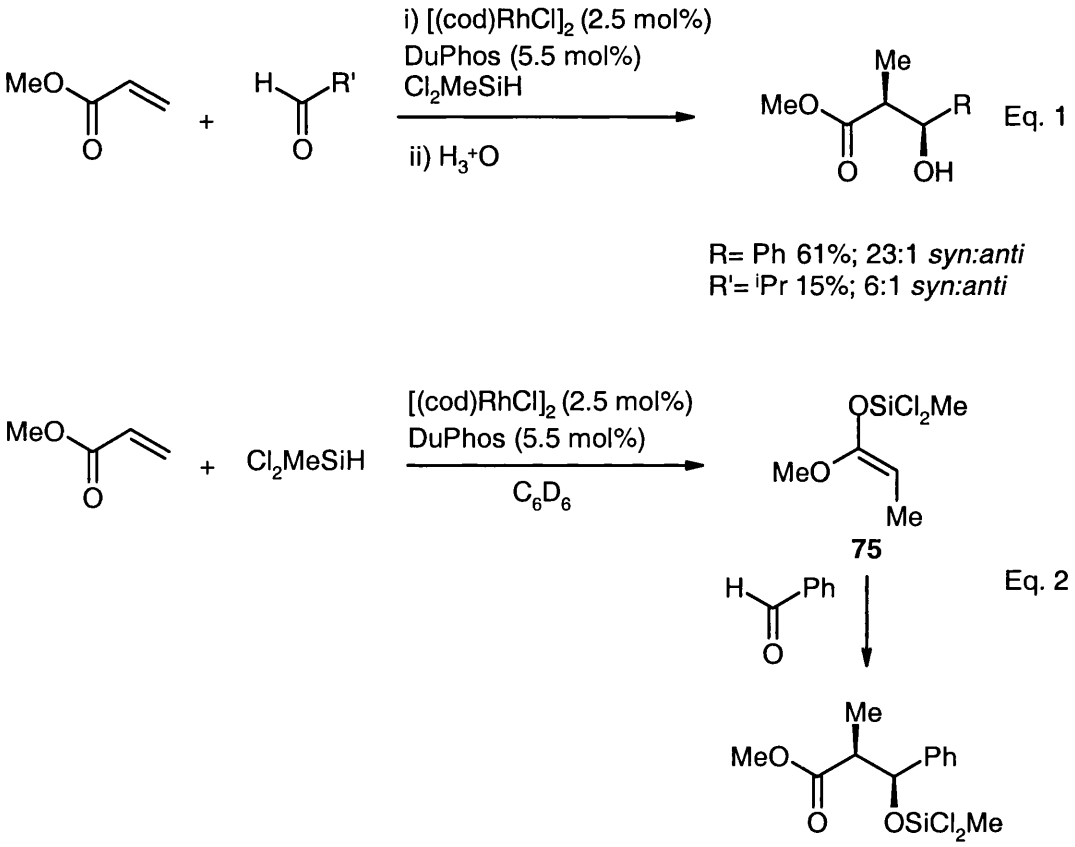
syn > *anti*

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

Scheme 32

Most recently, the scope of such rhodium-based catalytic systems has been extended through the development of further diastereoselective and also enantioselective variants. In particular, Morken[72] discovered an effective catalyst for the diastereoselective reductive aldol reaction of α,β-unsaturated esters and aldehydes with the aid of a high-throughput evaluation of 192 independent catalytic systems. The most active catalyst systems, $[(cod)RhCl]_2$-binap-cathecolborane (100% relative yield), and $[(cod)RhCl]_2$-DuPhos-Cl_2MeSiH (94% relative yield), showed *syn:anti* selectivity of 7:1 and 23:1, respectively. The catalysts were prepared *in situ* by premixing metals and ligands at 50°C in dichloroethane for 1 h. This approach has revealed a significant interdependence of metal, ligand and hydride source in terms of reactivity and selectivity, suggesting that an empirical catalyst development approach, where reaction variables are independently optimised, would not have revealed all highly active catalysts. Of all the catalysts examined, the synthetic utility of the catalytic system derived from $[(cod)RhCl]_2$, DuPhos (1,2-bis(2,5-dimethylphospholano)-benzene), and dichloromethylsilane was explored (Scheme 33, Equation 1). Good yields and high *syn* selectivities were achieved with aromatic aldehydes whereas aliphatic aldehydes resulted in diminished product yields but still with high *syn* selectivity.

The same group has also carried out some mechanistic studies employing *in situ* NMR analysis in order to identify the reactive intermediates in this Rh-DuPhos catalysed reductive aldol reaction.[73] For this purpose, the reaction was carried out in two steps. After one hour from the addition of dichloromethylsilane and methyl acrylate to the catalyst in C_6D_6, the reagents were completely converted to a new compound that is spectroscopically consistent with a single stereoisomer of the silyl ketene acetal **75**, which was determined to be the *E* isomer (Scheme 33, Equation 2).

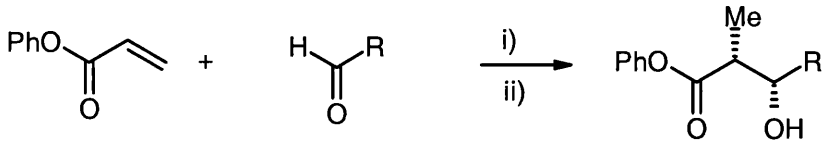


Scheme 33

Subsequent introduction of benzaldehyde led to rapid disappearance of the silyl ketene acetal and formation of a single stereoisomer of the reductive aldol adduct. In order to determine whether the rhodium catalyst was required for the coupling between the aldehyde and the silylketene acetal, this intermediate was distilled away from the metal complex. Addition of benzaldehyde to the metal-free and phosphine-free silyl ketene acetal provided the expected aldol product in high diastereoselection. This observation suggests that the role of the rhodium catalyst in this reductive aldol reaction is to catalyse the formation of the silicon enolate and not the aldol step. Comparison of these observations with the previously discussed work of both Revis and Hilty and Matsuda suggests that the nature of the silane and the catalyst used may be critical.

The first example of the intermolecular asymmetric catalytic reductive aldol was reported by Morken in 2000 using diethylmethylsilane and a rhodium complex derived from $[(cod)RhCl]_2$ and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

(BINAP).[74] Moderate diastereoselection and good to excellent levels of enantioselectivity were obtained with aromatic and aliphatic aldehydes (Scheme 34).



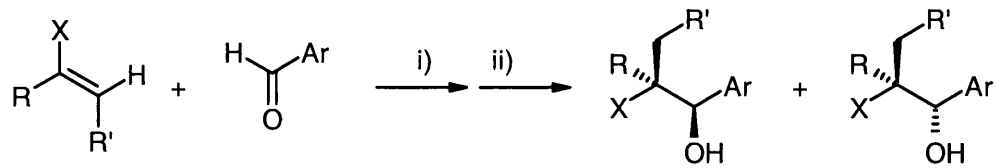
R= alkyl, aryl

2R,3R

i) $[(cod)RhCl]_2$ (2.5 mol%), *R*-binap (6.5 mol%), Et_2MeSiH
ii) $H_3{}^+O$

Scheme 34

In addition to rhodium, other transition metal catalysts based on Co (II), Pd (0) and Cu (I) have also been described for use in the catalytic reductive aldol reaction. A Co (II) based catalyst for the reductive aldol reaction of α,β-unsaturated nitriles, amides and esters with aromatic aldehydes has been described by Mukaiyama.[75] Two different cobalt catalytic systems have been investigated, bis(acetylacetonato)cobalt (II) ($Co(acac)_2$) and bis(dipivaloylmethanato) cobalt (II) ($Co(dpm)_2$), with the latter exhibiting the best catalytic activity (Scheme 35). The corresponding β-hydroxy nitriles, amides and esters were obtained in good to high yields (50-96%). In terms of diastereoselectivity, it is important to note that a certain extent of *syn* selectivity was observed in the reaction with conjugated amides (80:20), whereas in the presence of α,β-unsaturated nitriles and esters a 50:50 ratio of the two possible diastereomers was consistently obtained.

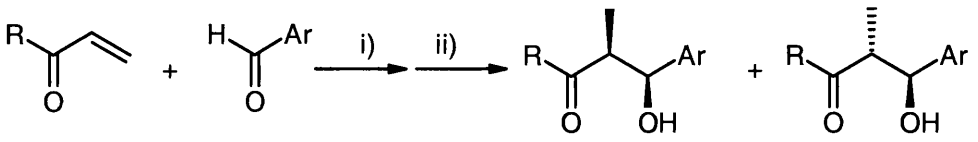


when X= CN, CO_2Me; R, R'= H or Me	50	:	50
when X= $CON(CH_3)_2$; R, R'= H or Me	80	:	20

i) $Co(dpm)_2$, $PhSiH_3$, r.t., 2-20 h
ii) $H_3{}^+O$

Scheme 35

Kiyooka[76] reported a mild aldol reaction of aryl aldehydes through palladium-catalysed hydrosilylation of α,β-unsaturated carbonyl compounds with trichlorosilane (Scheme 36).



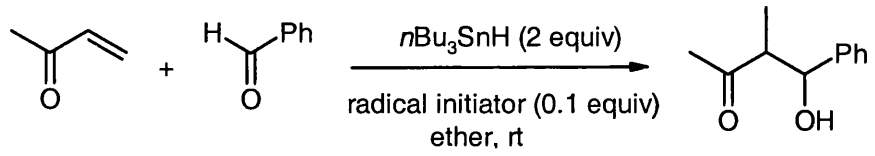
when R= O^{t}Bu	*syn*	>	*anti*
when R= $N(CH_3)_2$	*syn*	<	*anti*

i) $Pd(PPh_3)_4$, Cl_3SiH, r.t., 45 h
ii) H_3^+O

Scheme 36

Interestingly, he observed that reactions of aryl aldehydes with *N,N*-dimethylacrylamide took place very cleanly to give the corresponding aldol adducts with *anti* selectivity. However, when he carried out the reaction in the presence of *tert*-butyl acrylate, low yields were recovered with the expected *syn* selectivity. Use of triethylsilane instead of trichlorosilane resulted in no reaction.

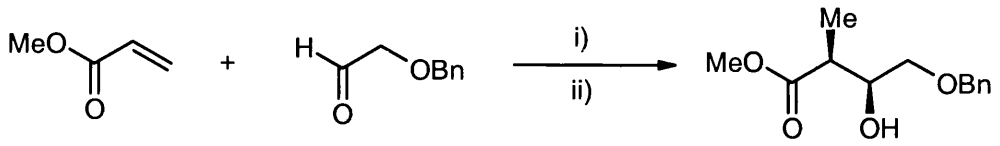
More recently, in 1999, Maruoka[77] has reported the hydrostannylation of α,β-unsaturated ketones with tri-*n*-butylstannane initiated by copper chloride in which the resulting tin enolates underwent subsequent aldol reaction with aldehydes under the influence of copper chloride as a Lewis acid catalyst (Scheme 37). Aldol products were uniformly obtained in good yield from either alkyl or aryl vinyl ketones with aliphatic and aromatic aldehydes. The presence of a β-substituent significantly lowered the reaction rate and only traces of product were isolated. Diastereoselectivity was moderate (*syn:anti* 3:1) regardless of the structure of substrates. Notably, the yield of the aldol products was dramatically lowered without copper chloride. Use of catalytic triethylboron as a radical initiator afforded the corresponding aldol product in only 3% yield presumably due to its weaker Lewis acidity.



radical initiator: none : 2%
Et_3B : 3%
CuCl : 72% (*syn:anti*= 3:1)

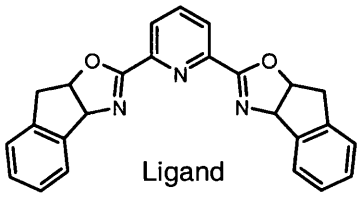
Scheme 37

Most recently, an enantioselective iridium (I) catalytic system has been described.[78] A catalytic amount of $[(cod)IrCl]_2$ and indane-pybox ligand was used in the reductive aldol reaction of diethylmethylsilane, methyl acrylate and various aldehydes leading to good enantio- and diastereocontrol (Scheme 38).



i) $[(cod)RhCl]_2$ (1 mol%), ligand (3 mol%), Et_2MeSiH
ii) H_3^+O

58% yield
98:2 *e.r*
9.5:1 *syn:anti*

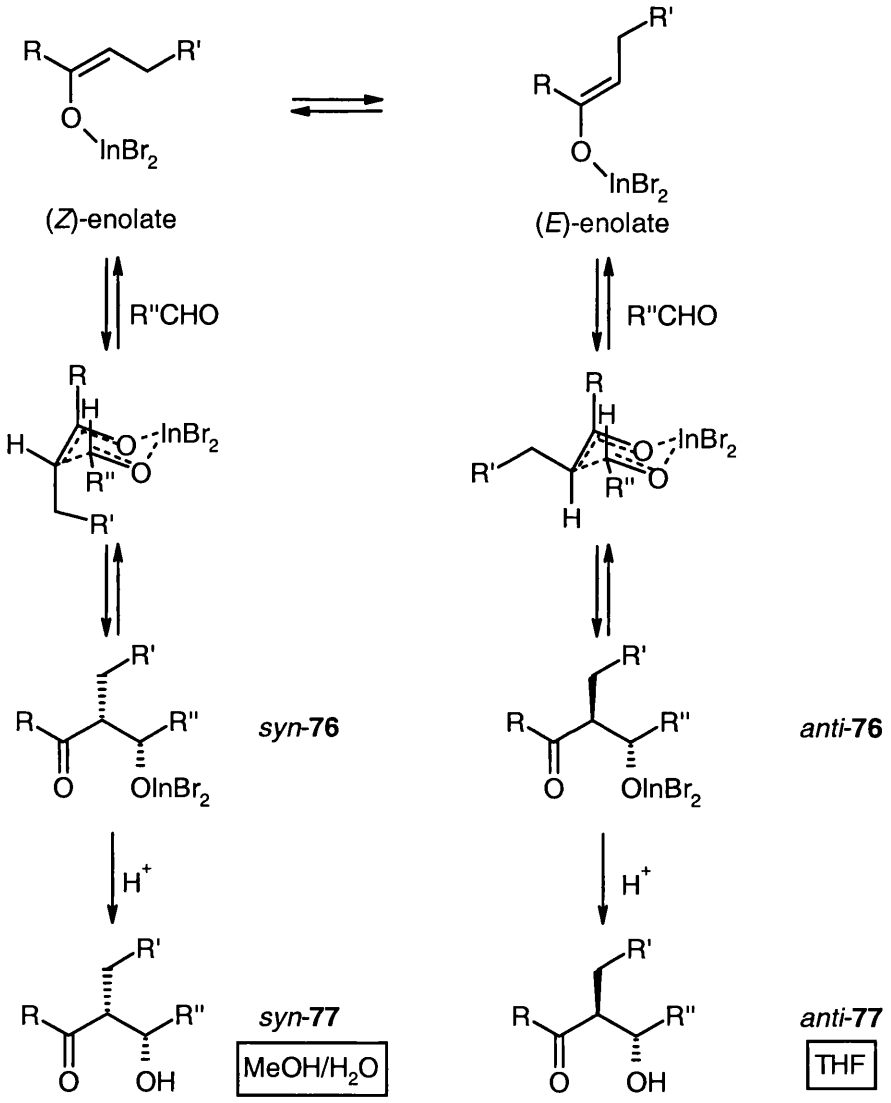


Ligand

Scheme 38

In most of the preceding examples, silanes are employed as the terminal reductant except for the Cu-catalysed reaction, which employed tributylstannane. In 2002, Baba[79] has reported an In-based catalytic system, dichloroindium hydride, which was generated by transmetallation between tri-*n*-butyltin hydride and indium trichloride. Interestingly, they found that under anhydrous conditions, the reductive aldol reaction of α,β-unsaturated ketones and aromatic aldehydes proceeded with high *anti*-selectivity, whereas in the presence of water and methanol as an additive and solvent respectively, the stereoselectivity was dramatically reversed. This constitutes the first example of a reductive aldol reaction in aqueous media.

Although the mechanism for the diastereoselective reductive aldol reaction was not clear, they have suggested the mechanistic pathway outlined in Scheme 39:

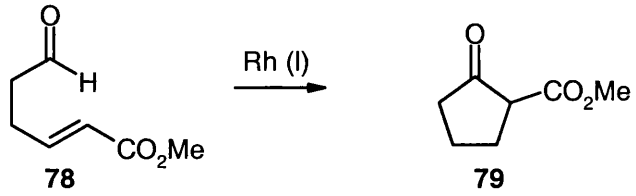


Scheme 39

Thus, the (*Z*)-enolate is generated initially because of the preferred 1,4-addition of the hydride to the cisoid form of the enone, and the enolate reacts then with the aldehyde to give the *syn*-indium aldolate by a Zimmerman-Traxler six-membered ring transition state. In aqueous media, *syn*-**76** is immediately protonated to give the *syn* β-hydroxy carbonyl, *syn*-**77**. In anhydrous THF, *syn*-**76** undergoes a retro aldol reaction sequence to give *anti*-**76** in which the overall transformation is controlled thermodynamically. Aldolate *anti*-**76** is protonated by water during the work-up to give *anti*-**77**.

1.4.2 Previous studies within our group

The approach taken by our own team was to investigate the inherent potential of the rhodium (I) catalysed tandem hydrosilylation-intramolecular aldol reaction of a 6-oxo-2-hexenoate as a stereoselective route to cyclopentanoids. Thus, in the first instance, Whitehead[60] investigated the rhodium (I) catalysed intramolecular hydroacylation of a terminally sustituted 4-pentenal, methyl 6-oxo-2-hexenoate **78**, and found that this methodology was incompatible with an electron deficient olefin in the form of an α,β-conjugated ester (Scheme 40). The ester functionality was chosen because after reduction it would provide the key 4-hydroxymethyl substituent common to a number of five-membered carbocyclic nucleosides.



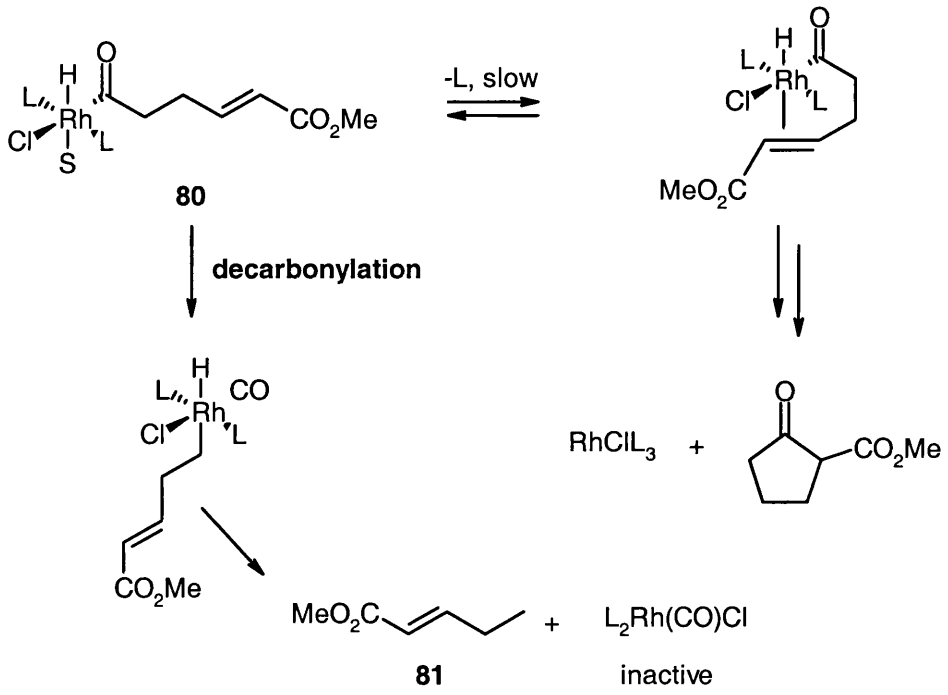
Scheme 40

The reaction was initially attempted with Wilkinson's catalyst. However, large amounts of catalyst (50-100 mol%) and long reaction times (48 h) were required to achieve only moderate yields (24-48%) of the cyclopentanone **79**. Contrarily to the observations of Lochow and Miller,[46] saturation of the reaction mixture with ethylene had no effect on the yield of the corresponding cyclopentanone. The reaction was then investigated in the presence of tertiary phosphine ligands other than triphenylphosphine. The catalysts of the type $RhClL_3$were prepared *in situ* from the commercially available chlorobis(cyclooctene)rhodium (I) dimer as catalyst precursor and the desired ligand (Equation 1). Although the yields were slightly improved with tri-*p*-tolylphosphine and tri-*p*-anisylphosphine (30-69%), large amounts of catalyst and long reaction times were still necessary. When the amount of catalyst was reduced to 10 mol%, the yield of the corresponding cyclopentanone was considerably reduced.

$$0.5\ [RhCl(cyclooctene)_2]_2 + nL \longrightarrow RhCl(cyclooctene)_{3-n}Ln \quad \text{with } n= 1\text{-}3$$

Equation 1

^{1}H NMR evidence suggested that although oxidative addition to the aldehyde occurred relatively easy to generate the acyl rhodium hydride complex **80**, the electron deficient nature of the olefin might possibly reduce the rate of olefin coordination (Scheme 41). If olefin coordination is slow, decarbonylation may be a competitive pathway. Although the product was not isolated, ^{1}H NMR showed the presence of methyl 2-pentenoate **81**, the decarbonylation product of hexenoate **78**.



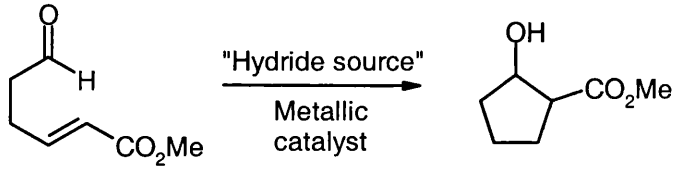
Scheme 41

The synthesis of carbocyclic nucleoside precursors by intramolecular hydroacylation can only be of synthetic preparative value if a small catalytic quantity of rhodium catalyst is used. For this reason, Whitehead also investigated the use of a number of cationic rhodium complexes such as $[Rh(diphos)]_2^{2+}ClO_4^{2-}$, which was previously reported by Bosnich[48] to give excellent yields of simple cyclopentanones with only 1-5 mol%. Unfortunately, when methyl 6-oxo-2-hexenoate **78** was submitted to these reaction conditions, no product whatsoever was detected by G.C. assay with any of the cationic rhodium catalysts used. In addition, ^{1}H NMR showed no evidence at all of any oxidative addition to the aldehyde.

The possibilities of catalyst poisoning by trace contaminants in the substrate, as well as competitive chelation or incorrect configuration of the catalyst were investigated

and it was found that none of this reasons was responsible for the lack of reactivity of the model substrate **78** towards intramolecular hydroacylation. It was then postulated that the incompatibility of pentenal **78** with cationic rhodium complexes and the large amount of Wilkinson's type catalysts required to produce acceptable yields of cyclopentanone **79** must be due to the effect of the terminal substituent.

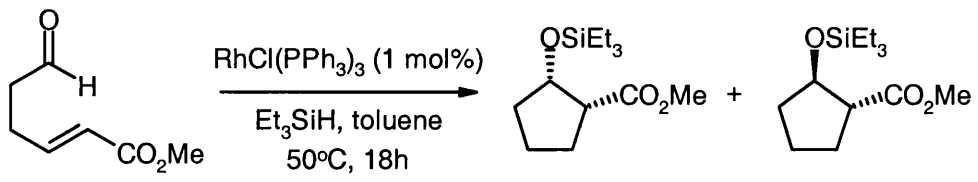
With the preceding constraints in mind, a more general and efficient methodology for the construction of carbocyclic nucleosides precursors was therefore sought. The presence of an ester group at the alkene terminus of 6-oxo-2-hexenoate **78** provided the opportunity for a tandem sequence involving conjugate reduction of the α,β-unsaturated system followed by intramolecular aldol reaction to afford the corresponding cyclopentanols **82** (Scheme 42).



78 **82**

Scheme 42

Thus, in a preliminary experiment, Whitehead[80] found that treatment of readily accessible (*E*)-6-oxo-2-hexenoate **78** with triethylsilane in toluene at 50°C in the presence of Wilkinson's catalyst (1 mol%) afforded the silylated cyclopentanols *syn*-**83** and *anti*-**83** in a 3:1 ratio and in 76% isolated yield (Scheme 43). This constituted the first example of an intramolecular tandem reductive-aldol reaction.



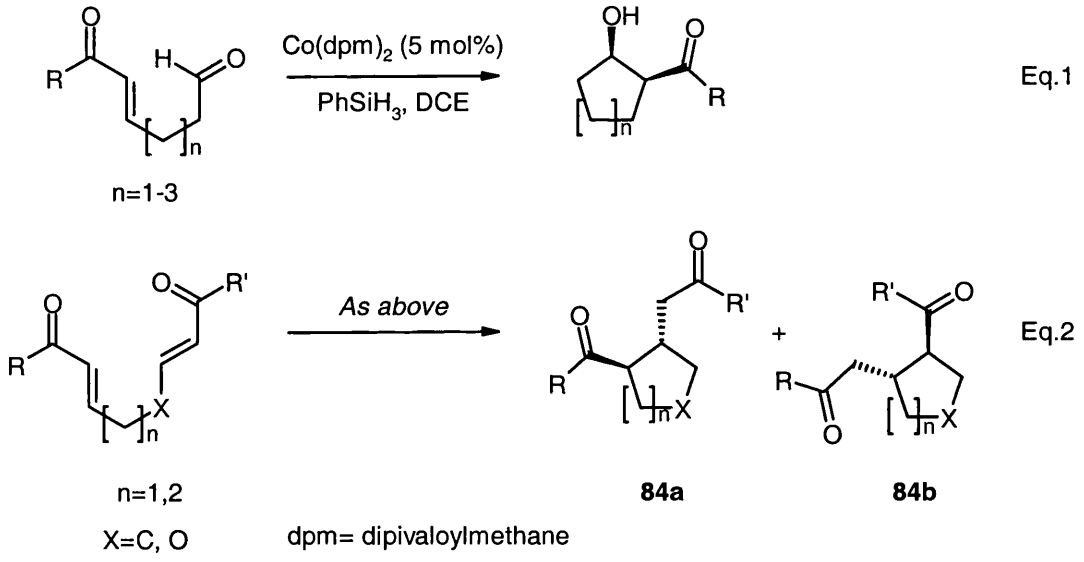
78 *syn*-**83** *anti*-**83**

Scheme 43

I.4.3 Recent advances in transition metal-catalysed intramolecular reductive-aldol processes and related cyclisations

I.4.3.1 Transition metal mediated intramolecular reductive-aldol reactions

Despite the burgeoning wealth of research in intermolecular tandem reductive-aldol processes, no intramolecular variants had been described before the start of this project. However, during the course of our own investigations, Krische[81] has reported a similar aldol cycloreduction but chosen to investigate oxo-enone substrates and to use a cobalt (II) catalyst. This methodology proved to be quite general for the formation of five, six and seven membered rings, albeit the latter in low yield (Scheme 44, Equation 1).

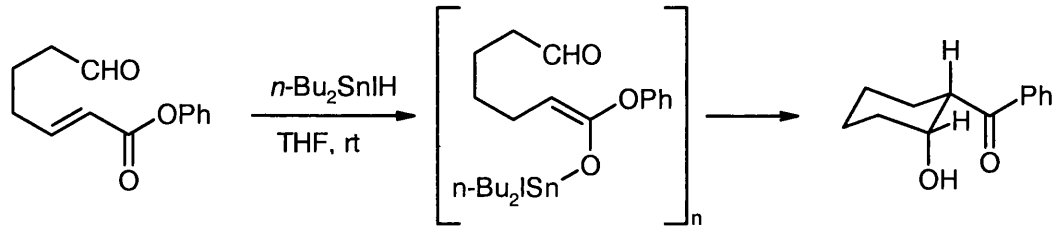


Scheme 44

Bis-enones have also been used as cyclisation precursors. In the case of symmetrical bis-enones, formation of the desired reductive-Michael cyclisation product was observed in good yield and with exclusive *anti* selectivity. However in the presence of unsymmetrical bis-enones, the catalyst was unable to distinguish the electronic effects between the two enone moieties, leading to a mixture of the two possible isomeric products **84a** and **84b** (Scheme 44, Equation 2).

Non-catalysed versions of this intramolecular tandem reductive-aldol reaction have also been reported recently by Baba[82] and Chiu.[83] The disadvantage of this

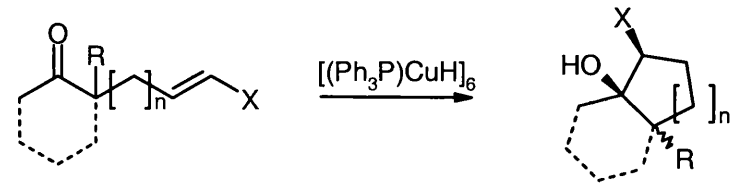
approaches is obviously the requirement for use of stoichiometric amounts of metal. Baba[82] has prepared a number of carbocycles from substrates bearing both enone and formyl moieties by using di-*n*-butyliodotin hydride (*n*-Bu_2SnIH). Linear substrates afforded the corresponding aldol adducts in good yield and *syn* selectivity (Scheme 45). However, the formation of more strained bicyclic products from cyclic precursors proved to be more difficult leading only to low yields.



(*Z*)-tin enolate 71%

Scheme 45

On the other hand, Chiu[83] has reported a conjugate reduction of α,β-unsaturated ketones, esters and nitriles by Stryker's catalyst, $[(PPh_3)CuH]_6$, to form copper enolates that undergo intramolecular aldol cyclisation to afford the corresponding five- and six-membered ring carbocycles. This tandem reaction proceeds in good yield and is generally *syn* distereoselective (Scheme 46).



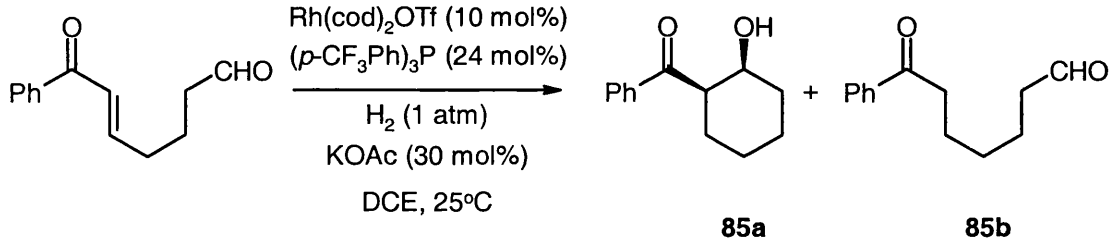
n=1,2

R= H, Me, CO_2Et
X= COR, CO_2Me, CN

Scheme 46

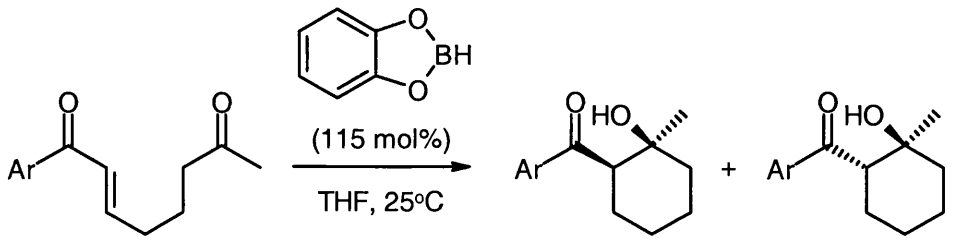
During the course of our own studies, Krische has described a reductive generation of enolates from enones using elemental hydrogen under rhodium catalysis and subsequent trapping by either aldehydes[84] or ketones[85]. The cyclisation substrates

were exposed to a number of rhodium sources under 1 atm of hydrogen. The majority of the rhodium catalysts screened afford products of 1,4-reduction, except $Rh(cod)_2OTf/PPh_3$ that gives equal amounts of *syn*-aldol product **85a** and 1,4-reduction product **85b** (Scheme 47). It was speculated that deprotonation of the intermediate (hydrido)Rh species would disfavour the 1,4-reduction pathway and also enhance the Lewis acidity of the metal which would promote coordination with the appendant aldehyde, thus, in turn, promoting the aldol cyclisation manifold. Thus, when the reaction was carried out in the presence of potassium acetate and *p*-$(CF_3Ph)_3P$ ligand, the yield of **85a** was increased to 89% with only traces of the 1,4-reduction product **85b** being observed.



Scheme 47

In 2003, the same group has reported a cycloreduction of enones in the presence of appendant ketones using boranes as the hydride source.[86] The formation of six-membered ring carbocycles proceeded very readily with high yield and *syn* distereoselectivity, whereas addition of rhodium (I) salts is required for the formation of five-membered rings to afford only very low yields of the corresponding carbocycle (Scheme 48).

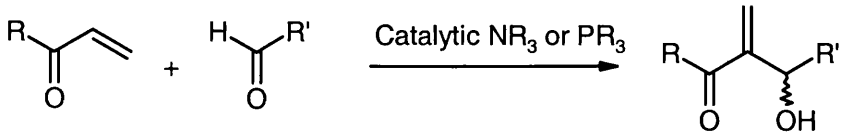


Scheme 48

I.4.3.2 Aldol cycloisomerisation (Intramolecular Morita-Baylis-Hillman reaction)

The catalytic cycloisomerisation of unsaturated precursors has attracted a lot of attention in the synthetic community as it represents an enviromentally friendly protocol for the synthesis of carbocycles from simple acyclic unsaturated precursors. As it employs the same type of cyclisation precursors as those which are envisaged for our own strategy, *viz.*, 6-oxo-2-hexenoates, and follows the same type of catalytic cycle except that the nucleophile is an organic molecule instead of an organometallic hydride, we have considered it appropriate to include such approaches in this introductory review.

The organocatalytic condensation of α,β-unsaturated carbonyl compounds with aldehydes was first introduced by Morita[87] in 1968 and later by Baylis and Hillman[88] (Scheme 49). This transformation is mediated by tertiary organic nucleophiles, such as amines and phosphines, which induce the generation of enolates from enones via conjugate addition followed by trapping of the enolate by an aldehyde. Subsequent elimination of the amine or phosphine then affords the corresponding α-hydroxyalkylated enone unit **86**.

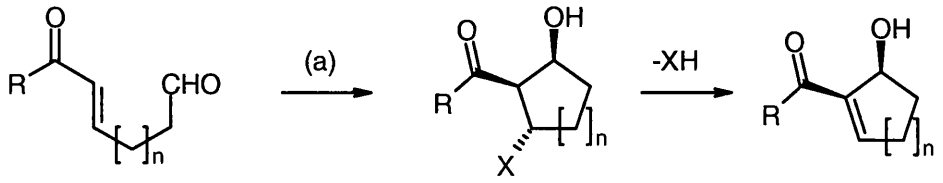


86

Scheme 49

It was not until 1992 that the first intramolecular Morita-Baylis-Hillman reaction was reported using DABCO as catalyst.[89] However this approach has displayed limited scope and applicability especially in view of the poor yields observed in the formation of six-membered rings. More recently, Murphy[90] has reported an intramolecular Morita-Baylis-Hillman reaction of different Michael acceptors mediated by secondary amines, phosphines and thiols (Scheme 50). Amine mediated cyclisations are limited to five- and six-membered ring systems with enones, whereas phosphines work best for the six- and seven-membered cyclisations, both

leading to the Baylis-Hillman products **87** in high yields. Thiols and thiolates were by far the most successful reactions proceeding for both the five- and six-membered substrates in 56-93% yield for the formation of the major adduct **88** with excellent stereoselectivity.



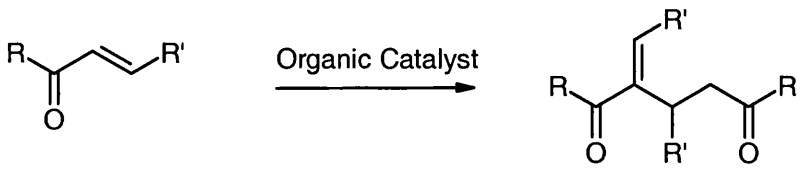
n= 1,2,3 **88** **87**

R= Alkyl, Ph (a) X= R_2N, R_3P^+, PhS

Scheme 50

I.4.3.3 Michael cycloisomerisation (Intramolecular Rauhut-Currier reaction)

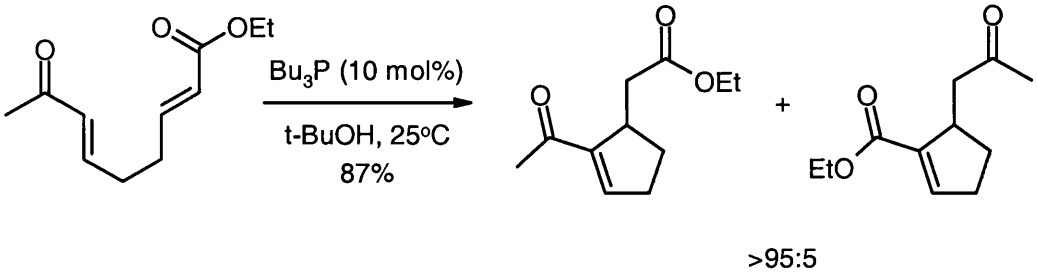
Predating the Morita-Baylis-Hillman reaction, the organocatalytic dimerization of electron deficient alkenes was first introduced by Rauhut and Currier in 1963.[91] This process is mechanistically related to the Morita-Baylis-Hillman reaction and can be considered as a vinylogous transformation (Scheme 51).



Scheme 51

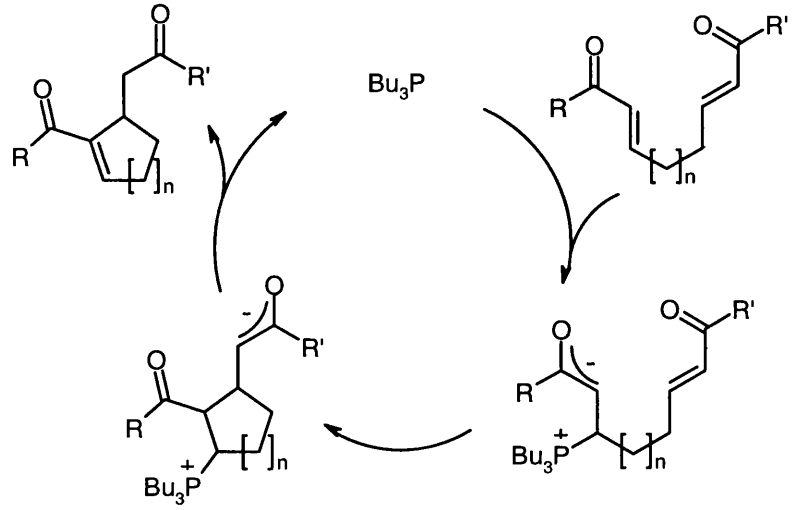
Recently an intramolecular variant of the Rauhut-Currier reaction has been simultaneously reported by two different groups, those of Roush[92] and Krische.[93] They both chose tri-*n*-butylphosphine as the catalyst in a polar solvent such as acetone or acetonitrile. Different symmetrical and unsymmetrical aliphatic and aromatic bis-enones and mixed substrates incorporating enone and enoate moieties were investigated. In all cases, the major product resulted from the addition of the phosphine to the more electrophilic of the two Michael acceptors, with the less electrophilic system serving as the Michael acceptor for the ring-closing step

(Scheme 52). In the absence of significant electronic differences, steric factors direct the regioselectivity.



Scheme 52

The mechanism for this Michael cycloisomerisation reaction, which may also be extended to the intramolecular Morita-Baylis-Hillman reaction, is detailed in Scheme 53:



Scheme 53

Thus, conjugate addition of tributylphosphine to the bis-enone provides the corresponding enolate which undergoes intramolecular conjugate addition to the appendant enone to afford a zwitterionic intermediate. Finally, proton transfer enables β-elimination of tributylphosphine to complete the catalytic cycle.

I.5 Project objectives

As we have hopefully highlighted above, methods involving carbocycle construction which feature initial regiospecific enolate formation *via* conjugate reduction followed by subsequent aldolisation or Michael reaction have seen many exciting developments in recent times.[94] Indeed, many of the references cited above were published during the course of the present thesis.

The aim of the present work is to define the scope of the tandem hydrosilylation-intramolecular aldol reaction as a general method for the synthesis of substituted carbocycles.

In particular:

i. To investigate the effect of substrate substitution pattern on reactivity and selectivity.

ii. To conduct a survey of alternative electrophiles other than aldehydes which can be incorporated into the substrate.

iii. To extend this study to generate larger ring sizes.

iv. To compare this methodology with the Rh (I) catalysed tandem intramolecular hydroboration aldol variant.

v. To investigate alternative transition metal catalysts to improve yields and diastereoselectivity in the synthesis of the corresponding carbocycles.

vi. To explore the use of asymmetric catalytic systems to probe the levels of enantioselectivity attainable on achiral substrates.

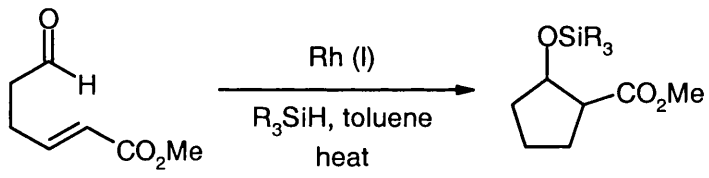
vii. To apply this methodology to the synthesis of biologically active carbocyclic nucleosides.

Chapter II Results and Discussion

II.1 Preliminary results in the Rh(I)-catalysed tandem hydrosilylation-aldol reaction

II.1.1 Introduction

In extending the scope and generality of this novel intramolecular reductive-aldol route to functionalised cyclopentanols, initial work was focused on determining the optimal experimental conditions which led to higher yields and levels of stereocontrol. Thus, a series of silanes, phosphine ligands and rhodium catalysts were screened and the effects of the temperature and amount of catalyst were investigated (Scheme 54). Methyl 6-oxo-2-hexenoate **78** was chosen as model substrate for the optimisation of the reaction conditions and its preparation will be the object of the following section.

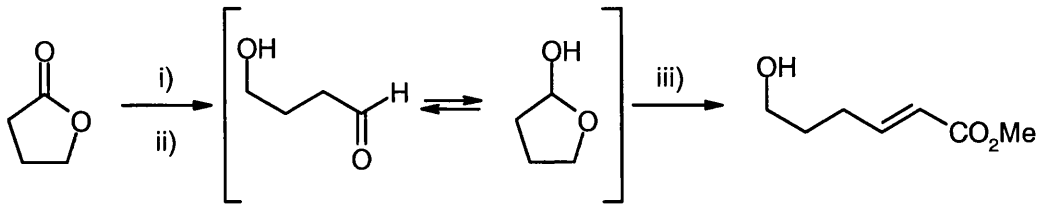


78

Scheme 54

II.1.2 Synthesis of the model substrate: methyl 6-oxo-2-hexenoate 78

The traditional route for the synthesis of this structural unit has generally involved reduction of a γ-lactone followed by Wittig olefination of the resultant lactol and subsequent oxidation.[95] Thus, preparation of methyl 6-oxo-2-hexenoate **78** was accomplished from commercially available γ-butyrolactone as shown in Scheme 55. Reduction with DIBAL at -70°C followed by *in situ* Wittig olefination of the corresponding lactol **89** using carbomethoxymethylene triphenylphosphorane led to hydroxy-ester **90** in low 34% yield as the single *E* diastereoisomer. Formation of the Wittig ylide by premixing the phosphonium salt with a base such as potassium *tert*-butoxide resulted in no significant improvement in yield or selectivity.



89 **90**

34% yield

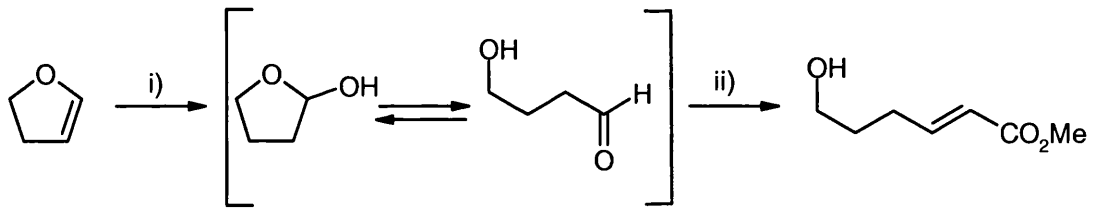
i) DIBAL (1.1 equiv), toluene, -70°C

ii) MeOH (3.0 equiv), -70°C

iii) $Ph_3P{=}CHCO_2Me$, toluene, 80°C

Scheme 55

In an attempt to improve this yield, a different approach starting from commercially available 2,3-dihydrofuran was then considered. Thus, addition of 1 equivalent of water and a catalytic amount of *p*-toluenesulfonic acid to a solution of 2,3-dihydrofuran in toluene gave butyrolactol **89**, which was subjected to *in-situ* Wittig olefination with carbomethoxymethylene triphenylphosphorane (Scheme 56).



89 **90**

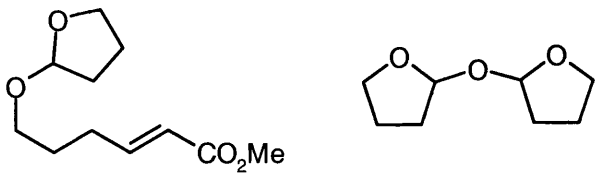
12% yield

i) H_2O (1.0 equiv), *p*-TsOH, toluene

ii) $Ph_3P{=}CHCO_2Me$, toluene, 80°C

Scheme 56

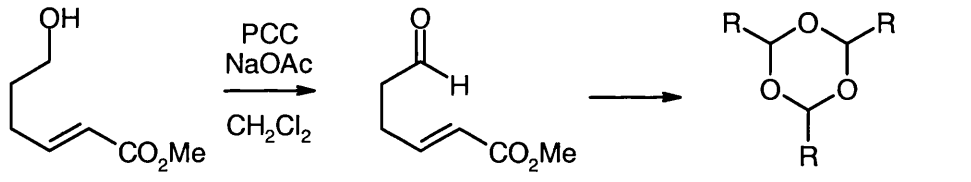
In this instance however, flash column chromatography afforded the hydroxy-ester **90** in an even lower 12% yield as a single *E* diastereoisomer together with two other side products, the THF-protected ester **91** and the dimer **92** in 34% and 27% yield respectively (Figure 8).



91 **92**

Figure 8

Nevertheless, subsequent pyridinium chlorochromate (PCC) oxidation[96] of methyl (*E*)-6-hydroxy-2-hexenoate **90** led to the required model substrate **78** albeit in a low 26% yield. It has been reported by several groups that aldehyde **78** readily undergoes trimerisation to the corresponding trioxane **93** (Scheme 57),[97] and indeed, trioxane **93** was present in the reaction mixture as a major contaminant. Addition of sodium acetate as a buffering agent to modify the slightly acidic nature of the reagent resulted in a reduction of the oligomerisation reaction and subsequently, an improved 39% yield of the desired aldehyde **78** was obtained. It is important to note that aldehyde **78** readily trimerises on standing at room temperature after several days. It is therefore desirable to prepare it freshly prior to use.

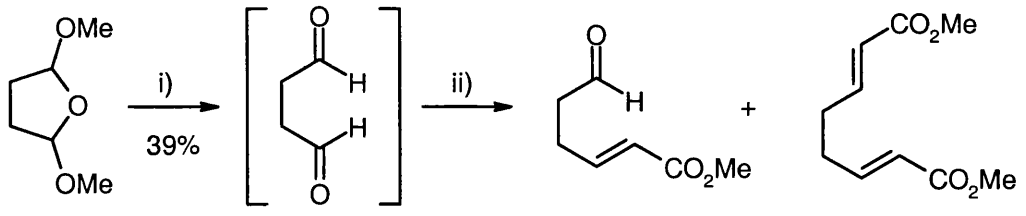


90 **78** **93**

39% yield R= $CH_2CH_2CH{=}CHCO_2Me$

Scheme 57

Direct Wittig olefination of freshly prepared succinaldehyde from 2,5-dimethoxy-tetrahydrofuran was also attempted for the preparation of the model substrate **78** according to a procedure reported by House (Scheme 58).[98] However, due to its ease to polymerisation, obtention of pure anhydrous succinaldehyde **94** proved to be very problematic and diester **95** was isolated as the major product in 30% yield whereas the desired aldehyde **78** was present in only 11% yield.



94 **78** **95**

11% 30%

i) HCl (0.6 N)

ii) $Ph_3P{=}CHCO_2Me$ (1.0 equiv), CH_2Cl_2, rt

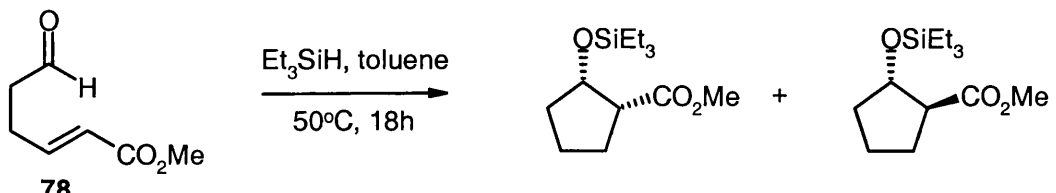
Scheme 58

In view of these limitations and constraints, and also because of our necessity for the use of such substrates, a more efficient alternative route for the preparation of methyl 6-oxo-2-hexenoates and related congeners was therefore sought, (*vide infra*). In the interim however, sufficient quantities of material could be accessed by the above routes for the key cyclisation studies.

II.1.3 Determination of the optimal reaction conditions

II.1.3.1 Effect of temperature and amount of catalyst

For a catalytic reaction to be of competitive synthetic value, a minimal amount of metallic catalyst is required. In the preliminary study, it was found that reaction of the model substrate **78** with excess triethylsilane and 1 mol% of rhodium catalyst in toluene at 50°C afforded the corresponding silylated *syn* and *anti* cyclopentenols in a 3:1 ratio in 81% yield.[80] Curiously, when the amount of metallic catalyst was increased from 1 mol% to 10 mol% a significant drop in yield was observed (64% yield) together with a reversal in stereoselectivity (*syn:anti* 1:2, Scheme 59). No reaction was observed when the rhodium catalyst was excluded from the reaction.



78

1 mol% $RhCl(PPh_3)_3$	81%	3	:	1
10 mol% $RhCl(PPh_3)_3$	64%	1	:	2
No catalyst	No reaction			

Scheme 59

The effect of temperature on the stereoselectivity of this reaction was also investigated and the results are summarised in Table 1. All reactions used 1 mol% Wilkinson's catalyst and were analysed after 4 h by ^{1}H NMR.

Temperature (°C)	*syn : anti*
25	No reaction
40	3:1
60	3:1
80	2:1
110	3:2

Table 1

As can be observed from Table 1, an increase in the reaction temperature resulted in a decrease in the *syn* selectivity, with 40-60°C being the range of temperature which led to the best results. The reason for both the reversal in selectivity when the amount of catalyst was increased and the decrease in the *cis* selectivity as the temperature was incrementally increased is not clear but will be discussed in further detail in Section 5.

II.1.3.2 Effect of silane, phosphine ligand and alternative rhodium catalysts

In the preliminary study of the rhodium (I) catalysed tandem hydrosilylation-intramolecular aldol reaction, optimal conditions (50°C and 1 mol% Rh) for the reaction of the model substrate methyl (*E*)-6-oxo-2-hexenoate (*E*)-**78** with Wilkinson's catalyst using triethylsilane as the hydride donor were established. The significant observation was also made that the stereochemical outcome of the reaction was not altered when the *Z* geometrical isomer of **78** was employed as substrate in an otherwise identical reaction, thereby indicating that the initial alkene geometry does not play a crucial role in influencing the possible transition states adopted for the subsequent intramolecular aldol reaction. As *E/Z* mixtures of α,β-unsaturated esters can therefore be used, this aspect is also clearly of preparative value since it obviates the necessity for separation of isomers by chromatography. At this stage, a catalyst and silane screen was also carried out and revealed several features of interest in terms of yield and selectivity. The results are summarised in

Table 2. Thus, increasing the bulk of the silane led to slightly lower *syn* selectivities and reduced yields of the corresponding cyclopentanol. The decreasing yield may be due to competing reactions such as 1,2-addition of the silane to the aldehyde or reductive elimination of the catalyst from the rhodium ester enolate which would give rise to the conjugate reduction product after work up. However none of these products were isolated. Finally, steric factors can certainly interfere as the bulk of the silane increases.

Silane[a]	Catalyst[b]	Ligand[d]	Yield (%)[h]	*syn:anti*
Et_3SiH	$RhCl(PPh_3)_3$	---	81	3.0:1.0
Me_2PhSiH	$RhCl(PPh_3)_3$	---	62	2.4:1.0
$MePh_2SiH$	$RhCl(PPh_3)_3$	---	49	2.8:1.0
Ph_3SiH	$RhCl(PPh_3)_3$	---	42	1.5:1.0
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	$P(Cy)_3$	79	2.5:1.0
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	DIPHOS[e]	78	3.3:1.0
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	$P(p\text{-Tol})_3$	27	1.0:2.0
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	$P(o\text{-Tol})_3$	53	2.0:1.0
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	$P(p\text{-An})_3$[f]	61	1.0:1.6
Et_3SiH	$[RhCl(C_8H_{14})_2]_2$[c]	$P(o\text{-An})_3$[f]	51	2.0:1.0
Et_3SiH	$RhH(PPh_3)_4$[g]	---	81	1.0:11.0

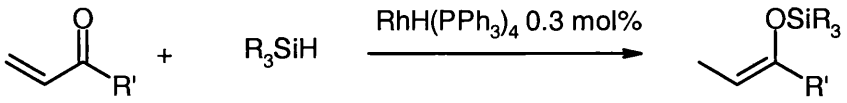
[a]2.1 equiv. of silane used. [b]1 mol% catalyst unless otherwise stated. [c]2.5 mol% catalyst [d]4 equiv. ligand with respect to catalyst unless otherwise stated. [e]2 equiv. ligand with respect to catalyst, DIPHOS (1,2-Bis(diphenylphosphino)ethane). [f]An = anisole. [g]Reaction complete after 6 h. [h]Yield of isolated products.

Table 2

The role of the ancilliary phosphine was also investigated. By modifying the phosphine ligands attached to the metal it was hoped to improve its catalytic activity. As previously stated by Larock[47] in his studies of the Rh (I)-catalysed intramolecular hydroacylation reaction, isolation of catalysts of type $RhClL_3$ with tertiary phosphines other than triphenylphosphine can be unsuccessful due to their increased solubility in a variety of solvents and their sensitivity towards oxygen. In view of these difficulties, all catalysts were prepared *in situ* by addition of the corresponding phosphine to a solution of chlorobis(cyclooctene) rhodium (I) dimer.

In most instances, the new catalysts compared favourably with the selectivity observed using Wilkinson's catalyst. However there are two notable exceptions to the general trend of *syn* selectivity when *p*-substituted triarylphosphines were used as ligands. In these cases, a reversal in selectivity was observed and the low yields could indicate decomposition of the complex and subsequent contamination with the phosphine oxide. The bidentate phosphine ligand (DIPHOS) provided the best combination of yield and *syn* selectivity. This result is very promising for future work in asymmetric catalysis since it suggests that chiral bidentate phosphines such as BINAP or CHIRAPHOS are compatible with this new methodology.

But the most intriguing observation of all however was that a complete reversal of stereoselectivity in favour of the *anti* cyclopentanol was noted when hydridotetrakis(triphenylphosphine) rhodium (I) was employed as the catalyst. Although the observed preference in our preliminary study[80] was relatively modest (*syn:anti;* 1:2) further work using carefully prepared rhodium catalyst reproducibly favours the *anti* product in high yield and with an excellent selectivity (*syn:anti;* 1.0:11.0). In addition, selection of hydridotetrakis(triphenylphosphine) rhodium (I) resulted in a significant reduction of the reaction time, from 16 h in the case of Wilkinson's catalyst to only 6 h. This result finds precedent in 1993, when Zheng[99] reported that hydridotetrakis(triphenylphosphine) rhodium (I) was an effective catalyst for the 1,4-addition of silanes to α,β-unsaturated carbonyl compounds (Scheme 60).



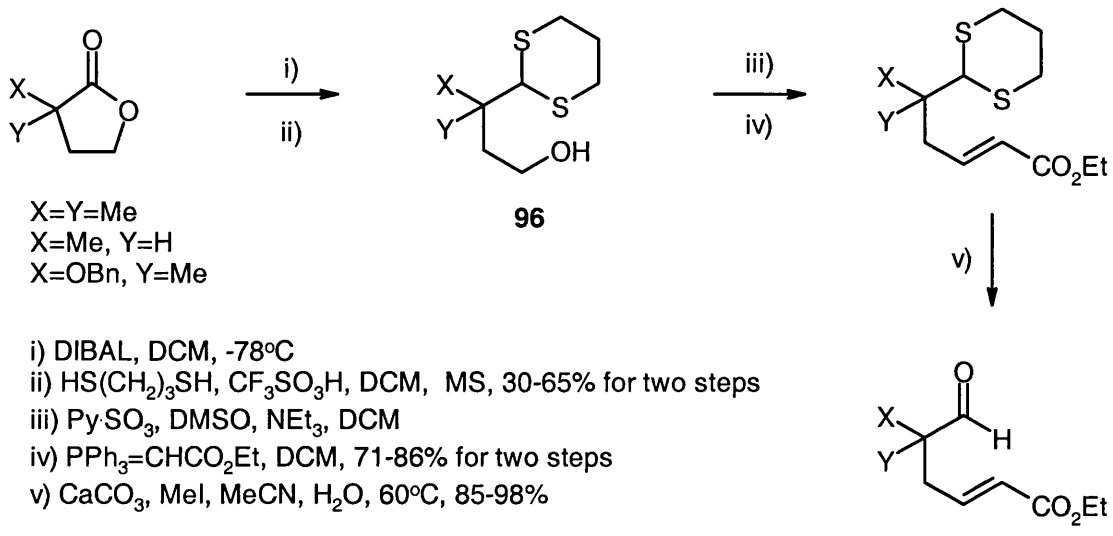
Scheme 60

In view to these results, we have therefore elected to use triethylsilane as the hydride source in all of our following studies on the tandem hydrosilylation-aldol reaction and to examine our two best catalytic systems, *viz.*, Wilkinson's catalyst and hydridotetrakis(triphenylphosphine) rhodium (I).

II.2 Synthesis of functionalised cyclopentanoids from 6-oxo-2-hexenoates *via* rhodium (I)-catalysed tandem hydrosilylation-aldol reaction

II.2.1 Previous synthesis of 6-oxo-2-hexenoate derivatives

6-Oxo-2-hexenoate units such as **78** are proving to be especially valuable building blocks in organic synthesis, especially for ring construction. Thus, it has served, *inter alia* as a dienophile,[95] as a key precursor for several variants of the tandem Michael-aldol reaction leading to functionalised cyclopentanols,[80],[90] and also as a substrate for the stereoselective synthesis of cyclobutanols.[100] As previously discussed in Section 1, this structural unit has traditionally been prepared by reduction of a γ-lactone followed by Wittig olefination of the resultant lactol and subsequent oxidation. Such a protocol avoids the problematic alternative of manipulating and controlling sensitive dialdehyde substrates, as we have seen in the generation and use of pure anhydrous succinaldehyde from 2,5-dimethoxytetrahydrofuran for the parent of the series. [98],[90b] Examination of the literature reveals however that the preparation of even more highly substituted analogues can often require long multistep routes, as in the recently reported syntheses of several 5,5-disubstituted 6-oxo-2-hexenoates[100a] which required a seven step sequence involving several protection and deprotection steps (Scheme 61).



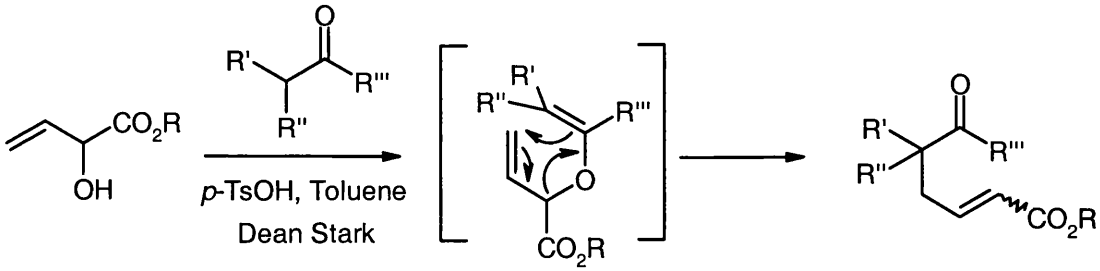
Scheme 61

Thus, substituted 6-oxo-2-hexenoates were prepared from γ-butyrolactone or α-benzyloxy-γ-butyrolactone by mono or dimethylation followed by reduction and ring-opening of the corresponding lactol with 1,3-propane dithiol. A number of subsequent synthetic transformations involving Swern oxidation of dithioacetals of type **96**, Wittig olefination, and final deprotection gave the required series of 6-oxo-2-hexenoates. In view of this situation we therefore set out to develop a simple atom efficient alternative route, especially to 5,5-disubstituted 6-oxo-2-hexenoates.

II.2.2 Preparation of cyclisation precursors *via* Claisen rearrangement

II.2.2.1 Synthesis of simple 6-oxo-2-hexenoate derivatives

Over the years the Claisen rearrangement has emerged as a valuable synthetic tool for the formation of new carbon-carbon bonds in terms of its broad applicability and atom efficiency.[101] It was therefore envisaged that the required 6-oxo-2-hexenoate unit **97** would be accessed from allyl alkenyl ether **98** *via* [3,3] sigmatropic rearrangement (Scheme 62). The intermediate **98** itself would be generated by *in situ* mild acid catalysed condensation and dehydration of a 2-hydroxy-3-butenoate **99** with an aldehyde. Precedent for such an approach exists in the synthesis of various substituted 4-pentenals from allyl alcohol itself[102] and this reaction can be easily run on large scale.[103] To the best of our knowledge however, Claisen rearrangements of substrates such as **97** possessing an electron withdrawing ester group have not previously been reported.



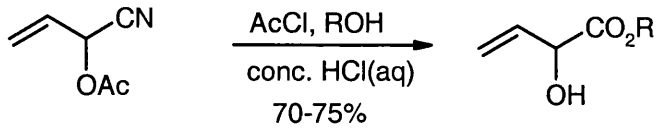
99a R= Me
99b R= *i*Pr

98

97

Scheme 62

In the first instance, the required 2-hydroxy-3-butenoates **99a-b** were easily prepared from commercially available 2-acetoxy-3-butenenitrile using a literature method.[104]



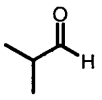
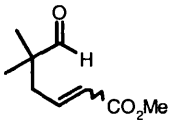
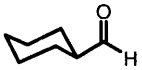
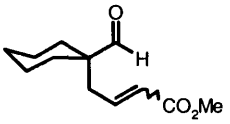
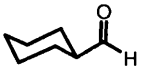
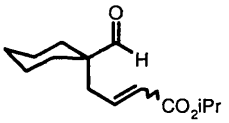
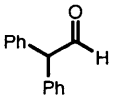
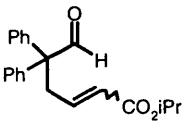
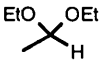
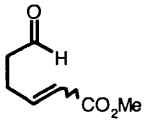
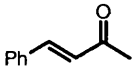
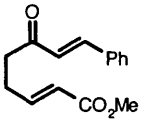
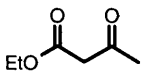
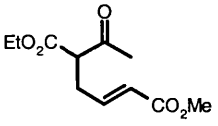
99a R=Me
99b R=*i*Pr

Scheme 63

As can be seen from Scheme 63, dissolution of 2-acetoxy-3-butenenitrile in a saturated hydrochloric acid solution of the appropriate alcohol afforded, after distillation, the desired 2-hydroxy-3-butenoates **99a-b** in 70-75% yield. A mixture of **99a-b** with slightly more than one molar equivalent of the carbonyl compound or derived acetal was then refluxed in toluene solution for 48 h in the presence of a catalytic amount of *para*-toluenesulfonic acid and using a Dean and Stark trap for the azeotropic removal of water. After [3,3] sigmatropic rearrangement of the allyl alkenyl ether intermediate **98**, the corresponding 6-oxo-2-hexenoate products **97**, produced as an *E:Z* mixture of geometrical isomers, were then isolated by flash chromatography (Scheme 62).

In order to evaluate the scope and utility of this simple preparation, a representative range of aliphatic and aromatic aldehydes, as well as alternative electrophiles including acetals, enones and β-keto esters was examined. The results of this study are shown in Table 3 and reveal several features of interest. Thus, as noted in Entries 1 and 2, reaction of methyl 2-hydroxy-3-butenoate **99a** with aliphatic aldehydes gave acceptable yields of the desired methyl 5,5-disubstituted 6-oxo-2-hexenoates with a slight preference for formation of the *E* geometrical isomer. Although the desired compound was isolated as the major product in both of these examples, this was also accompanied by the formation of a substituted 5-vinyl-[1,3]dioxolan-4-one derivative **100a-b** (Scheme 64) as a significant side product in 25-30% yield. A plausible mechanistic rationale is shown in Scheme 64 and involves two competing pathways for evolution of the hemiacetal intermediate **101**. Thus, if the desirable dehydration step to form the vinyl ether moiety is slow, intramolecular

transesterification can occur with loss of methanol. It was then postulated that replacement of the methyl ester moiety by the more bulky *iso*-propyl congener would favour the formation of the desired 6-oxo-2-hexenoate over the secondary product **100**.

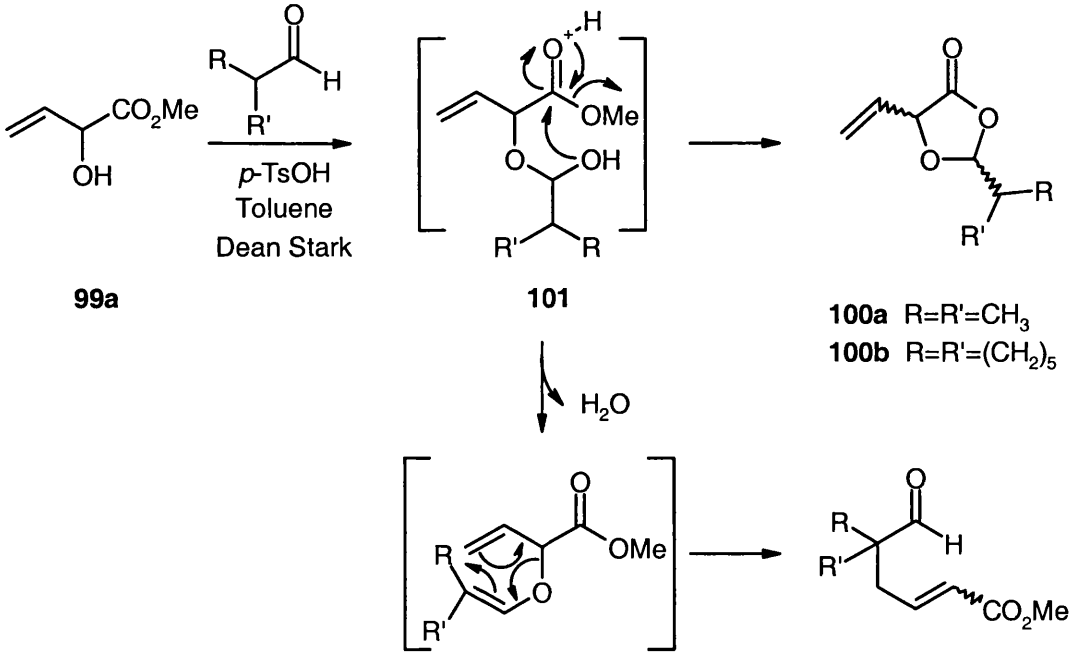
Entry	Electrophile	Product		Yield %[a]	Ratio *E:Z*
1			**102**	53	2:1
2			**103a**	49	1.5:1
3			**103b**	61	1.5:1
4			**104**	64	2:1
5			**78**	46[b]	2.2:1
6			**105**	58	Only *E*
7			**106**	39	Only *E*

[a]Isolated yields. [b]The reaction was carried out using a Soxhlet extractor in the presence of 4Å MS for the removal of ethanol.

Table 3

Gratifyingly, selection of *iso*-propyl 2-hydroxy-3-butenoate **99b** led to an improved 61% yield of the corresponding 6-oxo-2-hexenoate product **103b** (Entry 3). The reaction of diphenylacetaldehyde with reagent **99b** also proceeded in comparable yield and with a similar ratio of isomers (Entry 4). We also attempted to use

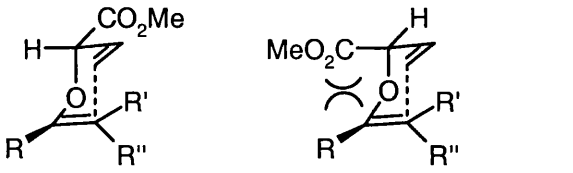
acetaldehyde itself for preparation of the non-substituted parent substrate but this reaction was unsuccessful, presumably because of volatility problems. Selection of the diethyl acetal however (Entry 5) circumvented this difficulty therefore suggesting that a similar solution could also be employed for aldehydes which are prone to oligomer formation. It was also possible to use ketonic substrates such as benzylidene acetone (Entry 6) or ethyl acetoacetate (Entry 7) to furnish even more highly functionalised building blocks containing an embedded 6-oxo-2-hexenoate unit.



99a **101** **100a** R=R'=CH_3 **100b** R=R'=$(CH_2)_5$

Scheme 64

From a stereochemical standpoint it is interesting to contrast the modest *E/Z* stereoselectivity observed in the use of aldehyde derivatives (Entries 1-5) with the exclusive formation of the *E* geometrical isomers noted for ketonic substrates (Entries 6 and 7). This is most readily explained in terms of a classical chair-like transition state in which the ketonic alkyl substituent R reinforces an equatorial preference for the alkoxycarbonyl group as shown in Figure 9, whereas in the case of aldehyde substrates (R=H) such an interaction is absent. Moreover the additional substituents (R', R'') may also encourage to some extent a boat-like pathway.



Favoured Disfavoured for larger R

R= CH=CHPh, R'=R"=H (Entry 6)
R= CH_3, R'= CO_2Et, R"=H (Entry 7)

Figure 9

II.2.2.2 Extension of the methodology to more complex carbocyclic skeletons

Having explored the scope of the reaction with various aldehydes and alternative electrophiles, we then wished to extend this methodology to more complex frameworks, such as natural occurring terpenes. In the first instance, we decided to examine the behaviour of the acyclic terpene citronellal (Figure 10). Unfortunately, only a complex mixture of polymerisation compounds was obtained as shown by the crude ^1H NMR spectrum.

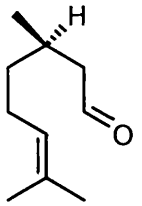
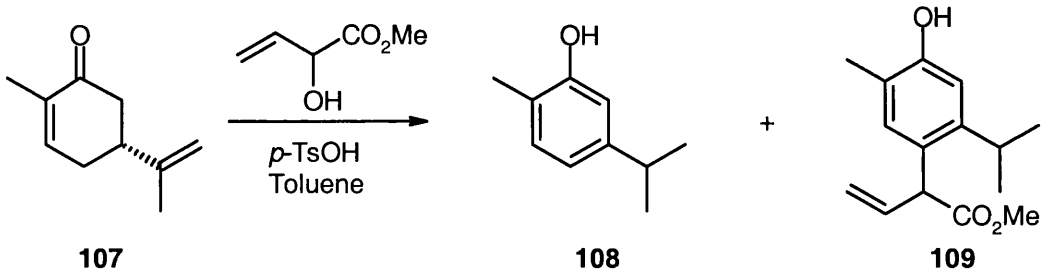


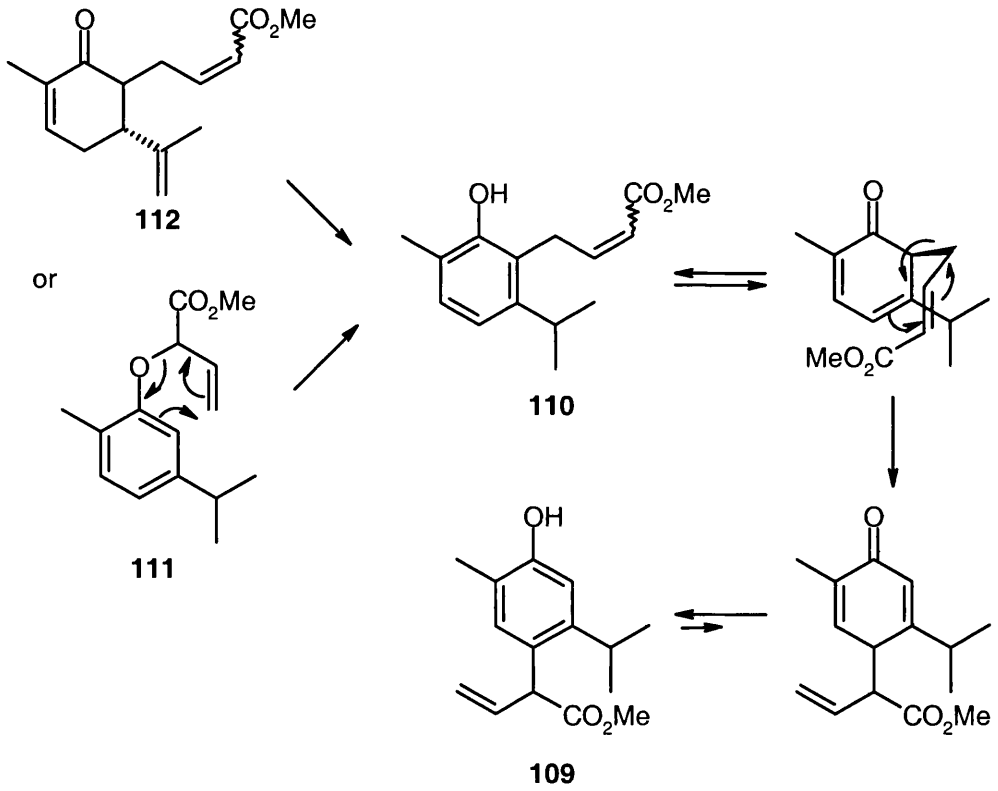
Figure 10

In order to prevent polymerisation problems, we then elected to study a ketonic substrate such as the monocyclic terpene (*R*)-carvone **107** (Scheme 65). As shown in Scheme 65, although the dominant process was the well precedented[105] acid catalysed double bond isomerisation to the phenol carvacrol **108** (78%), it was of particular interest to note that the sole adduct formed was phenol **109** (18%).



Scheme 65

The formation of phenol **109** certainly involves a second rearrangement of **110** (Scheme 66).



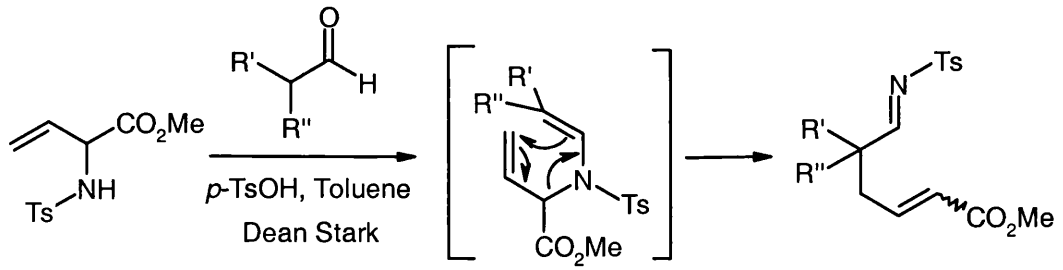
Scheme 66

Although the relative timing of the double bond isomerisation sequence is unknown, **110** can be generated either by [3,3] sigmatropic rearrangement of the aryl allyl ether **111** or by acid-catalysed isomerisation of the initially anticipated product **112**. Although the double Claisen-Cope migration phenomenon has been observed for phenolic ethers possessing two flanking *ortho* substituents, when one of the *ortho* positions is free, mixtures of *ortho* and *para* products are usually obtained.[106] In the

present instance however such an *ortho* intermediate **110** would possess substituents on four contiguous carbon centres and relief of steric congestion may well contribute a substantial driving force for the second Cope rearrangement.

II.2.2.3 Attempted preparation of 6-imino-2-hexenoate derivatives

With the aim of extending the scope of our rhodium cyclisation reaction, replacement of the aldehydic function by an imino group was therefore sought. As the aza-Claisen rearrangement of *N*-allyl enamines is a well precedented reaction,[107] we therefore envisaged the preparation of such substrates *via* the same type of Claisen rearrangement approach starting from a vinyl glycine derivative (Scheme 67). In order to increase the stability of the resultant 6-imino-2-hexenoate **113** after [3,3] sigmatropic rearrangement of **114** and also to enhance its electrophilic character, we therefore elected to protect the starting vinyl glycine as the corresponding *N*-*p*-toluenesulfonyl derivative **115**.

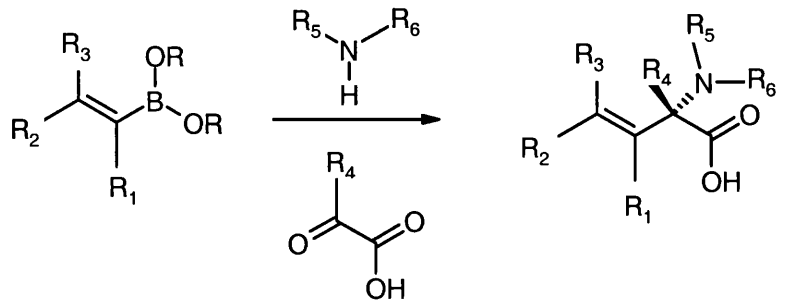


115 **114** **113**

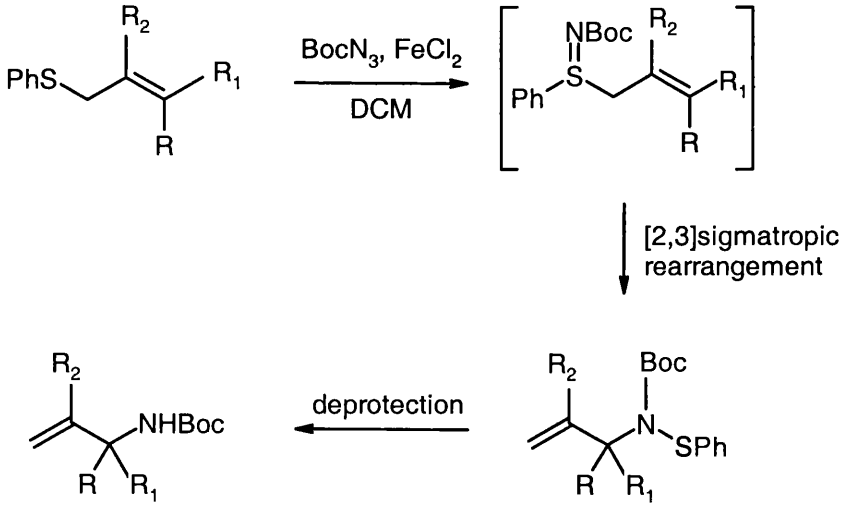
Scheme 67

There has been increasing interest in recent years for the discovery of practical methods of preparing novel α-amino acid derivatives containing β,γ-unsaturated side chains. Some amino acids of this type can profoundly alter the biological properties of certain natural amino acids, converting them from enzyme substrates to irreversible inhibitors with potential therapeutic utility.[108] Consequently, several methods for the synthesis of vinyl glycine and related β,γ-unsaturated α-amino acids have been reported.[109] Recent advances include a three-component variant of the Mannich reaction involving condensation of a vinylboronic acid with an amine and an α-keto acid as reported by Petasis (Scheme 68)[110] or the Fe (II)-catalysed

imidation of allyl sulfides and subsequent [2,3]-sigmatropic rearrangement reported by Bach (Scheme 69).[111]

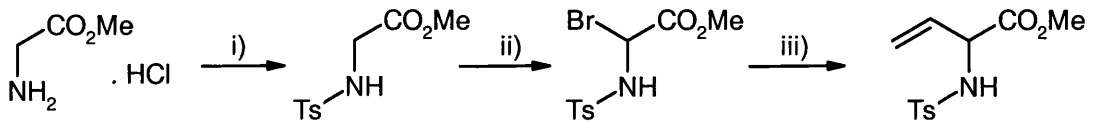


Scheme 68



Scheme 69

Vinyl glycine derivatives have also been traditionally prepared from the corresponding inexpensive amino acid precursors, such as methionine methyl ester [112] or glycine methyl ester.[113] In this context and in order to avoid the use of unpleasant sulphur compounds, we elected to prepare the required vinyl glycine derivative **115** from glycine methyl ester hydrochloride by adaptation of the procedure reported by Castelhano and Krantz (Scheme 70).[113]



116 **117** **115**

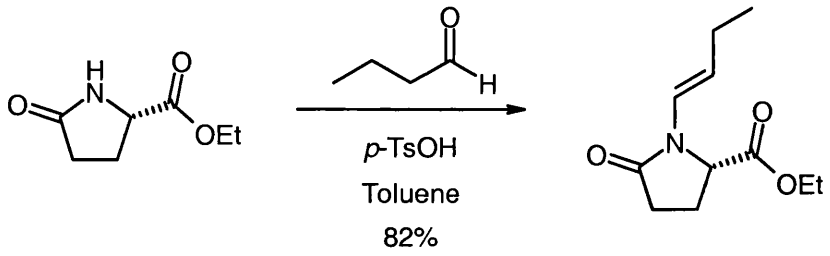
i) TsCl, NEt_3, THF, 98%
ii) Br_2, CCl_4
iii) Vinylmagnesium bromide (1M in THF), THF, -78°C, 24% (2 steps)

Scheme 70

Hence, in the first instance, commercially available glycine methyl ester hydrochloride was protected as its corresponding *p*-toluenesulfonyl derivative by reaction with tosyl chloride in the presence of two equivalents of triethylamine. Recrystallisation from *n*-pentane afforded *N*-protected glycine **116** in 98% yield. Bromination of **116** afforded the highly hydrolytically unstable bromoglycinate **117** which was immediately used in the next step without further purification. The formation of intermediate **117** was however confirmed by ^1H NMR which showed disappearance of both the methylene and the NH resonance present in **116** at 3.78 ppm and 5.05 ppm respectively and the appearance of a new signal at 6.00 ppm corresponding to the CH and the NH resonances in **117**. This coalescence of the NH and CH resonances has already been observed in a series of *N*-sulfonyl bromoglycinates[114] and it strongly suggests proton exchange on the NMR time-scale, presumably catalysed by traces of HBr. Subsequent displacement of the bromide atom in **117** with vinylmagnesium bromide at -78°C afforded, after column chromatography, the desired *N*-*p*-toluenesulfonyl vinyl glycine **115** in an overall 24% yield after two steps as a brown oil.

With the required precursor in hand, we then attempted the acid catalysed condensation of one mol of **115** with slightly more than one molar equivalent of isobutyraldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid as outlined in Scheme 67 (R'=R''=Me). After heating for three days in refluxing toluene, no evolution of water was observed in the Dean and Stark trap and t.l.c. revealed the sole presence of unreacted starting material. We therefore reasoned that the strong electron withdrawing character of the *N*-*p*-toluenesulfonyl protecting

group would significantly reduce the inherent nucleophilicity of the nitrogen atom, thus preventing condensation with the aldehyde. Examination of the literature discloses however several examples of condensation between proline derivatives with carbonyl compounds[115] as outlined in Scheme 71, suggesting that replacement of the *p*-toluenesulfonyl group at the nitrogen atom with a less electron withdrawing protective group such an acyl group may well encourage condensation.

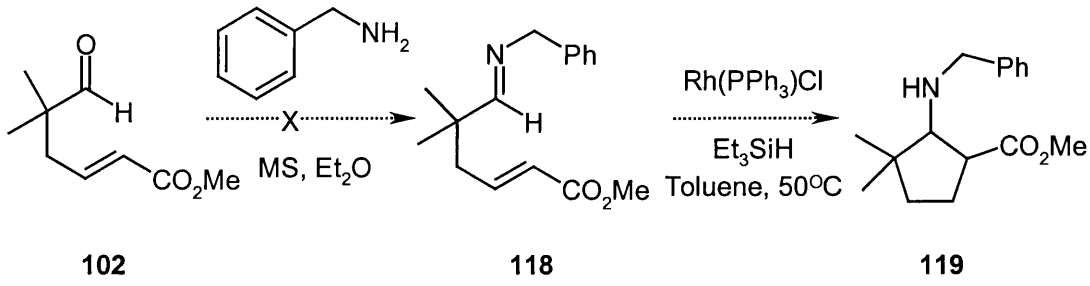


Scheme 71

In addition, Lewis acid catalysis of the Claisen rearrangement is well documented[116] and can considerably increase the reaction rate. Titanium tetrachloride has been reported to be a highly efficient catalyst for enamine formation from hindered carbonyl compounds and it was also found to be a suitable catalyst for the aza-Claisen rearrangement.[107b] Whereas the uncatalysed aza-Claisen rearrangement requires temperatures near to 250°C, the presence of a catalytic amount of titanium tetrachloride allows the reaction to occur at a convenient rate in refluxing benzene and at a slow rate even at room temperature. At this point, because of time constraints, we did not explore this transformation in further detail. Additional research in order to establish the feasibility of this transformation from a differently protected vinyl glycine derivative in the presence of alternative Lewis acid catalysts such as titanium tetrachloride is certainly of interest, as it would provide a simple and atom efficient method for the synthesis of 2-imino-6-hexenoate derivatives from a very inexpensive source.

Imines are traditionally prepared by an amination reaction from the appropriate aldehyde precursor. We therefore elected to attempt preparation of the corresponding 2-imino-6-hexenoate *via* direct condensation of the previously

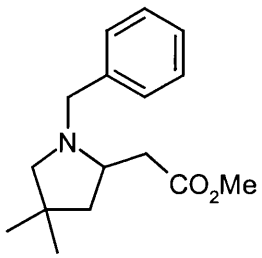
synthesised methyl 5,5-dimethyl-2-oxo-6-hexenoate **102** with benzylamine in the presence of 4Å molecular sieves for the removal of water (Scheme 72).



102 **118** **119**

Scheme 72

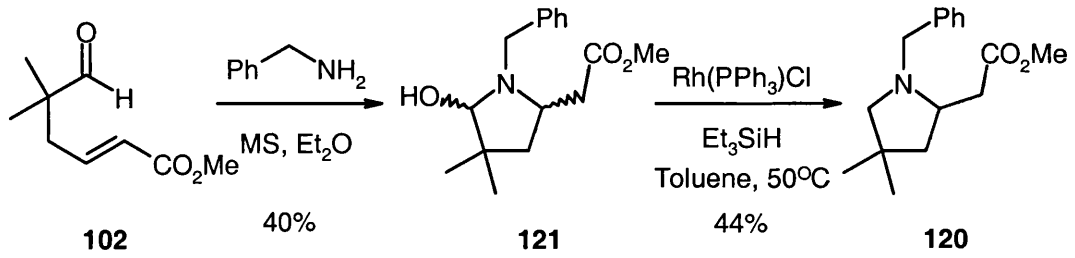
Thus, after filtration of the sieves and evaporation of the solvent, intermediate **118** was immediately subjected to our rhodium (I) cyclisation conditions. Surprisingly, none of the desired 2-amino-cyclopentane carboxylate **119** was obtained and instead the unexpected *N*-protected pyrrolidine **120** was the only product recovered after column chromatography (Figure 11).



120

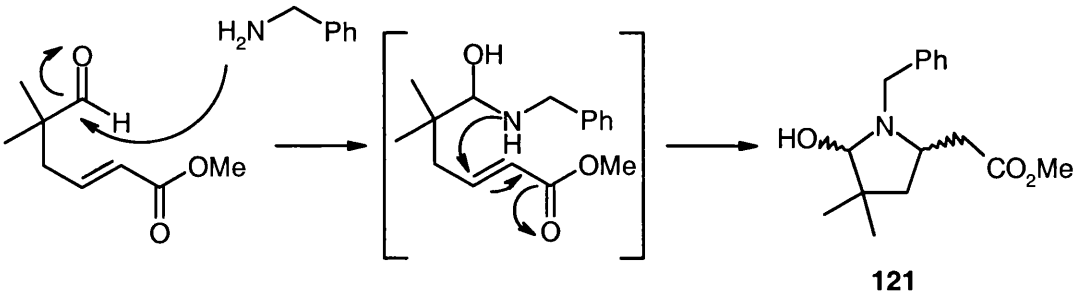
Figure 11

In view of this unexpected result, we therefore determined to isolate the initial product of condensation of benzylamine and aldehyde **102**. Careful analysis of the ^{1}H NMR spectrum revealed the absence of the expected imine **118**. Instead, 5-hydroxy-pyrrolidine **121** was obtained as a mixture of diastereomers in a 1:1 ratio and was further confirmed by the presence of a broad OH peak at 3480 cm^{-1} in the IR spectrum (Scheme 73).



Scheme 73

A plausible mechanistic rationale involves addition of benzylamine to the more reactive aldehydic function in the first instance and subsequent intramolecular Michael addition of the resulting hemiaminal. Thus, if the desirable dehydration step to form the required imine is slow, intramolecular 1,4-addition can occur to afford hydroxy-pyrrolidine **121** (Scheme 74). Finally, treatment of hydroxy-substituted pyrrolidine **121** with Wilkinson's catalyst and a hydride source such as triethylsilane afforded the reduction product **120** in 44% yield (Scheme 73). Although there was no precedent in the literature for this transformation, we decided not to pursue this study as it detracted from our main objectives.



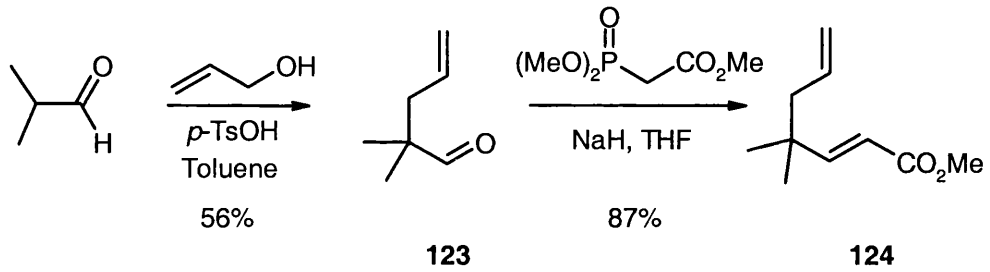
Scheme 74

II.2.3 Preparation of 4,4-disubstituted 6-oxo-2-hexenoate precursors

II.2.3.1 Synthesis of methyl 4,4-dimethyl-6-oxo-2-hexenoate **122**

The previously described methodology provides a simple access especially to 5,5-disubstituted 6-oxo-2-hexenoates. In order to investigate the effect of the substitution pattern in the cyclisation precursors, substitution in *C*-4 was also sought and the 4,4-dimethyl derivative was accordingly selected. The synthesis of methyl 4,4-dimethyl-6-oxo-2-hexenoate **122** has already been reported by a multistep process which

includes several protection and deprotection steps.[117] We have prepared it by an alternative procedure in three steps starting from isobutyraldehyde and allyl alcohol. Thus, 2,2-dimethyl-4-pentenal **123**, which is also commercially available, was synthesised by the method reported by Brannock[102] from allyl alcohol and isobutyraldehyde *via* Claisen rearrangement of the allyl alkenyl ether intermediate (Scheme 75). Fractional distillation of the reaction mixture afforded the desired product **123** in 56% yield.



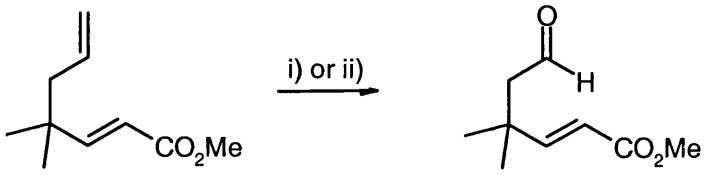
123 **124**

Scheme 75

Preparation of the α,β-unsaturated ester **124** from pentanal **123** was initially attempted using classical Wittig reaction conditions with carbomethoxymethylene triphenylphosphorane (1.2 equiv) in toluene at 80°C for 24 h. Disappointingly, only a very low 20% yield of the desired compound was recovered after column chromatography. Lithium cations affect the course of the Wittig reaction and its modified version, the Horner-Wadsworth-Emmons reaction (HWE), in many important ways. We then decided to attempt the Masamune-Roush[118] procedure utilising lithium chloride and an amine (DIPEA) with trimethylphosphonoacetate. After complete consumption of the starting material, purification of the reaction mixture by flash column chromatography afforded **124** in 35% yield as the *E* geometrical isomer. Significant improvements were finally made by changing the nature of the cation, from lithium to sodium, using the classical conditions of Horner- Wadsworth- Emmons olefination[119] with trimethylphosphonoacetate in the presence of sodium hydride which afforded **124** in a high 87% yield as a single *E* diastereoisomer.

Finally, selective ozonolysis of the terminal alkene in **124** is required to afford the desired aldehyde **122**. The presence of two double bonds in the substrate requires

precise control of the ozone flow in order to cleave the more electron rich double bond selectively over the other less reactive double bond. Veysoglu[120] has reported a convenient procedure for the selective cleavage of the more reactive olefinic linkage in a series of representative dienes. Control of these selective reactions is achieved by inclusion of a small amount of the appropriate ozonizable dye as an internal standard. Thus, a solution of commercially available Solvent Red 23 (Sudan III) in dichloromethane/ethanol (2:1) was used to allow selective cleavage of the terminal double bond in alkene **124** and ozonolysis was carried out until the red colour was just discharged (Scheme 76). However, in our case, this attempt was unsuccessful and ^{1}H-NMR analysis revealed a mixture of over oxidised products.

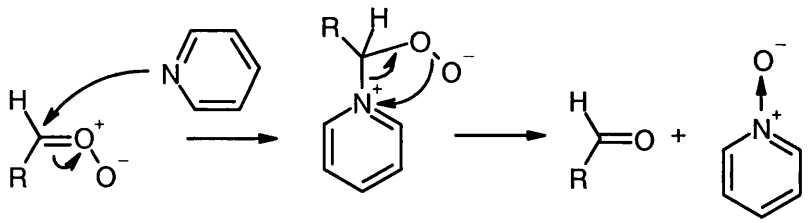


124 **122**

i) O_3, CH_2Cl_2/EtOH 2:1, -78°C, Sudan III
ii) O_3, CH_2Cl_2, -78°C, pyridine, then Me_2S, 48% yield

Scheme 76

An alternative method was therefore attempted. Slomp and Johnson[121] have reported the effect of pyridine for selective ozonolysis of compounds that possess two different double bonds. A possible explanation is that the pyridine slows the ozonolysis reactions enough so that difference in electronegativity of the two double bonds becomes important. A decrease in both the immediate ozone concentration and the electrophilic activity of the ozone could result from the formation of ozone complexes and the latter may have different selectivity characteristics from ozone itself. The pyridine, which probably solvates the carbonyl-ylide intermediate, could react with the latter to form pyridine oxide plus a second molecule of aldehyde. The reduction step is still necessary not to decompose ozonides as usual, but to reduce the pyridine-ozone complexes and the pyridine oxide (Scheme 77).

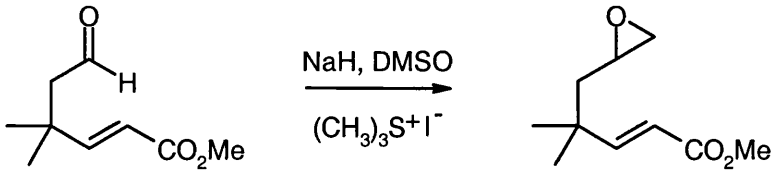


Scheme 77

In the event, one volume per cent of pyridine was added to a solution of the alkene **124** in dichloromethane. After reduction using an excess of dimethylsulfide, flash column chromatography afforded the aldehyde **122** in 48% yield (Scheme 76). Consequently, we have accomplished the synthesis of 4,4-dimethyl-6-oxo-2-hexenoate **122** by a shorter protocol than existing routes in the literature. Moreover, this method offers the advantage of permitting substituent variation at *C*-4 of the resulting 6-oxo-2-hexenoates by a simple choice of the appropriate starting aldehyde.

II.2.3.2 Synthesis of methyl 4,4-dimethyl-5-oxiranyl-2-pentenoate **125**

As previously mentioned, replacement of the aldehyde in the cyclisation substrates by alternative electrophiles also constitutes one of our main objectives. In this context, the oxirane functionality was envisaged as epoxides are very reactive electrophiles and can be readily accessed from aldehyde precursors. Several methods have been reported that enable direct transformation of aldehydes into epoxides, thus avoiding an intermediate olefination step.[122] In the first instance, Delmas procedure[123] was attempted from our previously synthesised aldehyde **122** using inexpensive trimethylsulfonium bromide with potassium hydroxide in acetonitrile and in the presence of a quantified amount of water (0.25 equiv). Unfortunately, although the present conditions proved to be quite general for the synthesis of epoxides from aromatic and heteroaromatic aldehydes they are not suitable for aliphatic aldehydes such as **122** and only starting material was recovered after column chromatography. Subsequently, we elected to prepare epoxide **125** by an alternative method using the Corey sulphur ylide epoxidation conditions[124] outlined in Scheme 78.



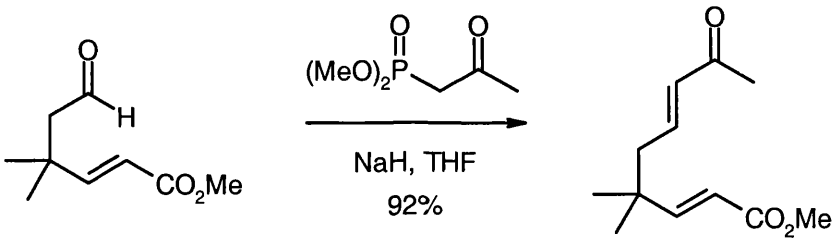
122 **125**

Scheme 78

Thus, the base, sodium methylsulfinylmethide, was prepared by heating a mixture of sodium hydride with excess dimethylsulfoxide and stirring under nitrogen at 75°C until evolution of hydrogen ceases. After cooling down to room temperature, a solution of trimethylsulfonium iodide in dimethylsulfoxide was added followed by aldehyde **122**. In this occasion, epoxide **125** was obtained in 33% yield after column chromatography as a clear oil.

II.2.3.3 Synthesis of methyl 4,4-dimethyl-8-oxo-2,6-nonadienoate **126**

Substrate **126** in which the aldehyde functionality was replaced by an enone moiety was initially selected with the intention of probing a non-rhodium catalysed tandem hydrometallation-Michael addition sequence. As previously discussed in the introductory review, Evans[66] has demonstrated that when boranes are used as hydride donors, α,β-unsaturated ketones undergo hydroboration even without the presence of the metallic catalyst whereas α,β-unsaturated esters are unreactive under the same conditions. In addition, several groups have recently reported related tandem hydrometallation-Michael addition processes using bis-enones as substrates.[81] For the case of unsymmetrical enones, as might have been anticipated, the reagent was unable to distinguish the electronic differences between the two enone moieties in the hydrometallation event, leading to a mixture of the two possible structural isomers. We anticipated however that the notable electronic difference between enone and enoate moieties in substrate **126** would presumably result in higher levels of chemoselectivity for the hydrometallation step. With these thoughts in mind, methyl 4,4-dimethyl-8-oxo-2,6-nonadienoate **126** was readily accessed from the previously synthesised aldehyde **122** by Horner-Wadsworth-Emmons olefination (Scheme 79).



122 **126**

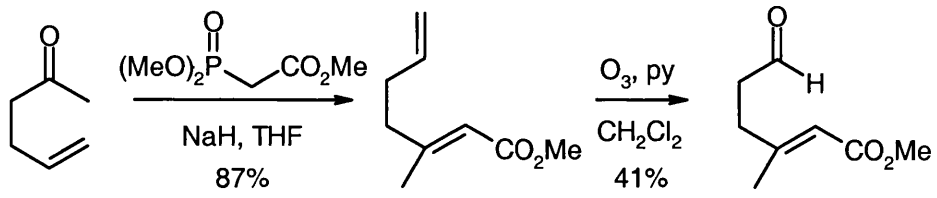
Scheme 79

Thus, treatment of aldehyde **122** with sodium hydride and dimethyl-(2-oxopropyl)-phosphonate in tetrahydrofuran afforded methyl 8-oxo-2,6-nonadienoate **126** in 92% yield after column chromatography.

II.2.4 Preparation of 6-oxo-2-hexenoate precursors containing alkyl substituents in *C*-3

II.2.4.1 Synthesis of methyl 3-methyl-6-oxo-2-hexenoate **127**

Substitution at *C*-3 was also sought. 6-Oxo-2-hexenoate **127** containing a methyl substituent at the desired position was accordingly prepared from commercially available 5-hexen-2-one. We note parenthetically that the Horner- Wadsworth-Emmons olefination using trimethylphosphonoacetate and sodium hydride proceeded much more efficiently (87% *versus* 43%) when the reaction was conducted in refluxing tetrahydrofuran rather than in 1,2-dimethoxyethane as previously reported for the corresponding ethyl ester congener (Scheme 80).[125]



128 **127**

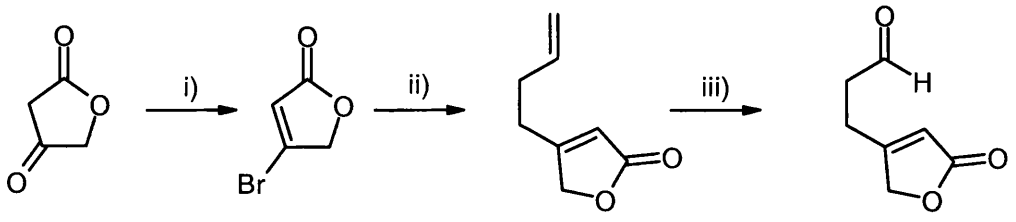
Scheme 80

Thus, alkene **128** was obtained in 87% yield as a 2:1 mixture of *E* and *Z* isomers, which were separated by chromatography. Finally, selective ozonolysis of the

terminal double bond of the *E* isomer of intermediate **128** in the presence of one volume percent of pyridine followed by reductive work up afforded the 3-substituted aldehyde **127** in 41% yield.

*II.2.4.2 Synthesis of 3-(5-oxo-2,5-dihydrofuran-3-yl)propionaldehyde **129***

Having synthesised the most simple 3-substituted 6-oxo-2-hexenoate, we then elected to prepare unsaturated lactone **129** with the intention of evaluating not only the feasibility of our rhodium cyclisation in the presence of a 3-substituted precursor but also the possibility of constructing more strained bicyclic products. Accordingly, 4-bromo-2(5*H*)-furanone **130** was prepared from tetronic acid following the procedure of Jas using oxalyl bromide and a catalylic amount of dimethylformamide in dichloromethane (Scheme 81).[126] After recrystallisation from diethyl ether, furanone **130** was obtained in 42% yield as light orange crystals. A subsequent palladium-catalysed substitution reaction of **130** with a homoallylzinc reagent prepared by a transmetallation sequence then afforded **131** in 54% yield as described by Negishi.[127] Finally, 3-(5-oxo-2,5-dihydrofuran-3-yl)-propionaldehyde **129** was obtained in 49% yield by selective ozonolysis of the terminal double bond of alkene **131** in the presence of one volume percent of pyridine followed by reductive work up with excess dimethylsulfide.



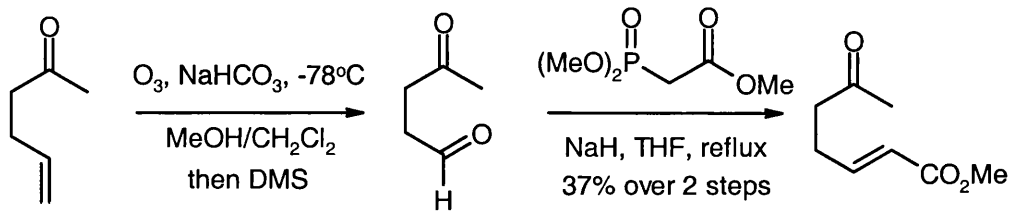
130 **131** **129**

i) $(COBr)_2$, DMF, CH_2Cl_2,42%
ii) Mg, C_4H_7Br, THF then $ZnBr_2$, $Pd(PPh_3)_4$, 54%
iii) O_3, pyridine, CH_2Cl_2, DMS, 49%

Scheme 81

II.2.5 Synthesis of methyl 6-oxo-2-heptenoate containing a ketone functionality

Since we also wished to examine the behaviour of a ketonic partner in the intramolecular aldolisation step, methyl 6-oxo-2-heptenoate **132** was accordingly prepared from commercially available 5-hexen-2-one by adaptation of a literature route (Scheme 82).[128]



133 **132**

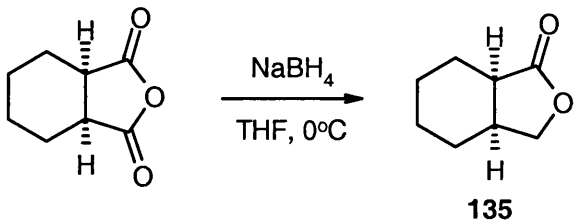
Scheme 82

Thus, standard ozonolysis followed by Horner-Wadsworth-Emmons reaction of aldehyde **133** with trimethylphosphonoacetate and sodium hydride in anhydrous tetrahydrofuran gave methyl ketone **132** (*E*:*Z* 3.6:1) in 37% yield over two steps.

II.2.6 Preparation of cyclic precursors containing an embedded 6-oxo-2-hexenoate unit

*II.2.6.1 Synthesis of methyl (E)-3-(2-formyl-cyclohexyl)-acrylate **134***

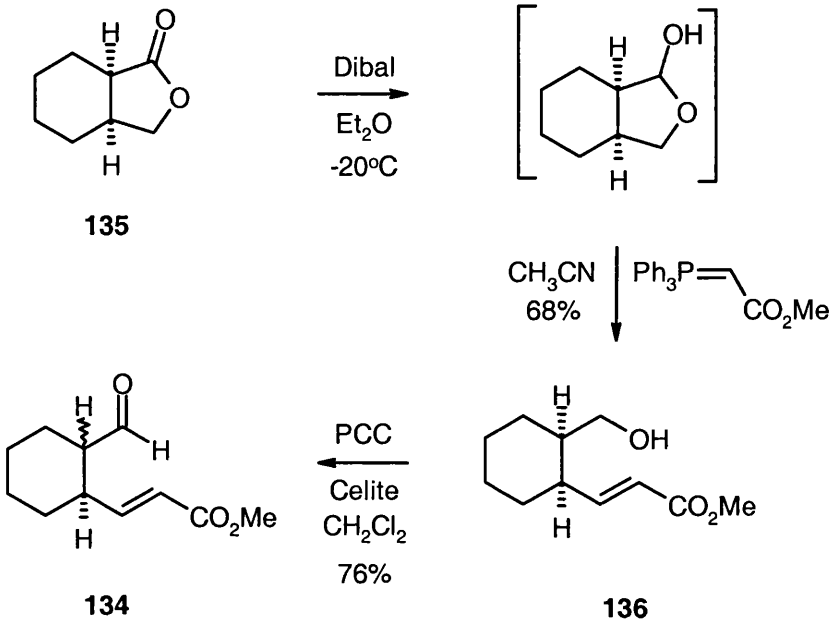
In order to assess the feasibility of generating an even more strained bicyclic system in the tandem cyclisation sequence, the cyclic substrate **134** was consequently synthesised from commercially available *cis*-cyclohexane-1,2-dioic acid anhydride. Thus, in the first instance, lactone **135** was obtained in 70% yield by reduction of the corresponding anhydride with sodium borohydride, using the general procedure of Bailey and Johnson (Scheme 83).[129]



135

Scheme 83

Subsequent treatment of lactone **135** with DIBAL in ether at –20°C resulted in rapid and quantitative reduction to the lactol, which was then reacted with carbomethoxymethylene triphenylphosphorane in acetonitrile to afford alcohol **136** in an overall 68% yield as the standard *E* isomer (Scheme 84).

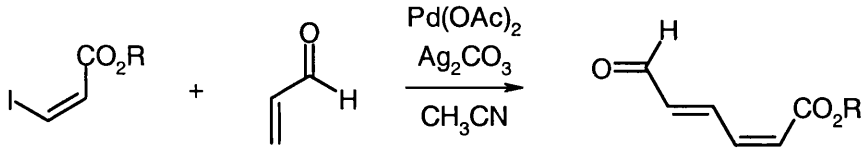


Scheme 84

Finally, oxidation of alcohol **136** with pyridinium chlorochromate (PCC) in the presence of celite gave, after column chromatography, the desired aldehyde **134** in 76% yield with some epimerization at the α centre of the newly formed aldehyde (*cis:trans* 6:1).

II.2.6.2 Synthesis of methyl (E)-3-(2-formyl-cyclohex-1-enyl)-acrylate **137**

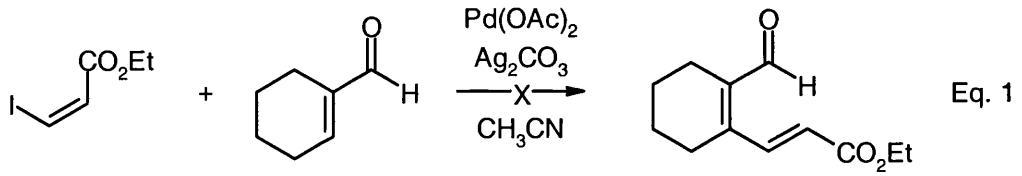
The viability of using a completely conjugated system in our cyclisation reaction was tested by selection of substrate **137a** which was envisaged *via* a Heck strategy. Gonzalez[130] has recently reported the synthesis of methyl 6-oxo-2,4-hexadienoate **138a** by a palladium-catalysed coupling of acrolein and methyl (*Z*)-3-iodopropenoate using silver carbonate as additive (Scheme 85).



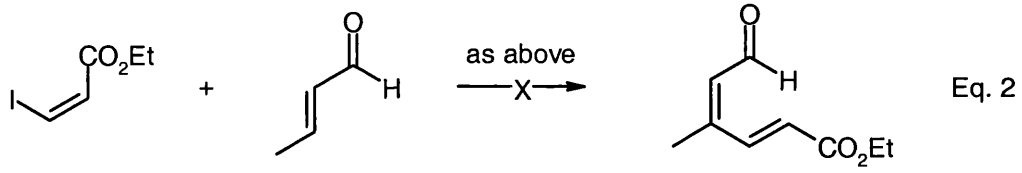
R= Me **138a**
R= Et **138b**

Scheme 85

In analogous fashion, 1-cyclohexene-1-carboxaldehyde and ethyl (*Z*)-3-iodopropenoate, both commercially available, were stirred in acetonitrile at room temperature in the presence of 0.05 equiv of palladium acetate and 1.5 equiv of silver carbonate (Scheme 86, Equation 1).



137a Eq. 1

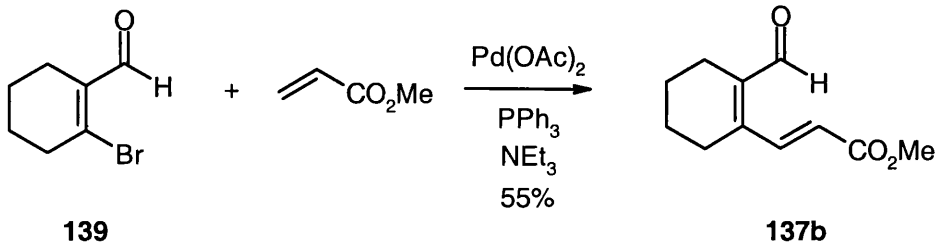


Eq. 2

Scheme 86

Unfortunately, coupling failed to occur and only starting material was recovered after 3 days. The literature conditions with acrolein and ethyl (*Z*)-3-iodo-propenoate were therefore reproduced in order to evaluate the effectiveness of this coupling procedure and indeed the desired product **138b** was obtained in a comparable yield to that reported by Gonzalez (Scheme 85).[130] However, when coupling was attempted in the presence of a disubstituted olefin such as crotonaldehyde, only starting material was recovered after filtration over silica, indicating that the present conditions are restricted to monosubstituted olefins (Scheme 86, Equation 2). It is well known that the yields and rates of reaction in Heck couplings decrease with increasing size and number of substituents around the double bond in the olefin.[131]

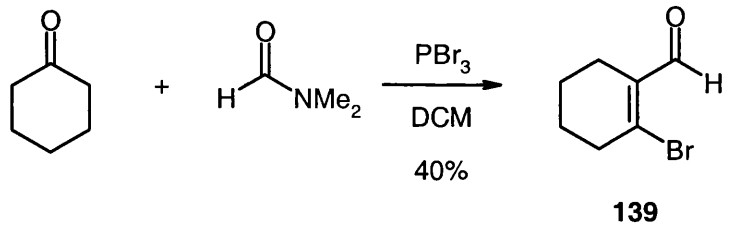
In order to circumvent this limitation, coupling was therefore attempted between 2-bromo-1-cyclohexenecarboxaldehyde **139** and a monosubstituted olefin, methyl acrylate, in the presence of triethylamine and a catalytic amount of $Pd[(PPh_3)_3]_2(OAc)_2$ at reflux (Scheme 87).



139 **137b**

Scheme 87

In this way, the desired substrate **137b** was obtained in 55% yield after column chromatography as a single *E* diastereoisomer. The required aldehyde **139** was available from cyclohexanone by the bromo analogue of the Vilsmeier reaction according to the procedure of Arnold and Holy (Scheme 88).[132]



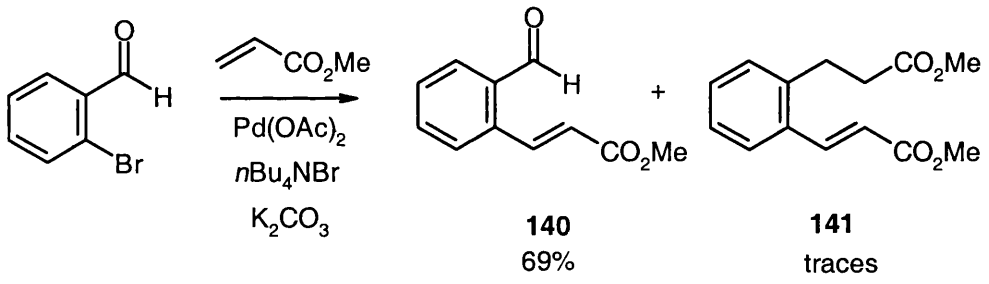
139

Scheme 88

Thus, the formylation reagent was prepared by addition of phosphorus tribromide to a solution of dimethylformamide in anhydrous dichloromethane at 0°C. The resulting yellow suspension was allowed to warm to room temperature and a solution of cyclohexanone was added dropwise. Careful hydrolysis of the dark red solution followed by column chromatography of the crude reaction mixture afforded bromo-aldehyde **139** in 40% yield as an orange oil. Since the instability of **139** and related compounds have previously been noted in the literature,[132a] this compound was prepared immediately before use.

II.2.6.3 Synthesis of methyl (E)-3-(2'-formylphenyl)-propenoate ***140***

In order to investigate the compatibility of a 4,5-fused aromatic ring in the cyclisation reaction, the benzoanulated substrate **140** was prepared from commercially available *o*-bromobenzaldehyde again by means of a Heck strategy. Rodrigo[133] has extensively studied the Heck reaction of various aryl bromides with methyl acrylate in the presence of a phase transfer catalyst such as tetra-*n*-butylammonium bromide. The observation was made that formation of the doubly substituted product **141** is favoured over the conventional Heck product **140** when the reaction is run in a concentrated solution in the presence of excess methyl acrylate (Scheme 89). We therefore reasoned that the use of moderate amounts of methyl acrylate and more dilute solutions would lead to the optimum yield of our desired Heck product **140** at the expense of the doubly substituted compound **141**.



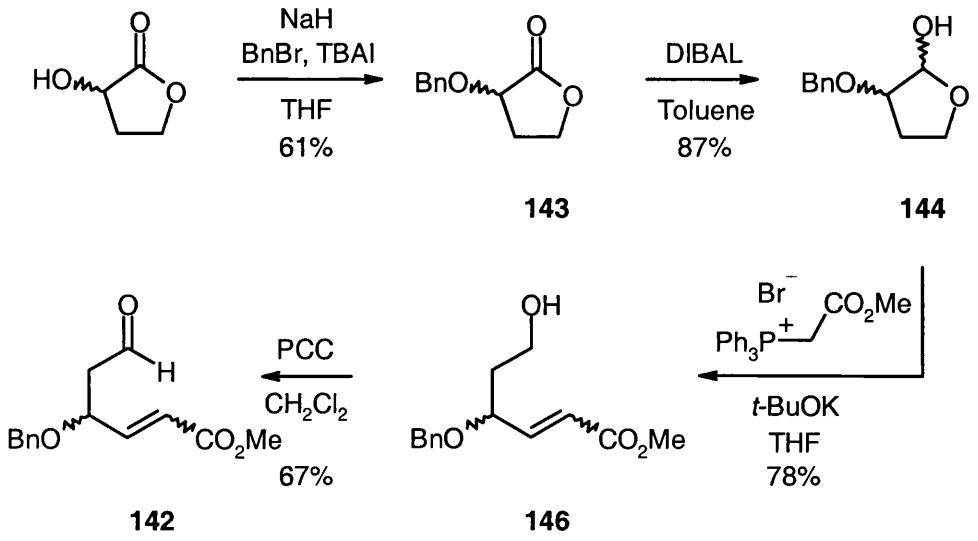
Scheme 89

Gratifyingly, coupling of *o*-bromobenzaldehyde (1 equiv) and methyl acrylate (5 equiv) in the presence of catalytic amounts of palladium acetate, potassium carbonate and a phase transfer catalyst gave the desired Heck product **140** which was obtained in 69% yield in pure form after column chromatography.

II.2.7 Preparation of cyclisation precursors containing heteroatomic substituents

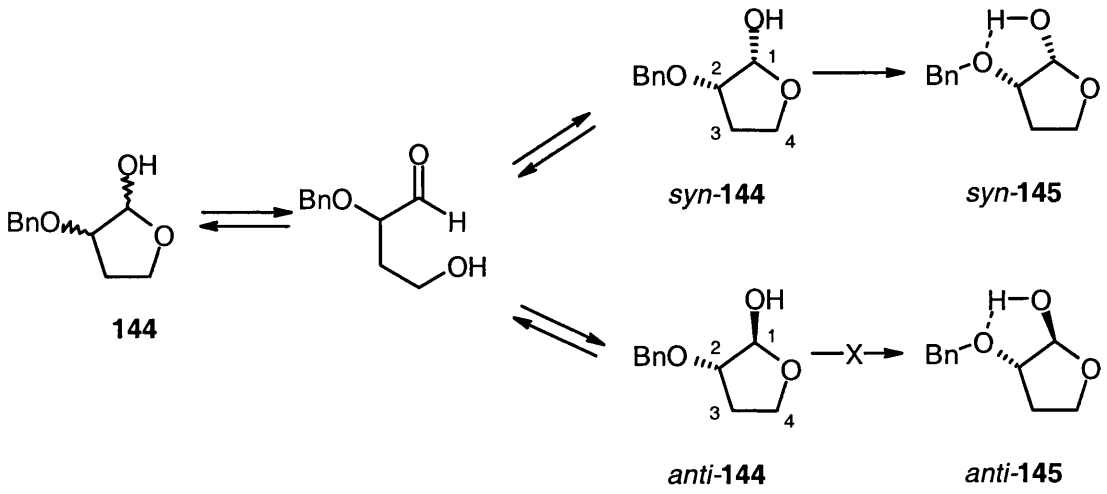
II.2.7.1 Synthesis of methyl 4-benzyloxy-6-oxo-2-hexenoate ***142***

Benzyl ether functionality was chosen to investigate whether tandem hydrosilylation cyclisation was compatible with heteroatomic substituents. Methyl 4-benzyloxy-6-oxo-2-hexenoate **142** was synthesised as shown in Scheme 90.



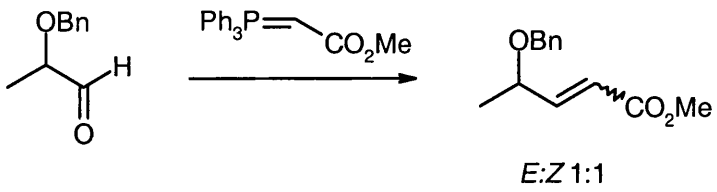
Scheme 90

Thus, commercially available racemic α-hydroxy-γ-butyrolactone was firstly protected using benzyl bromide and sodium hydride in the presence of a catalytic quantity of tetrabutylammonium iodide. The resulting α-benzyloxy-γ-butyrolactone **143** was then reduced to the corresponding lactol **144** with DIBAL, which gave a mixture of *syn* and *anti* diastereoisomers in a 2:1 ratio. The observed *cis* selectivity presumably arises *via* subsequent equilibration which favours the more thermodynamically stable *syn* lactol. The higher stability of the *syn* lactol *syn*-**144** would be most likely due to intramolecular hydrogen bonding interactions that would generate the *syn*-5,5-bicyclic chelate *syn*-**145** (Scheme 91). On the other hand, such intramolecular hydrogen bonding interaction would not be favoured in the *anti* lactol *anti*-**144** as it would generate a considerably more strained *anti*-5,5-bicyclic chelate *anti*-**145**. Alternatively, the pseudoaxial hydroxyl group may be favoured as a simple consequence of the anomeric effect. The structure of the *syn* and *anti* lactols **144** was unequivocally assigned on the basis of the values of coupling constants measured by ^1H NMR. Thus, the absence of coupling between adjacent protons (H_1 and H_2) in lactol *syn*-**144** corresponds typically to a dihedral angle close to 90°C indicating a *syn* relationship between these two protons.



Scheme 91

Wittig olefination of lactol **144** with carbomethoxymethyltriphenylphosphonium bromide and potassium *tert*-butoxide gave **146** in 78% yield as a mixture of *Z* and *E* diastereoisomers in a 1:4.3 ratio (Scheme 90). The stereoselectivity of the Wittig reaction depends strongly on both the structure of the ylide and the reaction conditions. The broadest generalisation is that unstabilised ylides give predominantly the *Z* alkene while stabilised ylides give mainly the *E* alkene.[134] Typically, stabilised phosphoranes give higher *E* selectivities than the one observed in the formation of **146** from lactol **144**. Such an observation however finds precedent in the literature as several examples of reactions between α-alkoxy aldehydes or lactols with stabilised phosphoranes have been reported to give reduced *E* selectivities (Scheme 92).[135]

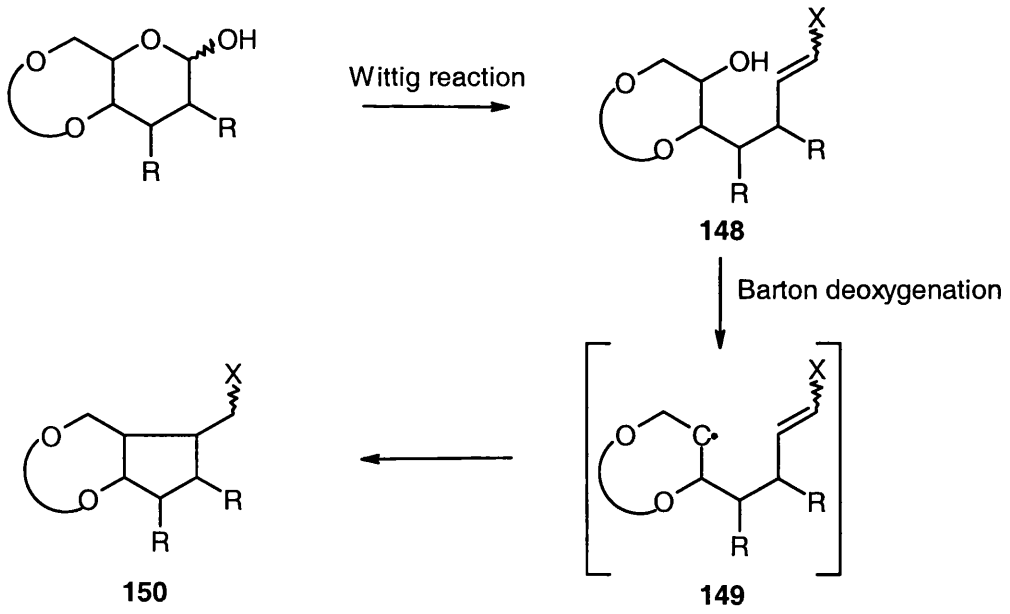


Scheme 92

Finally, the required benzyloxy aldehyde **142** was obtained in 67% yield as two separable diastereoisomers by subsequent oxidation of **146** with PCC.

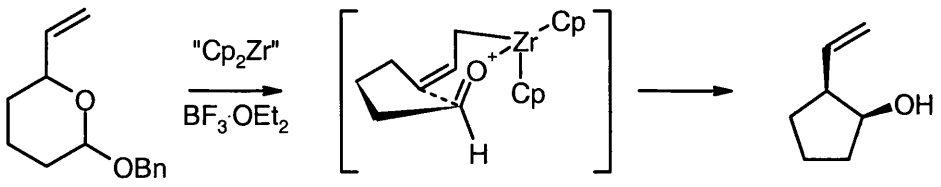
II.2.7.2 Synthesis of methyl 6-oxo-4,5-isopropylidenedioxy-2-hexenoate ***147***

The construction of carbocycles from sugars is an area that has attracted considerable attention in recent times, especially in view of the valuable synthetic utility of the resultant highly oxygenated carbocyclic products.[136] Some important and representative methodologies for achieving the conversion of carbohydrates into five-membered ring carbocycles are the radical cyclisation approach of RajanBabu[137] and the zirconium mediated ring contraction described by Taguchi.[138] RajanBabu has proposed a protocol for the conversion of carbohydrates into cyclopentanoids *via* the well-known hex-5-enyl radical cyclisation first introduced by Lamb[139] and Julia.[140] Thus, aldopyranose sugars readily undergo Wittig reaction to give hex-5-en-1-ols **148** which can then be converted to highly functionalised hex-5-enyl radicals **149** by any one of the variations of the Barton deoxygenation reaction[141] as shown in Scheme 93. Finally, hex-5-enyl radical cyclisation of **149** affords the corresponding cyclopentanoids **150**.



Scheme 93

On the other hand, Taguchi has reported a highly diastereoselective zirconium-mediated ring contraction of carbohydrate derivatives for the synthesis of highly functionalised enantiomerically pure carbocycles in the presence of $BF_3{\cdot}OEt_2$ *via* the reactive allylic zirconium intermediate **151** (Scheme 94).

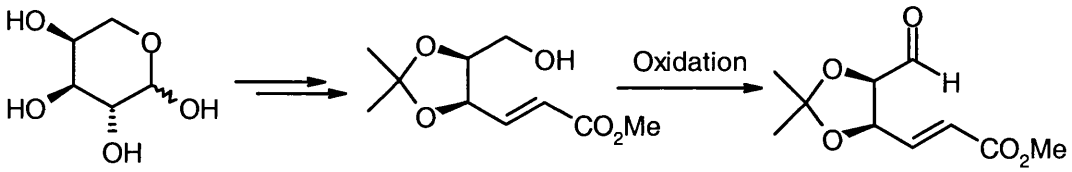


151 87% syn only

Scheme 94

In light of these observations, methyl 6-oxo-4,5-isopropylidenedioxy-2-hexenoate **147**, which could in principle be accessed from a carbohydrate, was chosen to investigate whether our tandem cyclisation sequence was compatible with the presence of increased peripheral substitution as well as heteroatoms in the substrate. If successful, our tandem cyclisation would therefore provide an alternative method for the conversion of carbohydrates into five-membered ring carbocycles.

In a preliminary study,[142] synthesis of the isopropylidene derivative **147a** was attempted from L-arabinose as outlined in Scheme 95.



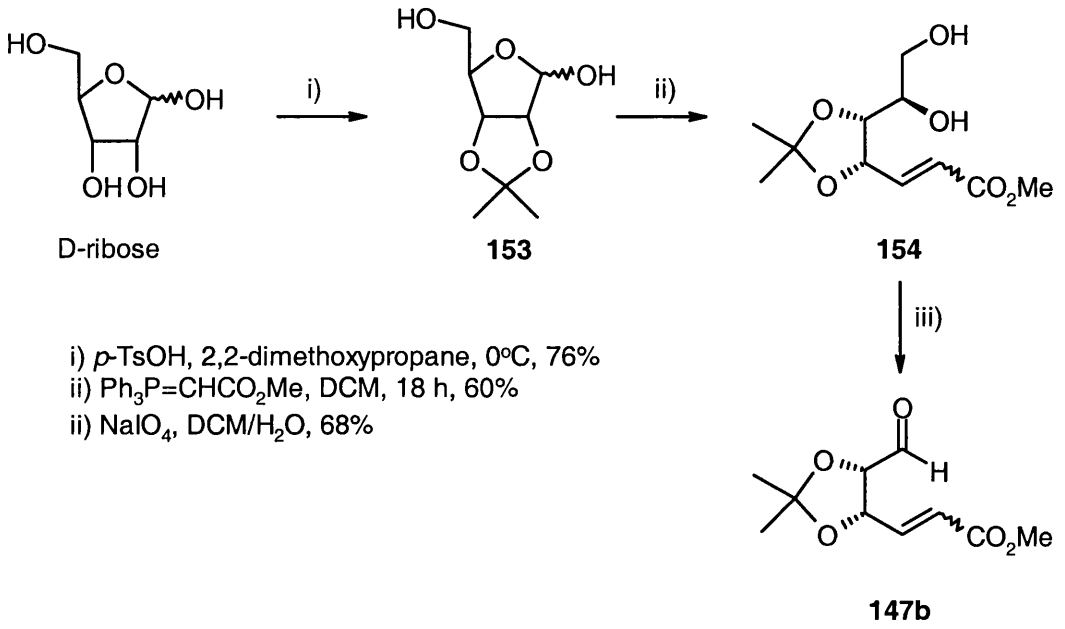
L-arabinose **152** **147a**

Scheme 95

Thus, L-arabinose was converted into 6-hydroxy-2-hexenoate **152** following a literature procedure[143] in a 25% overall yield. Despite a wide variety of oxidant conditions attempted (PCC, PDC, Dess-Martin periodinane, TPAP and NMO), isolation of the desired aldehyde **147a** in a preparatively useful yield was not possible.

An alternative strategy was therefore devised starting from D-ribose by adaptation of a literature route.[144] Thus, as shown in Scheme 96, a synthetic sequence involving formation of the acetonide followed by Wittig olefination and subsequent oxidative cleavage of the resultant diol could lead to the desired methyl 6-oxo-4,5-

isopropylidenedioxy-2-hexenoate **147**. It is important to note however that the compound expected from D-ribose is the opposite enantiomer to that derived from L-arabinose.

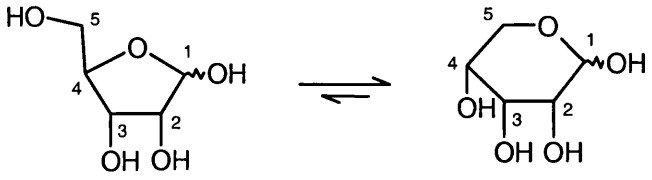


D-ribose **153** **154** **147b**

i) *p*-TsOH, 2,2-dimethoxypropane, 0°C, 76%
ii) $Ph_3P{=}CHCO_2Me$, DCM, 18 h, 60%
ii) $NaIO_4$, DCM/H_2O, 68%

Scheme 96

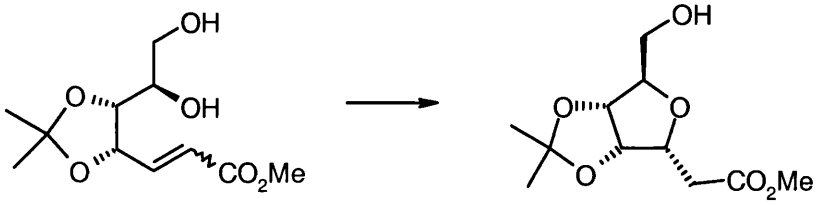
In the first instance, D-ribose was protected as its corresponding isopropylidene derivative. There has been intense research conducted on the precise conditions for this reaction with different carbohydrates, which proves to be highly dependant on the differing stereochemistries with varying degrees of success.[145] In particular, D-ribose is known to react mainly *via* the pyranose form **155**, with the furanoid ring **156** being the minor tautomer (Scheme 97).



furanoid D-ribose **156** pyranoid D-ribose **155**

Scheme 97

We found that the optimal conditions for protection of this particular carbohydrate involved 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid in acetone at 0°C. Consequently, reaction of D-ribose under these conditions gave, after stirring for 1 h, the corresponding isopropylidene derivative **153** in 76% yield. Subsequent Wittig olefination of **153** with carbomethoxymethylene triphenylphosphorane in anhydrous dichloromethane afforded diol **154** in 60% yield as a mixture of *E* and *Z* isomers, with the anomalous result that the *Z* diastereomer was the major isomer (*E*:*Z* 1:6). As discussed in the preceding section, Wittig reaction with stabilised ylides gives predominantly *E* alkenes. This reversal in stereochemistry however has been observed in other carbohydrate lactols of *ribo* configuration.[146] The *C*-4 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 *C*-1. On the other hand, the moderate yield obtained in this transformation could be explained by the tendency of the 6-oxo-2-hexenoate product **154** to undergo intramolecular 1,4-conjugate addition to give the tetrahydrofuran derivative **157** which was also obtained in 15% yield (Scheme 98). A comparison of the ^{1}H NMR spectrum of compound **157** with the existing literature spectroscopic data[147] revealed the presence of the single α-anomer.



154 **157**

Scheme 98

Attempts to separate the undesired tetrahydrofuran **157** from the mixture by column chromatography were mostly unsuccessful as the acidic nature of the silica also favoured cyclisation of the 6-oxo-2-hexenoate **154** leading to increasing quantities of side product **157**. Consequently, diol **154** was treated, without rigorous purification, with sodium periodate to give the desired aldehyde **147b**. At this stage, column chromatography allowed separation of the *E* and Z isomers which were obtained in a

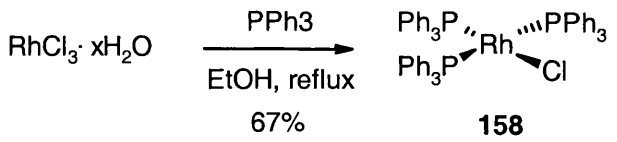
pure form in 68% overall yield as clear oils. With all of the above substrates in hand, the stage was now set for an extensive study of the scope of the Rh (I)-catalysed tandem reaction.

II.2.8 Studies on the Rh (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction

II.2.8.1 Preparation of the rhodium catalysts

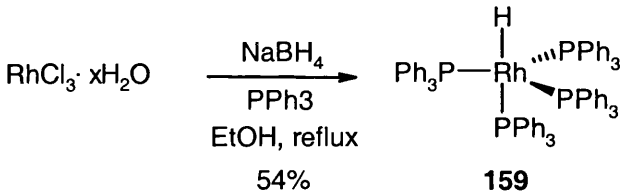
The increasing utility of triphenylphosphine complexes of transition metals as homogeneous catalysts highlights the desirability of convenient small-scale synthesis for this class of compounds. The basic technique employed involves the rapid, successive addition of alcoholic solutions of the appropriate transition metal salt and other reagents to a vigorously stirred, boiling, alcoholic solution of triphenylphosphine, which is subsequently heated under reflux until precipitation of the required product commences or until the reaction is complete. In the latter instances, the low solubility of most triphenylphosphine complexes in the alcoholic solvents employed in these reactions ensures the rapid crystallisation of the required product from the reaction solution on cooling. The success of these syntheses is critically dependent upon the maintenance of essentially homogeneous reaction conditions until the reaction sequence is complete. Failure to observe this precaution leads to precipitation of insoluble intermediates, which may fail to react further and hence contaminate the reaction product.

Following the results obtained in the preliminary study, we accordingly elected to examine two different rhodium complexes for the present study, tris(triphenylphosphine) rhodium chloride (I) (Wilkinson's catalyst) and hydridotetrakis(triphenylphosphine) rhodium (I). In the first instance, Wilkinson's catalyst **158**, was freshly prepared from rhodium trichloride trihydrate in boiling, degassed ethanol following a literature procedure (Scheme 99).[148] After the addition of a solution of triphenylphosphine in hot, degassed ethanol to the previously mentioned rhodium trichloride solution, the crystalline product was filtered from the hot solution, washed with small portions of anhydrous ether and dried under vacuum to afford the desired product in 67% yield as deep red crystals. Good analytical data were obtained without recourse to further purification procedures.



Scheme 99

Hydridotetrakis(triphenylphosphine) rhodium (I) **159** was prepared by the procedure described by Levison and Robinson.[149a] Thus, corresponding solutions of hydrated rhodium trichloride and sodium borohydride in warm ethanol were added rapidly and successively to a vigorously stirred solution of triphenylphosphine in boiling ethanol. After cooling down to 30°C, the resultant precipitate was filtered and washed to give the product in 54% yield as orange-yellow microcrystals (Scheme 100).



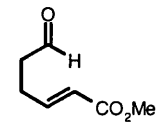
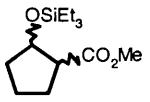
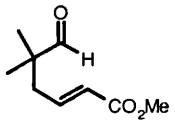
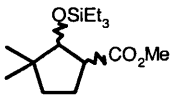
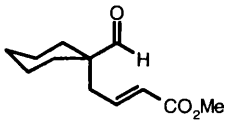
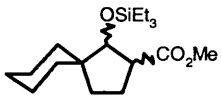
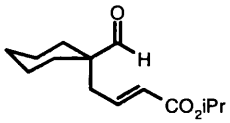
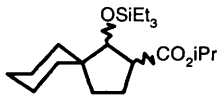
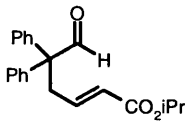
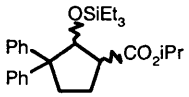
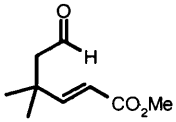
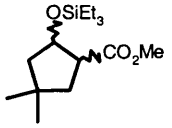
Scheme 100

Satisfactory elemental analysis and melting point values, together with a characteristic band at 2147 cm^{-1} attributable to υ (Rh-H) in the IR spectrum, confirmed the presence of **159** in high purity. Baker[149b] has reported the crystal structure of catalyst **159**. It was found that both the rhodium atom and one phosphorus atom lay on a three-fold axis, the arrangement of the four phosphorus atoms being regularly tetrahedral, and although the position of the hydrogen atom could not be determined, it was postulated that it might also lay on the three-fold axis in order to be consistent with the crystal symmetry.

II.2.8.2 Rhodium (I)-catalysed tandem cyclisation of 3,4 or 5-substituted 6-oxo-2-hexenoate derivatives

With both rhodium catalysts in hand, we then elected to examine the synthetic utility of our tandem hydrosilylation-aldol sequence for the synthesis of substituted cyclopentanoids. The variety of variously functionalised 4,4 and 5,5-disubstituted 6-oxo-2-hexenoate derivatives previously described were accordingly submitted to our

optimised cyclisation conditions (2.1 molar equiv of triethylsilane and 1 mol% of rhodium catalyst in toluene at 50°C) and compared with the unsubstituted parent substrate in order to probe such issues as chemoselectivity and the influence of the substitution pattern on the tandem sequence. The results are shown in Table 4.

Entry	Substrate		Product		Rh[a]	%[b]	*syn:anti*[c]
1		**78**		**83**	A	81	3.0:1.0
					B	81	1.0:11.0
2		**102**		**160**	A	56	1.0:1.0
					B	62	6.4:1.0
3		**103a**		**161**	A	54	2.0:1.0
4		**103b**		**162**	B	59	1.0:2.0
5		**104**		**163**	B	68	1.0:2.5
6		**122**		**164**	A	93	2.2:1.0
					B	61	1.0:11.0

[a] A = $RhCl(PPh_3)_3$; B = $RhH(PPh_3)_4$. [b] Isolated yields after chromatography on silica gel.
[c] Diastereomeric ratio in the crude material determined by ^1H NMR.

Table 4

Thus, as shown in Table 4, both aliphatic and aromatic substituents are compatible with our tandem reaction conditions leading to the corresponding substituted cyclopentanoids **160**-**164** in good to excellent yields (54 -93%) and, at times, with high degrees of stereoselectivity (*syn:anti* 1:11). Comparison of Entries 2 to 6 reveals that whilst geminal substitution at *C*-5 (Entries 2-5) leads to a reduction in yield relative to the unsubstituted parent substrate **83** (Entry 1) this is not necessarily

the case for the *C*-4 *gem* dimethyl group (Entry 6). Although all five cases might be anticipated to benefit from the Thorpe- Ingold effect,[150] it would therefore appear that the intramolecular aldol step is more sensitive to the presence of a neighbouring quaternary carbon atom than is the initial hydrosilylation step. Comparison of Entries 3 and 4 also demonstrates that no significant difference in yield was observed when the methyl ester **103a** was replaced by its *iso*-propyl analogue in **103b**.

In terms of stereoselectivity, comparison of the two catalysts **158** (A) and **159** (B) reinforces the observation made in the parent system (Entry 1) that the outcome can be significantly influenced by this choice. Thus, whilst Wilkinson's catalyst consistently exhibits a modest *syn* preference for formation of the β-triethylsiloxy ester unit, selection of hydridotetrakis(triphenylphosphine) rhodium generally favours the *anti* congener. However, an exception to this broad generalisation is observed in the cyclisation of 5,5-dimethyl-6-oxo-2-hexenoate **102**. When the reaction was carried out in the presence of Wilkinson's catalyst the corresponding cyclopentanol **160** was obtained as a 1:1 mixture of *syn* and *anti* isomers, whereas selection of hydridotetrakis(triphenylphosphine) rhodium led to an anomalous *syn* stereoselectivity in a very good 6.4:1 ratio. It is important to note that the diastereoisomeric ratios with hydridotetrakis(triphenylphosphine) rhodium are self evidently much more strongly influenced by the exact nature of the substrate substitution pattern and can, at times, be excellent (Entries 1 and 6).

In all cases, the structure of the major diastereoisomer was assigned on the basis of the values of coupling constants measured in ^{1}H NMR. In general, coupling constant J (H^1 –H^2)= 3.5 -6.5 Hz indicates *syn* relative stereochemistry whereas J (H^1 –H^2)= 5.5 -9.5 Hz accounts for the *anti* isomer (Figure 12).

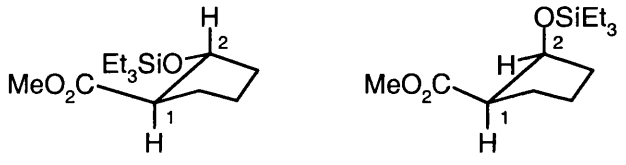


Figure 12

This assignment is in agreement with Mohrle's[151] ^{1}H NMR work on methyl 2-hydroxycyclopentane carboxylate. He observed that in the *syn* isomer of the corresponding cyclopentanol, H^1 appeared at lower field compared to the *anti* isomer. A similar trend in chemical shift was observed for H^2. Moreover, the band width of H^1 and H^2 was smaller for the *syn* isomer than for the corresponding *anti* isomer. Mohrle's criteria remained applicable to the silyl protected cyclopentanols as verified by bidimensional COSY and NOESY spectroscopy. Further proof supporting this assignment was provided by X-ray crystallographic analysis of compound **163** (see appendices), since the minor *syn* diastereoisomer crystallised out of the mixture of isomers giving suitable crystals (Figure 13).

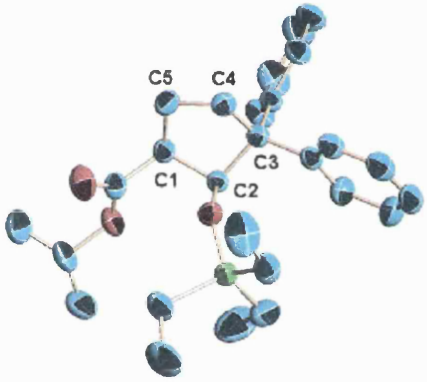
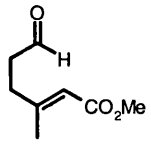
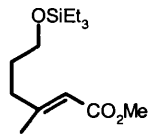
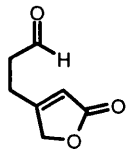
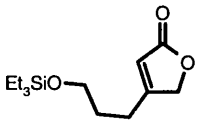


Figure 13

We then investigated the compatibility of our tandem sequence with the previously synthesised 3-substituted 6-oxo-2-hexenoates and the results are summarised in Table 5. In this instance, reaction of 3-methyl-6-oxo-2-hexenoate **127** with triethylsilane using either chlorotris(triphenylphosphine) rhodium (I) or hydridotetrakis(triphenylphosphine) rhodium (I) gave the 6-triethylsilyloxy-2-hexenoate **165** in 35% and 39% yield respectively. We then attempted cyclisation of the more reactive lactone **129** with Wilkinson's catalyst and yet again the analogous reduced silyl ether **166** was obtained in 43% yield.

Entry	Substrate		Product		Catalyst[a]	Yield(%)[b]
1		**127**		**165**	A	35
					B	39
2		**129**		**166**	A	43

[a] A = $RhCl(PPh_3)_3$; B = $RhH(PPh_3)_4$. [b] Isolated yields after chromatography on silica gel.

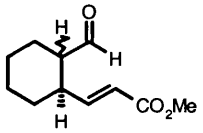
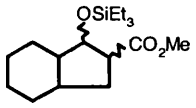
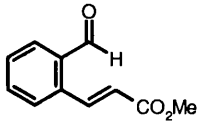
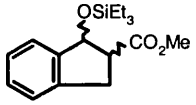
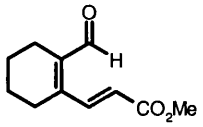
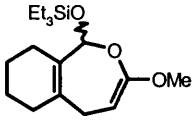
Table 5

Thus, in stark contrast to the results obtained for 4- and 5-substituted precursors, our examination of substrates possessing a trisubstituted α,β-unsaturated lactone or ester unit reveals that the incorporation of the additional alkyl substitution at this site completely blocks the conjugate addition step and simple hydrosilylation of aldehydic functionality then becomes the dominant process.

II.2.8.3 Rhodium (I)-catalysed tandem cyclisation of cyclic 6-oxo-2-hexenoate derivatives

In order to evaluate the feasibility of constructing even more strained bicyclic systems *via* our tandem cyclisation reaction, previously synthesised cyclic 6-oxo-2-hexenoate derivatives were then investigated and the results are summarised in Table 6. Thus, substrate **134** was successfully cyclised in a high 81% yield into the corresponding bicyclic product **167** using hydridotetrakis(triphenylphosphine) rhodium (I) (Entry 1). However, as the aldehyde precursor **134** was a mixture of *cis* and *trans* isomers, a very complex mixture of diastereomers of the corresponding product **167** was obtained after cyclisation and determination of the diastereomeric ratio by means of ^1H NMR spectroscopy was not possible. The presence of a 4,5-fused aromatic ring was also compatible with our new methodology as shown in Entry 2. Benzoanulated substrate **140** led to the corresponding indane **168** using either Wilkinson's catalyst or hydridotetrakis(triphenylphosphine) rhodium (I) in 61% and 69% yield respectively. It is important to note however that when the reaction was carried out in the presence of 1 mol% of rhodium catalyst at 50°C, close

monitoring by t.l.c. indicated no reaction after 3 hours. The amount of catalyst was therefore increased to 3 mol% and yet again no product was observed. We then decided to increase the temperature to 70°C and gratifyingly all of the starting material was then consumed within 16 hours. In terms of stereochemistry, the results were consistent with the usual trend of selectivity previously observed, that is, the modest preference of Wilkinson's catalyst for the *syn* isomer of the β-triethylsiloxy ester unit and the predominance of the *anti* diastereoisomer with hydridotetrakis(triphenylphosphine) rhodium (I). It is noteworthy that in the latter instance a remarkably high degree of *anti* selectivity (1:20) in the corresponding indane **168** was obtained. We then attempted the cyclisation of the fully conjugated system **137b** (Entry 3). To our surprise, the expected product was not formed and the hexahydro-benzo[c]oxepin **169** was isolated after column chromatography and characterised by ^{1}H NMR. The appearance of a singlet at 6.02 ppm corresponding to OC*H*OSiEt$_3$ and the presence of an olefinic proton at 5.35 ppm, indicated that cyclisation of the ester enolate *via* oxygen to give the seven membered ring **169** had occurred. In this latter instance, formation of the silyl ether functionality by reductive elimination to give the product must be fast and hence preclude the reverse reaction.

Entry	Substrate		Product		Rh[a]	Yield[b]	*syn:anti*[c]
1		**134**		**167**	B	81[d]	---
2		**140**		**168**	A	61[e]	1.5:1.0
					B	69[e]	1.0:20.0
3		**137b**		**169**	B	88	---

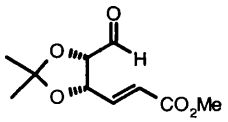
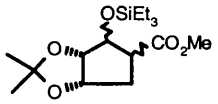
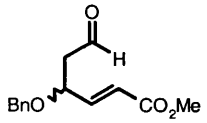
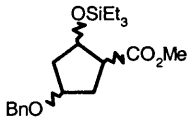
[a]A = $RhCl(PPh_3)_3$; B = $RhH(PPh_3)_4$. [b]Isolated yields (%) after chromatography on silica gel. [c]Diastereomeric ratio in the crude material determined by ^{1}H NMR. [d]Isolated as a complex mixture of diastereomers. [e]Using 3 mol% of catalyst at 70°C.

Table 6

Comparison of these results reveals that the success of the intramolecular aldol addition step can be subject to very subtle conformational and stereoelectronic restrictions. Thus, whilst Entries 1 and 2 provide a very encouraging basis for construction of the linearly fused bicyclo [4.3.0] system in both the hydrindane **167** (Entry 1) and indane skeletons **168** (Entry 2), the isolation of the hexahydro-benzo[c]oxepin **169** from the fully conjugated precursor **137b** was unexpected.

II.2.8.4 Rhodium (I)-catalysed tandem cyclisation of 6-oxo-2-hexenoate derivatives containing heteroatomic substituents

In view of the ever increasing importance of constructing carbocycles from the chiral pool of carbohydrates,[136] it was also of interest to examine substrates containing ancillary isopropylidene and benzyl ether functionalities. The results are shown in Table 7.

Substrate		Product		Rh[a]	%[b]	*a:b:c:d*[c]
	**147b**		**170**	A	65	2.0:5.4:2.0:1.0[d]
				B	81	5.4:4.0:2.0:1.0[d]
	**142**		**171**	A	81	1.5:1.0:1.0:1.7[e]
				B	72	1.2:1.0:1.2:1.7[e]

[a] A = $RhCl(PPh_3)_3$; B = $RhH(PPh_3)_4$. [b] Isolated yields (%) after chromatography on silica gel. [c] Diastereomeric ratio in the crude material determined by ^1H NMR. [d] See Figure 14 for assignment of the structures. [e] See Figure 16 for assignment of the structures.

Table 7

Hence, cyclisation of chiral substrate **147b** afforded bicycle **170** in good yield (65-81%) suggesting that our tandem hydrosilylation reaction was compatible with the presence of heteroatoms in the substrate. As far as stereochemistry is concerned, when more than two stereogenic centres are present, proton assignment and subsequent determination of all possible diastereoisomers by experimental means was extremely difficult. To our delight however, in this instance careful column chromatography allowed the separation of three of the four possible isomers of

compound **170** and their structure and relative predominance was determined by ^1H NMR (Figure 14).

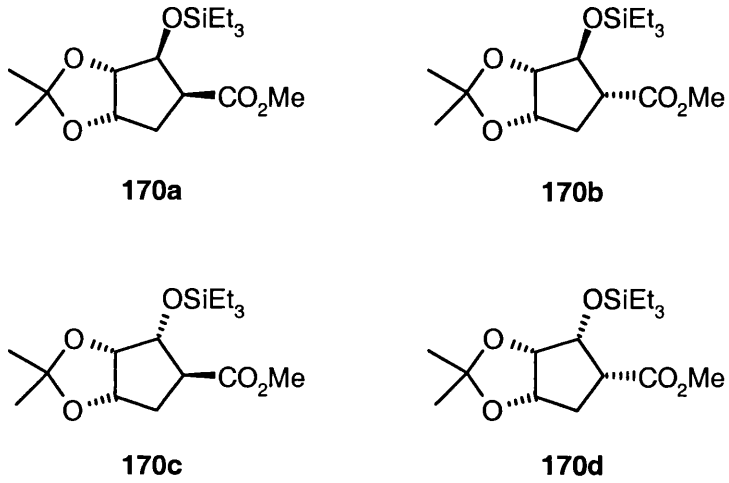


Figure 14

A coupling constant J (H_2 –H_3)= 0.0 -0.7 Hz was observed for both isomers **170a** and **170b**, indicating a dihedral angle close to 90°C, which implies the pseudoequatorial configuration of H_2. The configuration of H_1 was assigned on the basis of NOE experiments (Figure 15). A strong NOE effect between H_1 and H_{5eq} in the major isomer **170a** indicates that H_1 occupies an axial position, whereas in **170b** the NOE effect was observed between H_1 and H_{5ax}, indicating that, in this case, it occupies an equatorial position.

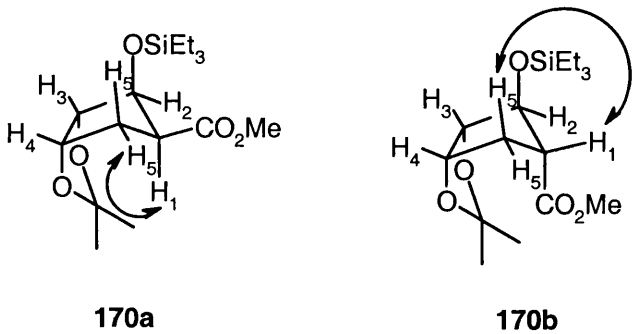


Figure 15

Structure of isomer **170c** was unequivocally assigned on the basis of the typical coupling constant of J (H_1 –H_2)= 12.4 Hz for a diaxial configuration. The minor

isomer **170d** was not isolated after column chromatography but its structure was tentatively deduced as the all *cis* isomer.

The effect of a benzyloxy substituent in the 4 position of the 6-oxo-2-hexenoate **142** was then investigated. Thus, 4-benzyloxy-6-oxo-2-hexenoate **142** was treated with triethylsilane and 1 mol% of the rhodium (I) catalyst leading to the corresponding trisubstituted silyl protected cyclopentanol **171** in very good yields and with slight selectivity for isomer **171d** (Figure 16). Once again, careful column chromatography allowed the separation of three of the four possible diastereoisomers of compound **171** and the corresponding structures were assigned on the basis of the values of coupling constants measured in ^{1}H NMR.

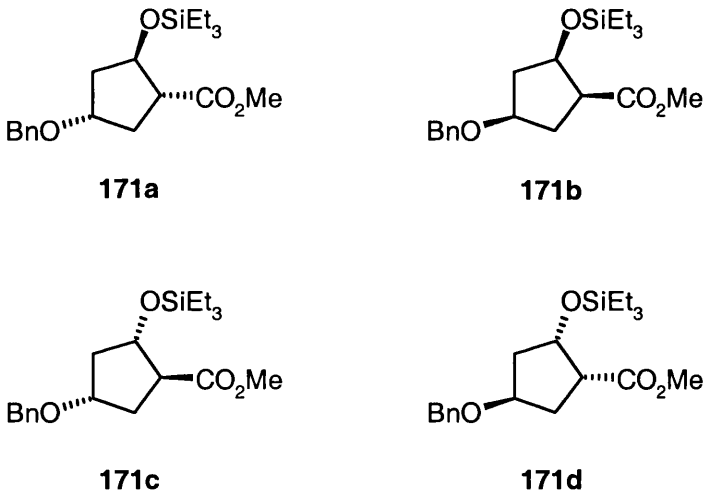
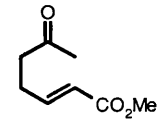
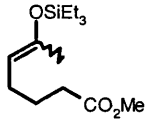
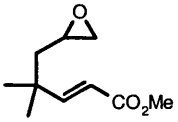
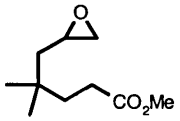
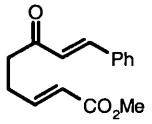
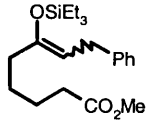
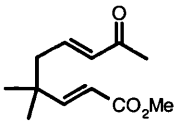
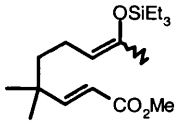


Figure 16

The functional group tolerance exhibited in these latter two cyclisations provides an indication that this approach may be of promise for cyclopentanoid construction from carbohydrates.

II.2.8.5 Rhodium (I)-catalysed tandem cyclisation of substrates containing alternative electrophiles

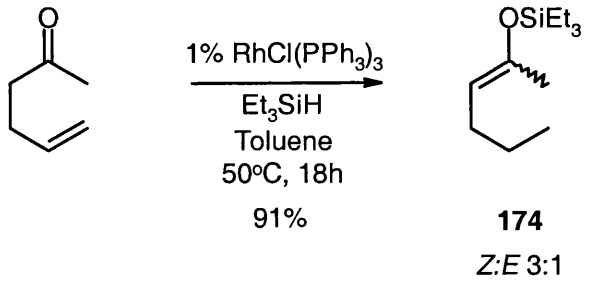
At this stage, in order to extend the scope of the reaction, cyclisation was also carried out on several substrates where the aldehyde functionality was replaced by alternative electrophilic acceptor groups. The results are shown in Table 8.

Entry	Substrate		Product		Catalyst[a]	Yield(%)[b]
1		**127**		**172**	A	83
					B	61
2		**132**		**173**	A	68
					B	60
3		**105**		**175**	A	74
4		**126**		**176**	B	91

[a] A = $RhCl(PPh_3)_3$; B = $RhH(PPh_3)_4$. [b] Isolated yields (%) after chromatography on silica gel.

Table 8

In the event, aldehyde functionality proved to be crucial in order to achieve cyclisation. Thus, as shown in Entries 1 and 2, replacement of the aldehyde either by a methyl ketone or by an epoxide only led to the formation of the acyclic products **172** and **173**, even although the reduction of the acrylate unit by the silane in both cases implies formation of a hydrometallated ester enolate intermediate. In the case of the methyl ketone **127** (Entry 1), the regiospecific and highly stereoselective (*E:Z* 1:5) formation of the silyl enol ether product **172** was not anticipated but certainly of interest, especially since the control of regioselectivity in the case of unsymmetrical ketones[152] is always useful in organic synthesis. In order to understand this transformation commercially available 5-hexen-2-one was also subjected to the standard cyclisation conditions in the presence of Wilkinson's catalyst. As shown in Scheme 101, regiospecific formation of silyl enol ether **174** with concomitant double bond reduction occurred once again in excellent yield and with moderate stereoselectivity (*E:Z* 1:3), thereby establishing that the ester group is not essential for this reaction to occur.



Scheme 101

A speculative intermediate is shown in Figure 17 and implies that substrate coordination around a silyl hydridorhodium intermediate may well direct the regiospecificity of the sequence and also produce molecular hydrogen for subsequent reduction of the double bond. The reason why the analogous aldehyde precursor did not behave in this way still remains unclear.

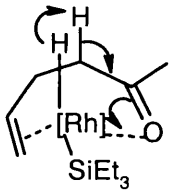


Figure 17

The two enone substrates **105** and **126** shown in Entries 3 and 4 were initially selected with the intention of probing a non-rhodium catalysed tandem hydrometallation-Michael addition sequence in which, as demonstrated by Evans[66] for hydroboration, the α,β-unsaturated ketone unit should be the first point of attack. In the event however, only the acyclic products **175** and **176** derived from 1,4-addition of the organosilane to the enones were isolated in the rhodium catalysed reactions and no evidence for a subsequent tandem Michael reaction was adduced. It is interesting to note however that the use of Wilkinson's catalyst (Entry 3) led to reduction of both the enone and the enoate whereas in the presence of hydridotetrakis(triphenylphosphine) rhodium (I) (Entry 4) reduction occurred exclusively at the enone moiety. This unexpected result suggests that the latter catalyst offers the advantage of being highly chemoselective for hydrosilylation of the enone moiety in the presence of α,β-unsaturated esters.

II.2.8.6 Conclusions

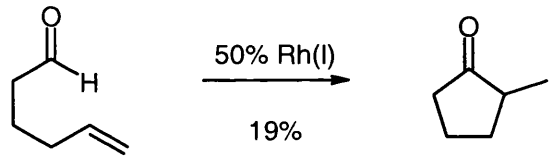
In summary, we have developed a highly stereoselective cyclisation sequence *via* a rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction that can be used to prepare a range of usefully functionalised cyclopentanoids in good yields under very mild conditions. The scope and limitations of this novel reaction have been established. Thus, both aliphatic and aromatic substitutions at *C*-4 and *C*-5 of the 6-oxo-2-hexenoate precursor were tolerated, however the presence of alkyl substitution at the β position of the ester completely blocks the conjugate addition step. Access to even more strained bicyclic systems such as the hydrindane and indane skeletons is feasible *via* our methodology, thus strongly encouraging us for further applications in synthesis. The presence of oxygen heteroatoms is also tolerated providing a promising alternative approach for the construction of carbocycles from the natural pool of carbohydrates. Finally, although our tandem cyclisation sequence proved to be quite general in terms of substitution around the substrate, aldehyde functionality was crucial in order to achieve cyclisation. The stereochemical outcome is highly dependant on the catalyst precursor. While Wilkinson's catalyst consistently exhibits a modest *syn* selectivity, selection of hydridotetrakis(triphenylphosphine) rhodium generally favours the *anti* isomer. Moreover, as a generalisation, the latter catalyst proved to be a more efficient precatalyst for tandem hydrosilylation-aldol reactions and gave the best results in terms of steroselectivity.

II.3 Rhodium (I)-catalysed tandem hydrosilylation-aldol reaction for the construction of larger ring sizes

II.3.1 Synthesis of functionalised six-membered ring carbocycles

II.3.1.1 Introduction

Following the reasonable success of our rhodium (I)-catalysed tandem sequence in the preparation of highly functionalised cyclopentanoids, we therefore elected to investigate the application of this methodology for the generation of larger ring sizes. In particular, stereoselective methods for the synthesis of six-membered ring carbocycles from readily available acyclic precursors have traditionally received a lot of attention especially in view of the abundance of this motif in a wide range of biologically active natural products. In this context, Larock[47] first investigated the cyclisation of 5-hexenals into the corresponding cyclohexanones in an attempt to complement the existing hydroacylation methodology (Scheme 102).

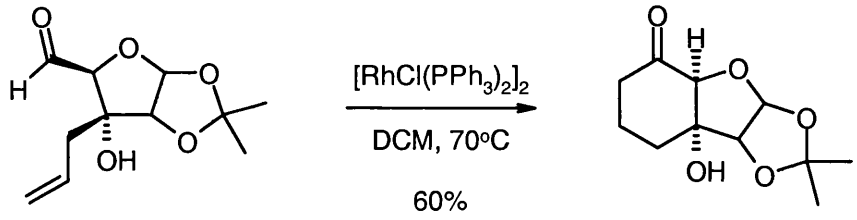


177

Scheme 102

The desired cyclohexanone was not however obtained, and instead, 2-methylcyclopentanone **177** was isolated in 19% yield. Large amounts of rhodium catalyst were required to obtain only very low yields of the corresponding cyclopentanone **177** as a consequence of extensive decarbonylation and subsequent poisoning of the catalyst.

The first and as yet only example of the preparation of a cyclohexanone derivative by hydroacylation of a hexanal precursor was reported by Gable and Benz (Scheme 103).[153]



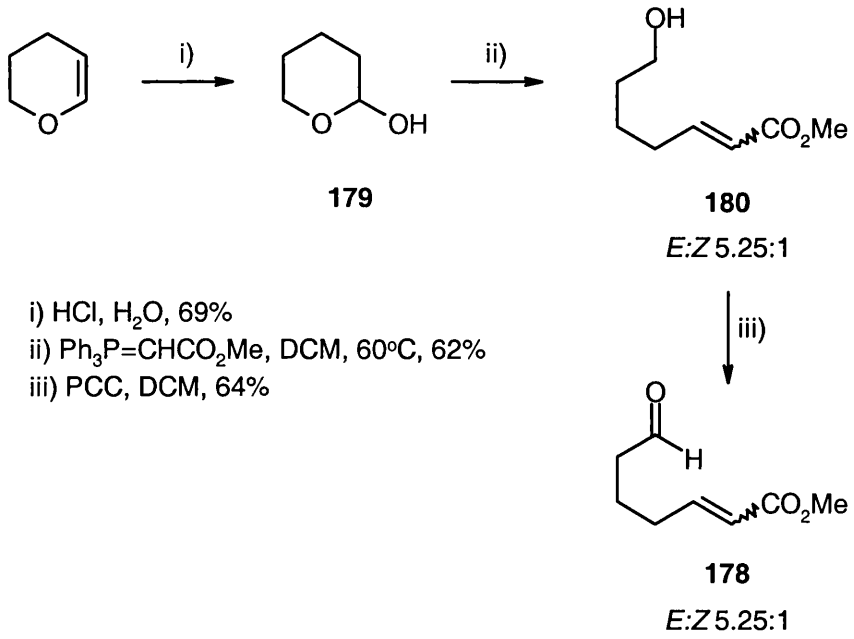
Scheme 103

A plausible rationale for the success of the hydroacylation reaction in this particular example is that the formation of the alternative fused 5,5,5 tricyclic product may be inhibited by ring strain.

In view of these limitations we therefore envisaged the preparation of the corresponding cyclohexanoids by our novel tandem hydrosilylation-aldol sequence and the synthesis of the required cyclisation precursors will accordingly be the object of the following section.

II.3.1.2 Preparation of methyl 7-oxo-2-heptenoate ***178***

Substrate **178** was accessed by a general route from tetrahydropyran-2-ol **179**[154] as shown in Scheme 104.

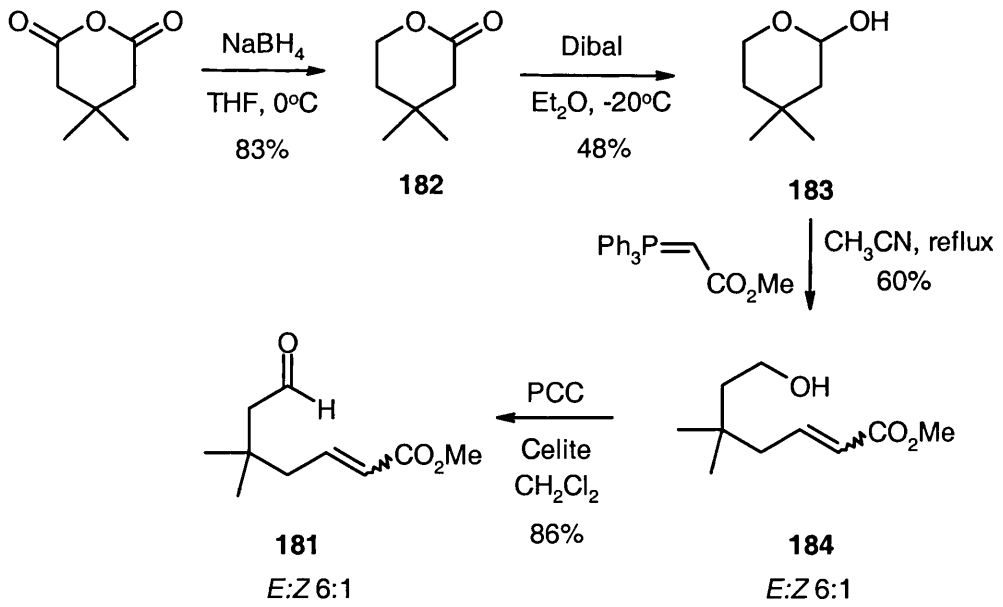


Scheme 104

Thus, acid catalysed hydration of commercially available 3,4-dihydropyran afforded, after distillation of the crude reaction mixture, pyranol **179** in 69% yield as a clear oil.[155] Subsequent Wittig olefination of the lactol **179** using carbomethoxymethylene triphenylphosphorane gave the desired 7-hydroxy-2-heptenoate **180** in 62% yield as a mixture of *E* and *Z* isomers in a 5.25:1 ratio. Finally, oxidation of the hydroxyl group to the aldehyde using pyridinium chlorochromate afforded the desired 7-oxo-2-heptenoate **178** in 64% yield.

*II.3.1.3 Preparation of methyl 5,5-dimethyl-7-oxo-2-heptenoate **181***

Increased substitution around the 7-oxo-2-heptenoate moiety was sought in order to investigate the effects of the substitution pattern in the tandem cyclisation and to generate even more substituted cyclohexanoids. Accordingly, the *gem* dimethyl derivative **181** was selected by analogy with the previously synthesised dimethyl-6-oxo-2-hexenoates since it would, in principle, benefit from a Thorpe-Ingold effect.[150] Therefore, substrate **181** was prepared in four steps from commercially available 3,3-dimethyl glutaric anhydride following a literature route reported by Little and Muller (Scheme 105).[156]



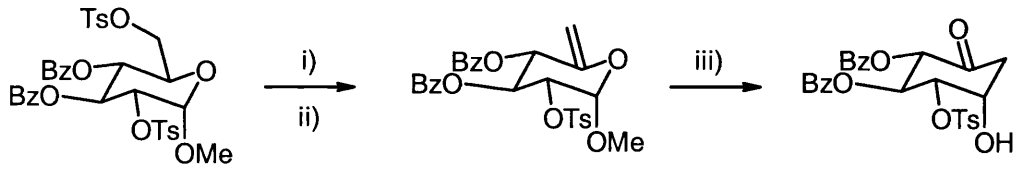
Scheme 105

In the first instance, 3,3-dimethyl glutaric anhydride was added to a stirred suspension of sodium borohydride in anhydrous tetrahydrofuran at 0°C. After 4

hours, the desired lactone **182** was obtained in 83% yield as a clear oil of sufficient purity to be used in the next step. Subsequent DIBAL reduction of **182** afforded lactol **183** in 48% yield and this was then submitted to Wittig olefination using carbomethoxymethylene triphenylphosphorane in anhydrous acetonitrile to give the corresponding 7-hydroxy-2-heptenoate **184** in 60% yield as a mixture of geometrical isomers in a *E:Z* 6:1 ratio. Unfortunately, flash column chromatography did not allow isomer separation. Consequently, the mixture was treated with Corey's PCC oxidant and after 2 hours at room temperature, the desired methyl 5,5-dimethyl-7-oxo-2-heptenoate **181** was isolated by column chromatography in 86% yield as a mixture of geometrical isomers.

*II.3.1.4 Preparation of methyl 4-(5-formyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-butenoate **185***

As discussed in Section II.2.7.2, the synthesis of carbocycles of various ring sizes from carbohydrate precursors is an area which has received a lot of attention in recent years.[136] The Ferrier[157] reaction constitutes one of the most well known strategies for the conversion of sugars into six-membered ring carbocycles (Scheme 106). In the first instance, the sugar derivative **186** is transformed into the enol ether **187** which, upon heating in aqueous acetone with mercury (II) salts, affords the chiral cyclohexanone **188** by ring opening followed by intramolecular aldol ring closure of the intermediate mercury enolate.



186 **187** **188**

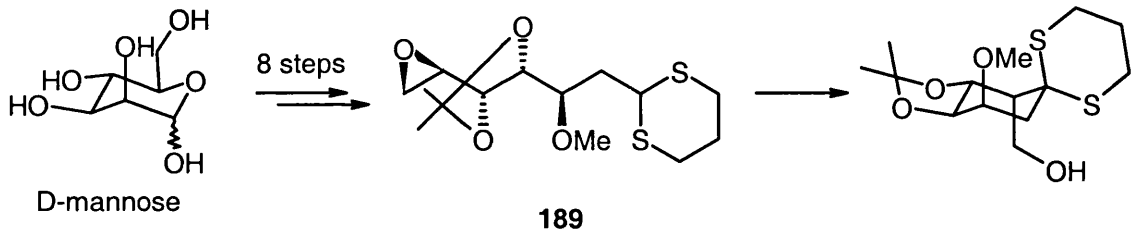
i) NaI, Ac_2O
ii) AgF, pyridine
iii) $HgCl_2$, aq. acetone

Scheme 106

The Ferrier mercuric ion mediated conversion of 6-deoxyhex-5-enopyranosyl compounds to deoxyinososе derivatives has been shown to exhibit general applicability[158] in the synthesis of cyclitol derivatives, inosamines and other

compounds of interest in the areas of aminoglycoside antibiotics[159] as well as pseudo-oligosaccharides.[160] The main disadvantage of this methodology, however, is the use of undesirable mercuric salts which render this approach unattractive especially for large scale syntheses.

More recently, Krohn[161] has reported a flexible new method for converting sugars into cyclohexanoids. This approach comprised addition of 2-lithio-1,3-dithiane to the free anomeric centre of a protected sugar such as mannose, reductive elimination of the newly formed hydroxyl group, and appropriate activation of one of the hydroxyl groups in the chain to form an epoxide, which acts as the electrophile, followed by base-induced cyclisation (Scheme 107).



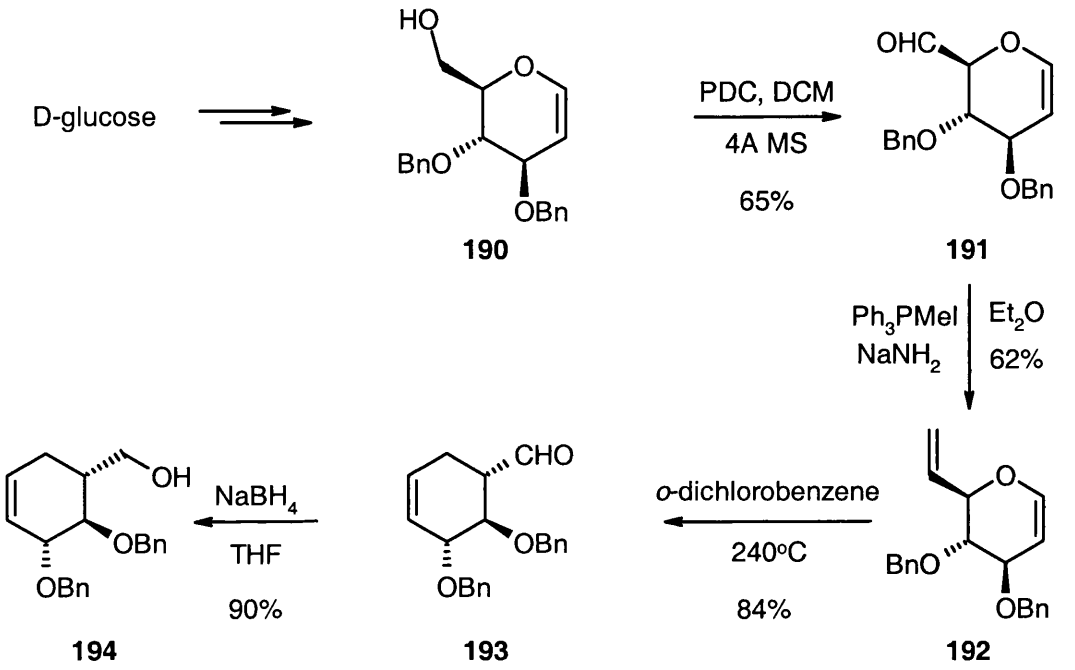
189

Scheme 107

This methodology has been applied for the synthesis of validatol and 4-*epi*-validatol from mannose and glucose respectively.[162] Although this approach has proven to be very flexible for the synthesis of carbocycles of various ring sizes it does however require a long multistep sequence for the preparation of the epoxy dithiane intermediate **189** (8 steps from mannose).

The increasing biological importance of pseudo-sugars has led to the development of several methods for their synthesis in optically pure form.[163] Pseudo-sugars are 2,3,4,5-tetrahydroxy-1-(hydroxyl-methyl)cyclohexanes in which the oxygen atom has been replaced by a methylene group. Pseudo-D-glucose, pseudo-D-galactose and pseudo-D-fructose have been suggested as replacements for their sugar congeners as non-nutritive sweeteners.[164] Moreover, pseudo-sugars and related carbocyclic compounds have been found in some antibiotics such as validamycins as well as enzyme inhibitors such as adiposins.[165] In this context, Nagarajan[166] has recently

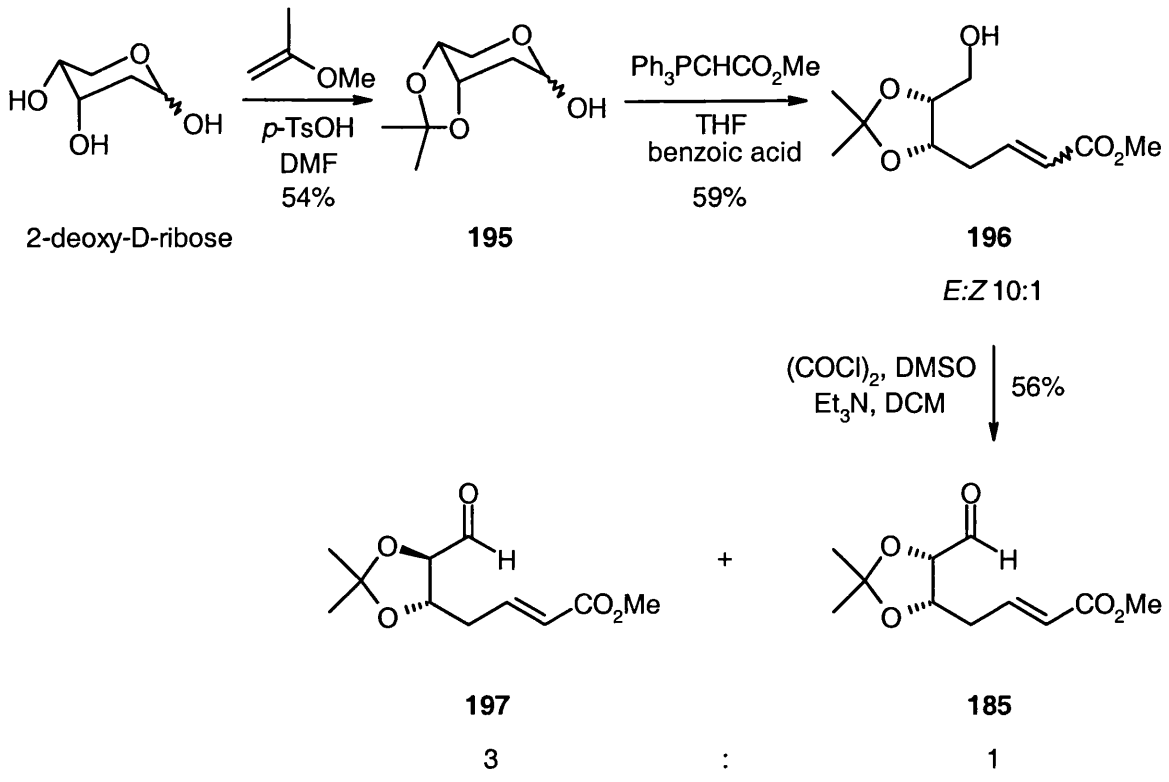
reported a short and versatile synthesis of pseudo-sugars from naturally occurring carbohydrates using the Claisen rearrangement as the key step (Scheme 108).



Scheme 108

Thus, compound **190**, which could be readily derived from D-glucose, was oxidised using pyridinium dichromate (PDC) to the aldehyde **191**. Subsequent methylenation of **191** with a combination of methyltriphenylphosphonium iodide and sodamide gave **192** which was heated in a sealed tube in *o*-dichlorobenzene at 240°C to afford the rearranged chiral carbocycle **193** in 84% yield. As a consequence of its instability, product **193** was immediately reduced using sodium borohydride to give compound **194**. Nagarajan has prepared a number of pseudo-sugars starting from this highly functionalised chiral synthon **194**.

Although several methodologies for the conversion of sugars into highly functionalised six-membered ring carbocycles have recently been reported, there is still a synthetic need for more efficient and straightforward approaches. In this context, we wished to prepare compound **185** which could in principle be readily accessed from 2-deoxy-D-ribose as outlined in Scheme 109, in order to probe whether our tandem sequence would also constitute a suitable approach for the construction of cyclohexanoids from the chiral pool of carbohydrates.



Scheme 109

Thus, 2-deoxy-D-ribose was reacted with one molar equivalent of 2-methoxypropene in the presence of a catalytic quantity of *p*-toluenesulfonic acid and dessicant ($CaSO_4$) in anhydrous dimethylformamide at 0°C. After one hour, an additional stoichiometric amount of 2-methoxypropene was added and stirring was continued for a further two hours. Neutralisation of the reaction mixture followed by column chromatography furnished the desired deoxyribopyranose 3,4-acetonide **195** in 54% yield. Treatment of the protected carbohydrate **195** with carbomethoxymethylene triphenylphosphorane in dry tetrahydrofuran containing a trace of benzoic acid at reflux effected Wittig olefination to the corresponding α,β-unsaturated ester **196** as a mixture of geometrical isomers in a *E:Z* 10:1 ratio. Finally, oxidation of the primary hydroxyl group in **196** into the aldehyde would lead to the desired methyl 4-(5-formyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-butenoate **185**. Therefore, oxidation was firstly carried out under the classical Swern conditions[167] using oxalyl chloride, dimethylsulfoxide and an excess of triethylamine. Under these conditions, epimerisation occurred at the α centre of the newly formed aldehyde leading to a mixture of the desired compound **185** and its 5-epimer **197** in an overall 56% yield

and in a 1:3 ratio as observed by ^{1}H NMR. Further proof supporting this observation was obtained from NOE experiments. Thus, strong NOE effects were observed between H_4 and Me_a and between H_5 and Me_b respectively, confirming the *anti* relative stereochemistry of such protons in compound **197** (Figure 18).

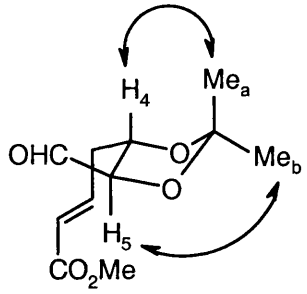
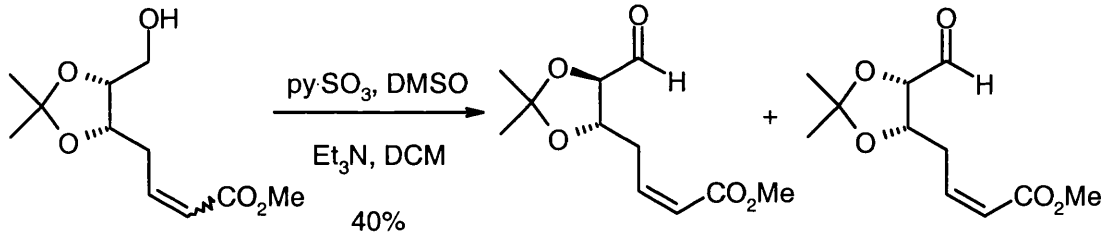


Figure 18

Alternatively, oxidation of **196** under the Parikh and Doering conditions[168] using pyridine-sulfur trioxide complex in dimethylsulfoxide and in the presence of triethylamine led to a similar result with the 5-epimer **197** being the major compound albeit in a lower yield (Scheme 110).



196 **197** **185**

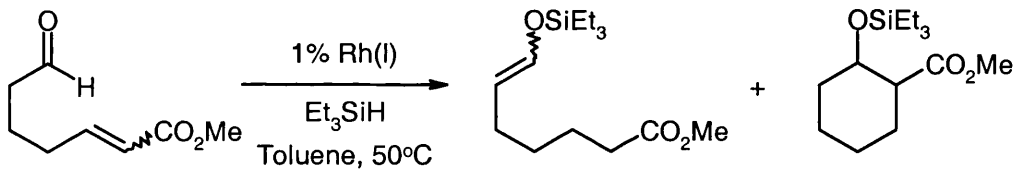
3 : 1

Scheme 110

As both isomers were easily separable by column chromatography and as both of them could be used for the purpose of our study, no further attempts in trying to prevent epimerisation were made at this stage.

II.3.1.5 Rh (I)-catalysed tandem cyclisation for the construction of cyclohexanoids

Having synthesised a variety of differently substituted 7-oxo-2-heptenoates we therefore elected to investigate the applicability of our tandem cyclisation for the synthesis of functionalised six-membered rings. Thus, in the first instance, the unsubstituted parent substrate **178** was submitted to our optimised reaction conditions (2.1 molar equiv of triethylsilane and 1 mol% of catalyst at 50°C) using Wilkinson's catalyst (Scheme 111). Unfortunately, only traces of the cyclised product **198** were observed by ^{1}H NMR, the major product being the reduced silyl enol ether **199** analogous as the previously obtained from methyl 6-oxo-2-heptenoate **127** (See Section II.2.8.5, Table 8, Entry 1).



178 **199** **198**

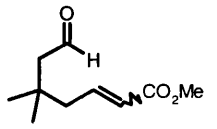
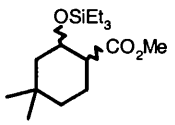
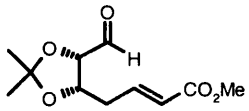
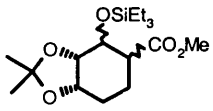
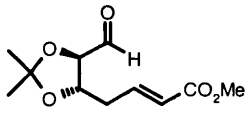
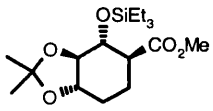
$RhCl(PPh_3)_3$	66% (*E:Z* 4.6:1)	traces
$RhH(PPh_3)_4$	traces	65% (*syn:anti* 1:3)

Scheme 111

To our delight, however, selection of hydridotetrakis(triphenylphosphine) rhodium (I) under the same reaction conditions afforded the desired 2-triethylsilyloxy-cyclohexane carboxylate derivative **198** in 65% yield with *anti* selectivity. In the latter instance, only traces of the silyl enol ether **199** were observed by ^{1}H NMR spectroscopy.

The structure of the major diastereoisomer was assigned on the basis of coupling constant values observed in ^{1}H NMR. By contrast with the previously discussed five-membered rings, typical coupling constants in the corresponding six-membered rings are greatly differentiated between axial-axial and axial-equatorial configurations, being J= 9.0 -12.5 Hz and J= 3.5 -5.5 Hz respectively.

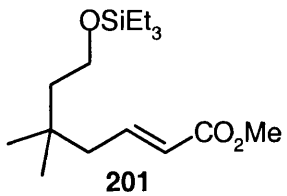
In view of this promising result, we then examined the compatibility of the previously synthesised substituted 7-oxo-2-heptenoate derivatives with our cyclisation methodology using hydridotetrakis(triphenylphosphine) rhodium (I) as catalyst. The results are summarised in Table 9.

Entry	Substrate		Product		Yield[a]	*syn:anti*[b]
1		**181**		**200**	37	1.0:1.0
2		**185**		**202**	47[c]	---
3		**197**		**203**	41[d]	---

[a]Isolated yields (%) after chromatography on silica gel. [b]Diastereomeric ratio in the crude material determined by ^{1}H NMR. [c]Isolated as a complex mixture of diastereomers. [d]Isolated as a single enantiomer.

Table 9

Thus, although the presence of both alkyl and heteroatomic substituents is tolerated in our hydrosilylation-aldol sequence, the yields were reduced relative to the unsubstituted parent substrate **178**. As shown in Entry 1, cyclisation of substrate **181** led to the corresponding silyl protected cyclohexanol **200** in 37% yield but with no selectivity. The low yield was due to simple competing hydrosilylation of the aldehydic functionality leading to the silyl ether **201** in 35% yield (Figure 19)

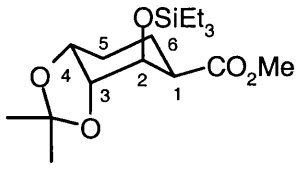


201

Figure 19

Substrate **185** containing the isopropylidene functionality was cyclised into the highly functionalised six membered ring carbocycle **202** in 47% yield (Entry 2). In

the latter instance, the diasteromeric ratio could not be determined by ^{1}H NMR due to overlapping of signals in the characteristic region of the spectrum. Column chromatography allowed, however, the separation of one of the four possible isomers which was identified to be the *syn* isomer **202a** showed in Figure 20.

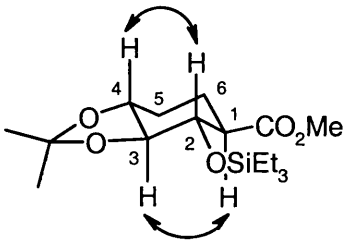


202a

Figure 20

The assignment was made on the basis of the values of coupling constants measured in ^{1}H NMR. Thus, examination of the signal at 2.71 ppm corresponding to H_1 indicates that this proton occupies an axial position based on the presence of two small coupling constants ($J_{H1ax\text{-}H2eq}$= 3.5 Hz and $J_{H1ax\text{-}H6eq}$= 5.7 Hz), which indicates axial-equatorial relationship, and the presence of a big coupling constant ($J_{H1ax\text{-}H6ax}$= 8.9 Hz) characteristic of a *trans* diaxial configuration.

In a similar manner, cyclisation of substrate **197** gave the corresponding cyclohexanoid **203** in 41% yield as a single enantiomer (Figure 21). As for substrate **200**, the reduced yields in both **202** and **203** relative to the unsubstituted parent substrate could be explained by the formation of significant amounts of the silyl ethers derived from the hydrosilylation of the aldehydic function.



203

Figure 21

The structure of isomer **203** was unequivocally assigned on the basis of two typical diaxial coupling constants ($J_{H1ax\text{-}H6ax}$= 12.5 Hz and $J_{H1ax\text{-}H2ax}$= 9.5 Hz). Further

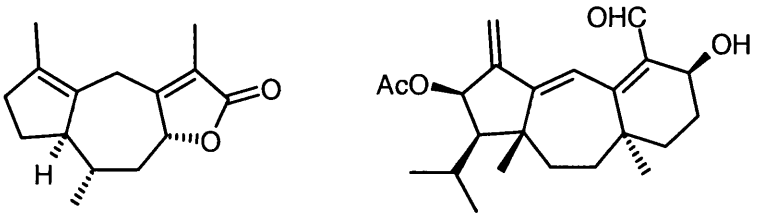
support for this assignment was obtained from NOE experiments. Hence, a strong NOE effect between H_4 and H_2 and between H_3 and H_1 unambiguously confirmed this configuration. The stereospecificity of our tandem cyclisation in this particular example could be attributed to the greater stability of isomer **203** in which all four substituents occupy an equatorial position.

The tolerance of the ancillary isopropylidene functionality exhibited in these latter two cyclisations, together with the ready availability of the cyclisation precursors which were obtained in only three steps from the natural sugar, provides an indication that this approach may be of promise for the construction of six-membered ring carbocycles from carbohydrates and promises an excellent alternative to the Ferrier rearrangement involving highly toxic mercuric salts.

II.3.2 Extension of the Rh (I) tandem cyclisation for the synthesis of larger ring sizes

II.3.2.1 Introduction

Cycloheptene-containing polycyclic natural products are widely present in nature, some of these exhibiting important biological activities. In particular, the bicyclo[5.3.0]decane ring system is prevalent in nature and has been identified as the key structural unit in a number of biologically active compounds including the guianes and the tricyclic guanacastenes, as well as the guaianolide sesquiterpenes which are characterised by a γ-lactone ring fused to the 5-7 core. Representative examples of these include the americanolides,[169] some of which exhibit activity against the human colon cancer cell line, and the unique diterpene guanacastepene which was found to possess novel and potent antibacterial properties (Figure 22).[170]



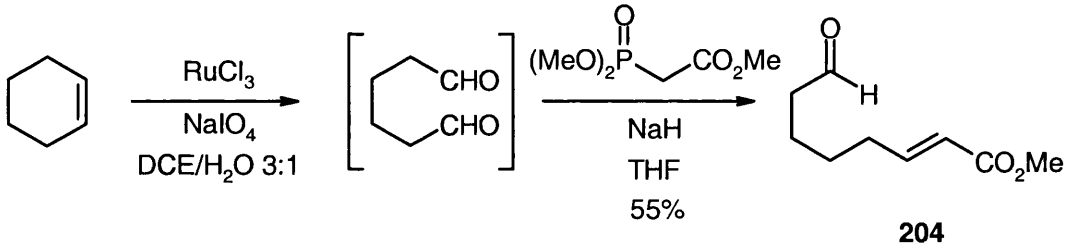
Americanolide D **Guanacastepene**

Figure 22

Despite many synthetic studies however, efficient and highly stereoselective methods for the construction of seven membered ring carbocyclic skeletons still pose a formidable synthetic challenge. In this context, we therefore elected to study the applicability of our novel rhodium (I) hydrosilylation-aldol sequence for the construction of seven-membered rings and even larger ring sizes.

II.3.2.2 Preparation of methyl 8-oxo-2-octenoate **204**

Substrate **204** was synthesised in one step from commercially available cyclohexene *via* oxidative cleavage of the cyclic olefin followed by *in situ* Horner- Wadsworth-Emmons olefination of the resultant adipaldehyde as outlined in Scheme 112.



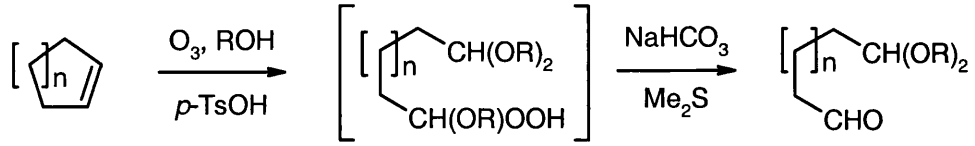
Scheme 112

Cleavage of olefins is a synthetically useful transformation that permits the degradation of large compounds and more importantly the introduction of oxygen functionality into molecules. Conversion of olefins which are not fully substituted into aldehydes has been traditionally accomplished by ozonolysis followed by reductive workup[171] as well as using a combination of osmium tetroxide-sodium periodate known as Lemieux-Johnson reagent.[172] In the latter instance however, the main disadvantage is the use of a highly toxic oxidant. Very recently, Yang[173] has reported a convenient oxidation protocol to cleave olefins to carbonyl compounds using ruthenium trichloride as catalyst. In particular, aliphatic olefins were converted in good to excellent yields into the corresponding alkyl aldehydes using a combination of ruthenium trichloride (3.5 mol%) and sodium periodate (1.5 equiv) in a mixture of 1,2-dichloroethane and water. Thus, as shown in Scheme 112, reaction of cyclohexene under the above reaction conditions afforded unstable adipaldehyde which was immediately submitted to *in situ* Horner- Wadsworth-Emmons olefination with trimethylphosphonoacetate providing methyl 8-oxo-2-

octenoate **204** in 55% overall yield as a single *E* diastereomer. The desired compound **204** was however accompanied by the doubly substituted diester (ca. 20%) which was easily separated by chromatography on silica gel.

*II.3.2.3 Preparation of methyl 9-oxo-2-nonenoate **205** and methyl 10-oxo-2-decenoate **206***

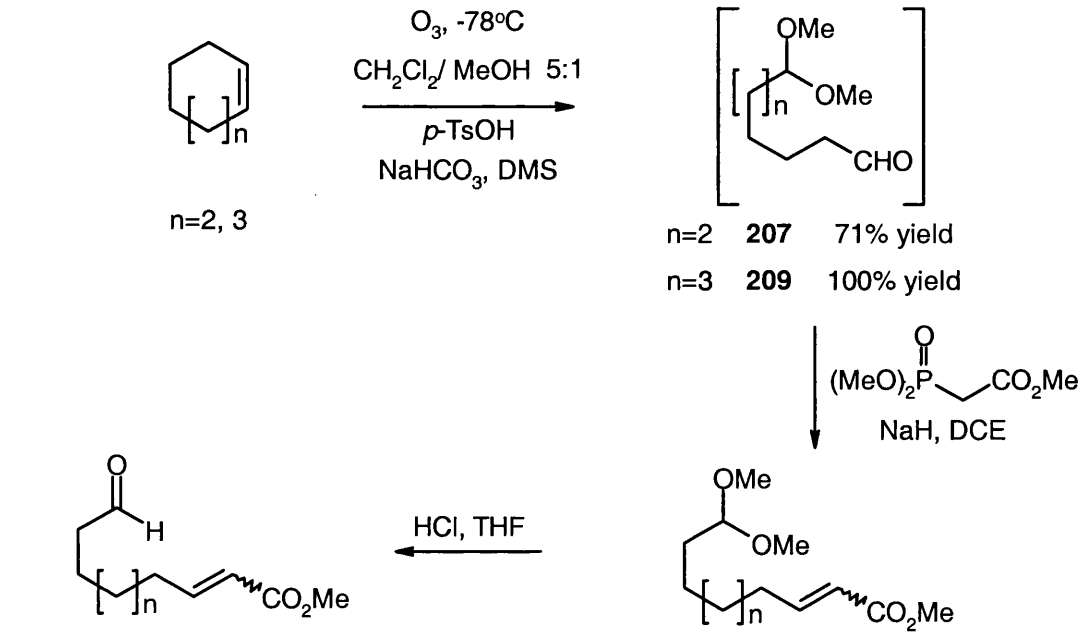
In order to extend our methodology to even larger ring sizes and hence to explore its potential limitations, we initially envisaged the preparation of methyl 9-oxo-2-nonenoate **205** and its higher homologue **206** by a similar synthetic approach to that previously described for the preparation of octenoate **204**. In the event however, we elected to attempt an ozonolytic cleavage of the corresponding olefin under the classical Schreiber conditions[174] in order to obtain terminally differentiated products and, hence, to prevent the possible formation of the doubly substituted diester side product. It is well known that ozonolytic cleavage of cyclic olefins in the presence of an alcohol affords the open chain product with an aldehyde and a α-alkoxy hydroperoxide at the terminus.[175] Schreiber[174] has reported that simple modifications of the ozonolytic workup procedure for these peroxides can give rise to a variety of products with differentiated terminal functionality. In particular, addition of *p*-toluenesulfonic acid to the ozonolysis reaction mixture led to an acetal-alkoxy hydroperoxide. Neutralisation of the acid with sodium bicarbonate and subsequent reduction with dimethylsulfide then affords the corresponding acetal-aldehyde in a one-pot operation (Scheme 113).



Scheme 113

Accordingly, ozonolytic cleavage of commercially available cycloheptene afforded the corresponding aldehyde-acetal **207** in 71% as a clear oil of sufficient purity for further use (Scheme 114). At this stage, Horner- Wadsworth- Emmons olefination could only take place at the aldehydic terminus giving the ester-acetal **208** in quantitative yield as a mixture of *E* and *Z* isomers in a *E:Z* 6:1 ratio. Final acidic

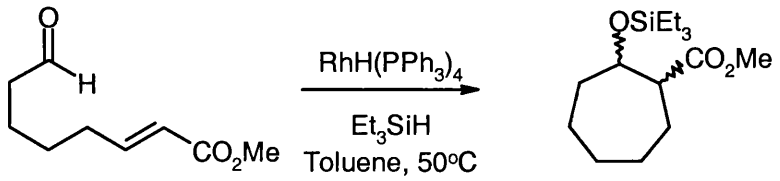
hydrolysis of the dimethyl acetal functionality afforded, after chromatography on silica gel, the desired methyl 9-oxo-2-nonenoate **205** in 56% yield. In an analogous manner, cyclooctene was quantitatively oxidised into aldehyde-acetal **209**. Subsequent Horner- Wadsworth- Emmons olefination with trimethylphosphonoacetate afforded the ester-acetal **210** in 84% yield as a mixture of geometrical isomers in a *E:Z* 5.2:1 ratio. Finally, deprotection of the acetal functionality under acidic conditions gave the homologue methyl 10-oxo-2-decenoate **206** in 80% yield.



Scheme 114

II.3.2.4 Rh (I)-catalysed tandem cyclisation for the construction of larger ring sizes

Previously synthesised methyl 8-oxo-2-octenoate **204** was reacted with triethylsilane and hydridotetrakis(triphenylphosphine) rhodium (I) in toluene at 50°C in order to investigate the feasibility of generating substituted cycloheptanoids by our tandem cyclisation methodology. To our delight, octenoate **204** furnished the seven-membered ring analogue **211** in comparable yield (68%) but with a reversal in terms of stereoselectivity relative to the six-membered ring congener **198** (Scheme 115).



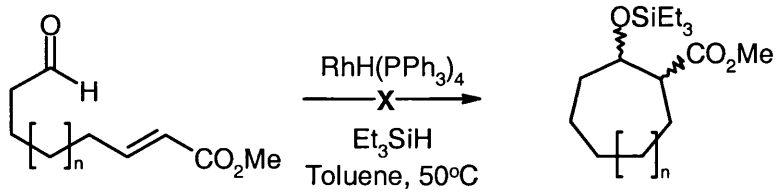
204 68% **211**

syn:anti 2.5:1

Scheme 115

Column chromatography did not allow the separation of isomers. Nevertheless, they were unambiguously assigned on the basis of the coupling constants and chemical shifts measured in ^{1}H NMR. Analogous criteria to those previously applied to the assignment of five and six-membered rings remained pertinent to the corresponding cycloheptanoid. Thus, coupling constant $J_{H1\text{-}H2}$= 8.3 Hz indicates *anti* relative stereochemistry whereas $J_{H1\text{-}H2}$= 6.8 Hz accounts for the *syn* isomer.

Having established the applicability of our tandem sequence for the construction of functionalised seven-membered rings, we then elected to investigate the extension of this methodology for the generation of even larger ring sizes. Thus, the previously synthesised methyl 9-oxo-2-nonenoate **205** and its higher homologue **206** were submitted to our optimised reaction conditions using tetrakis(triphenylphosphine) rhodium hydride until total consumption of the starting material was observed (Scheme 116).



n=2 **205**
n=3 **206**

Scheme 116

In both cases the reactions were very sluggish, and led to a complex mixture of compounds as shown by t.l.c. All attempts to isolate these compounds by column

chromatography were unsuccessful. However, careful examination of the crude ^{1}H NMR revealed the presence of acyclic compounds derived from 1,4-conjugate addition of the organosilane to the α,β-unsaturated ester as well as products of hydrosilylation of the aldehydic function. The presence of the desired cyclised products however could not be clearly determined by ^{1}H NMR but in the event, the very low yield and the impossibility of isolation of the desired carbocycle from the reaction mixture made this transformation unsuitable for the construction of eight- or nine-membered rings. Several methodologies such as ring closing metathesis have also exhibited similar behaviour, leading to very sluggish reactions when increasing the ring size from seven to the kinetically and thermodynamically disfavoured eight-membered ring systems as a consequence of *trans* annular interactions.[176] Virtually only substrates incorporating cyclic conformational constraints[177] or rigid acyclic conformational control elements to avoid formation of dimers and oligomers[178] have led to successful eight-membered ring closures.

II.3.3 Conclusions

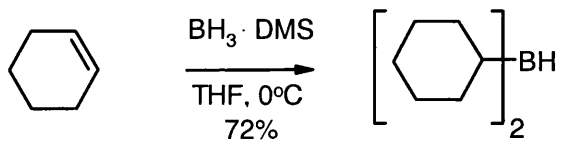
From the preceding study, it has been demonstrated that the rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction is a suitable method for the construction of functionalised cyclohexanoids from the corresponding 7-oxo-2-heptenoate derivatives in good yields and with moderate selectivity. Although a range of substituents is tolerated in the substrates, substitution led to reduced yields relative to the unsubstituted parent. Moreover, the tolerance of the isopropylidene functionality indicates that our approach may be of promise for cyclohexanoid construction from carbohydrates. Seven-membered ring carbocycles can also be accessed by our tandem reaction in good yield and with moderate *anti* selectivity. Attempts to generate even larger ring sizes from the corresponding acyclic precursors were mostly unsuccessful leading to a very complex mixture of acyclic compounds and hence suggesting that our method is not viable for the preparation of eight- and nine-membered ring carbocycles. Significantly, and in contrast to the hydroacylation protocol, the applicability of this approach for the preparation of highly functionalised five-, six- and seven-membered rings constitutes a significant synthetic improvement.

II.4 Alternative hydride donors and transition metal catalyst systems

II.4.1 Hydroboration *versus* hydrosilylation

As previously discussed in the introductory review, Evans and Fu[66] reported that Rh (I) complexes catalysed both the 1,4-addition of silicon hydrides and boranes to α,β-unsaturated systems. This mild method for conjugate reduction was compatible with a wide variety of functional groups. In particular, they noted that while α,β-unsaturated ketones which can readily adopt a *cis* conformation underwent conjugate reduction with catecholborane at room temperature in the absence of catalyst, α,β-unsaturated esters required catalytic quantities of Wilkinson's catalyst to react. The resulting boron enolates may then be reacted with an electrophile such as the proton to afford the corresponding carbonyl compounds or eventually with an aldehyde to afford aldol products. One year later, Boldrini[67] reported a similar one-pot, two-step procedure consisting of the conjugate addition of dialkylboranes to β-substituted (*E*)-α,β-unsaturated ketones followed by reaction of the resultant boron enolates with aldehydes. In this context, we therefore elected to investigate the effect of using boranes in the hydrometallation step, in order to probe such issues as chemoselectivity and stereoselectivity in our tandem sequence and thus to establish a comparison with the hydrosilylation variant.

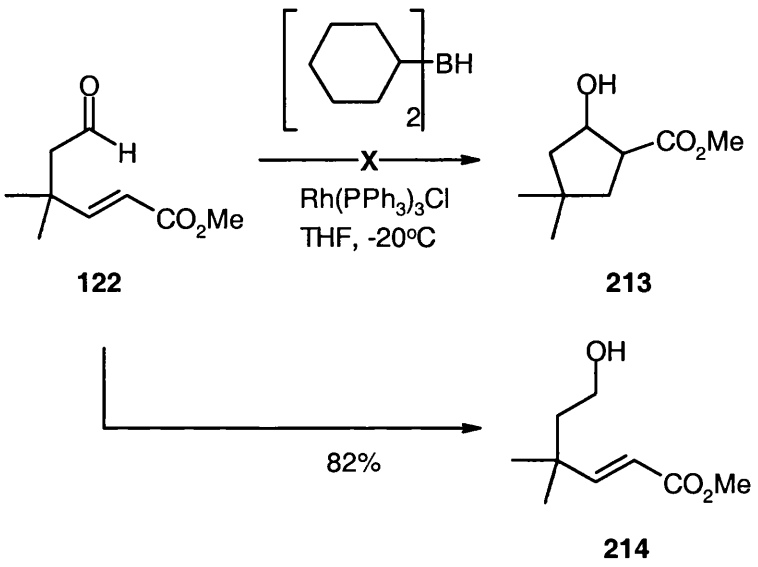
The rhodium (I)-catalysed tandem hydroboration-intramolecular aldol reaction was firstly attempted using dicyclohexylborane as hydride source, as this dialkylborane was found to give higher yields of the corresponding aldol adducts as reported by Boldrini.[67] Thus, dicyclohexylborane **212** was prepared from commercially available cyclohexene according to the procedure described by Brown (Scheme 117).[179]



212

Scheme 117

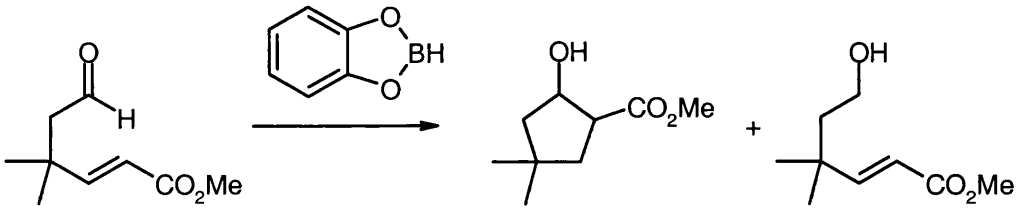
Subsequently, to a solution of methyl 4,4-dimethyl 6-oxo-2-hexenoate **122** in anhydrous tetrahydrofuran, was added Wilkinson's catalyst (2 mol%) and the reaction mixture was cooled to -20°C. Excess dicyclohexylborane **212** was then added and the suspension was stirred at the same temperature until complete consumption of the starting material (Scheme 118).



Scheme 118

After quenching the reaction with water, ^{1}H NMR of the crude mixture revealed the absence of the expected cyclopentanol **213**. Instead, column chromatography permitted the isolation of 6-hydroxy-2-hexenoate **214** in which the aldehyde functionality has been reduced to the corresponding primary alcohol, suggesting that in the presence of a borane hydride donor, hydroboration of the aldehyde takes place preferentially over 1,4-addition of the borane to the conjugated ester.

The rhodium (I)-catalysed tandem hydroboration-intramolecular aldol variant was then explored using the same model substrate **122** but in the presence of commercially available catecholborane, following an analogous procedure to that reported by Evans[66] for the intermolecular congener. However, as in the preceding experiment using dicyclohexylborane, 6-hydroxy-2-hexenoate **214** was the only compound isolated after column chromatography (Scheme 119).



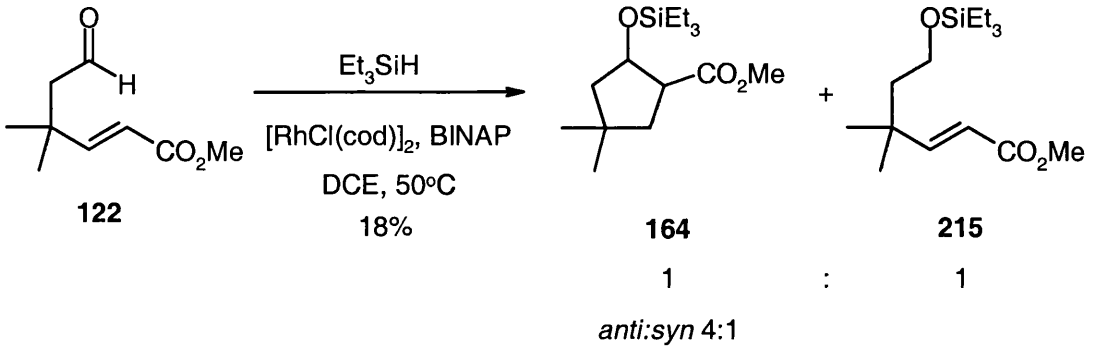
122 **213** **214**

1) $Rh(PPh_3)_3Cl$, THF, -20°C	0%	63%
2) $[RhCl(cod)]_2$, BINAP, DCE, 50°C then rt	0%	61%

Scheme 119

As already mentioned in Chapter 1, Morken[72] carried out a high-throughput evaluation of 192 independent catalytic systems for the intermolecular reductive aldol reaction of α,β-unsaturated esters and aldehydes. Among the most active catalysts, a combination of chloro(1,5-cyclooctadiene)rhodium (I) dimer, cathecolborane and the chiral ligand BINAP gave the best yields of the corresponding aldol adducts. Therefore, the use of catecholborane was further investigated under these conditions. Once again, only the acyclic alcohol **214** was isolated from the reaction mixture in 61% yield (Scheme 119).

The preceding catalytic system was then evaluated using triethylsilane as hydride source instead of catecholborane (Scheme 120). In the event, the corresponding cyclopentanoid product **164** was obtained together with the reduction product **215** as a 1:1 mixture in an overall 18% yield. Although column chromatography failed to separate both compounds, careful examination of the ^1H NMR spectrum of the mixture revealed that the cyclopentanoid **164** was obtained with *anti* selectivity in a 4:1 ratio. In addition, the chiral ligand BINAP was selected to investigate the degree of enantioselectivity attained in this transformation. However, in view of the low yield and the impossibility of obtaining a pure sample of the corresponding cyclopentanol **164**, the enantiomeric excess was not determined.

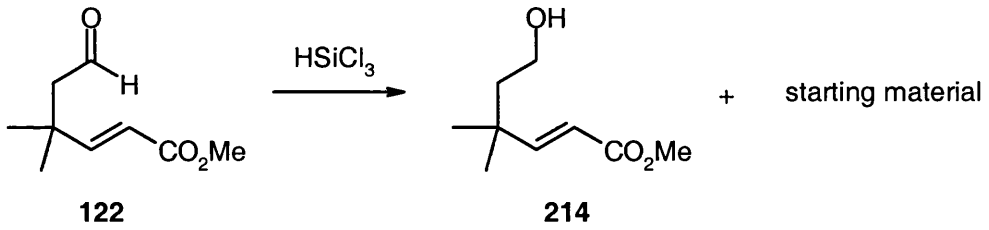


Scheme 120

Although boranes have been successfully used in the intermolecular variant of this tandem reductive aldol reaction, we have consequently demonstrated that they are not suitable for the intramolecular version as a consequence of chemoselectivity problems. On the other hand, the use of silanes in the presence of chloro(1,5-cyclooctadiene)rhodium (I) dimer and a very bulky ancillary phosphine such as BINAP also resulted in decreased yield and chemoselectivity compared to our previously investigated rhodium catalysts, Wilkinson's catalyst and hydridotetrakis(triphenylphosphine) rhodium (I). It would therefore be of interest to investigate the role of less bulky chiral ancillary phosphines in order to probe the levels of enantioselectivity attainable on achiral substrates.

II.4.2 Alternative transition metal catalysts

Having explored the role of boranes in the hydrometallation step, we then elected to investigate the use of a variety of silanes in the presence of a transition metal other than rhodium. Kiyooka[76] reported a mild reaction of aryl aldehydes and α,β-unsaturated amides and *tert*-butyl esters with trichlorosilane catalysed by tetrakis(triphenylphosphine) palladium (0). However, under these conditions, our model substrate **122** was completely unreactive even after 48 hours at 50°C (Scheme 121).



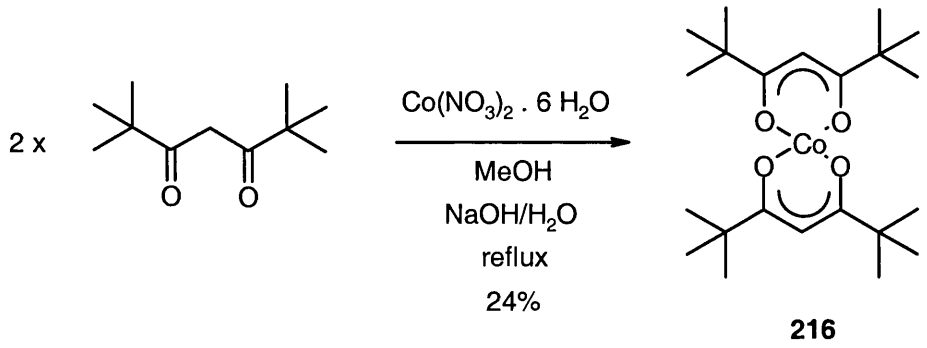
122 **214**

1) $Pd(PPh_3)_4$, DCM, 50°C	0%	95%
2) $CoCl_2$, DMI, CH_3CN, 70°C	49%	21%

Scheme 121

Also using readily available trichlorosilane, Chauhan and Boudjouk[180] have reported the conjugate reduction of a variety of α,β-unsaturated esters and cyclic ketones catalysed by cobalt chloride in the presence of small amounts of DMI (1,3-dimethyl-2-imidazolidinone) or DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone). The reactions were performed under very mild conditions and products were obtained in high yields. Selective reduction of the C=C double bond may give the appropriate enolate intermediate to undergo the desired intramolecular aldol cyclisation. Consequently, to a mixture of anhydrous cobalt chloride and DMI in anhydrous acetonitrile, was added 6-oxo-2-hexenoate **122** followed by trichlorosilane and the resulting mixture was refluxed at 70°C. Once again however, after 24 hours, alcohol **214** was isolated after preparative t.l.c. in 49% yield together with some unreacted starting material (Scheme 121).

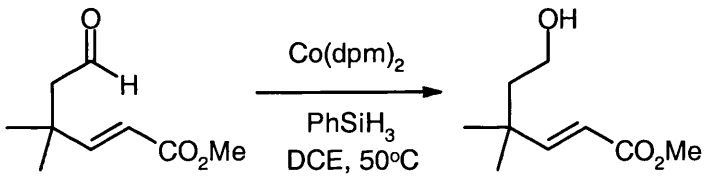
As previously described in the introductory review, during the course of our own investigations, Krische[81] has described an effective catalytic system, bis(dipivaloylmethanido) cobalt (II) and phenylsilane, for the intramolecular tandem hydrosilylation-aldol reaction of oxo-enone substrates. We have therefore envisaged applying these conditions to our oxo-enoate model substrate **122** in order to compare this catalytic system with our previously studied rhodium catalysts. In the first instance, the catalyst, bis(dipivaloylmethanido) cobalt (II) **216**, was prepared according to the procedure described by Cotton[181] from 2,2,6,6-tetramethylheptane-3,5-dione, cobalt nitrate hexahydrate and sodium hydroxide in methanol (Scheme 122).



216

Scheme 122

Recrystalisation from hot diethyl ether followed by sublimation at 110°C afforded compound **216** as ruby-red crystals in 24% yield. Subsequent treatment of substrate **122** with bis(dipivaloylmethanido) cobalt (II) and phenylsilane in anhydrous dichloroethane failed however to give the expected cyclisation compound and the corresponding reduction product **214** was obtained in 86% yield (Scheme 123).

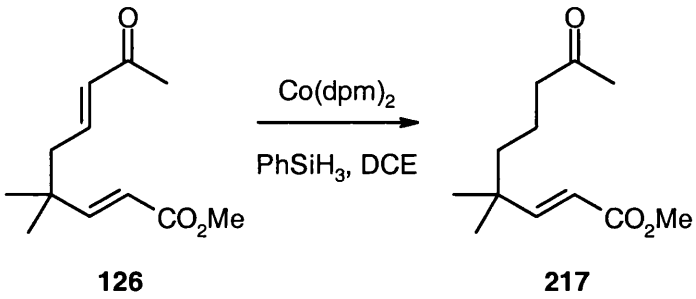


122 **214**

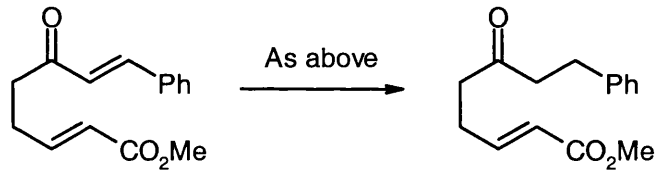
Scheme 123

Krische[81] has also applied the preceding conditions to bis-enone substrates in order to investigate a related tandem hydrosilylation-intramolecular Michael addition sequence. In the presence of unsymmetrical enones however, the catalyst was unable to discriminate between the two enone moieties, leading to a mixture of the two possible regioisomers. In this context, we envisaged applying the above conditions to substrates **105** and **126** both bearing simultaneously an enone and an enoate moiety. We reasoned that, since the conjugated ester had already proven to be unreactive under these conditions, hydrosilylation could occur exclusively at the enone moiety and subsequent intramolecular Michael addition would afford the desired cyclopentanol, preventing the regioselectivity problem observed by Krische. Thus, substrates **126** and **105** were treated with 5 mol% of $Co(dpm)_2$ and 2.4 equiv of phenylsilane in anhydrous 1,2-dichloroethane, and the reaction mixture was heated at

50°C during 24 hours (Scheme 124). In both cases, reaction was very sluggish and no cyclic products were observed by ^{1}H NMR spectroscopy. Instead, only acyclic products derived from the reduction of the enone moiety **217** and **218** were recovered after column chromatography, confirming the lack of reactivity of the conjugated ester under these conditions not only towards hydrometallation but also towards the intramolecular Michael addition of the corresponding cobalt enolates.



126 **217**



105 **218**

Scheme 124

In the event, from this study of palladium and cobalt catalysts with a variety of silanes, it has been demonstrated that the previously investigated combination of triethylsilane and a rhodium catalyst, either hydridotetrakis(triphenylphosphine) rhodium (I) or chlorotris(triphenylphosphine) rhodium (I), exhibits the best chemoselectivity for the tandem hydrosilylation-intramolecular aldol reaction of 6-oxo-2-hexenoates.

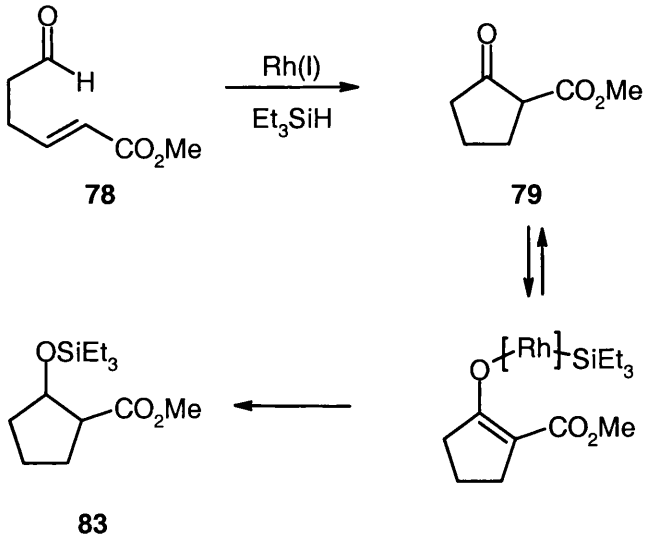
II.5 Mechanistic considerations and stereochemistry

II.5.1 Introduction

One of the key factors in developing a stereoselective method is the capability 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, some understanding of the reaction mechanism is therefore required. Moreover, the remarkable differences in behaviour exhibited by the two rhodium catalysts used in our own study, both, in terms of yield and selectivity, strongly encouraged us to gain deeper insight into the mechanism of this transformation.

II.5.2 Verification of the mechanistic pathway

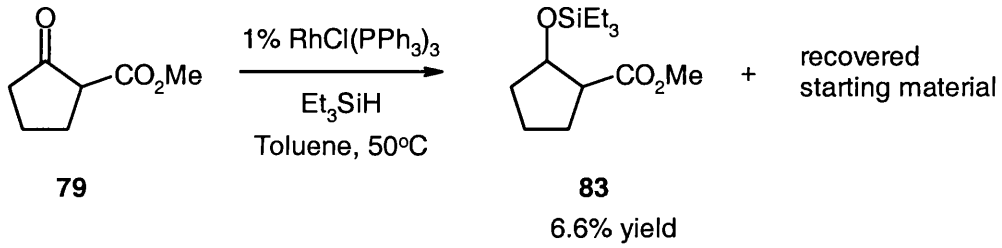
From a mechanistic standpoint, it was of interest to determine whether the transformation described was indeed a consequence of intermolecular hydrosilylation followed by an intramolecular aldol reaction, and not in fact intramolecular hydroacylation followed by hydrosilylation as outlined in Scheme 125, with the silane inhibiting in some way the competing decarbonylation reaction previously observed.



78 **79** **83**

Scheme 125

To this end, reduction of the ester, methyl-2-oxocyclopentane carboxylate **79**, was attempted using an excess of triethylsilane in the presence of 1 mol% of Wilkinson's catalyst. Under identical conditions to those that yielded 81% of the products *syn*-**83** and *anti*-**83** from methyl (*E*)-6-oxo-2-hexenoate **78**, only traces of the β-triethylsiloxy ester were formed (Scheme 126).

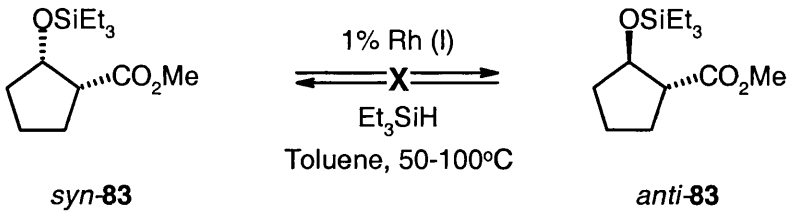


79 **83**
6.6% yield

Scheme 126

This experiment provides strong presumptive evidence that the mechanism of this transformation follows the tandem hydrosilylation-aldol cyclisation sequence, with hydroacylation of methyl 6-oxo-2-hexenoate **78** followed by hydrosilylation being, at most, a minor competing pathway.

We have also demonstrated that the *syn*-substituted cyclopentanol *syn*-**83** was not interconverted to the *anti* isomer *anti*-**83** when resubmitted to the reaction conditions, either in the presence of Wilkinson's catalyst or in the presence of $RhH(PPh_3)_4$ (Scheme 127). It was then established that even at elevated temperatures, the kinetic *syn* isomer did not equilibrate to the thermodynamic *anti* isomer.

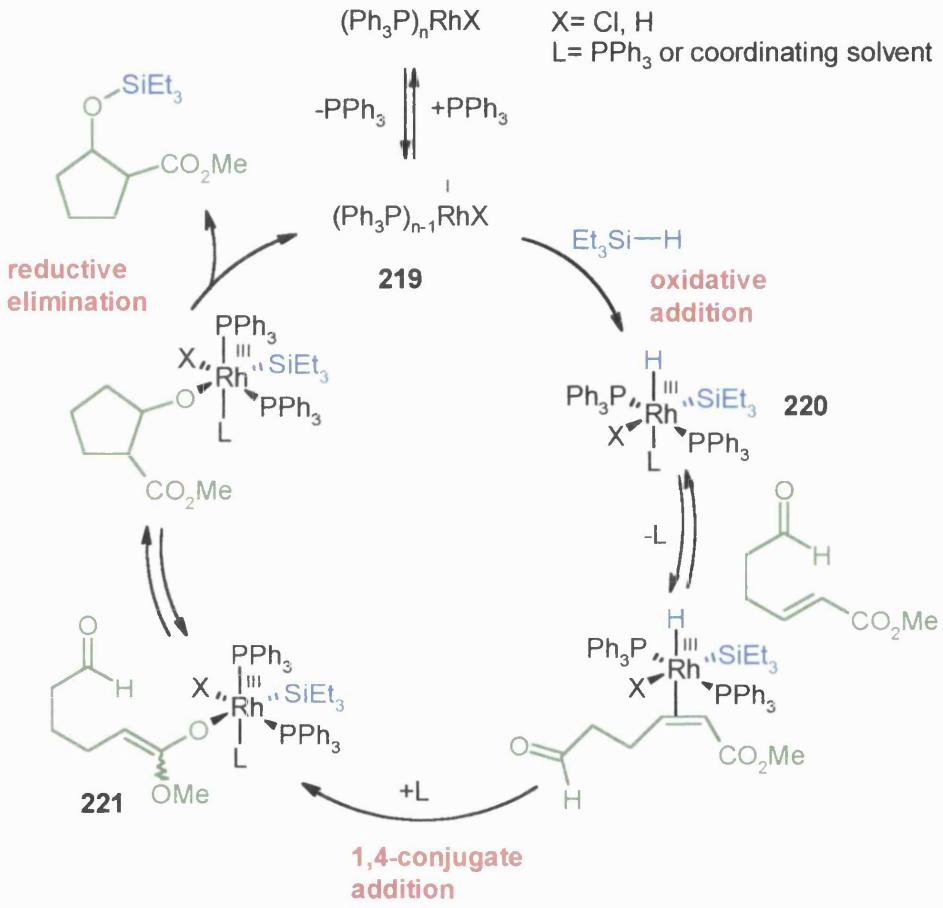


syn-**83** *anti*-**83**

Scheme 127

As in the intermolecular variant of this reaction using enones and aldehydes,[70] the intermediacy of an oxygen bound rhodium ester enolate of the type suggested by

Heathcock[71] seems most likely. The influence of the ancillary phosphine ligands and the replacement of the chlorine atom by a hydride ligand on the stereochemical outcome of our reactions both provide strong support for this possibility. A possible pathway for the catalytic aldol cycloreduction is depicted in Scheme 128.



Scheme 128

In contrast to group 10 metals, such as nickel, palladium and platinum which typically operate within catalytic cycles shuttling between the (0) and (II) oxidation states, rhodium typically shuttles between the (I) and (III) oxidation states in catalytic reactions with organometallics. Thus, oxidative addition of triethylsilane to the active species of the rhodium (I) catalyst **219** provides the hydridosilyl rhodium (III) intermediate **220** which, after coordination with the unsaturated ester, undergoes conjugate 1,4-hydride addition to afford the rhodium (III) ester enolate **221**. Subsequent intramolecular aldol trapping of enolate **221** followed by reductive elimination liberates the carbocyclic silyl ether product with concomitant

regeneration of the active catalytic species. It is interesting to note that a rhodium complex may catalyse both, the 1,4-addition and the aldol reaction, in one catalytic cycle. The chemoselectivity at both of the two steps is very high, the intermediates **220** and **221** reacting firstly with the enoate and then the aldehyde, respectively, with perfect selectivity.

Further insight into the cycloreduction mechanism requires an understanding of the interaction of Wilkinson's catalyst with triethylsilane. In this context, we have considered it relevant to refer to the related alkene hydrogenation reaction. The catalytic cycle of alkene hydrogenation has been the subject of intense research.[182] Thus, the active species of the catalyst appears to contain two tertiary phosphine ligands. However, the precise mechanism of formation of such species from the tri-tertiary phosphine complex $RhClL_3$ still remains unclear. Although it was first suggested that $RhCl(PPh_3)_3$ would rapidly dissociate in solution to form the solvated species $RhClS(PPh_3)_2$, this hypothesis was somewhat discredited by molecular weight and ^{31}P NMR measurements which demonstrated that, in the absence of oxygen, $RhCl(PPh_3)_3$ remains essentially undissociated ($K=3x10^{-3}M$) in benzene solution. According to the Tolman's 16/18 electron rule, this observation suggested that the equilibrium would involve a 16 to 14 electron species transformation (Equation 2).

$$\underset{16e}{(Ph_3P)_3RhCl} \rightleftharpoons \underset{14e}{(Ph_3P)_2RhCl} + PPh_3$$

Equation 2

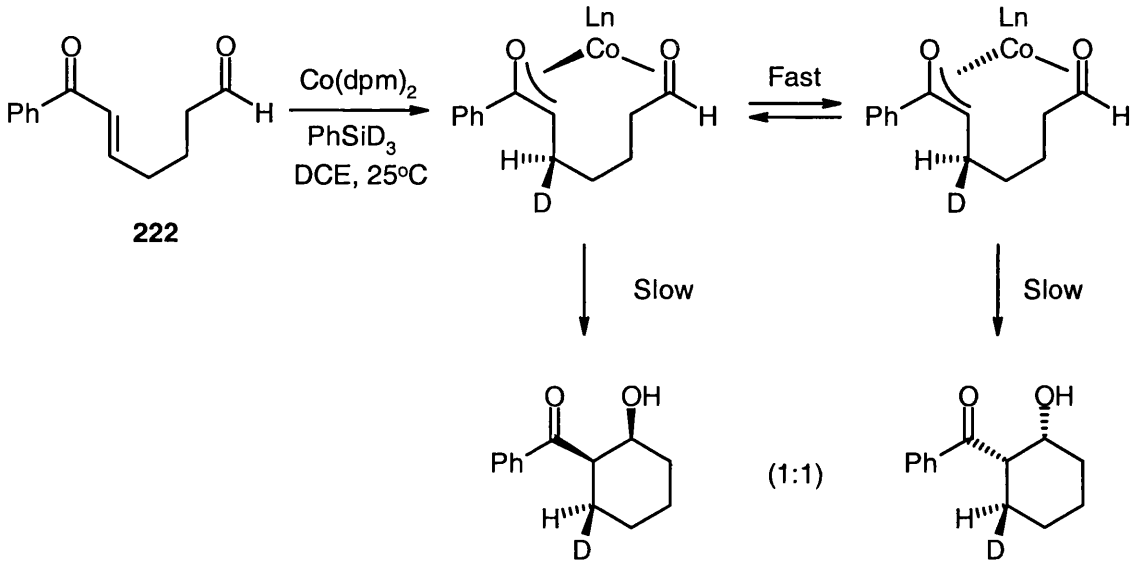
On the other hand, in the presence of a suitable coordinating solvent such as ethanol or in the presence of oxygen, this objection could be overcome *via* the sequence outlined in Equation 3.

$$\underset{16e}{(Ph_3P)_3RhCl} + S \rightleftharpoons \underset{18e}{(Ph_3P)_3RhClS} \rightleftharpoons \underset{16e}{(Ph_3P)_2RhClS} + PPh_3$$

Equation 3

Thus, the solvated di-tertiary phosphine species $RhClS(PPh_3)_2$ is believed to be the true catalyst with $RhCl(PPh_3)_3$ being merely the precursor. As oxidative addition of the Rh (I) to an aldehyde is comparatively slow, the active species of the low valence transition metal catalyst adds preferentially to the silane leading to the hydrido-metal intermediates required for initiation of the catalytic cycle.

The mechanism of a related hydrosilylation-intramolecular aldol reaction of oxo-enone substrates of type **222** in the presence of a cobalt catalyst has been probed through deuterium labelling studies employing d^3-phenylsilane (Scheme 129).[183]

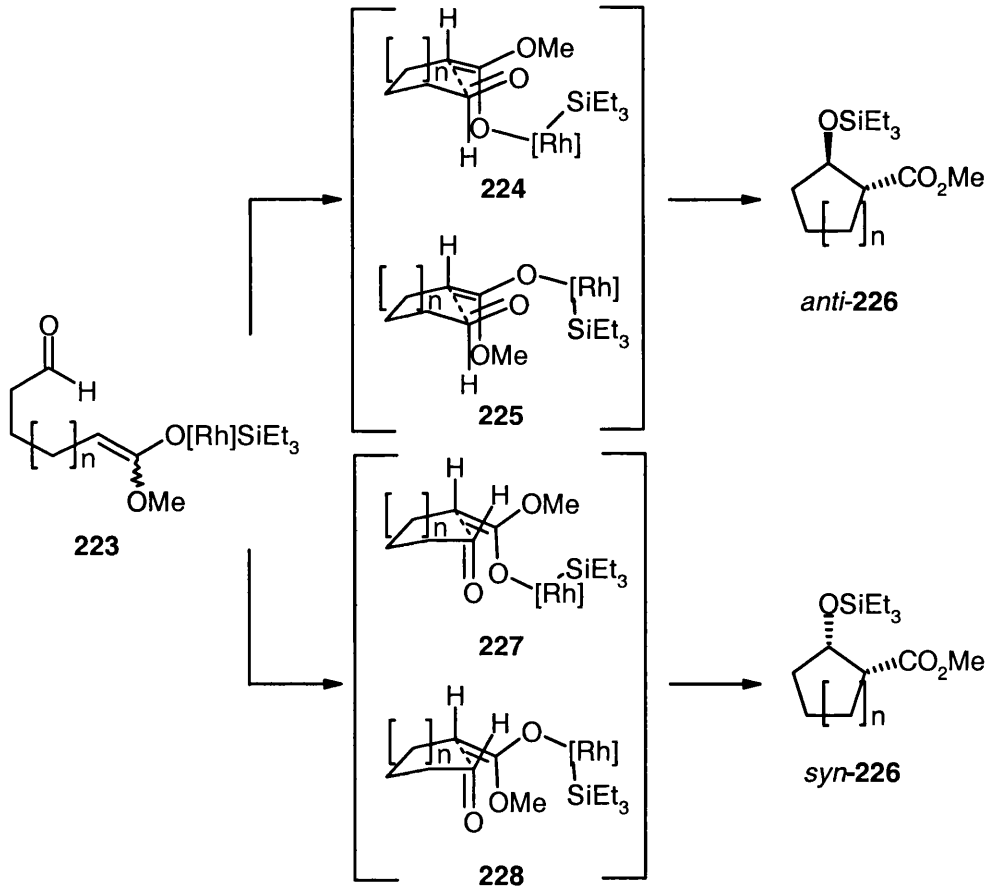


Scheme 129

As demonstrated by neutron diffraction analysis, a single deuterium is incorporated at the β-position of the enone as an equimolecular mixture of epimers, suggesting that β-hydride elimination is slow with respect to aldehyde addition. Related deuterium labelling studies on the $Mn(dpm)_3$-phenylsilane catalyst system for enone conjugate reduction also revealed incorporation of a single deuterium at the β-position.[184] The formation of the deuterated product as a 1:1 mixture of epimers suggested that π-facial interconversion of the kinetically formed metallo-enolate was faster than the intramolecular aldol reaction. Both isomerisation and aldehyde addition are likely to occur through the η^1-haptomer of the enolate, as supported by related studies involving Ni (II) enolates.[185]

II.5.3 Stereochemistry

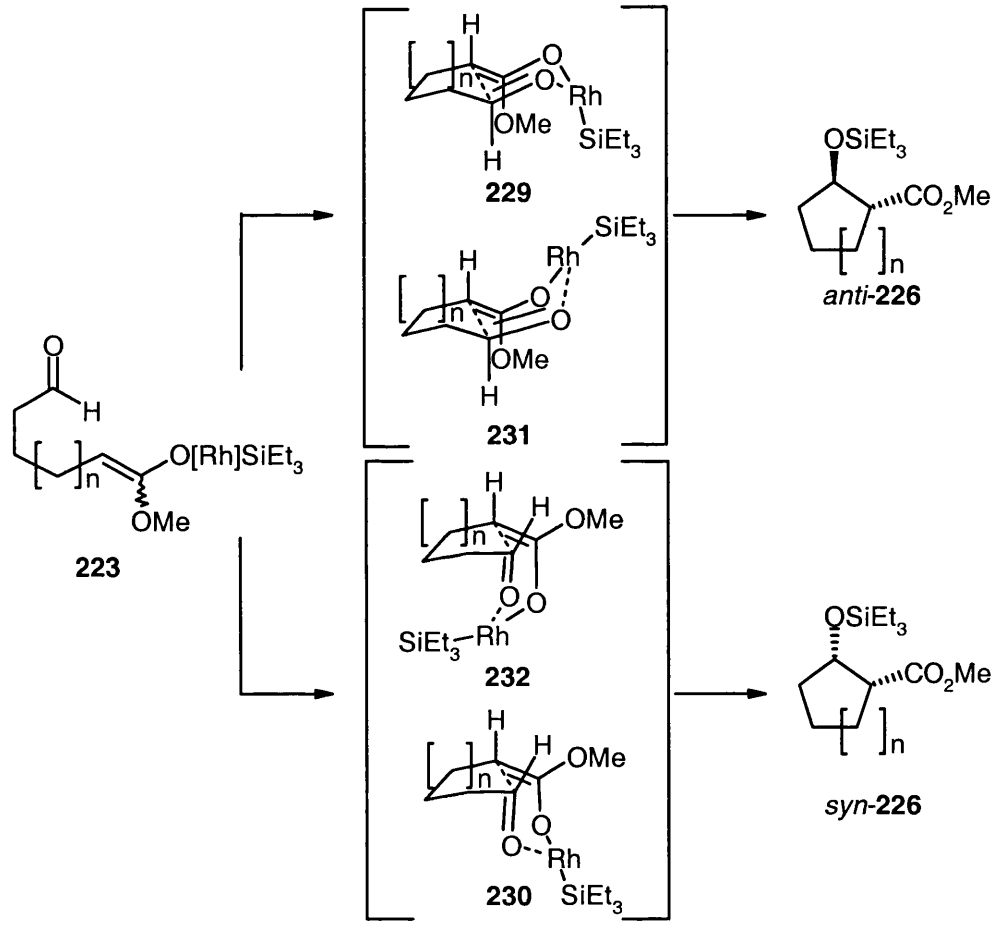
As anticipated on the basis of a hydrometallative mechanism, and as demonstrated from our preliminary results in the rhodium-catalysed tandem sequence discussed in Section 1, the stereochemical outcome is independent of the initial alkene geometry. Therefore, the stereoselectivity of this reaction can be formally rationalised in terms of the preferential formation of one stereoisomer of the rhodium ester enolate intermediate **223**. Moreover, two differing conformational types of transition state for the intramolecular aldol step could be invoked, involving an "open" transition state or a "chelated" Zimmerman-Traxler type transition state.[186] Thus, in an "open" transition state, the stereochemistry of the rhodium ester enolate should not have an influence on the stereochemical outcome, its conformation being the most important controlling factor (Scheme 130).



Scheme 130

Consequently, the favoured transition states **224** and **225** in both of which the aldehyde substituent occupies an equatorial position, lead to the *anti* carbocyclic

product *anti*-**226** whereas the less favoured conformations **226** and **227** lead to the *syn* diastereoisomer *syn*-**226**. Alternatively, in a "chelated" Zimmerman-Traxler type transition state, the transition metal may act as a Lewis acid to form a six-membered ring chelate. In these cases, the stereochemistry of the rhodium ester enolate is crucial in determining the stereochemical outcome of the reaction (Scheme 131).



Scheme 131

Thus, the chelated chair-like transition states **229** and **230** are considerably favoured with respect to the **231** and **232** transition states which invoke more strained boat-like conformations. Moreover, it is well known that the presence of *trans* double bonds in medium ring sizes is highly strained. Therefore, the presence of two transoid double bonds in the nine-membered ring transition state **229** is significantly disfavoured compared to the transition state **230** in which the enolate double bond adopts a cisoid conformation. Consequently, the more strained (*E*)-enolate **229** cyclises with an all-equatorial orientation leading to the *anti*-carbocyclic product

anti-**226**, whereas the preferred (*Z*)-enolate **230** undergoes the intramolecular aldol reaction *via* a chelated chair-like transition state and provides the *syn*-substituted product *syn*-**226** in which one of the substituents occupies an axial position. We have therefore reasoned that with 1 mol% of hydridotetrakis(triphenylphosphine) rhodium (I), the high degree of *anti* selectivity is likely to arise through the more favoured conformation **224** in an "open" transition state. The moderate *syn* selectivity observed upon selection of Wilkinson's catalyst may arise through the predominant formation of the *Z*-rhodium enolate **230** in a less strained "chelated" chair-like transition state. Both, the presence of a chlorine atom, which will significantly increase the Lewis acidity of the rhodium ester enolate, as well as the presence of a free coordination site around the transition metal centre, will favour the evolution of the reaction *via* a chelated transition state.

As discussed in a previous section, an increase in temperature resulted in a reduction of the *syn* selectivity when the reaction was carried out with 1 mol% of Wilkinson's catalyst. Although the reason is not clear, it may be due to a change either in transition state or in the (*Z*)/(*E*) rhodium enolate ratio. It was also found that increasing the amount of Wilkinson's catalyst to 10 mol% led to a reversal in selectivity (*syn:anti* 1:2). The reason for this observation is again not clear but an excess catalyst in the form of H-Rh(III)-$SiEt_3$ may act as a external source of Lewis acid which assists the formation of a chelated transition state. The predominant formation of an (*E*)-rhodium enolate **229** would then give rise to the *anti* carbocyclic product *anti*-**226**.

Although in the first instance it could be argued that the two rhodium complexes used in this study might well have converged to a common catalytic intermediate through oxidative addition of the silane to Wilkinson's catalyst and subsequent reductive elimination of chlorotriethylsilane, the experimental observations clearly do not substantiate this hypothesis. Consequently, the presence or absence of the rhodium chlorine bond will clearly influence the outcome of the reaction both in terms of the polarity of the rhodium hydride bond and the stereochemical outcome in the initial hydrometallation step. Moreover, it will significantly alter the Lewis acidic nature of the rhodium ester enolate intermediate and therefore the evolution of the reaction *via* either a "chelated" or an "open" transition state.

II.6 Application: Asymmetric formal total synthesis of (-)-carbovir and its related analogue abacavir

II.6.1 Introduction

As previously described in the introductory review, the development of efficient synthetic routes to carbocyclic nucleoside analogues has attracted considerable attention in recent years, not only as a consequence of their interesting biological activities but also because of the constant challenge associated with stereoselective construction of 5-membered ring carbocycles. Since our previous work on the rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction had proven to be a promising approach towards functionalised cyclopentanols, we have therefore elected to apply this tandem sequence to the synthesis of biologically active carbocyclic nucleosides such as carbovir and its related analogue abacavir.

II.6.2 Biological activity

(-)-Carbovir **9**, which was first prepared by Vince's group in 1988, was shown to have similar potency to the clinically approved nucleoside AZT **3** in selectively inhibiting HIV reverse transcriptase (Figure 23).[11],[28]

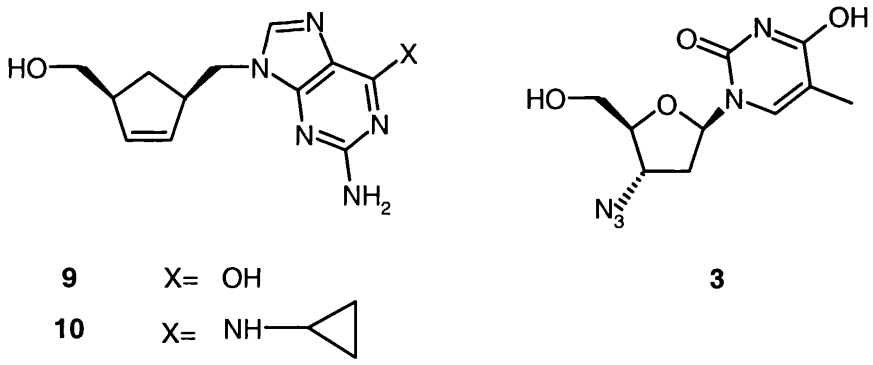


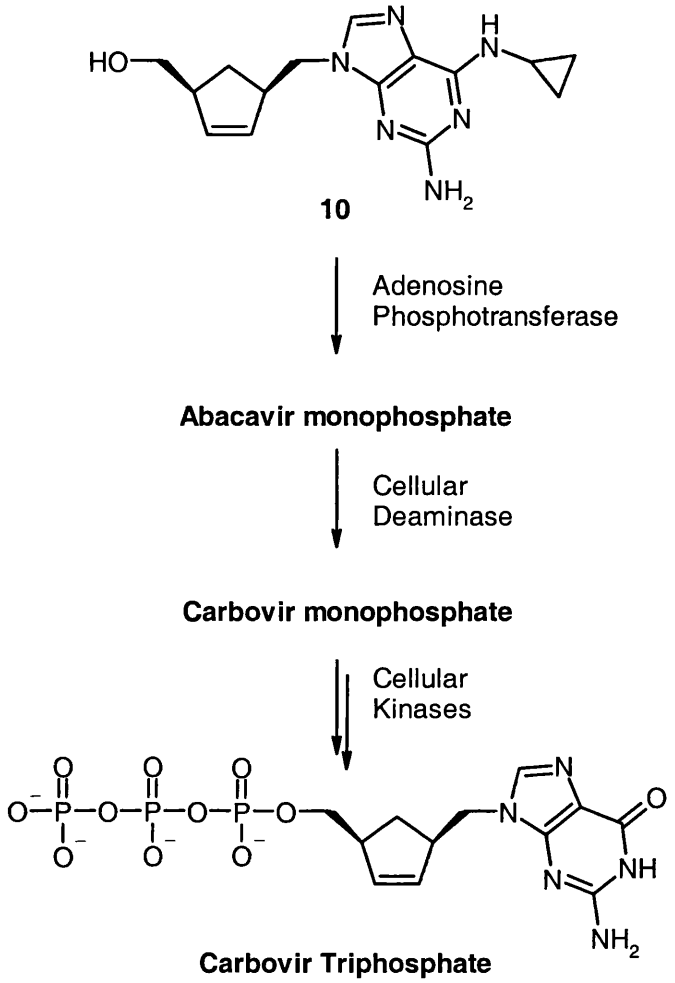
Figure 23

Human inmmunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), requires reverse transcriptase to copy its single-stranded RNA genome into a double-stranded DNA for integration into the host cell genome. Although almost all aspects of HIV-1's replication cycle have been targeted for therapy, most of the drugs that have been effective in clinical trials

are nucleoside reverse transcriptase inhibitors.[187] However, the effectiveness of these agents is often limited by their toxicity to the host through their interaction with mitochondrial polymerase γ[188] and the ability of the virus to mutate and hence gain resistance.[189] Other factors that limit the antiviral activity of such inhibitors are uptake, transport, metabolism and incorporation of the drug. In particular, (-)-carbovir **9** was removed from a clinical trial test due to its pharmacokinetic and toxicological deficiencies.

More recently, abacavir (1592U89 or Ziagen) **10**,[190] a new reverse transcriptase inhibitor with higher oral bioavailability and the capacity to penetrate the central nervous system, has been approved by the Food and Drug Administration (FDA) for treatment of acquired immunodeficiency syndrome (Figure 23). Abacavir and carbovir are both characterised by the presence of a 2',3'-unsaturated bond in the cyclopentyl ring. Unlike all clinically approved nucleoside analogues (AZT or Zidovudine, d4T or Stavudine, 3TC or Lamivudine, ddC or Zalcitabine and ddI or Didanosine), abacavir contains a novel carbocyclic ring instead of the sugar ring. Moreover, the promising pharmacokinetic profile of abacavir was attributed to its modified amino group at the 6 position of the purine ring.[190]

The metabolic activation of this analogue is unique and the mechanism in outlined in Scheme 132. Thus, abacavir is phosphorylated by adenosine phosphotransferase to the corresponding monophosphate derivative and further metabolised in several steps to the active congener carbovir triphosphate. This compound is a guanosine analogue containing a 2'-3'-unsaturation in its planar carbocyclic deoxyribose ring that acts on HIV-1 reverse transcriptase as a molecular target, resulting in chain termination of DNA synthesis.[191]

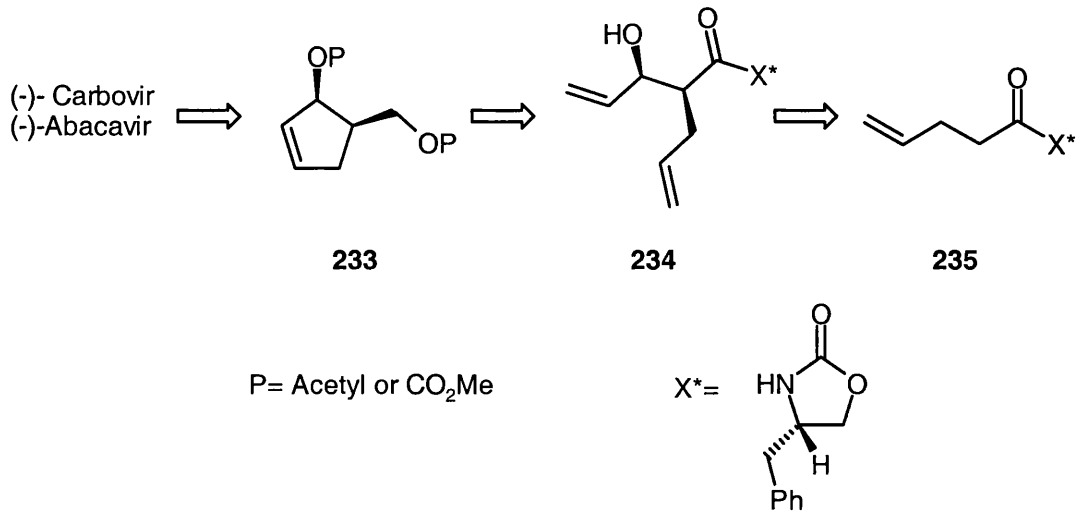


Scheme 132

II.6.3 Previous strategies for the synthesis of (-)-carbovir and its related analogue abacavir

The fascinating antiviral potency of (-)-carbovir and abacavir has triggered a significant synthetic effort for the preparation of such carbocyclic nucleosides and their analogues. As previously mentioned in the introductory review, most of the synthetic approaches to these carbocyclic nucleosides rely on the use of cyclopentadiene as the source of the carbocyclic sugar. Beside the clear advantage of being a very inexpensive starting material, the main disadvantage is the necessity of introducing chirality into the carbocyclic ring, which often involves classical resolution or desymmetrisation of a *meso* intermediate. Only few syntheses involving stereoselective cyclisation methods for the generation of the cyclopentyl moiety have been reported and most of them rely on a metathesis ring closing strategy and on the use of chiral auxiliaries to establish the absolute configuration of

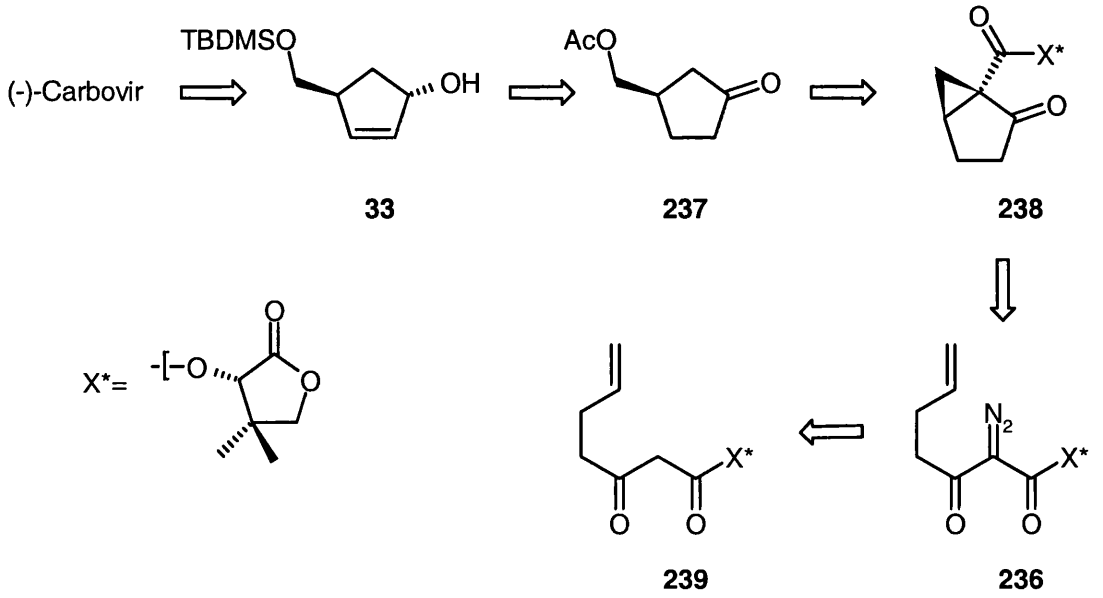
the pseudo-sugar. In this context and as previously discussed in the introductory review, Crimmins[37] has reported an efficient and general strategy based on an asymmetric aldol/ring closing metathesis sequence for the synthesis of (-)-carbovir and abacavir (Scheme 133).



Scheme 133

This strategy offered the advantage of establishing the asymmetry of the molecule prior to ring closure. Thus, the corresponding carbocyclic nucleosides were obtained after assembly of the appropriate 5-membered ring carbocycle **233** and the heterocyclic base *via* a Trost-type allylic substitution.[192] Cyclopentane **233** was accessed by ring closing metathesis of **234**, itself resulting from an asymmetric aldol reaction of intermediate **235**, which incorporates the chiral auxiliary (*S*)-4-benzyl-2-oxazolidinone, hence providing the relative and absolute stereochemistry of the cyclisation precursor **234**.

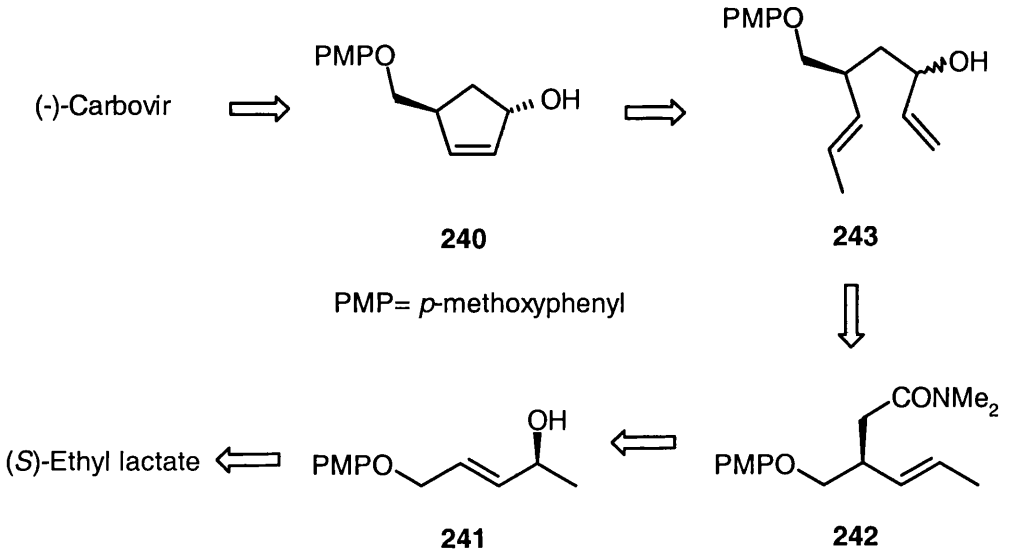
Tanimori[193] has reported an enantioselective synthesis of the carbocyclic moiety of (-)-carbovir **33**, based on intramolecular cyclopropanation of a chiral α-diazo-β-ketoester **236** and taking advantage once again of the asymmetry induced by a chiral auxiliary (Scheme 134).



Scheme 134

Thus, preparation of (-)-carbovir from the functionalised cyclopentane **33** was previously described by Asami,[34] which itself could be obtained from cyclopentanone **237** by classical synthetic transformations. Carbocycle **237** was prepared from **238** by opening the cyclopropane ring by acetate anion in order to install the 4-hydroxymethyl group. Cyclopropane **238** could in turn be obtained by a diastereoselective rhodium (II)-catalysed intramolecular cyclopropanation of chiral α-diazo-β-ketoester **236**, the key step in this strategy, which could be readily accessed from the β-ketoester **239**.

Very recently, Florent[194] has reported an enantioselective formal total synthesis of (-)-carbovir *via* a similar, although differently protected, carbocyclic moiety to that described by Tanimori **240**, but using (*S*)-ethyl lactate as the source of chirality instead of a chiral auxiliary as in the preceding examples. The two key steps of this strategy are a Claisen [3,3] sigmatropic rearrangement of the asymmetric alcohol **241** to afford amide **242** and as in Crimmins strategy, a ruthenium-catalysed ring closing metathesis of the 1,5-diene **243** for the formation of the five-membered carbocycle **240** (Scheme 135). The main disadvantage of this strategy however is the obtention of a 1:1 mixture of diastereomers in the last step of the synthesis, the expected compound **240** and its *syn* diastereomer.

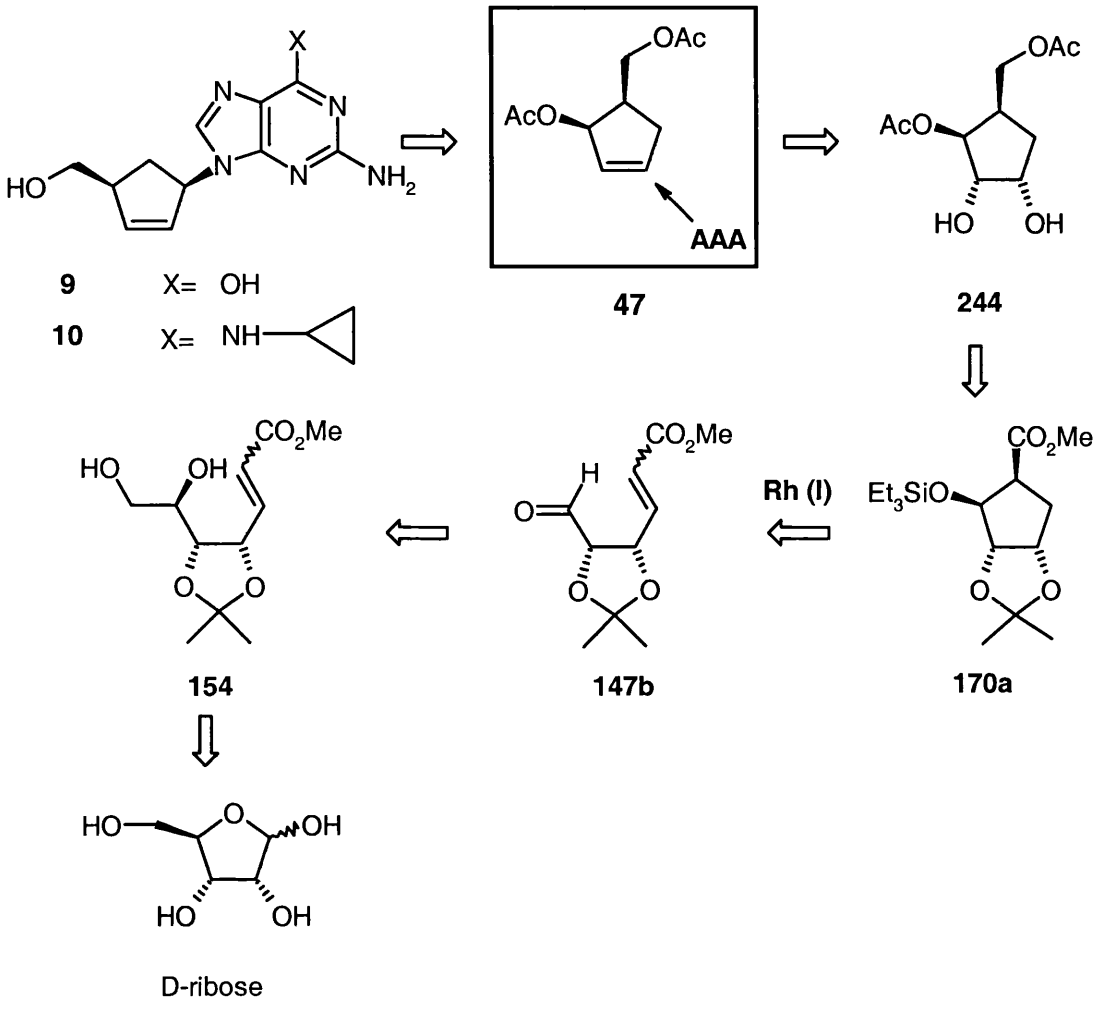


Scheme 135

Despite the fact that there are many synthetic approaches to (-)-carbovir and its related analogue abacavir, there is nevertheless a need for alternative and perhaps more efficient stereoselective strategies for the preparation of the carbocyclic moiety of such carbocyclic nucleosides.

II.6.4 Our retrosynthetic approach

Since our rhodium (I)-catalysed tandem sequence had proven to be a promising reaction for the construction of functionalised carbocycles from the chiral pool of carbohydrates, we have therefore envisaged the preparation of the carbocyclic moiety of (-)-carbovir and abacavir starting from D-ribose. Consequently, our strategy to such carbocyclic nucleosides requires that the rhodium (I)-catalysed tandem hydrosilylation-aldol cyclisation to form the pseudo sugar ring can establish the appropriate relative stereochemistry for the Trost-type asymmetric allylic alkylation (AAA) to assemble the heterocyclic base and the carbocyclic ring. On the other hand, the absolute stereochemistry would be induced by the chirality of the inexpensive natural carbohydrate D-ribose, avoiding the need for introduction and subsequent removal of chiral auxiliaries and hence shortening the synthetic pathway (Scheme 136).



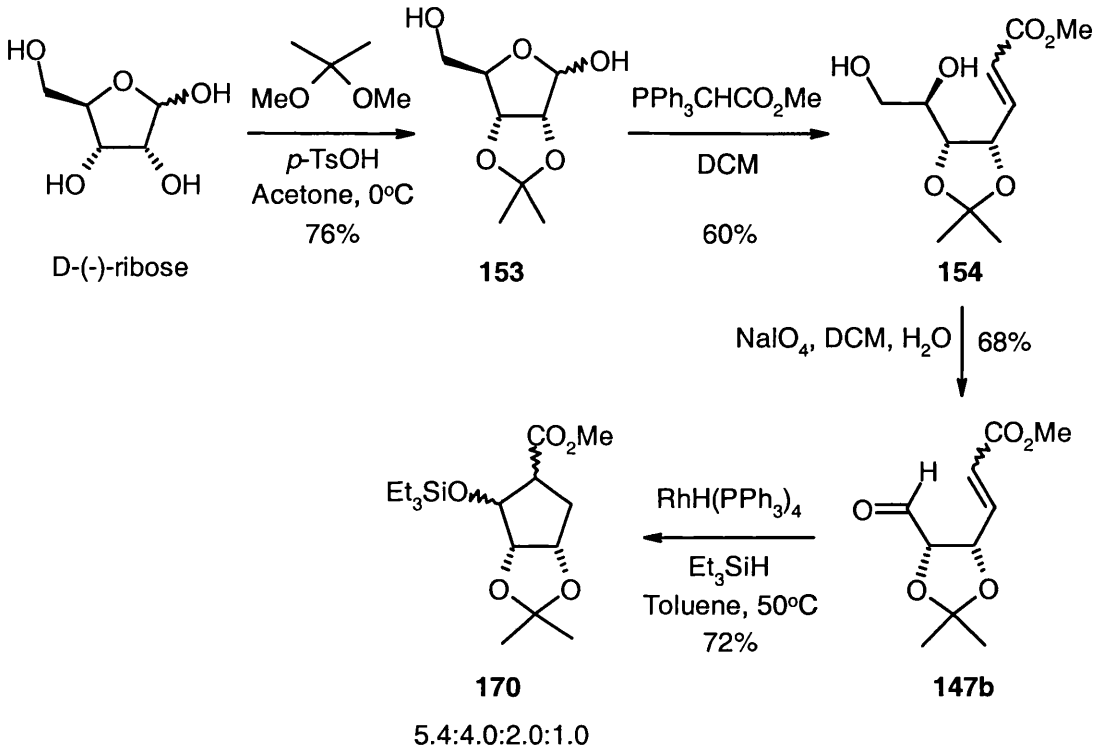
Scheme 136

Thus, it was envisaged that the aldehydic cyclisation precursor **147b** could be readily obtained from D-ribose after protection of the sugar as the corresponding isopropylidene derivative and subsequent Wittig olefination and oxidation. The tetrasubstituted carbocycle **170a** could then be accessed from **147b** *via* rhodium (I)-catalysed tandem cyclisation, provided that the cyclisation occurs with the desired stereoselectivity. Cyclic diol **244** could be readily prepared from **170a** after reduction of the methyl ester functionality and several selective protection and deprotection steps. Finally, the required carbocyclic diacetate **47** could be obtained by deoxygenation of the *cis*-diol **244**. Optically pure diacetate **47** has previously been prepared by a variety of methods[37],[195] and constitutes a highly valuable building block for the introduction of the pseudo-ribose moiety present in the structure of the

antiviral drug (-)-carbovir **9** and abacavir **10** by palladium-catalysed asymmetric allylic alkylation (AAA).

II.6.5 Asymmetric synthesis of the carbocyclic moiety of (-)-carbovir and abacavir

As we have in fact already described (Sections II.2.7.2 and II.2.8.4), the key highly functionalised carbocyclic intermediate **170** required for our synthetic approach was obtained in only four steps from commercially available D-(-)-ribose (Scheme 137).



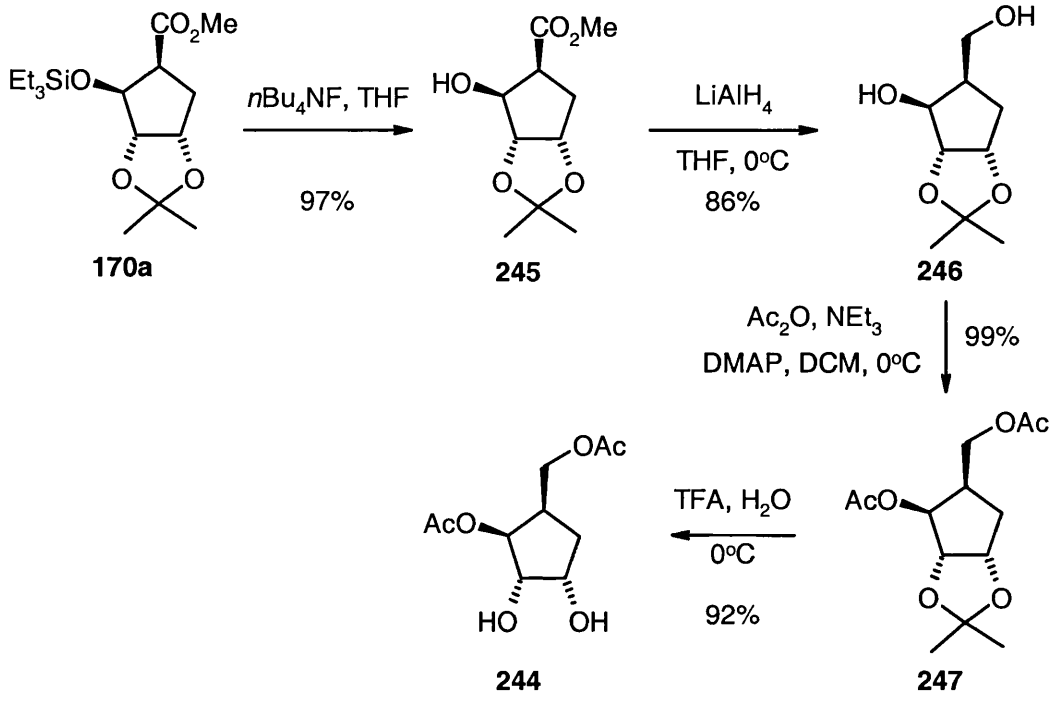
Scheme 137

Thus, protection of D-(-)-ribose as its isopropylidene congener **153** using 2,2-dimethoxypropane and a catalytic quantity of *p*-toluenesulfonic acid proceeded in 76% yield. Subsequent Wittig olefination with carbomethoxymethylene triphenylphosphorane afforded diol **154** in 60% yield with *Z* selectivity (*E:Z* 1:6). Oxidative cleavage of diol **154** with sodium periodate gave the aldehydic cyclisation precursor **147b** in 68% yield. Finally, rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction of a *Z/E* mixture of 6-oxo-2-hexenoate **147b** led to the highly substituted five-membered ring carbocycle **170** in 72% yield as a mixture of

diastereomers in a 5.4:4.0:2.0:1.0 ratio. Careful column chromatography allowed the separation of three of the four possible isomers, with the major isomer being that presenting the correct stereochemistry **170a** and therefore constituting a 31% yield.
As discussed in a previous section, the moderate yield obtained in the Wittig olefination of lactol **153** is due to the reactivity of ester **154** which readily undergoes intramolecular Michael-addition to afford the corresponding tetrahydrofuran derivative. The Wittig reaction of sugar lactols with stabilised ylides such as alkoxy-carbonylmethylene triphenylphosphoranes has been intensively investigated,[196] and this behaviour has often been observed. The extent to which the intramolecular Michael process occurs depends not only on the reaction conditions but also on the nature of the substrate. Although it is likely that conformationally restricted substrates such as isopropylidene derivatives could inhibit the intramolecular 1,4-addition, this is certainly not so in our case. Clive[197] has recently reported that use of bulky *O*-alkyl groups in the Wittig reagent such as *tert*-butyl or benzyl groups largely suppresses the intramolecular Michael reaction and allows the resulting unsaturated ester to be easily isolated. In addition, Martin[198] has recently reported that higher yields and improved *E* selectivities are obtained in the Wittig reaction of sugar lactols when replacing the corresponding triphenylphosphorane by its tributyl congener. The above observations suggest that further improvements in the yield of this transformation could be presumably achieved by replacement of the standard Wittig reagent with a more bulky phosphorane, provided that the rhodium-catalysed tandem sequence is then compatible with the presence of a *tert*-butyl ester functionality.

With the appropriate carbocycle precursor **170a** in hand, preparation of the *syn* diol **244** was very straightforward (Scheme 138). Thus, in the first instance, selective deprotection of the triethylsilyl ether was accomplished with tetra-*n*-butylammonium fluoride in tetrahydrofuran at room temperature, leading to the cyclopentanol **245** in 97% yield. Reduction of the ester functionality using lithium aluminium hydride afforded diol **246** in 86% yield which was quantitatively converted to the diacetate **247** by exposure to acetic anhydride, triethylamine and 4-(dimethylamino)pyridine at 0°C in anhydrous dichloromethane. Finally, selective deprotection of the acetonide protecting group was sought. In the first instance, deprotection was attempted by acidic hydrolysis with hydrochloric acid 2.0 M. Under these conditions, however,

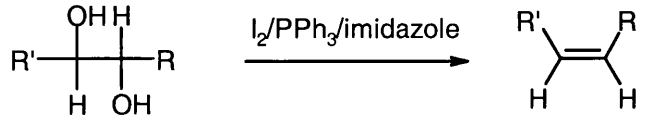
both acetate-protecting groups were removed whereas the isopropylidene functionality remained intact. We therefore elected to change the hydrolysis conditions and to use a 9:1 mixture of trifluoroacetic acid and water. In the event, the desired *syn* diol **244** was obtained after column chromatography in 92% yield.



Scheme 138

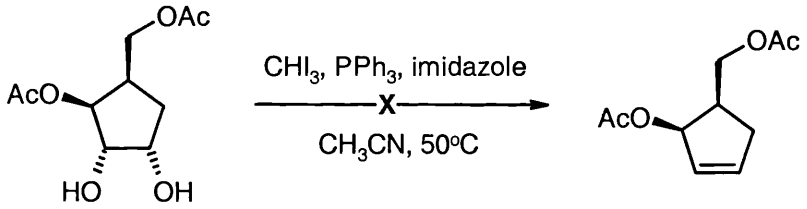
With ready access to the diacetate **244**, several possible routes to the olefinic carbocyclic moiety were therefore investigated. The generation of versatile olefinic functionality by deoxygenation of a 1,2-diol is a useful transformation in organic synthesis. In the ribonucleoside series several methods are known which will effect the deoxygenation of the 2'-3' vicinal diol function to the corresponding olefin.[199] In general, these require derivatisation of the vicinal diol in a separate step prior to the actual deoxygenation reaction. The cited methods include the Corey-Winter reaction,[200] bromoacetylation-debromoacetylation,[201] elimination of 2-methoxy-1,3-dioxolane derivatives,[202] the Barton reduction of bis-*O,O'*-dithiocarbonates,[203] the Tipson-Cohen reaction,[204] the Hanessian elimination of 1-(dimethylamino)methylene acetals[205] and the recently developed deoxygenation of vicinal dimesylates with telluride dianion.[206] In contrast to these methods, the Garegg-Samuelsson[207] procedure using iodine, triphenylphosphine and imidazole

will accomplish the conversion of the diol directly to the olefin in one step under mild conditions with the desired product being easily isolated from the unwanted organic and inorganic products (Scheme 139). Moreover, this procedure is not restricted to deoxygenation of *cis*-1,2-cyclic diols and has also been reported to deoxygenate a variety of *trans*-1,2-diols in the carbohydrate series.[208]



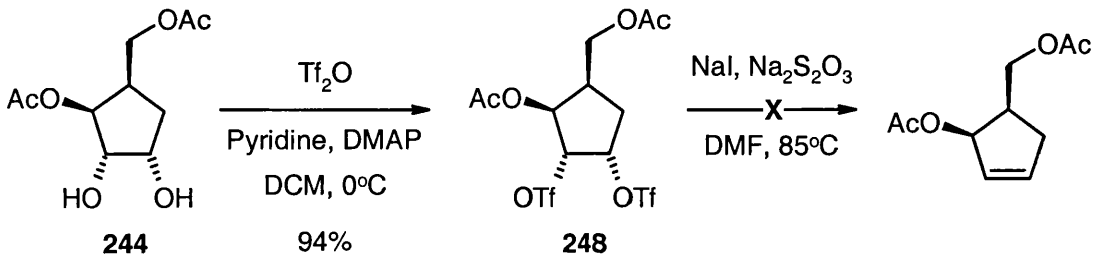
Scheme 139

In view of the above advantages, we therefore elected to attempt the deoxygenation of diol **244** using this reaction but replacing iodine by iodoform since it has been shown to significantly improve the yield of this transformation.[209] To our surprise however, only starting material was obtained after 24 hours at 50°C as shown by ^1H NMR (Scheme 140).



Scheme 140

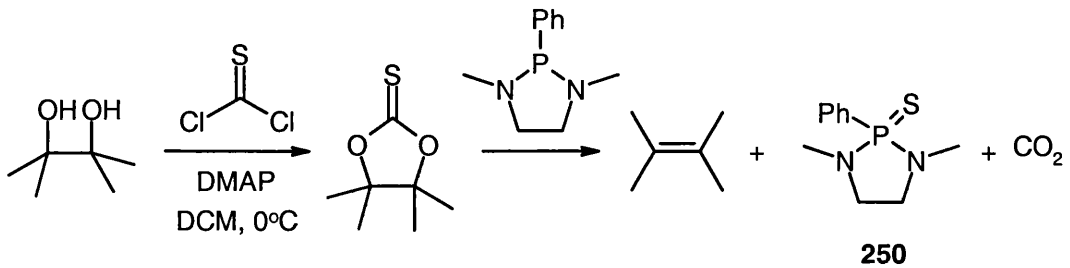
Since the direct conversion of the 1,2-diol into the corresponding olefin failed to occur, we therefore elected to convert it into the bistriflate derivative in order to attempt the classical Tipson-Cohen conditions[204] using sodium iodide in dimethylformamide (Scheme 141).



Scheme 141

Thus, substrate **244** was readily converted to the bistriflate **248** by reaction with triflic anhydride, pyridine and 4-(dimethylamino)pyridine in dry dichloromethane at 0°C in 94% yield. A significant shift of the ^{1}H NMR resonances corresponding to the C*H*OH in **244** from 4.00 and 4.22 ppm to 5.14 and 5.40 ppm respectively, confirmed the formation of the bistriflate derivative. However, due to its potential instability, compound **248** was not purified but immediately exposed to sodium iodide and sodium thiosulfate pentahydrate in dry dimethylformamide and heated at 85°C overnight. Disappointingly, although all the starting material was consumed, examination of the crude ^{1}H NMR spectrum revealed a complex mixture of compounds with no evidence of the expected olefinic carbocycle.

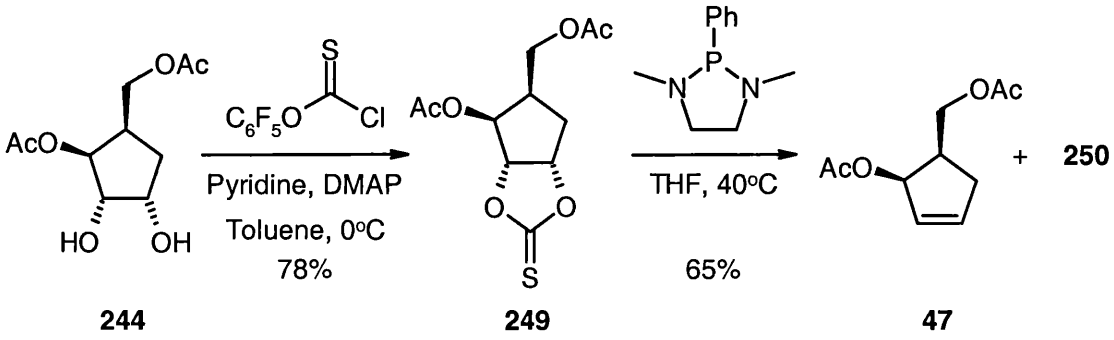
Despite the large number of procedures for the conversion of 1,2-diols to the corresponding olefins, only a few possess the mildness and efficiency necessary for their use in the multistep synthesis of complex molecules. In view of the fact that the most promising protocols failed with this sensitive substrate, a milder method was therefore required. At this stage, we turned our attention to the Corey-Winter reaction[200] which involves prior conversion of a diol to a cyclic thionocarbonate and subsequent cleavage to the olefin. Traditionally, conversion of the diol to the corresponding thionocarbonate has been accomplished using thiocarbonyldiimidazole at reflux in toluene (110°C) or xylene (140°C). Furthermore, the cleavage of the cyclic thionocarbonate to the olefin has been carried out at reflux in trimethylphosphite (111°C) or triethylphosphite (156°C). More recently, Corey and Hopkins[210] have reported a milder variant of the preceding procedure for the deoxygenation of 1,2-diols which efficiently affords olefins from thionocarbonates at 25-40°C using neat 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine. In addition, the thionocarbonate could also be obtained in high yield from thiophosgene and 4-(dimethylamino)pyridine at 0°C (Scheme 142).



250

Scheme 142

We therefore elected to attempt the conversion of diol **244** into the corresponding cyclic olefin **47** using the above Corey-Hopkins conditions, but using pentafluorophenyl chlorothionoformate instead of thiophosgene for safety reasons (Scheme 143).[211]

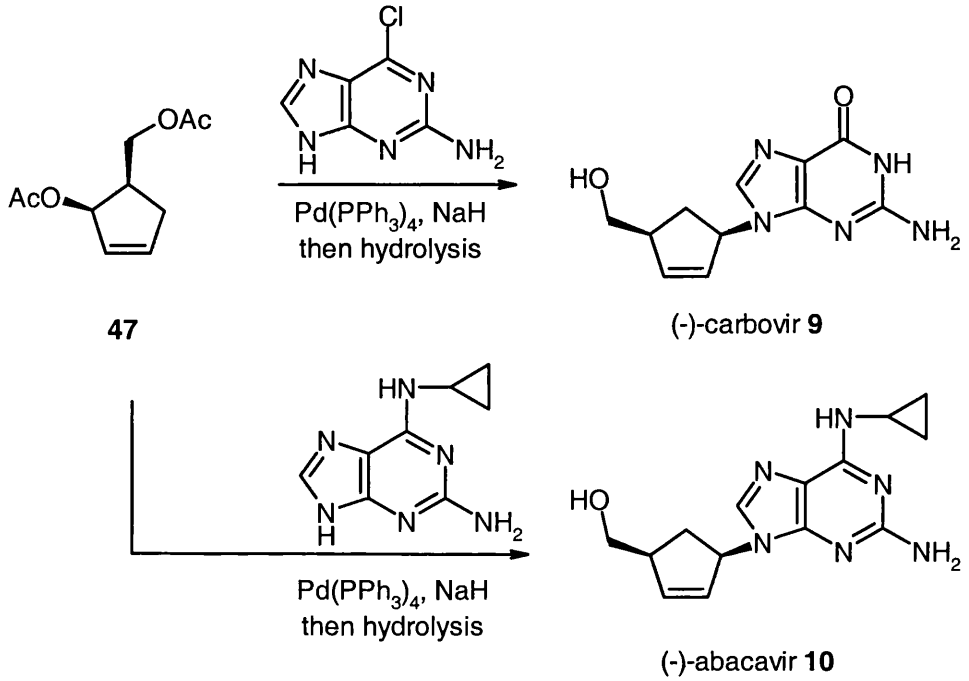


244 **249** **47**

Scheme 143

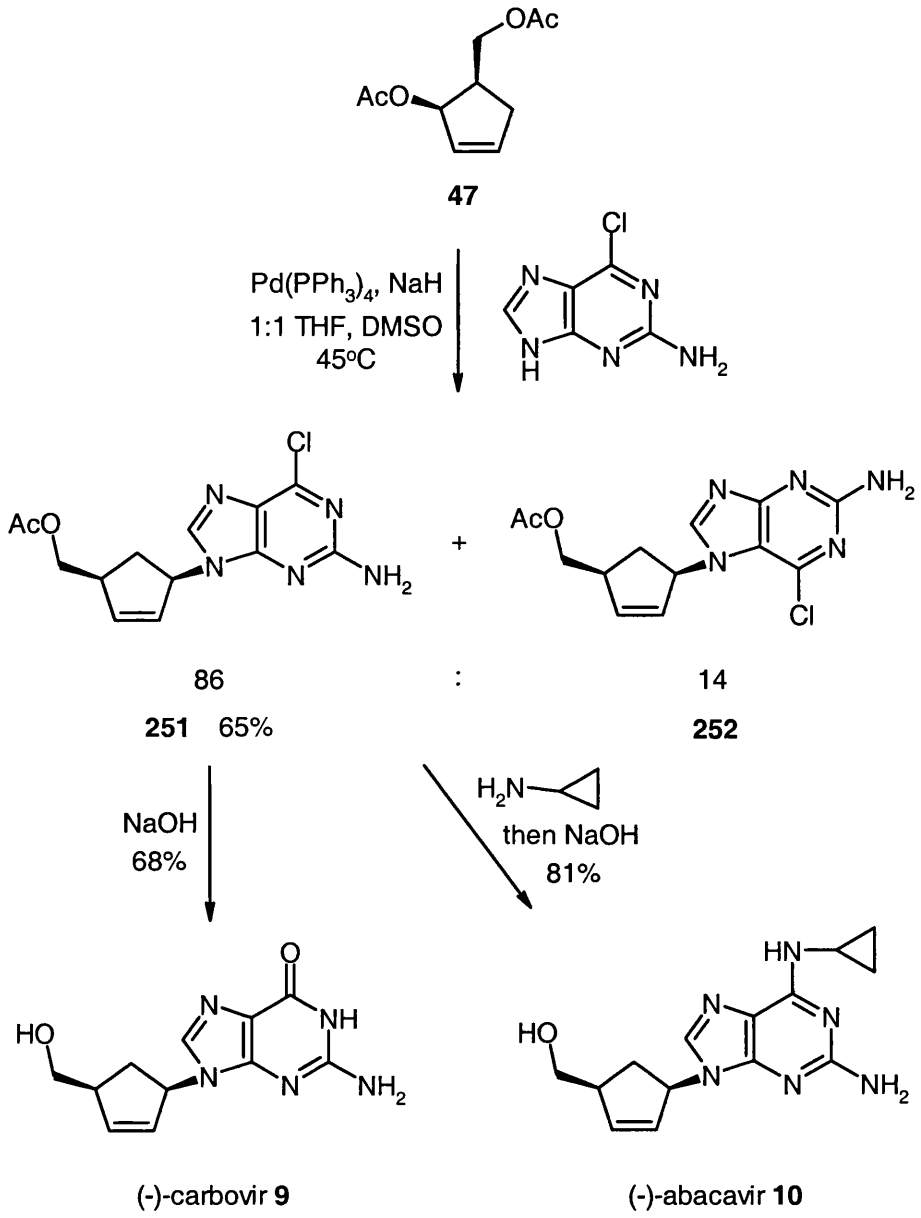
Thus, cyclic thionocarbonate **249** was readily accessed from diol **244** by exposure to pentafluorophenylchlorothionoformate, pyridine and 4-(dimethylamino)pyridine in toluene at 0°C. Column chromatography afforded the desired cyclic thionocarbonate **249** in 78% yield. Subsequent treatment of **249** with three equivalents of 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine in anhydrous tetrahydrofuran at 40°C, afforded after four hours, the desired cyclic olefin **47** in 65% yield. Isolation of the product was accomplished by chromatography on silica gel. Interestingly, when a 6:4 mixture of petroleum ether/ethyl acetate was used as eluant, both the cyclic olefin **47** and the side product of the reaction **250** co-eluted. Dichloromethane proved to be a suitable eluant system allowing the separation of the relatively non-polar side product **250** which was rapidly eluted, and therefore the isolation of the desired cyclic olefin **47** in a pure form. All spectroscopic and analytical data of compound **47** were in agreement with the previously reported literature values.[195a],[37]

With the appropriate carbocyclic intermediate **47** in hand, palladium-catalysed coupling with 2-amino-6-chloropurine and 2-amino-6-(cyclopropylamino)purine would therefore lead respectively, after subsequent hydrolysis, to carbovir **9** and abacavir **10**, as previously described by Crimmins (Scheme 144).[37]



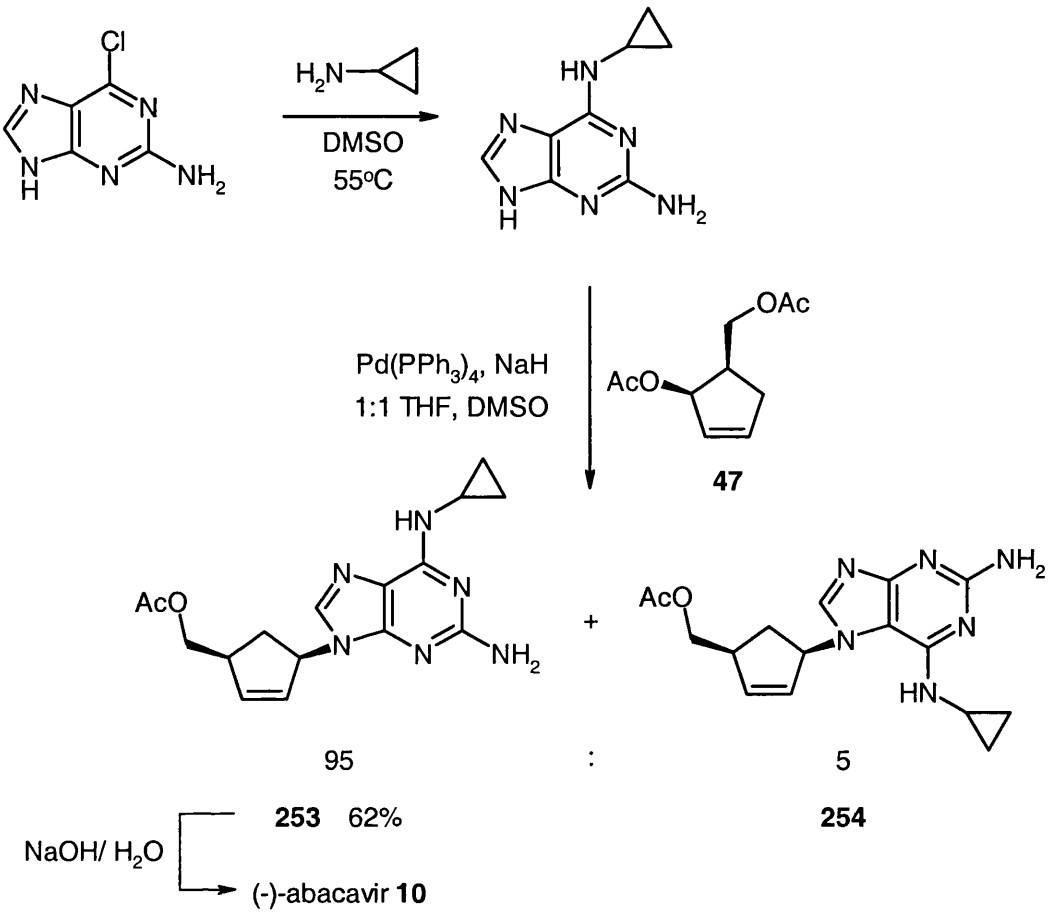
Scheme 144

It was found that reaction of diacetate **47** with 2-amino-6-chloropurine in the presence of tetrakis(triphenylphosphine) palladium (0) and sodium hydride in a 1:1 mixture of tetrahydrofuran and dimethylsulfoxide at 45°C °C led to an 86:14 mixture of the desired chloropurine acetate **251** in 65% isolated yield and its N7 regioisomer **252** (Scheme 145). The identification of the two regioisomers was accomplished by ^{1}H NMR, as the proton at position 8 of the desired N9 isomer (ca. δ 7.85 ppm) is typically upfield of the N7 isomer (ca. δ 8.05 ppm). The problem of N9/N7 regioselectivity has previously been reported in the classic Vorbruggen coupling of purine bases with sugars,[212] but it has only been recently recognised in palladium-catalysed couplings by Benneche and Gundersen.[213] They noted that not only coupling of purines with allylic esters and carbonates gave the N9/N7 mixture of regioisomers, but also that the presence of more bulky groups at position 6 of the purine can considerably influence the regioselectivity of the coupling reaction. As shown in Scheme 145, final hydrolysis of chloropurine acetate **251** with sodium hydroxide 0.5 N afforded (-)-carbovir **9** in 68% yield whereas treatment with cyclopropylamine in ethanol followed by basic hydrolysis led to (-)-abacavir **10** in 81% yield.



Scheme 145

Based on the observations of Benneche and Gundersen,[213] it was therefore envisaged that direct coupling of 2-amino-6-(cyclopropylamino)purine with diacetate **47** might improve the N9/N7 regioselectivity (Scheme 146). In the event, the desired acetate was obtained as a N9/N7 mixture of regioisomers **253**/**254** in an improved 95:5 ratio. The desired N9 isomer **253**, obtained in 62% yield after column chromatography, was readily hydrolysed under basic conditions to afford (-)-abacavir.



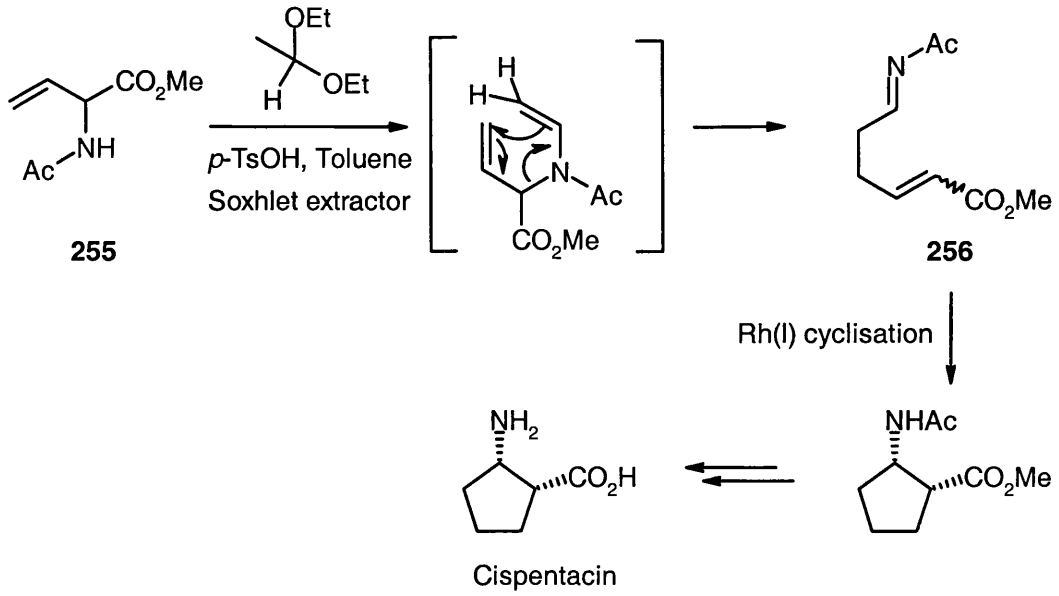
Scheme 146

In summary, an efficient asymmetric formal total synthesis of the potent and highly selective inhibitors of human immunodeficiency virus, (-)-carbovir and (-)-abacavir, has been accomplished by exploiting the rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol sequence for stereoselective generation of the pseudo-sugar fragment of the nucleosides. In particular, the enantioselective construction of the carbocyclic moiety of such 2',3'-dideoxy-carbocyclic nucleosides, has been achieved in only 10 steps and in an overall 3.8% yield. To the best of our knowledge, this constitutes the shortest asymmetric route to such carbocyclic nucleosides starting from the chiral pool of carbohydrates and involving a stereoselective cyclisation approach for synthesis of the five-membered ring moiety.

II.7 Conclusions and perspectives

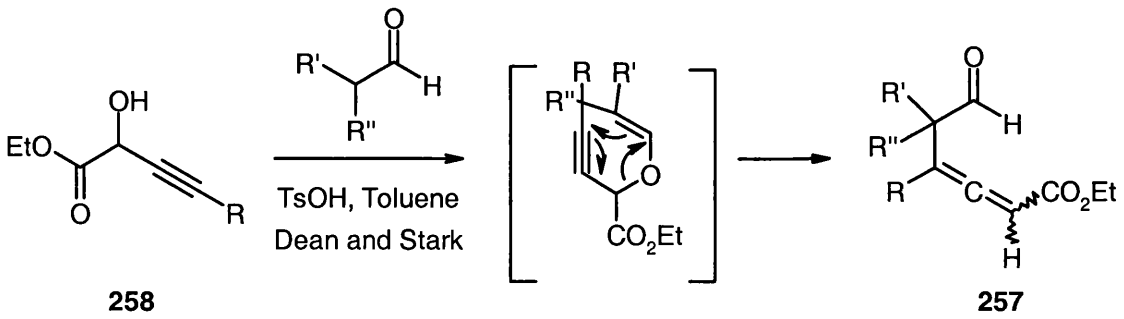
The foregoing discussion of our results has revealed several important findings and fulfilled our main objective of providing a highly stereoselective novel rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction as a general method for the preparation of substituted carbocycles of various ring sizes under very mild conditions. Furthermore, in many instances the required 6-oxo-2-hexenoate precursors can be easily prepared in a highly atom efficient way using a [3,3] sigmatropic rearrangement sequence. In addition, we have also demonstrated the applicability of our tandem methodology to the synthesis of the cyclopentanoid moiety of the antiviral carbocyclic nucleoside (-)-carbovir and its highly potent related analogue (-)-abacavir.

Thus, we have developed a simple atom efficient route to substituted 6-oxo-2-hexenoate derivatives by direct condensation of 2-hydroxy-3-butenoate esters and aldehydes. This Claisen based protocol was used to successfully prepare a range of aliphatic and aromatic 5,5-disubstituted 6-oxo-2-hexenoates in good yields and in a shorter and environmentally cleaner route to that existing in the literature for comparable substrates. This methodology proved to be compatible with the use of alternative electrophiles, such as enones and β-keto esters, permitting the incorporation of additional functionality for further elaboration. However, attempts to extend this methodology to the synthesis of 6-imino-2-hexenoate from *N-p*-toluenesulfonyl vinyl glycine *via* the related aza-Claisen rearrangement proved to be unsuccessful. Further research is therefore recommended in order to establish the feasibility of this transformation from a more nucleophilic glycine derivative such as *N*-acyl vinyl glycine **255** as it would provide a simple atom efficient approach to 6-imino-2-hexenoate derivatives. Moreover, if successful, the rhodium-catalysed tandem cyclisation of the resulting 6-imino-2-hexenoate **256** may provide an efficient synthesis of the potent antifungal agent Cispentacin[214] after deprotection of the amino group and acid hydrolysis of the ester as shown in Scheme 147.



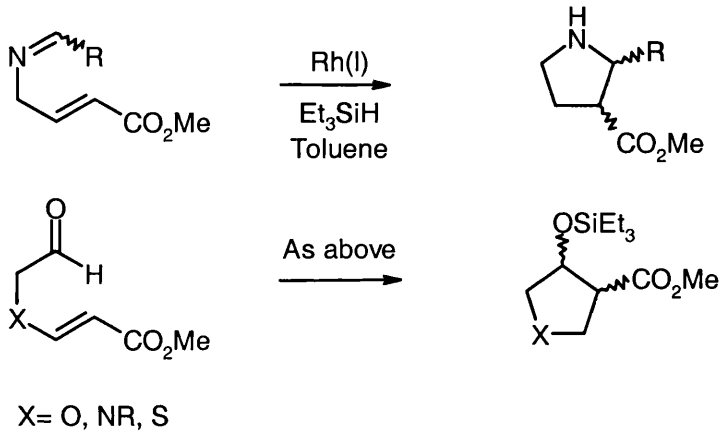
Scheme 147

The previous [3,3] sigmatropic rearrangement methodology could also be further extended to the synthesis of synthetically useful allenes **257** from direct coupling of propargylic alcohols and aldehydes *via* a Saucy-Marbet type rearrangement (Scheme 148).[215] The propargylic alcohol precursor **258** could be readily accessed by addition of differently substituted terminal acetylenes to ethyl glyoxylate mediated by zinc triflate or alternatively by the direct reaction of the corresponding acetylenic Grignard reagent with ethyl glyoxylate. In addition, chiral propargylic alcohols could be obtained from the same precursors by the Carreira procedure[216] using zinc triflate and *N*-methyl ephedrine in order to obtain the corresponding chiral allenes which are not only highly versatile intermediates in synthesis but also very resourceful substrates for potential tandem reactions.



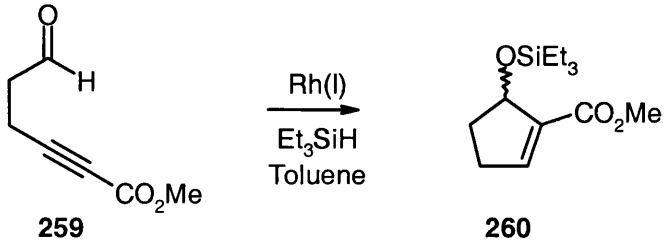
Scheme 148

On the other hand, the scope and limitations of the rhodium (I)-catalysed tandem hydrosilylation-aldol cyclisation have been established. A range of substituents in the substrate is tolerated, although aldehyde functionality proved to be crucial. However, as previously mentioned, it would be interesting to investigate whether replacement of the aldehyde by an imine may be compatible with our tandem sequence. Alternatively, the incorporation of heteroatoms into the substrate chain may also provide access to a range of substituted pyrrolidines, tetrahydrofurans or tetrahydrothiophenes (Scheme 149).

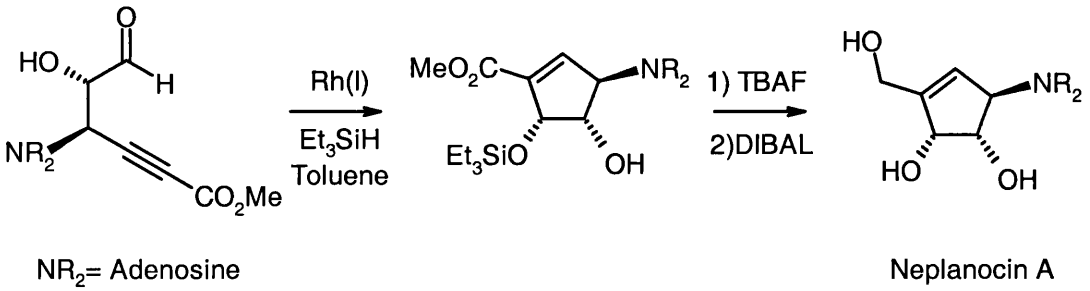


Scheme 149

Replacing the α,β-unsaturated ester with alternative Michael acceptors such as nitrile, nitro or sulfonyl groups would lead to a more general synthesis of cyclopentanols. In addition, 6-oxo-2-hexynoate **259** may cyclise to give the corresponding substituted cyclopentenol **260** (Scheme 150). This approach, if successful, could then be extended to the synthesis of the potent anti-cancer carbocyclic nucleoside Neplanocin A (Scheme 151).



Scheme 150

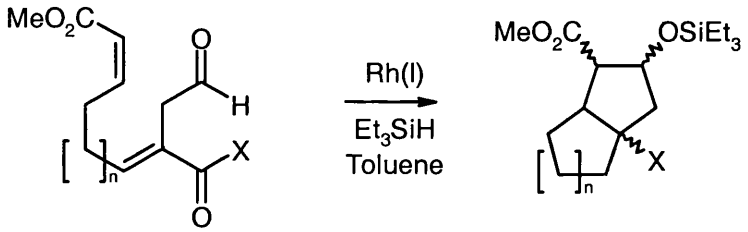


NR_2= Adenosine

Neplanocin A

Scheme 151

The possibility of tandem cascade reactions as a means to fused carbocycles also requires investigation, but will require fine tuning of differentiated Michael acceptors (Scheme 152).



X= alkyl, aryl

Scheme 152

The extension of our tandem sequence to the synthesis of larger ring sizes has also been investigated. From this study, it has been demonstrated that the rhodium (I)-catalysed tandem hydrosilylation-intramolecular aldol reaction is a suitable method for the construction of functionalised six- and seven-membered rings in good yields and with moderate selectivity.

We note parenthetically that the related tandem hydroboration-intramolecular aldol reaction was also investigated. However, when boranes are used as hydride donors, hydroboration of the aldehyde functionality becomes the dominant process. In addition, alternative catalytic systems containing a transition metal other than rhodium have also been evaluated. From this study, it was demonstrated that the combination of triethylsilane and a rhodium catalyst, either hydridotetrakis(triphenylphosphine) rhodium (I) or chlorotris(triphenylphosphine) rhodium (I), gave the best results in terms of yield, stereo- and chemo-selectivity.

The stereochemical outcome proved to be highly dependant on the catalyst precursor, with hydridotetrakis(triphenylphosphine) rhodium (I) giving the best results in terms of selectivity. As previously described, a number of asymmetric catalytic systems have been successfully employed in intramolecular hydroacylation chemistry to afford enantiomerically enriched cyclopentanones.[54]-[57] Screening of a number of chiral catalysts to probe the levels of enantioselectivity attainable on achiral substrates would also be of interest in the present case.

Finally, the constant demand for efficient synthetic routes to chiral carbocyclic nucleosides has prompted us to investigate the applicability of our methodology to the synthesis of biologically active carbocyclic nucleosides. In this context, we have successfully completed an asymmetric formal total synthesis of the potent antiviral agent (-)-carbovir and its related analogue (-)-abacavir in only 10 steps starting from D-ribose. Further applications of the rhodium (I)-catalysed tandem hydrosilylation-aldol chemistry to the synthesis of alternative carbocyclic nucleosides as well as more complex biologically active carbocyclic natural products can certainly be envisaged.

Chapter III Experimental Section

III.1 General experimental procedures

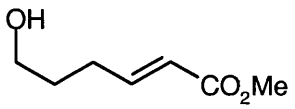
Melting points were determined using a Reichert hot stage apparatus and are uncorrected. Pressure was measured using a standard Gallenkamp manometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (using the sodium D line; 589 nm) and $[\alpha]^{T}_{D}$ are given in units of 10^{-1} deg dm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1605 FT-IR spectrometer as thin films on NaCl or as KBr discs and are reported in cm^{-1}. Mass spectra were recorded on a Micromass 70-SE spectrometer using a cesium ion gun for FAB. X-ray crystallography was performed using a Bruker Smart Apex, CDD diffractometer. Elementary analyses and accurate mass measurements were performed at Christopher Ingold Laboratories, University College London.

Nuclear magnetic resonance spectra were recorded using a Bruker AMX-300 or a Bruker AMX-400 or a Bruker Avance 500. Chemical shifts (δ) are quoted in parts per million (ppm) relative to tetramethylsilane. The ^{1}H NMR spectra are referenced to the residual chloroform peak at 7.26 ppm. Coupling constants (*J*) are reported in Hertzs. ^{13}C NMR spectra were fully decoupled and are referenced to the middle peak of chloroform at 77.0 ppm. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; or a combination of these. Column chromatography was performed using BDH silica gel (40-60 μm). Analytical thin layer chromatography was performed on pre-coated aluminium-backed plates (Merck Keisekgel 60 F_{254}) and visualised by 254 nm UV or by staining with basic potassium permanganate solution followed by heat.

All cyclisations and air and/or moisture sensitive reactions were carried out in oven-dried glassware under a nitrogen atmosphere using standard Schlenk techniques. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use and degassed immediately prior to use. Toluene was distilled from sodium. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone ketyl. Dichloromethane, dichloroethane, acetonitrile, dimethylformamide and dimethylsulfoxide were distilled from calcium hydride. Methanol was distilled from magnesium turnings and iodine.

III.2 Preparation of the cyclisation precursors

Methyl (*E*)-6-hydroxy-2-hexenoate 90[95]



$C_7H_{12}O_3$

M= 144.17 g.mol^{-1}

Procedure A:

To a stirred solution of γ-butyrolactone (4.0 g, 47.5 mmol) in 60 mL of anhydrous toluene at -70°C under a positive nitrogen pressure, DIBAL (1.0 M solution in toluene) (50 mL, 50.0 mmol) was added dropwise. The resulting solution was stirred at -70°C for a total of 2 h. The reducing agent was quenched with anhydrous MeOH (10 mL) before the addition of carbomethoxymethylene triphenylphosphorane (18.6 g, 55.0 mmol). The reaction mixture was heated at 80°C for 18 hours. The heat was removed and the solution was concentrated under reduced pressure. *Tert*-butyl methyl ether was then added and the resulting white crystalline precipitate of triphenylphosphine oxide was removed by filtration and the filtrate concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (70:30) to yield the desired product (0.9 g, 34%) as a single *E* diastereoisomer as a colourless liquid.

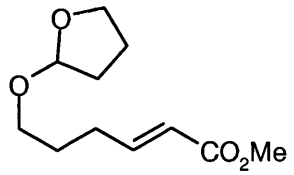
Procedure B:

A mixture of 2,3-dihydrofuran (3.0 g, 43.0 mmol), one equivalent of water (0.8 g, 43.0 mmol) and 10 mg of *p*-toluenesulfonic acid was stirred in 20 mL of toluene at room temperature during 7 hours. The solution becomes homogenous and carbomethoxymethylene triphenylphosphorane (17.3 g, 52.0 mmol) was added and the reaction mixture heated at 80°C for 14 hours. The heat was removed and the solution was concentrated under reduced pressure. Diethyl ether was then added and the resulting white crystalline precipitate of triphenylphosphine oxide was removed by filtration and the filtrate concentrated *in vacuo*. The resulting crude oil was

purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to yield the desired product (0.7 g, 12%) as a single *E* diastereomer as a colourless liquid, together with methyl (*E*)-6-(tetrahydro-furan-2-yloxy)-hex-2-enoate **91** and 2-(tetrahydro-furan-2-yloxy)-tetrahydrofuran **92** in 34% and 27% yield respectively.

Rf (P.E./EtOAc, 6:4): 0.20; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.85-1.98 (m, 2H, $HOCH_2CH_2CH_2$), 2.51 (dtd, *J*=7.0 Hz, *J*=8.1 Hz, *J*=1.6 Hz, 2H, CH_2CH_2CH=), 3.87 (t, *J*=6.4 Hz, 2H, $HOCH_2$), 3.93 (s, 3H, OCH_3), 6.06 (dt, *J*=15.7 Hz, *J*=1.6 Hz, 1H, CH=$CHCO_2CH_3$), 7.20 (dt, *J*=15.7 Hz, *J*=7.0 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 28.9 (CH_2), 31.3 (CH_2), 51.8 (OCH_3), 62.2 (CH_2OH), 121.7 (CH=$CHCO_2CH_3$), 149.2 (CH=$CHCO_2CH_3$), 167.4 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3427 (O-H), 1724 (C=O), 1656 (C=C); **LRMS** (FAB^+) *m/z*: 145 (M+H, 18%), 113 (M-OCH_3, 40%), 71 (100%).

Methyl (*E*)-6-(tetrahydro-furan-2-yloxy)-hex-2-enoate 91[218]



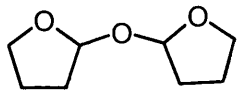
$C_{11}H_{18}O_4$

M= 214.25 $g.mol^{-1}$

Rf (P.E./EtOAc, 6:4): 0.46; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.62-1.67 (m, 2H, CH_2CH_2CH=), 1.77-1.86 (m, 4H, CH_2 furan ring), 2.20 (dtd, *J*=7.0 Hz, *J*=8.1 Hz, *J*=1.6 Hz, 2H, CH_2CH_2CH=), 3.32 (dt, *J*=9.8 Hz, *J*=6.6 Hz, 1H, CH_aH_bO furan ring), 3.60 (dt, *J*=9.8 Hz, *J*=6.6 Hz, 1H, CH_aH_bO furan ring), 3.65 (s, 3H, OCH_3), 3.76-3.82 (m, 2H, OCH_2CH_2), 5.01 (dd, *J*=4.0 Hz, *J*=1.7 Hz, 1H, $OCHO$), 5.76 (dt, *J*=15.7 Hz, *J*=1.6 Hz, 1H, CH=$CHCO_2CH_3$), 6.90 (dt, *J*=15.7 Hz, *J*=7.0 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 23.8 (CH_2 furan ring), 28.5 (CH_2CH_2CH=), 29.4 (CH_2 furan ring), 32.6 (CH_2CH=), 51.6 (OCH_3), 66.5 (CH_2O), 67.6 (CH_2O), 100.2 ($OCHO$), 121.5 (CH=$CHCO_2CH_3$), 149.3 (CH=$CHCO_2CH_3$),

167.3 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 1724 (C=O), 1658 (C=C); **LRMS** (FAB^+) *m/z*: 215 (M+H, 30%); 71 (100%).

2-(Tetrahydro-furan-2-yloxy)-tetrahydrofuran 92[219]

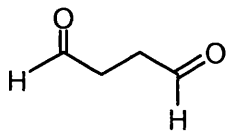


$C_8H_{14}O_3$

M= 158.19 $g.mol^{-1}$

Rf (P.E./EtOAc, 6:4): 0.56; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.07-2.21 (m, 8H, CH_2), 4.05-4.17 (m, 4H, CH_2O), 5.67 (dd, *J*=4.2 Hz, *J*=0.9, 2H, OC*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 23.9 (CH_2), 32.4 (CH_2), 67.2 (CH_2O), 100.2 (O*C*HO); **FTIR** (film) ν cm^{-1}: 2955, 2883, 1458, 1443, 1366, 1325, 1292, 1240, 1109, 1074.

1,4-Butanedial 94[98]



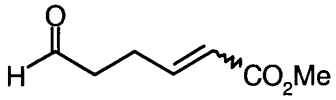
$C_4H_6O_2$

M= 86.09 $g.mol^{-1}$

A mixture of 2,5-dimethoxytetrahydrofuran (24 g, 181 mmol) and aqueous hydrochloric acid 0.6 N (150 mL) was stirred at room temperature for 30 min and then neutralised (pH=7 to 8) with sodium carbonate and extracted with dichloromethane (3 x 25 mL). The aqueous phase was reacidified with concentrated hydrochloric acid (7 mL), again stirred for 30 min, neutralised and extracted. This process was performed a total of five times after which the combined methylene chloride extracts were dried over $MgSO_4$, filtered and concentrated. Distillation of the residual yellow liquid (10 g) separated 1,4-butanedial **94** (6 g, 39%) as a clear oil

(bp= 30°C/0.2 mmHg; lit.,[98] 31-35°C/0.2 mmHg) which was immediately used in the next step without further purification.

Methyl 6-oxo-2-hexenoate 78[95]



$C_7H_{10}O_3$

M= 142.15 g.mol^{-1}

Procedure A

A solution of (*E*)-methyl-6-hydroxy-2-hexenoate **90** (0.6 g, 4.2 mmol) in anhydrous dichloromethane (8 mL) was added in one portion to a stirred suspension of the oxidising agent pyridinium chlorochromate (PCC) (1.3 g, 6.2 mmol) and the buffering agent sodium acetate (0.1 g, 1.9 mmol) in anhydrous dichloromethane (6 mL). The resulting black solution was stirred for 4 h with careful monitoring by tlc. The reaction mixture was poured into ether and the black gum was extracted with additional ether until the gum had transformed into a granular solid. The combined organic layers were passed through a short pad of florisil® and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (70:30) to afford the desired product (225 mg, 39%) as a colourless liquid.

Procedure B

A mixture of methyl 2-hydroxy-3-butenoate **99a** (2.0 g, 17.2 mmol), acetaldehyde diethyl acetal (3.1 g, 25.8 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux using a Soxhlet extractor containing freshly conditioned 4Å molecular sieves for 4 days. The sieves were replaced 5 times with a freshly conditioned batch. Column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) gave aldehyde **78** (1.1 g, 46%) as two diastereomers in a *E:Z* 2.2:1 ratio as a colourless oil.

Procedure C

A solution of freshly prepared 1,4-butanedial **94** (6.0 g, 70.0 mmol) in dry degassed dichloromethane (15 mL) was added to a solution of carbomethoxymethylene triphenylphosphorane (23.3 g, 70.0 mmol) in anhydrous degassed dichloromethane (15 mL). After this time, the solution was concentrated under reduced pressure, diethyl ether was added and the resulting white crystalline precipitate of triphenylphosphine oxide was removed by filtration and the filtrate concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to yield the desired product **78** (1.1 g, 11%) as a single *E* diastereomer as a colourless liquid together with diester **95** (4.1 g, 30%).

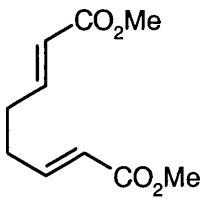
***E* isomer (*E*)-78**

Rf (P.E./EtOAc, 6:4): 0.50; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.73-2.78 (m, 2H, C*H*$_2$CH=), 2.85 (t, *J*=7.3 Hz, 2H, C*H*$_2$CHO), 3.94 (s, 3H, OC*H*$_3$), 6.08 (dt, *J*=15.7 Hz, *J*=1.5 Hz, 1H, CH=C*H*CO$_2$CH$_3$), 7.16 (dt, *J*=15.7 Hz, *J*=6.7 Hz, 1H, C*H*=CHCO$_2$CH$_3$), 9.97 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 24.8 (*C*H$_2$CH=), 42.2 (*C*H$_2$CHO), 51.9 (O*C*H$_3$), 122.5 (CH=*C*HCO$_2$CH$_3$), 147.0 (*C*H=CHCO$_2$CH$_3$), 167.0 (*C*O$_2$CH$_3$), 200.5 (*C*HO); **FTIR** (film) ν cm^{-1}: 2953, 2849, 2731, 1724, 1659, 1437, 1165; **LRMS** (EI$^+$) *m/z*: 142 (M, 15%), 127 (M-CH$_3$, 50%), 111 (M-OCH$_3$, 55%), 54 (100%).

***Z* isomer (*Z*)-78**

Rf (P.E./EtOAc, 6:4): 0.54; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.83 (td, *J*=7.6 Hz, *J*=1.3 Hz, 2H, C*H*$_2$CHO), 3.17 (qd, *J*=7.6 Hz, *J*=1.5 Hz, 2H, C*H*$_2$CH=), 3.93 (s, 3H, OC*H*$_3$), 6.04 (dt, *J*=11.4 Hz, *J*=1.5 Hz, 1H, CH=C*H*CO$_2$CH$_3$), 6.46 (dt, *J*=11.4 Hz, *J*=7.6 Hz, 1H, C*H*=CHCO$_2$CH$_3$), 9.99 (t, *J*=1.3 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.1 (*C*H$_2$), 43.3 (*C*H$_2$), 51.5 (O*C*H$_3$), 121.0 (CH=*C*HCO$_2$CH$_3$), 148.0 (*C*H=CHCO$_2$CH$_3$), 166.8 (*C*O$_2$CH$_3$), 201.4 (*C*HO).

Methyl (2*E*,6*E*)-octa-2,6-dien-1,6-dioate 95[220]

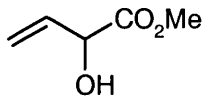


$C_{10}H_{14}O_4$

M= 198.09 g.mol^{-1}

Rf (P.E./EtOAc, 9:1): 0.51; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.42-2.44 (m, 4H, CH_2CH_2), 3.78 (s, 6H, OCH_3), 5.92 (d, *J*=15.7 Hz, 2H, $CH{=}CHCO_2CH_3$), 6.91-7.02 (m, 2H, $CH{=}CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 30.8 (CH_2), 51.8 (OCH_3), 122.4 ($CH{=}CHCO_2CH_3$), 147.4 ($CH{=}CHCO_2CH_3$), 167.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3027, 2950, 1720 (C=O), 1659 (C=C), 1612, 1436, 1275; **LRMS** (ES$^+$) *m/z:* 199 (M+H, 100%), 185 (33%), 167 (M-OCH_3, 58%); **HRMS** (ES$^+$) *m/z:* Requires 199.0974 for $C_{10}H_{15}O_4$ (M+H), found 199.0970.

Methyl 2-hydroxy-3-butenoate 99a[104]



$C_5H_8O_3$

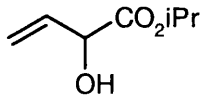
M= 116.11 g.mol^{-1}

A stirred solution of 2-acetoxy-3-butenenitrile (10.0 g, 80.0 mmol) in 15 mL of methanol was brought to reflux. A saturated solution of hydrochloric acid in methanol (14.4 mL), prepared from acetyl chloride in methanol (5:1), was added dropwise. A concentrated aqueous solution of hydrochloric acid (3.7 mL) was then added and the mixture was refluxed for a total of 6 h. The heat was removed and the solution was cooled at 0°C. The NH_4Cl formed was filtered off and the filtrate was concentrated under reduced pressure. The residue was washed with a saturated

aqueous solution of $NaHCO_3$ and extracted several times with ether. The organic extracts were dried over $MgSO_4$, filtered and concentrated under *vacuo*. Distillation of the reaction mixture gave the desired product (6.5 g, 70%) as a clear oil, (bp: 40°C/10 mmHg, lit.,[104] 65°C/20 mmHg).

Rf (EtOAc): 0.50; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 3.28 (br, 1H, O*H*), 3.95 (s, 3H, OC*H*$_3$), 4.83-4.85 (m, 1H, C*H*OH), 5.43 (dd, J_{cis}=10.5 Hz, J_{gem}=1.6 Hz, 1H, CH_aH$_b$=CH), 5.65 (dd, J_{trans}=17.0 Hz, J_{gem}=1.6 Hz, 1H, CH$_a$*H*$_b$=CH), 6.10 (ddd, J_{trans}=17.0 Hz, J_{cis}=10.5 Hz, *J*=5.2 Hz, 1H, CH$_2$=C*H*); **^{13}C NMR** ($CDCl_3$, 300 MHz) δ ppm: 53.3 (O*C*H$_3$), 71.9 (*C*HOH), 117.6 (*C*H$_2$=CH), 134.6 (CH$_2$=*C*H), 174.1 (*C*O$_2$CH$_3$); **FTIR** (film) cm^{-1}: 3465 (O-H), 1728 (C=O), 1643 (C=C); **LRMS** (CI$^+$) *m/z*: 117 (M+H, 100%); 101 (M-CH$_3$, 36%).

<u>*iso*-Propyl 2-hydroxy-3-butenoate</u> <u>99b</u>[104]



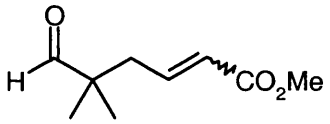
$C_7H_{12}O_3$

M= 144.17 g.mol^{-1}

A stirred solution of 2-acetoxy-3-butenenitrile (40.0 g, 320 mmol) in 60 mL of methanol was brought to reflux. A saturated solution of hydrochloric acid in *iso*-propanol (60 mL), prepared from acetyl chloride in methanol (5:1), was added dropwise. A concentrated aqueous solution of hydrochloric acid (15 mL) was then added and the mixture was refluxed for a total of 6 h. The heat was removed and the solution was cooled at 0°C. The NH_4Cl formed was filtered off and the filtrate was concentrated under reduced pressure. The residue was washed with a saturated aqueous solution of $NaHCO_3$ and extracted several times with ether. The organic extracts were dried over $MgSO_4$, filtered and concentrated under *vacuo*. Distillation of the reaction mixture gave the desired product (34.6 g, 75%) as a clear oil, (bp: 30°C/0.15 mmHg, lit.,[104] bp: 105°C/15 mmHg).

Rf (EtOAc): 0.53; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.40 (d, *J*=6.3 Hz, 3H, CH_3), 1.43 (d, *J*=6.3 Hz, 3H, CH_3), 3.14 (br, 1H, OH), 4.74 (br, 1H, CHOH), 5.20-5.26 (m, 1H, $OCH(CH_3)_2$), 5.39 (dt, J_{cis}=11.9 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH), 5.64 (dt, J_{trans}=17.0 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH), 6.06 (ddd, J_{trans}=17.0 Hz, J_{cis}=11.9 Hz, *J*=4.9 Hz, 1H, CH_2=CH); **^{13}C NMR** ($CDCl_3$, 300 MHz) δ ppm: 22.0 ($CH(CH_3)_2$), 70.8 (OCH), 71.9 (OCH), 117.1 (CH_2=CH), 134.9 (CH_2=CH), 173.1 (CO_2iPr); **FTIR** (film) cm^{-1}: 3454 (O-H), 2985, 2940, 1736 (C=O), 1641 (C=C), 1456, 1377, 1201, 1102, 921; **LRMS** (CI^+) *m/z*: 162 ($M+NH_4$, 73%); 145 (M+H, 90%); 129 ($M-CH_3$, 82%), 55 (100%).

Methyl 5,5-dimethyl-6-oxo-2-hexenoate 102



$C_9H_{14}O_3$

M= 170.09 $g.mol^{-1}$

A mixture of methyl 2-hydroxy-3-butenoate **99a** (2.0 g, 17.2 mmol), isobutyraldehyde (1.9 g, 26 mmol) and a small amount of *p*-toluenesulfonic acid (10 mg) in 10 mL of toluene, was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to afford the desired product **102** (1.5 g, 53%) as two separable diastereomers in a *E:Z* 2:1 ratio as a colourless oil, together with 2-*iso*-propyl-5-vinyl-[1,3]dioxolan-4-one **100a** which was isolated in 25% yield as a 2:1 mixture of diastereomers.

***E* isomer (*E*)-102**

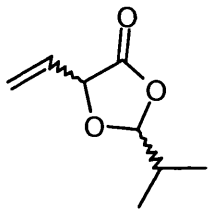
Rf (P.E./EtOAc, 8:2): 0.20; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.14 (s, 6H, $C(CH_3)_2$), 2.41 (dd, *J*=7.8 Hz, *J*=1.4 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.93 (dt, *J*=15.6 Hz, *J*=1.4 Hz, 1H, $CH=CHCO_2CH_3$), 6.93 (dt, *J*=15.6 Hz, *J*=7.8 Hz, 1H, $CH=CHCO_2CH_3$), 9.60 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.8

($C(CH_3)_2$), 39.7 (CH_2), 46.2 ($C(CH_3)_2$), 51.9 (OCH_3), 124.6 ($=CHCO_2CH_3$), 144.2 ($CH=CHCO_2CH_3$), 166.8 (CO_2CH_3), 205.0 (*C*HO); **FTIR** (film) ν cm^{-1}: 1803 (CH=O), 1730 (C=O), 1645 (C=C); **LRMS** (EI^+) *m/z*: 171 (M+H, 50%), 139 (M-OCH_3, 100%), 109 (M-CO_2CH_3, 79%), 81 (73%), 41 (33%); **HRMS** (EI^+) *m/z*: Requires 170.09429 for $C_9H_{14}O_3$ (M), found 170.09400.

Z isomer (*Z*)-102

Rf (P.E./EtOAc, 8:2): 0.25; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.05 (s, 6H, $C(CH_3)_2$), 2.83 (dd, *J*=7.8 Hz, *J*=1.6 Hz, 2H, CH_2), 3.65 (s, 3H, OCH_3), 5.84 (dt, *J*=11.6 Hz, *J*=1.6 Hz, 1H, $CH=CHCO_2CH_3$), 6.11 (dt, *J*=11.6 Hz, *J*=7.8 Hz, 1H, $CH=CHCO_2CH_3$), 9.50 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.7 ($C(CH_3)_2$), 35.9 (CH_2), 46.6 ($C(CH_3)_2$), 51.5 (OCH_3), 122.2 ($=CHCO_2CH_3$), 145.0 ($CH=CHCO_2CH_3$), 166.9 (CO_2CH_3), 205.5 (*C*HO); **FTIR** (film) ν cm^{-1}: 1797 (CH=O), 1724 (C=O), 1656 (C=C); **LRMS** (EI^+) *m/z*: 170 (M, 8%), 141 (58%), 109 (M-CO_2CH_3, 87%), 81 (70%), 41 (100%); **HRMS** (EI^+) *m/z*: Requires 170.09429 for $C_9H_{14}O_3$ (M), found 170.09417.

2-*iso*-Propyl-5-vinyl-[1,3]dioxolan-4-one 100a



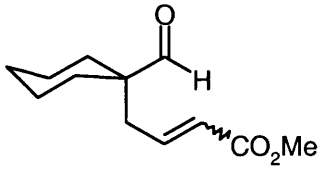
$C_8H_{12}O_3$

M= 156.08 $g.mol^{-1}$

Rf (P.E./EtOAc, 8:2): 0.52; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.04 (d, *J*=6.9 Hz, 6H, $CH(CH_3)_2$, *major + minor*), 1.94 (m, 1H, $CH(CH_3)_2$, *major + minor*), 4.65 (dt, *J*=5.2 Hz, *J*=1.5 Hz, 1H, OCHCO, *major*), 4.85 (m, 1H, OCHCO, *minor*), 5.27 (d, *J*=4.7 Hz, 1H, OCHO, *major*), 5.40 (m, 1H, OCHO, *minor*), 5.46 (dt, J_{cis}=10.5 Hz, *J*=1.5 Hz, 1H, CH_aH_b=CH, *major + minor*), 5.55 (dt, J_{trans}=16.9 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH, *minor*), 5.62 (dt, J_{trans}=17.0 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH,

major), 6.01 (ddd, J_{trans}=17.0 Hz, J_{cis}=10.5 Hz, J=5.2 Hz, 1H, CH_2=C*H*, *major* + *minor*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 16.1 (C(CH_3)$_2$, *major* + *minor*), 32.5 (*C*H(CH_3)$_2$, *major*), 33.0 (*C*H(CH_3)$_2$, *minor*), 75.5 (CH_2=CH*C*HO, *minor*), 76.0 (CH_2=CH*C*HO, *major*), 108.2 (O*C*HO, *major*), 108.9 (O*C*HO, *minor*), 119.3 (*C*H_2=CH, *minor*), 120.5 (*C*H_2=CH, *major*), 130.0 (CH_2=*C*H, *minor*), 130.3 (CH_2=*C*H, *major*), 171.5 (*C*O_2R, *minor*), 171.6 (*C*O_2R, *major*); **FTIR** (film) ν cm^{-1} : 1798 (C=O), 1640 (C=C); **LRMS** (ES^+) *m/z*: 157 (M+H, 100%); **HRMS** (ES^+) *m/z:* Requires 157.0863 for $C_8H_{13}O_3$ (M+H), found 157.0865.

4-(1-Formyl-cyclohexyl)-but-2-enoic acid methyl ester 103a



$C_{12}H_{18}O_3$

M= 210.13 $g.mol^{-1}$

A mixture of methyl 2-hydroxy-3-butenoate **99a** (3.0 g, 25,8 mmol), cyclohexanecarboxaldehyde (2.9 g, 25.8 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to afford the desired product **103a** (2.7 g, 49%) as two separable diastereomers in a *E:Z* 1.5:1 ratio as a colourless oil, together with 2-cyclohexyl-5-vinyl-[1,3]dioxolan-4-one **100b** which was isolated in 30% yield as a single diastereomer.

***E* isomer (*E*)-103a**

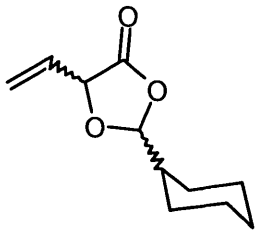
Rf (P.E./EtOAc, 8:2): 0.28; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.24-1.50 (m, 4H, CH_2), 1.62-1.70 (m, 4H, CH_2), 1.96-2.00 (m, 2H, CH_2), 2.44 (dd, *J*=8.0 Hz, *J*=1.3 Hz, 2H, CH_2CH=), 3.84 (s, 3H, OCH_3), 5.96 (dt, *J*=15.6 Hz, *J*=1.3 Hz, 1H, =C*H*CO_2CH_3), 6.93 (dt, *J*=15.6 Hz, *J*=8.0 Hz, 1H, C*H*=CHCO_2CH_3), 9.66 (s, 1H,

C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.6 (*C*H_2), 25.8 (*C*H_2), 31.4 (*C*H_2), 38.8 (*C*H_2), 50.1 (*C*Cy), 51.9 (O*C*H_3), 124.6 (=*C*HCO_2CH_3), 143.7 (*C*H=CHCO_2CH_3), 166.7 (*C*O_2CH_3), 206.1 (*C*HO); **FTIR** (film) ν cm^{-1}: 1799 (CH=O), 1732 (C=O), 1656 (C=C); **LRMS** ($APCI^+$) *m/z*: 211 (M+H, 44%), 179 (M-OCH_3, 100%), 149 (39%); **HRMS** (CI^+) *m/z*: Requires 211.13341 for $C_{12}H_{19}O_3$ (M+H), found 211.13323.

Z isomer (*Z*)-<u>103a</u>

Rf (P.E./EtOAc, 8:2): 0.33; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.24-1.50 (m, 4H, C*H*$_2$), 1.62-1.70 (m, 4H, C*H*$_2$), 1.96-2.02 (m, 2H, C*H*$_2$), 3.05 (dd, *J*=7.8 Hz, *J*=1.7 Hz, 2H, C*H*$_2$CH=), 3.89 (s, 3H, OC*H*$_3$), 5.76 (dt, *J*=11.6 Hz, *J*=1.7 Hz, 1H, =C*H*CO_2CH_3), 6.30 (dt, *J*=11.6 Hz, *J*=7.8 Hz, 1H, C*H*=CHCO_2CH_3), 9.72 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.7 (*C*H_2), 25.7 (*C*H_2), 31.2 (*C*H_2), 34.8 (*C*H_2), 50.6 (*C*Cy), 51.5 (O*C*H_3), 122.0 (=*C*HCO_2CH_3), 144.8 (*C*H=CHCO_2CH_3), 166.9 (*C*O_2CH_3), 206.4 (*C*HO).

<u>2-Cyclohexyl-5-vinyl-[1,3]dioxolan-4-one</u> <u>100b</u>



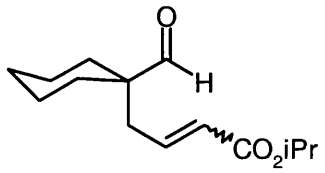
$C_{11}H_{16}O_3$

M= 196.24 $g.mol^{-1}$

Rf (P.E./EtOAc, 8:2): 0.50; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.24-1.50 (m, 4H, C*H*$_2$), 1.62-1.70 (m, 4H, C*H*$_2$), 1.96-2.11 (m, 3H, C*H* and C*H*$_2$), 4.62 (m, 1H, OC*H*CO), 5.41 (dt, J_{cis}=10.5 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH), 5.41-5.43 (m, 1H, OC*H*O), 5.62 (dt, J_{trans}=17.0 Hz, J_{gem}=1.5 Hz, 1H, CH_aH_b=CH), 6.01 (ddd, J_{trans}=17.0 Hz, J_{cis}=10.5 Hz, *J*=5.2 Hz, 1H, CH_2=C*H*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.2 (*C*H_2), 27.0 (*C*H_2), 43.0 (*C*H), 75.8 (CH_2=CH*C*HO), 108.8 (O*C*HO),

119.9 (CH_2=CH), 130.5 (CH_2=CH), 172.0 (CO_2R); **FTIR** (film) ν cm^{-1}: 1723 (C=O), 1646 (C=C); **LRMS** (ES^+) *m/z*: 197 (M+H, 100%); **HRMS** (ES^+) *m/z:* Requires 197.11776 for $C_{11}H_{17}O_3$ (M+H), found 197.11772.

4-(1-Formyl-cyclohexyl)-but-2-enoic acid *iso*-propyl ester 103b



$C_{14}H_{22}O_3$

M= 238.16 $g.mol^{-1}$

A mixture of *iso*-propyl 2-hydroxy-3-butenoate **99b** (3.0 g, 20,8 mmol), cyclohexanecarboxaldehyde (2.3 g, 20.8 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to afford the desired product **103b** (3.0 g, 61%) as two separable diastereomers in a *E:Z* 1.5:1 ratio as a colourless oil.

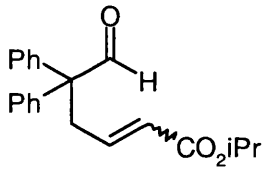
***E* isomer (*E*)-103b**

Rf (P.E./EtOAc, 8:2): 0.48; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.18 (d, *J*=6.3 Hz, 6H, OCH(CH_3)$_2$), 1.19-1.32 (m, 4H, CH_2), 1.39-1.57 (m, 4H, CH_2), 1.78-1.90 (m, 2H, CH_2), 2.24 (dd, *J*=7.8 Hz, *J*=1.2 Hz, 2H, CH_2=CH), 4.97 (m, 1H, OC*H*(CH_3)$_2$), 5.73 (dt, *J*=15.5 Hz, *J*=1.2 Hz, 1H, =C*H*CO_2iPr), 6.70 (dt, *J*=15.5 Hz, *J*=7.8 Hz, 1H, C*H*=CHCO_2iPr), 9.41 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.2 (OCH(CH_3)$_2$), 22.6 (CH_2), 25.8 (CH_2), 31.2 (CH_2), 38.9 (CH_2CH=), 50.1 (*C*Cy), 68.1 (OCH(CH_3)$_2$), 125.6 (=*C*HCO_2iPr), 143.0 (*C*H=CHCO_2iPr), 165.8 (CO_2iPr), 206.2 (*C*HO); **FTIR** (film) ν cm^{-1}: 2934, 2856, 1798, 1719, 1655, 1452, 1273, 1200; **LRMS** (CI^+) *m/z:* 239 (M+H, 58%), 209 (83%), 167 (100%); **HRMS** (CI^+) *m/z:* Requires 239.16471 for $C_{14}H_{23}O_3$ (M+H), found 239.16435.

Z isomer (*Z*)-<u>103b</u>

Rf (P.E./EtOAc, 8:2): 0.52; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.18 (d, *J*=6.3 Hz, 6H, OCH(CH_3)$_2$), 1.19-1.32 (m, 4H, CH_2), 1.39-1.57 (m, 4H, CH_2), 1.78-1.90 (m, 2H, CH_2), 2.88 (dd, *J*=6.8 Hz, *J*=1.6 Hz, 2H, CH_2=CH), 5.00 (m, 1H, OC*H*(CH_3)$_2$), 5.75 (dt, *J*=11.5 Hz, *J*=1.6 Hz, 1H, =C*H*CO_2iPr), 6.11 (dt, *J*=11.5 Hz, *J*=6.8 Hz, 1H, C*H*=CHCO_2iPr), 9.40 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.3 (OCH(CH_3)$_2$), 22.5 (CH_2), 26.0 (CH_2), 27.2 (CH_2), 38.9 (CH_2CH=), 50.7 (*C*Cy), 68.0 (O*C*H(CH_3)$_2$), 123.2 (=*C*HCO_2iPr), 144.1 (*C*H=CHCO_2iPr), 166.0 (CO_2iPr), 206.5 (*C*HO).

<u>*iso*-Propyl 5,5-diphenyl-6-oxo-2-hexenoate 104</u>



$C_{21}H_{22}O_3$

M= 322.16 g.mol^{-1}

A mixture of *iso*-propyl 2-hydroxy-3-butenoate **<u>99b</u>** (1.5 g, 10.4 mmol), 2,2-diphenylacetaldehyde (2.0 g, 10.4 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford the desired product (2.2 g, 64%) as two separable diastereomers in a *E:Z* 2:1 ratio as a colourless oil.

E isomer (*E*)-<u>104</u>

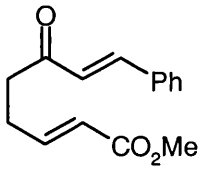
Rf (P.E./EtOAc, 9:1): 0.53; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.11 (d, *J*=6.3 Hz, 6H, CH(CH_3)$_2$), 3.11 (dd, *J*=7.4 Hz, *J*=1.1 Hz, 2H, CH_2=CH), 4.88 (m, 1H, C*H*(CH_3)$_2$), 5.62 (dt, *J*=15.6 Hz, *J*=1.1 Hz, 1H, =C*H*CO_2iPr), 6.62 (dt, *J*=15.6 Hz, *J*=7.4 Hz, 1H, C*H*=CHCO_2iPr), 7.08-7.33 (m, 10H, Ph), 9.74 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.2 (CH(CH_3)$_2$), 37.4 (CH_2), 63.9 (CPh_2), 67.8

(*C*H(CH$_3$)$_2$), 125.4 (=*C*HCO$_2$iPr), 128.1 (Ph), 129.3 (Ph), 139.3 (Ph), 144.1 (*C*H=CHCO$_2$iPr), 165.9 (*C*O$_2$iPr), 197.9 (*C*HO); **FTIR** (film) ν cm^{-1}: 2982, 2936, 1796, 1720, 1656, 1277, 908, 735; **LRMS** (FAB$^+$) *m/z:* 323 (M+H, 23%), 307 (12%), 263 (16%), 245 (5%), 167 (17%), 154 (100%); **HRMS** (FAB$^+$) *m/z:* Requires 323.16471 for $C_{21}H_{23}O_3$ (M+H), found 323.16428.

Z isomer (*Z*)-104

Rf (P.E./EtOAc, 9:1): 0.56; **^{1}H NMR** (CDCl$_3$, 300 MHz) δ ppm: 1.11 (d, *J*=6.3 Hz, 6H, CH(C*H*$_3$)$_2$), 3.35 (dd, *J*=7.0 Hz, *J*=1.5 Hz, 2H, C*H*$_2$=CH), 4.91 (m, 1H, C*H*(CH$_3$)$_2$), 5.64 (dt, *J*=11.6 Hz, *J*=1.5 Hz, 1H, =C*H*CO$_2$iPr), 6.02 (dt, *J*=11.6 Hz, *J*=7.0 Hz, 1H, C*H*=CHCO$_2$iPr), 7.08-7.35 (m, 10H, Ph), 9.72 (s, 1H, C*H*O); **^{13}C NMR** (CDCl$_3$, 75.5 MHz) δ ppm: 22.3 (CH(*C*H$_3$)$_2$), 39.7 (*C*H$_2$), 63.7 (*C*Ph$_2$), 67.9 (*C*H(CH$_3$)$_2$), 123.4 (=*C*HCO$_2$iPr), 128.1 (Ph), 129.2 (Ph), 139.5 (Ph), 144.8 (*C*H=CHCO$_2$iPr), 166.1 (*C*O$_2$iPr), 198.0 (*C*HO).

Methyl (2*E*, 7*E*)-6-oxo-8-phenyl-2,7-octadienoate 105



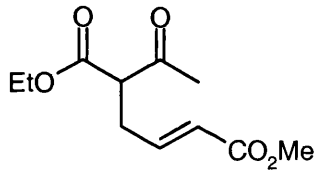
$C_{15}H_{16}O_3$

M= 244.11 g.mol^{-1}

A mixture of methyl 2-hydroxy-3-butenoate **99a** (2.0 g, 17.2 mmol), dibenzylideneacetone (2.5 g, 17.2 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to afford the desired product (2.4 g, 58%) as a single *E*-diastereomer as a yellow oil.

Rf (P.E./EtOAc, 8:2): 0.37; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.56 (qd, *J*=6.9 Hz, *J*=1.4 Hz, 2H, CH_2CH=), 2.82 (t, *J*=6.9 Hz, 2H, CH_2CO), 3.70 (s, 3H, OCH_3), 5.86 (dt, *J*=15.6 Hz, *J*=1.4 Hz, 1H, =$CHCO_2CH_3$), 6.72 (d, *J*=16.2 Hz, 1H, CH=CHPh), 6.99 (dt, *J*=15.6 Hz, *J*=6.9 Hz, 1H, CH=$CHCO_2CH_3$), 7.37-7.54 (m, 5H, Ph), 7.60 (d, *J*=16.2 Hz, 1H, CH=CHPh); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.7 (CH_2CH=), 39.1 (CH_2CO), 51.8 (OCH_3), 122.1 (=$CHCO_2CH_3$), 126.2 (CH=CHPh), 128.7 (Ph), 129.3 (Ph), 131.0 (Ph), 134.8 (Ph), 143.3 (CH=CHPh), 148.0 (CH=$CHCO_2CH_3$), 167.2 (CO_2CH_3), 198.4 (CO); **FTIR** (film) ν cm^{-1}: 3055, 1719, 1659, 1612, 1578, 1265, 739, 704; **LRMS** (FAB^+) *m/z:* 245 (M+H, 100%), 213 (78%), 167 (39%); **HRMS** (FAB^+) *m/z:* Requires 245.11776 for $C_{15}H_{17}O_3$ (M+H), found 245.11782.

(2*E*)-5-Acetyl-hex-2-enedioic acid 6-ethyl ester 1-methyl ester 106



$C_{11}H_{16}O_5$

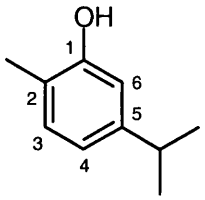
M= 228.10 $g.mol^{-1}$

A mixture of methyl 2-hydroxy-3-butenoate **99a** (1.0 g, 8.6 mmol), ethyl 3-oxo-butenoate (1.12 g, 8.6 mmol) and *p*-toluenesulfonic acid (3 mg), was heated under reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to afford the desired product (0.77 g, 39%) as a single *E* diastereomer as a yellow oil.

Rf (P.E./EtOAc, 8:2): 0.55; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.28 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 2.26 (s, 3H, CH_3CO), 2.73 (td, *J*=7.2 Hz, *J*=1.5 Hz, 2H, CH_2CH=), 3.57 (t, *J*=7.2 Hz, 1H, $CHCOCH_3$), 3.72 (s, 3H, OCH_3), 4.21 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.88 (dt, *J*=15.6 Hz, *J*=1.5 Hz, 1H, =$CHCO_2CH_3$), 6.86 (dt, *J*=15.6 Hz, *J*=7.2 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 14.1

(OCH_2CH_3), 29.2 (CH_3CO), 30.2 (CH_2CH=), 51.5 (OCH_3), 58.2 ($CHCOCH_3$), 61.8 (OCH_2CH_3), 123.4 (=$CHCO_2CH_3$), 144.4 (CH=$CHCO_2CH_3$), 166.4 (CO_2R), 168.6 (CO_2R), 201.2 ($COCH_3$); **FTIR** (film) ν cm^{-1}: 1720 (C=O), 1660 (C=C), 1437, 1361, 1271, 1154, 737; **LRMS** (ES^+) *m/z:* 246 ($M+NH_4$, 100%), 229 (M+H, 34%); **HRMS** (ES^+) *m/z:* Requires 229.1074 for $C_{11}H_{17}O_5$ (M+H), found 229.1076.

5-*iso*-Propyl-2-methyl-phenol 108[221]



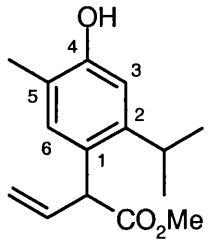
$C_{10}H_{14}O$

M= 150.22 $g.mol^{-1}$

A mixture of methyl 2-hydroxy-3-butenoate **99a** (2.0 g, 17 mmol), (*R*)-(-)-carvone (2.58 g, 17 mmol) and a small amount of *p*-toluenesulfonic acid (50 mg) in toluene (100 mL), was heated under reflux for 72 h with provision of a Dean-Stark apparatus for the removal of water. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10). The desired compound was not present in the mixture but instead phenol **108** (2.0 g, 78%) was isolated together with tetrasubstituted phenol **109** (0.76 g, 18%) as orange oils.

Rf (P.E./EtOAc, 8:2): 0.82; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.32 (d, *J*=6.9 Hz, 6H, $CH(CH_3)_2$), 2.32 (s, 3H, CH_3), 2.90-3.04 (m, 1H, $CH(CH_3)_2$), 4.92 (s, 1H, OH), 6.76 (d, *J*=1.5 Hz, 1H, H_6), 6.82 (dd, *J*=7.7 Hz, *J*=1.5 Hz, 1H, H_4), 7.02 (d, *J*=7.7 Hz, 1H, H_3); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 15.7 (CH_3), 24.4 ($CH(CH_3)_2$), 34.1 ($CH(CH_3)_2$), 113.4 (Ph), 119.1 (Ph), 121.3 (Ph), 131.2 (Ph), 148.8 (Ph), 154.1 (Ph); **FTIR** (film) ν cm^{-1}: 3423 (O-H), 2961, 2928, 2870, 1618 (C=C), 1589 (C=C), 1521 (C=C), 1502 (C=C), 1460, 1258, 937, 866, 812; **LRMS** (EI^+) *m/z:* 150 (M, 100%), 133 (M-OH, 25%).

Methyl 2-(4-hydroxy-2-isopropyl-5-methylphenyl)-3-butenoate 109

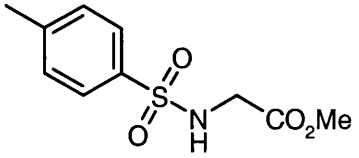


$C_{15}H_{20}O_3$

M= 248.14 g.mol^{-1}

Rf (P.E./EtOAc, 8:2): 0.63; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.20 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 1.24 (d, *J*=6.8 Hz, 3H, $CH(CH_3)_2$), 2.22 (s, 3H, CH_3), 3.10-3.14 (m, 1H, $CH(CH_3)_2$), 3.71 (s, 3H, OCH_3), 4.57 (dt, *J*=6.8 Hz, *J*=1.3 Hz, 1H, $CHCO_2CH_3$), 4.85 (s, 1H, OH), 5.04 (dt, J_{trans}=17.2 Hz, J_{gem}=1.3 Hz, 1H, $CH=CH_aH_b$), 5.21 (dt, J_{cis}=11.5 Hz, J_{gem}=1.3 Hz, 1H, $CH=CH_aH_b$), 6.25 (ddd, J_{trans}=17.2 Hz, J_{cis}=11.5 Hz, *J*=6.8 Hz, 1H, $CH=CH_2$), 6.47 (s, 1H, H_3), 6.75 (s, 1H, H_6); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 15.7 (CH_3), 24.1 ($CH(CH_3)_2$), 24.3 ($CH(CH_3)_2$), 29.2 ($CH(CH_3)_2$), 50.5 ($CHCO_2CH_3$), 52.5 (OCH_3), 112.7 (Ph), 117.3 ($CH=CH_2$), 121.8 (Ph), 127.5 (Ph), 131.3 (Ph), 136.8 ($CH=CH_2$), 146.2 (Ph), 153.7 (Ph), 174.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3435 (O-H), 3055, 2964, 2930, 2870, 1717 (C=O), 1639 (C=C), 1620 (C=C), 1589 (C=C), 1504 (C=C), 1435, 1267, 739, 704; **LRMS** (EI$^+$) *m/z:* 248 (M, 30%), 189 (M-CO_2CH_3, 44%), 149 (M-$CH(CH=CH_2)CO_2CH_3$, 66%), 147 (100%); **HRMS** (EI$^+$) *m/z:* Requires 248.1432 for $C_{15}H_{20}O_3$ (M), found 248.1422.

Methyl (toluene-4-sulfonylamino)-acetate 116[222]



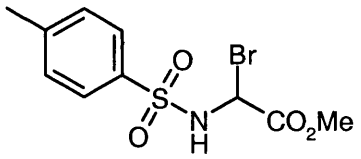
$C_{10}H_{13}NO_4S$

M= 243.06 g.mol^{-1}

A suspension of glycine methyl ester hydrochloride (10 g, 80 mmol) and triethylamine (7.7 g, 174 mmol) in tetrahydrofuran (300 mL), was stirred at room temperature for 15 min. *p*-Toluenesulfonyl chloride was added (16.6 g, 87 mmol) and the mixture was heated at reflux under nitrogen for 48 h. The solids were filtered off and the filtrate acidified until pH=2. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Recrystallisation from *n*-pentane afforded the desired product **116** (19 g, 98%) as a white solid, (mp= 92°C, lit.,[222] 92-93°C).

Rf (P.E./EtOAc, 6:4): 0.52; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.42 (s, 1H, CH_3), 3.64 (s, 3H, OCH_3), 3.78 (d, *J*=5.6 Hz, 2H, CH_2NH), 5.05 (t, *J*=5.6 Hz, 1H, N*H*), 7.31 (d, *J*=8.2 Hz, 2H, Ph), 7.75 (d, *J*=8.2 Hz, 2H, Ph); **^{13}C NMR** ($CDCl_3$, 300 MHz) δ ppm: 21.5 (CH_3), 44.1 (CH_2), 52.6 (OCH_3), 127.3 (Ph), 129.8 (Ph), 136.3 (Ph), 143.9 (Ph), 169.3 (CO_2CH_3); **FTIR** (film) cm^{-1}: 3277 (N-H), 1745 (C=O), 1598 (C=C), 1495 (C=C), 1438, 1331, 1161, 815, 664, 557; **LRMS** (ES^+) *m/z*: 509 (2M+Na, 53%), 487 (2M+H, 26%), 266 (M+Na, 39%), 244 (M+H, 100%); **HRMS** (ES^+) *m/z:* Requires 244.0634 for $C_{10}H_{14}NO_4S$ (M+H), found 244.0644.

Methyl 2-bromo-(toluene-4-sulfonylamino)-acetate 117



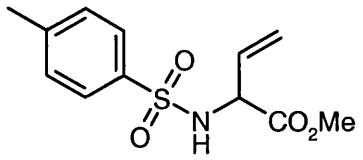
$C_{10}H_{12}BrNO_4S$

M= 322.18 $g.mol^{-1}$

A solution of bromine (7.7 g, 48 mmol) in carbon tetrachloride (50 mL) was added dropwise to a slurry of compound **116** (6.0 g, 24 mmol) in carbon tetrachloride (50 mL) and the mixture was heated at reflux under nitrogen for 5 h. The solvent was removed *in vacuo* and the resulting residue was used in the next step without further purification.

Rf (P.E./EtOAc, 6:4): 0.79; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.35 (s, 1H, C*H*$_3$), 3.75 (s, 3H, OC*H*$_3$), 5.99-6.11 (m, 2H, C*H*Br and N*H*), 7.24 (d, *J*=8.2 Hz, 2H, Ph), 7.72 (d, *J*=8.2 Hz, 2H, Ph).

Methyl 2-(toluene-4-sulfonylamino)-3-butenoate 115



$C_{12}H_{15}NO_4S$

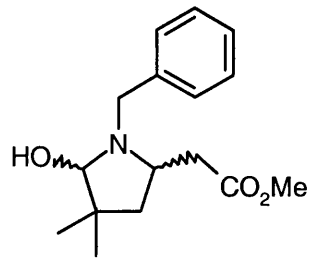
M= 269.08 g.mol^{-1}

To a solution of compound **117** (10.5 g, 31 mmol) in anhydrous tetrahydrofuran (200 mL) at -78°C, was added vinylmagnesium bromide 1.0M in tetrahydrofuran (62 mL, 62 mmol) *via* syringe. After 3 h, the reaction was quenched with citric acid. The solids were filtered off and the filtrate acidified with an aqueous solution of hydrochloric acid 1N (200 mL). Ether was added and the organic portion was washed with water and then brine. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (70:30) to afford the desired product **115** (1.6 g, 24% over 2 steps) as a brown oil.

Rf (P.E./EtOAc, 6:4): 0.58; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.44 (s, 1H, C*H*$_3$), 3.61 (s, 3H, OC*H*$_3$), 4.36-4.40 (m, 1H, C*H*NH), 5.26 (dd, *J*=10.3 Hz, *J*=1.6 Hz, 1H, CH=C*H*$_{cis}$H), 5.31 (m, 1H, N*H*), 5.50 (dd, *J*=17.1 Hz, *J*=1.6 Hz, 1H, CH=C*H*$_{trans}$H), 5.78 (ddd, *J*=17.1Hz, *J*=10.3 Hz, *J*=5.5 Hz, 1H, C*H*=CH$_2$), 7.31 (d, *J*=8.2 Hz, 2H, Ph), 7.75 (d, *J*=8.2 Hz, 2H, Ph); **^{13}C NMR** ($CDCl_3$, 300 MHz) δ ppm: 21.9 (*C*H$_3$), 53.2 (O*C*H$_3$), 58.2 (*C*HNH), 119.2 (=*C*H$_2$), 127.7 (Ph), 130.0 (Ph), 132.1 (*C*H=CH$_2$), 137.4 (Ph), 144.1 (Ph), 170.5 (*C*O$_2$CH$_3$); **FTIR** (film) cm^{-1}: 3283 (N-H), 1744 (C=O), 1599 (C=C), 1437, 1341, 1266, 1164, 738, 704, 668; **LRMS** (ES$^+$) *m/z*: 561 (2M+Na, 88%), 539 (2M+H, 24%), 287 (M+NH$_4$, 29%), 292 (M+Na, 28%), 270

(M+H, 100%); **HRMS** (ES^+) *m/z:* Requires 270.0800 for $C_{12}H_{16}NO_4S$ (M+H), found 270.0800.

Methyl (1-benzyl-4,4-dimethyl-5-hydroxy-pyrrolidin-2-yl)-acetate 121



$C_{16}H_{23}NO_3$

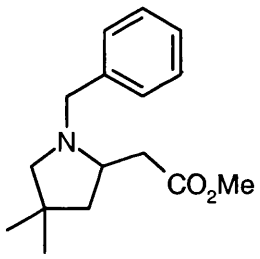
M= 277.35 $g.mol^{-1}$

A mixture of benzylamine (250 mg, 2.35 mmol) and methyl (*E*)-5,5-dimethyl-6-oxo-2-hexenoate **102** (400 mg, 2.35 mmol) in anhydrous diethyl ether (8 mL) was stirred at room temperature overnight over 4Å molecular sieves (2.0 g). After 30 min a white precipitate was observed but it was disappeared after stirring overnight. The molecular sieves were removed by filtration and the filtrate was evaporated under reduced pressure. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (70:30) to afford hydroxy-pyrrolidine **121** (260 mg, 40%) as a 1:1 mixture of diastereomers as a yellow oil.

Rf (P.E./EtOAc, 7:3): 0.32; **^{1}H NMR** (DMSO, 400 MHz) δ ppm: 0.79 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.29 (dd, *J*=12.8 Hz, *J*=4.3 Hz, 1H, $C(CH_3)_2CH_2CH$), 1.37 (dd, *J*=12.4 Hz, *J*=7.8 Hz, 1H, $C(CH_3)_2CH_2CH$), 1.61 (dd, *J*=12.4 Hz, *J*=7.2 Hz, 1H, $C(CH_3)_2CH_2CH$), 1.94 (dd, *J*=12.8 Hz, *J*=9.6 Hz, 1H, $C(CH_3)_2CH_2CH$), 2.11 (dd, *J*=14.9 Hz, *J*=9.3 Hz, 1H, $CH_2CO_2CH_3$), 2.24 (dd, *J*=15.0 Hz, *J*=9.4 Hz, 1H, $CH_2CO_2CH_3$), 2.50 (dd, *J*=14.9 Hz, *J*=7.1 Hz, 1H, $CH_2CO_2CH_3$), 2.59 (dd, *J*=15.0 Hz, *J*=4.1 Hz, 1H, $CH_2CO_2CH_3$), 3.10-3.12 (m, 1H, CH_2CHCH_2), 3.26-3.30 (m, 1H, CH_2CHCH_2), 3.48 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.60 (d, *J*=14.0 Hz, 1H, NCH_2Ph), 3.63 (d, *J*=7.0 Hz, 1H, CHOH), 3.79 (d, *J*=14.0 Hz, 1H, NCH_2Ph), 3.83 (d, *J*=6.0 Hz, 1H, CHOH), 3.84 (d, *J*=14.0 Hz, 1H,

NCH_2Ph), 3.90 (d, *J*=14.0 Hz, 1H, NCH_2Ph), 4.66 (d, *J*=7.0 Hz, 1H, CHO*H*), 4.80 (d, *J*=6.0 Hz, 1H, CHO*H*), 7.18-7.33 (m, 10H, Ph); **^{13}C NMR** (DMSO, 100 MHz) δ ppm: 23.8 (C(CH_3)$_2$), 24.1 (C(CH_3)$_2$), 26.3 (C(CH_3)$_2$), 29.0 (C(CH_3)$_2$), 39.1 (C(CH$_3$)$_2$), 40.1 (C(CH$_3$)$_2$), 40.3 (CH_2), 40.4 (CH_2), 40.8 (CH_2), 42.4 (CH_2), 49.1 (CH_2Ph), 51.1 (OCH_3), 51.1 (OCH_3), 53.0 (CH_2Ph), 55.3 (CH_2CHCH_2), 57.2 (CH_2CHCH_2), 90.8 (*C*HOH), 94.1 (*C*HOH), 126.4 (Ph), 126.6 (Ph), 128.0 (Ph), 128.1 (Ph), 128.5 (Ph), 139.5 (Ph), 140.5 (Ph), 172.0 (CO_2CH_3), 172.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3480 (O-H), 1732 (C=O); **LRMS** (EI$^+$) *m/z*: 260 (M-OH, 43%), 218 (M-CO_2CH_3, 75%), 144 (100%), 91 (97%); **HRMS** (EI$^+$) *m/z:* Requires 260.1638 for $C_{16}H_{22}NO_2$ (M-OH), found 260.1651.

Methyl (1-benzyl-4,4-dimethyl-pyrrolidin-2-yl)-acetate 120



$C_{16}H_{23}NO_2$

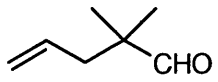
M= 261.17 g.mol^{-1}

According to the general procedure for the rhodium tandem cyclisation reaction (see Section III.3), reaction of methyl (1-benzyl-4,4-dimethyl-5-hydroxy-pyrrolidin-2-yl)-acetate **121** (100 mg, 0.36 mmol), triethylsilane (94 mg, 0.81 mmol) and tris(triphenylphosphine) rhodium chloride (7.5 mg, 8.1 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), pyrrolidine **120** (41 mg, 44%) as a colourless oil.

Rf (P.E./EtOAc, 7:3): 0.52; **^{1}H NMR** (DMSO, 300 MHz) δ ppm: 0.90 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.37 (dd, *J*=12.7 Hz, *J*=7.8 Hz, 1H, C(CH$_3$)$_2$CH_2), 1.78 (dd, *J*=12.7 Hz, *J*=8.0 Hz, 1H, C(CH$_3$)$_2$CH_2), 1.94 (d, *J*=9.1 Hz, 1H, CH_2NBn), 2.30 (dd, *J*=14.8 Hz, *J*=8.8 Hz, 1H, CH_2CO$_2$CH$_3$), 2.56 (d, *J*=9.1 Hz, 1H, CH_2NBn), 2.61 (dd,

J=14.8 Hz, *J*=4.2 Hz, 1H, C*H*$_2$CO$_2$CH$_3$), 2.88-2.98 (m, 1H, CH$_2$C*H*CH$_2$), 3.58 (s, 3H, OC*H*$_3$), 3.79 (d, *J*=14.0 Hz, 1H, NC*H*$_2$Ph), 3.89 (d, *J*=13.3 Hz, 1H, NC*H*$_2$Ph), 7.09-7.24 (m, 5H, Ph); **^{13}C NMR** (DMSO, 75.5 MHz) δ ppm: 29.0 (C(*C*H$_3$)$_2$), 30.4 (C(*C*H$_3$)$_2$), 36.4 (*C*(CH$_3$)$_2$), 40.3 (C(CH$_3$)$_2$*C*H$_2$), 47.0 (*C*H$_2$CO$_2$CH$_3$), 51.8 (O*C*H$_3$), 58.7 (N*C*H$_2$Ph), 61.5 (CH$_2$*C*HCH$_2$), 68.2 (N*C*H$_2$), 127.1 (Ph), 128.5 (Ph), 128.8 (Ph), 140.3 (Ph), 173.2 (*C*O$_2$CH$_3$); **FTIR** (film) ν cm^{-1}: 1732 (C=O); **LRMS** (EI$^+$) *m/z:* 261 (M, 8%), 246 (M-CH$_3$, 31%), 202 (M-CO$_2$CH$_3$, 54%), 91 (100%); **HRMS** (EI$^+$) *m/z:* Requires 261.17287 for C$_{16}$H$_{23}$O$_2$N (M), found 261.17296.

2,2-Dimethyl-4-pentenal 123[103]



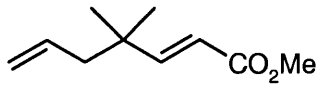
C$_7$H$_{12}$O

M= 112.17 g.mol^{-1}

A mixture of isobutyraldehyde (32.4 g, 448.0 mmol), allyl alcohol (17.4 g, 300.0 mmol) and *p*-toluenesulfonic acid (0.1 g) in 60 mL of *p*-cymene, was heated at reflux for 48 h with provision of a Dean-Stark apparatus for the removal of water. During this time, the water layer (5 mL) was separated. Fractional distillation of the reaction mixture gave the desired product (18.8 g, 56%) as a colourless oil, (bp: 120-122°C; lit.,[103] 124-126°C).

Rf (EtOAc): 0.77; **^{1}H NMR** (CDCl$_3$, 300 MHz), δ ppm: 1.10 (s, 6H, C(C*H*$_3$)$_2$), 2.14 (d, *J*=7.4 Hz, 2H, C*H*$_2$CH=), 4.95-5.06 (m, 2H, C*H*$_2$=CH), 5.56- 5.74 (m, 1H, C*H*=CH$_2$), 9.68 (s, 1H, C*H*O); **^{13}C NMR** (CDCl$_3$, 75.5 MHz) δ ppm: 21.5 (C(*C*H$_3$)$_2$), 41.8 (*C*H$_2$), 46.0 (*C*(CH$_3$)$_2$), 118.8 (*C*H$_2$=CH), 134.3 (CH$_2$=*C*H), 206.0 (*C*HO); **FTIR** (film) ν cm^{-1}: 1705 (C=O).

Methyl (*E*)-4,4-dimethylhept-2,6-dienoate 124



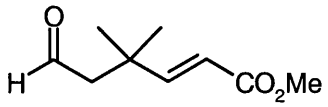
$C_{10}H_{16}O_2$

M= 168.23 g.mol^{-1}

A suspension of 80% sodium hydride dispersion in mineral oil (6.8 g, 225.6 mmol) in 200 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while trimethyl phosphonoacetate (41.0 g, 225.6 mmol) in 200 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for further 1 h at 0°C. Then, a solution of 4,4-dimethyl pentenal **123** (23.0 g, 205.0 mmol) in 250 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) afforded the desired product (30.3 g, 87%) as a single *E* diastereomer as a colourless oil.

Rf (P.E./EtOAc 8:2): 0.67; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.98 (s, 6H, $C(CH_3)_2$), 2.04 (d, *J*=7.4 Hz, 2H, CH_2CH=), 3.66 (s, 3H, OCH_3), 4.92-5.02 (m, 2H, $CH=CH_2$), 5.56- 5.72 (m, 1H, $CH=CH_2$), 5.66 (d, *J*=15.7 Hz, 1H, $CH=CHCO_2CH_3$), 6.88 (d, *J*=15.7 Hz, 1H, $CH=CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.4 ($C(CH_3)_2$), 37.1 ($C(CH_3)_2$), 46.8 (CH_2), 51.8 (OCH_3), 117.9 ($=CHCO_2CH_3$), 118.2 ($CH=CH_2$), 134.6 ($CH=CH_2$), 158.3 ($CH=CHCO_2CH_3$), 167.9 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 2964, 2872, 1719 (C=O), 1653 (C=C), 1265; **LRMS** (APCI$^+$) *m/z*: 169 (M+H, 10%); 137 ($M-OCH_3$, 10%); 127 (63%); 109 ($M-CO_2CH_3$, 100%); **HRMS** (ES$^+$) calcd for $C_{10}H_{17}O_2$ (M+H) 169.1239, found 169.1232.

Methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate 122[117]



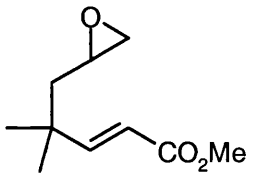
$C_9H_{14}O_3$

M= 170.09 g.mol^{-1}

A solution of methyl (*E*)-4,4-dimethylhept-2,6-dienoate **124** (30.0 g, 178.3 mmol) and pyridine (5 mL, 1% vol) in anhydrous dichloromethane (500 mL) was cooled to -78°C. A stream of ozone was bubbled through the solution, and the reaction was carefully monitored by t.l.c. After consumption of the starting material the flask was flushed with nitrogen. Dimethylsulfide was added (11.1 g, 1.8 mol) and the mixture was allowed to warm to room temperature overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford the desired aldehyde (14.6 g, 48%) as a yellow oil.

Rf (P.E./EtOAc 9:1): 0.28; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.30 (s, 6H, $C(CH_3)_2$), 2.52 (d, *J*=2.7 Hz, 2H, CH_2CHO), 3.83 (s, 3H, OCH_3), 5.89 (d, *J*=16.0 Hz, 1H, $CH=CHCO_2CH_3$), 7.13 (d, *J*=16.0 Hz, 1H, $CH=CHCO_2CH_3$), 9.84 (t, *J*=2.7 Hz, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 27.2 ($C(CH_3)_2$), 36.2 ($C(CH_3)_2$), 52.0 (OCH_3), 54.6 (CH_2), 118.9 ($=CHCO_2CH_3$), 155.9 ($CH=CHCO_2CH_3$), 167.3 (CO_2CH_3), 201.6 (CHO); **FTIR** (film) ν cm^{-1}: 2930, 2853, 2729, 1730 (C=O), 1654 (C=C), 1462; **LRMS** (APCI$^+$) *m/z*: 171 (M+H, 8%); 155 (M-CH_3, 46%); 139 (M-OCH_3, 100%).

Methyl (*E*)-4,4-dimethyl-5-oxiranyl-2-pentenoate 125



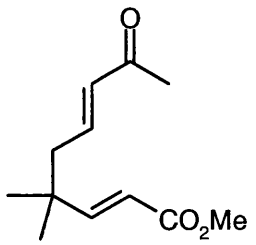
$C_{10}H_{16}O_3$

M= 184.23 g.mol^{-1}

A mixture of 60% sodium hydride dispersion in mineral oil (0.13 g, 3.2 mmol) and excess anhydrous dimethylsulfoxide (5 mL) was stirred under nitrogen at 75°C until the evolution of hydrogen ceases (1h). The solution was then cooled down to room temperature, diluted with an equal volume of dry tetrahydrofuran to avoid freezing and then cooled in an ice-salt bath. A solution of trimethyl sulfonium iodide (0.66 g, 3.2 mmol) in 3 mL of dry dimethylsulfoxide was added and the mixture stirred for 5 min. Aldehyde **122** was then added (0.5 g, 2.9 mmol) and stirring was continued at salt-ice temperature for further 15 min, then for 1 h at room temperature. The mixture was diluted with 3 volumes of water and extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford epoxide **125** (0.18 g, 33%) as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.28; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.11 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.47-1.54 (m, 2H, CH_2), 2.34 (dd, *J*=5.0 Hz, *J*=2.7 Hz, 1H, CH_aHO), 2.66 (dd, *J*=5.0 Hz, *J*=4.1 Hz, 1H, CHH_bO), 2.80-2.82 (m, 1H, C*H*O), 3.67 (s, 3H, OCH_3), 5.67 (d, *J*=16.0 Hz, 1H, =C*H*CO_2CH_3), 6.93 (d, *J*=16.0 Hz, 1H, C*H*=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.7 (*C*H_3), 27.3 (*C*H_3), 37.0 (*C*$(CH_3)_2$), 45.2 (*C*H_2), 47.0 (*C*H_2O), 49.4 (*C*HO), 51.9 (O*C*H_3), 118.3 (=*C*HCO_2CH_3), 157.6 (*C*H=$CHCO_2CH_3$), 167.7 (*C*O_2CH_3); **FTIR** (film) ν cm^{-1}: 3054, 2969, 2931, 2874, 1717 (C=O), 1652 (C=C), 1436, 1265; **LRMS** (FAB$^+$) *m/z:* 185 (M+H, 66%), 169 (M-CH_3, 8%), 154 (M+H-OCH_3, 100%); **HRMS** (FAB$^+$) *m/z:* Requires 185.11775 for $C_{10}H_{17}O_3$ (M+H), found 185.11746.

Methyl (2*E*, 6*E*)-4,4-dimethyl-8-oxo-2,6-nonadienoate 126[223]



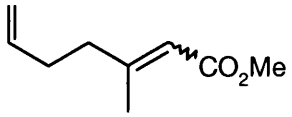
$C_{12}H_{18}O_3$
M= 210.13 g.mol^{-1}

A suspension of 80% sodium hydride dispersion in mineral oil (0.26 g, 9.7 mmol) in 15 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while dimethyl-(2-oxopropyl)-phosphonate (1.6 g, 9.7 mmol) in 15 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for further 1 h. at 0°C. Then, a solution of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (1.5 g, 8.9 mmol) in 20 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. Purification by flash column chromatography employing P.E. 30-40°C/EtOAc (80:20) as eluant afforded enoate **126** (1.7 g, 92%) as a colourless oil.

R_f (P.E. /EtOAc, 9:1): 0.66; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.10 (s, 6H, $C(CH_3)_2$), 2.22 (s, 3H, CH_3CO), 2.28 (dd, *J*=7.6 Hz, *J*=1.2 Hz, 2H, CH_2CH=), 3.74 (s, 3H, OCH_3), 5.76 (d, *J*=16.0 Hz, 1H, =$CHCO_2CH_3$), 6.07 (dt, *J*=15.8 Hz, *J*=1.2 Hz, 1H, =$CHCOCH_3$), 6.65 (dt, *J*=15.8 Hz, *J*=7.6 Hz, 1H, CH=$CHCOCH_3$), 6.93 (d, *J*=16.0 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.8 ($C(CH_3)_2$), 27.5 ($COCH_3$), 37.5 ($C(CH_3)_2$), 45.2 (CH_2), 51.9 (OCH_3), 118.7

(=*C*HCO$_2$CH$_3$), 134.3 (=*C*HCOCH$_3$), 143.6 (*C*H=CHCOCH$_3$), 156.9 (*C*H=CHCO$_2$CH$_3$), 167.5 (*C*O$_2$CH$_3$), 198.4 (*C*OCH$_3$); **FTIR** (film) ν cm^{-1}: 2964, 2845, 1724 (C=O), 1655 (C=C), 1628, 1437, 1367, 1256, 1171; **LRMS** (ES$^+$) *m/z:* 233 (M+Na, 96%), 211 (M+H, 65%), 179 (M-OCH$_3$, 100%); **HRMS** (ES$^+$) *m/z:* Requires 211.1335 for $C_{12}H_{19}O_3$ (M+H), found 211.1334.

Methyl 3-methyl-2,6-heptadienoate 128[224]



$C_9H_{14}O_2$

M= 154.10 g.mol^{-1}

A suspension of 80% sodium hydride dispersion in mineral oil (3.6 g, 121.2 mmol) in 100 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while trimethyl phosphonoacetate (22.1 g, 121.2 mmol) in 100 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for further 1 h. at 0°C. Then, a solution of 5-hexen-2-one (10.0 g, 101.9 mmol) in 150 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. Purification by flash column chromatography employing P.E. 30-40°C/EtOAc (80:20) as eluant afforded enoate **128** (13.7 g, 87%) as two diastereomers in a *E:Z* 2:1 ratio as a colorless oil.

***E* isomer (*E*)-128**

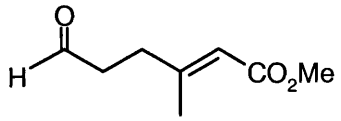
***R*f** (P.E./EtOAc, 8:2): 0.73; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 2.09 (d, *J*=1.3 Hz, 3H, C*H*$_3$), 2.16-2.18 (m, 4H, C*H*$_2$), 3.61 (s, 3H, OC*H*$_3$), 4.89 (dq, *J*=10.1 Hz, *J*=1.8

Hz, 1H, CH=CH_{cis}H), 4.96 (dq, *J*=17.1 Hz, *J*=1.8 Hz, 1H, CH=CHH_{trans}), 5.60 (m, 1H, =C*H*CO_2CH_3), 5.66-5.78 (m, 1H, C*H*=CH_2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 18.7 (*C*H_3), 31.4 (*C*H_2), 40.1 (*C*H_2), 50.7 (O*C*H_3), 115.3 (=*C*H_2), 115.4 (=*C*HCO_2CH_3), 137.2 (*C*H=CH_2), 159.4 (*C*=$CHCO_2CH_3$), 167.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3078, 2926, 2853, 1720, 1651, 1435, 1225, 1151; **LRMS** (DCI^+) *m/z:* 155 (M+H, 100%), 139 (M-CH_3, 8%), 123 (M-OCH_3, 26%), 95 (M-CO_2CH_3, 63%); **HRMS** (DCI^+) *m/z:* Requires 155.10719 for $C_9H_{15}O_2$ (M+H), found 155.10696.

Z isomer (Z)-128

Rf (P.E./EtOAc, 8:2): 0.78; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.82 (d, *J*=1.3 Hz, 3H, C*H*$_3$), 2.16-2.18 (m, 2H, C*H*$_2$), 2.66 (t, *J*=7.5 Hz, 2H, C*H*$_2$C=), 3.60 (s, 3H, OC*H*$_3$), 4.89 (dq, *J*=10.1 Hz, *J*=1.8 Hz, 1H, CH=CH_{cis}H), 4.96 (dq, *J*=17.1 Hz, *J*=1.8 Hz, 1H, CH=CHH_{trans}), 5.60 (m, 1H, =C*H*CO_2CH_3), 5.66-5.78 (m, 1H, C*H*=CH_2); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 25.5 (*C*H_3), 32.6 (*C*H_2), 33.1 (*C*H_2), 51.1 (O*C*H_3), 115.2 (=*C*H_2), 116.5 (=*C*HCO_2CH_3), 138.3 (*C*H=CH_2), 160.3 (*C*=$CHCO_2CH_3$), 167.0 (CO_2CH_3).

Methyl (*E*)-3-methyl 6-oxo-2-hexenoate 127[225]



$C_8H_{12}O_3$

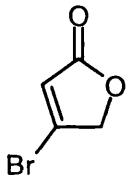
M= 156.18 $g.mol^{-1}$

A solution of methyl (*E*)-3-methyl-2,6-heptadienoate **128** (15.0 g, 97.3 mmol) and pyridine (1.7 mL, 1% vol) in anhydrous dichloromethane (170 mL) was cooled to -78°C. A stream of ozone was bubbled through the solution, and the reaction was carefully monitored by TLC. After consumption of the starting material the flask was flushed with nitrogen. Dimethylsulfide was added (6.0 g, 970 mmol) and the mixture was allowed to warm to room temperature overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The resulting

crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford aldehyde **127** (6.23 g, 41%) as a colorless oil.

Rf (P.E./EtOAc, 9:1): 0.37; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 2.15 (d, *J*=1.3 Hz, 3H, C*H*$_3$), 2.45 (td, *J*=7.6 Hz, *J*=1.1 Hz, 2H, C*H*$_2$CHO), 2.61 (td, *J*=7.6 Hz, *J*=1.3 Hz, 2H, C*H*$_2$CH$_2$CHO), 3.65 (s, 3H, OC*H*$_3$), 5.61 (m, 1H, =C*H*CO$_2$CH$_3$), 9.77 (t, *J*=1.1 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 500 MHz) δ ppm: 19.1 (*C*H$_3$), 33.0 (*C*H$_2$), 41.8 (*C*H$_2$), 51.3 (O*C*H$_3$), 116.4 (=*C*HCO$_2$CH$_3$), 157.7 (*C*=CHCO$_2$CH$_3$), 167.2 (*C*O$_2$CH$_3$), 200.8 (*C*HO); **FTIR** (film) ν cm^{-1}: 2951, 2845, 2729, 1719, 1649, 1437, 1362, 1229, 1153; **LRMS** (ES$^+$) *m/z:* 157 (M+H, 100%), 313 (2M+H, 26%); **HRMS** (ES$^+$) *m/z:* Requires 157.0863 for $C_9H_{15}O_2$ (M+H), found 157.0865.

4-Bromo-5*H*-furan-2-one 130[126]



$C_4H_3BrO_2$

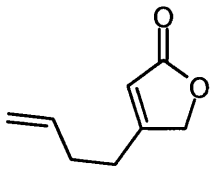
M= 162.97 g.mol^{-1}

To a suspension of tetronic acid (9.0 g, 90 mmol) in anhydrous dichloromethane (200 mL) was added dimethylformamide (9 mL, 117 mmol). The mixture was cooled at 0°C and oxalyl bromide (23.3 g, 108 mmol) was added over 60 min. After the addition, the suspension was stirred for 1 h at 0°C and for a further 2 h at room temperature. Water was added (250 mL) and the organic layer was extracted with ether (4 x 100 mL). The organic layers were successively washed with water, saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Recrystallisation from ether gave the desired compound (6.2 g, 42%) as orange crystals (mp: 77°C; lit.,[126] 77°C).

Rf (P.E./EtOAc, 8:2): 0.39; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 4.81 (d, *J*= 1.9 Hz, 2H, C*H*$_2$O), 6.31 (t, *J*= 1.9 Hz, 1H, C*H*CO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm:

75.3 (CH_2), 122.3 (*C*HCO), 146.4 (*C*Br), 172.1 (CO_2R); **IR** (KBr) ν cm^{-1}: 1742 (C=O); 1598 (C=C); **LRMS** (EI^+) *m/z*: 164/162 (M, 90%); 83 (M-Br, 100%).

4-But-3-enyl-5*H*-furan-2-one 131[127]



$C_8H_{10}O_2$

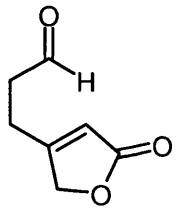
M= 138.16 $g.mol^{-1}$

To magnesium turnings (0.38 g, 15.3 mmol) and a small piece of iodine covered with anhydrous tetrahydrofuran (5 mL), were added at room temperature under nitrogen a small portion (<1/10) of homoallylic bromide (2.07 g, 15.3 mmol) in 14 mL of tetrahydrofuran. The remainder of the bromide was added dropwise over 1 h and stirring was continued at room temperature until complete disparition of the magnesium. The supernatant solution of the Grignard reagent was added at 0°C to anhydrous zinc bromide (3.45 g, 15.3 mmol) dissolved in 14 mL of tetrahydrofuran by using a double-tipped needle. After stirring for 30 min at 0°C, the reaction mixture was allowed to warm up to room temperature and the supernatant was added to a suspension of tetrakis(triphenylphosphine)palladium (0) (530 mg, 0.46 mmol) in 15 mL of tetrahydrofuran, followed by the addition of 4-bromo-5*H*-furan-2-one **130** (2.5 g, 15.3 mmol) in 15 mL of tetrahydrofuran. After the reaction mixture was stirred first at 0°C (1 h) and then at room temperature (overnight), it was quenched with saturated aqueous NH_4Cl, extracted with *n*-hexane, washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After filtration and evaporation of the volatile compounds under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (80:20) to give **131** (2.05 g, 54%) as a yellow oil.

Rf (P.E./EtOAc, 8:2): 0.33; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.50-2.57 (m, 2H, CH_2=CHCH_2), 2.70 (td, *J*= 7.4 Hz, *J*= 1.5 Hz, 2H, CH_2=CHCH_2CH_2), 4.93 (d, *J*=

1.5 Hz, 2H, CH_2O), 5.23-5.31 (m, 2H, CH=CH_2), 5.95-6.06 (m, 1H, CH_2=C*H*), 6.04-6.06 (m, 1H, C*H*CO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 28.1 (*C*H_2), 31.4 (*C*H_2CH=CH_2), 73.4 (*C*H_2O), 116.2 (*C*HCO), 116.9 (*C*H_2=CH), 136.4 (*C*H=CH_2), 169.9 (*C*=CHCO), 174.3 (*C*O_2R); **FTIR** (film) ν cm^{-1}: 2854, 1750 (C=O), 1630 (C=C); **LRMS** (ES^+) *m/z:* 161 (M+Na, 10%), 139 (M+H, 100%); **HRMS** (ES^+) *m/z:* Requires 161.0577 for $C_8H_{10}O_2Na$ (M+Na), found 161.0578.

3-(5-Oxo-2,5-dihydrofuran-3-yl)propionaldehyde 129



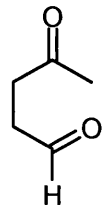
$C_7H_8O_3$
M= 140.13 $g.mol^{-1}$

A solution of 4-but-3-enyl-5*H*-furan-2-one **131** (0.6 g, 4.3 mmol) and pyridine (0.2 mL, 1% vol) in anhydrous dichloromethane (20 mL) was cooled to -78°C. A stream of ozone was bubbled through the solution, and the reaction was carefully monitored by TLC. After consumption of the starting material the flask was flushed with nitrogen. Dimethylsulfide was added (0.27 g, 43.4 mmol) and the mixture was allowed to warm to room temperature overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with EtOAc to afford aldehyde **129** (0.33 g, 49%) as a yellow oil.

Rf (EtOAc): 0.35; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.50-2.57 (m, 2H, C$H_2$$CH_2$CHO), 2.70 (t, *J*=7.4 Hz, 2H, CH_2CHO), 4.93 (d, *J*=1.5 Hz, 2H, OCH_2), 6.04-6.06 (m, 1H, =C*H*CO_2R), 9.79 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.1 (*C*$H_2$$CH_2$CHO), 41.4 (*C*$H_2$CHO), 73.4 (O$CH_2$), 116.4 (=*C*H$CO_2$R), 168.7 (*C*=CH$CO_2$R), 173.8 (*C*$O_2$R), 199.4 (*C*HO); **FTIR** (film) ν cm^{-1}: 2853, 1744, 1636,

1391, 1182; **HRMS** (FAB^+) *m/z:* Requires 141.05516 for $C_7H_9O_3$ (M+H), found 141.05505.

4-Oxo-pentanal 133[128]

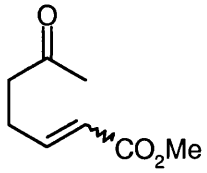


$C_5H_8O_2$

M= 100.11 $g.mol^{-1}$

Ozone was bubbled through a solution of 5-hexen-2-one (8.0 g, 82 mmol) and sodium bicarbonate (13.7 g, 163 mmol) in 160 mL of 1:1 methanol/dichloromethane at -78°C during 5 h. Dimethylsulfide was added (50 g, 810 mmol) and the mixture was allowed to warm to room temperature overnight. The resulting crude reaction mixture was diluted with brine (200 mL) and extracted with ether. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude oil was immediately used in the next step without further purification.

Methyl 6-oxo-2-heptenoate 132[125]



$C_8H_{12}O_3$

M= 156.18 $g.mol^{-1}$

A suspension of 80% sodium hydride dispersion in mineral oil (1.8 g, 60 mmol) in 70 mL of dry tetrahydrofuran under positive nitrogen pressure was stirred in an ice

bath while trimethylphosphonoacetate (9.1 g, 50 mmol) in 70 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for further 1 h at 0°C. Then, a solution of crude 4-oxo-pentanal **133** (5.0 g, 50 mmol) in 100 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for 15 min, slowly brought to reflux and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford the desired product (4.62 g, 37% over two steps) as two separable diastereomers in a *E:Z* 3.6:1 ratio as yellow oils.

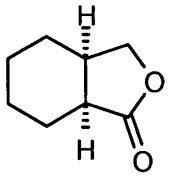
***E* isomer (*E*)-132**

Rf (P.E./EtOAc, 8:2): 0.25; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.35 (s, 3H, CH_3), 2.62-2.70 (qd, *J*=6.8 Hz, *J*=1.6 Hz, 2H, CH_2CH=), 2.81 (t, *J*=6.8 Hz, 2H, CH_2CO), 3.91 (s, 3H, OCH_3), 6.03 (dt, *J*=15.6 Hz, *J*=1.6 Hz, 1H, $CHCO_2CH_3$), 7.11 (dt, *J*=15.6 Hz, *J*=6.8 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.4 (CH_2), 30.3 (CH_3), 41.9 (CH_2), 51.8 (OCH_3), 122.1 (=$CHCO_2CH_3$), 147.8 (CH=$CHCO_2CH_3$), 167.2 (CO_2CH_3), 207.0 ($COCH_3$); **FTIR** (film) ν cm^{-1}: 2999, 2953, 1720 (C=O), 1658 (C=C), 1437, 1367, 1275, 1160; **LRMS** (EI^+) *m/z*: 157 (M+H, 55%), 124 (90%), 113 (M-$COCH_3$, 100%), 97 (M-CO_2CH_3, 30%), 81 (70%), 43 (95%).

***Z* isomer (*Z*)-132**

Rf (P.E./EtOAc, 8:2): 0.30; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.31 (s, 3H, CH_3), 2.72 (t, *J*=7.2 Hz, 2H, CH_2CO), 3.01 (qd, *J*=7.2 Hz, *J*=1.4 Hz, 2H, CH_2CH=), 3.83 (s, 3H, OCH_3), 5.92 (dt, *J*=11.5 Hz, *J*=1.4 Hz, 1H, $CHCO_2CH_3$), 6.37 (dt, *J*=11.5 Hz, *J*=7.2 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 23.7 (CH_2), 30.1 (CH_3), 43.0 (CH_2), 51.4 (OCH_3), 120.6 (=$CHCO_2CH_3$), 148.8 (CH=$CHCO_2CH_3$), 167.0 (CO_2CH_3), 207.8 ($COCH_3$).

cis-Hexahydro-isobenzofuran-1-one 135[226]



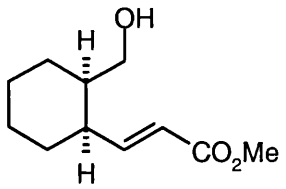
$C_8H_{12}O_2$

M= 140.18 g.mol^{-1}

To a cold (0°C) stirred suspension of sodium borohydride (3.7 g, 97 mmol) in anhydrous tetrahydrofuran (20 mL), was added, over 30 min, a solution of *cis*-1,2-cyclohexanecarboxylic anhydride (10.0 g, 65 mmol) in dry tetrahydrofuran (45 mL). The resulting solution was allowed to warm to room temperature and stirred for a further 3.5 h. The solution was then cooled to 0°C and quenched by the addition of aqueous hydrochloric acid 6N. The upper organic layer was separated. The aqueous layer was then extracted with ether (3 x 75 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford a colourless oil of sufficient purity for further use (7.19 g, 70%).

Rf (P.E./EtOAc, 6:4): 0.60; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.98-1.05 (m, 3H, CH_2), 1.34-1.45 (m, 3H, CH_2), 1.57-1.60 (m, 1H, CH_2), 1.86-1.91 (m, 1H, CH_2), 2.18-2.26 (m, 1H, CH), 2.39-2.41 (m, 1H, CH), 3.72 (d, J=8.8 Hz, 1H, CH_aH_bO), 3.97 (dd, J=8.8 Hz, J=5.0 Hz, 1H, CH_aH_bO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.9 (*C*H_2), 23.3 (*C*H_2), 23.8 (*C*H_2), 27.6 (*C*H_2), 35.8 (*C*H), 39.8 (*C*H), 72.1 (*C*H_2O), 178.8 (*C*O_2R); **FTIR** (film) ν cm^{-1}: 1770 (C=O); **LRMS** (EI$^+$) *m/z*: 140 (M, 11%), 95 (6%), 85 (16%), 81 (100%).

Methyl (*E*)-*cis*-3-(2-hydroxymethyl-cyclohexyl)-acrylate 136



$C_{11}H_{18}O_3$

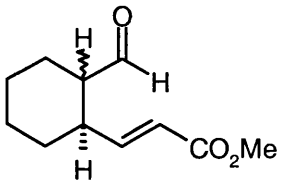
M= 198.12 g.mol^{-1}

To a stirred solution of hexahydro-isobenzofuran-1-one **135** (5.5 g, 38.7 mmol) in 100 mL of anhydrous ether at -20°C under positive nitrogen pressure, DIBAL (1.22 M solution in toluene) (33.3 mL, 40.6 mmol) was added dropwise over 1 h. The resulting solution was stirred at -20°C for an additional 0.5 h, and was then quenched by the addition of methanol (30 mL). The solution was allowed to warm to room temperature and stirred overnight. The resulting suspension was diluted with 50 mL of 30% aqueous solution of Rochelle's salt and was stirred for 30 min. The organic layer was separated and washed with 30% aqueous solution of Rochelle's salt. The combined aqueous layers were extracted with ether. The organic layers were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford the crude lactol that was added to a stirred solution of carbomethoxymethylene triphenylphosphorane (18.55 g, 55 mmol) in 150 mL of dry acetonitrile and heated at reflux under a nitrogen atmosphere for 2 days. The heat was removed and most of the solvent was removed *in vacuo*. Ether (25 mL) was added and the mixture was stirred for an additional 2 h. The resulting mixture was filtered and the filtrate washed with 15 mL of ether. The solvent was removed *in vacuo* and 20 mL of 70% ether in pentane was added. After stirring for further 30 min, the suspension was filtered again and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the alcohol **136** (5.22 g, 68%) as a single *E* diastereoisomer as a colourless oil.

Rf (P.E./EtOAc, 8:2): 0.33; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.30-1.74 (m, 8H, C*H*$_2$), 1.86-1.97 (m, 1H, C*H*CH$_2$OH), 2.72-2.78 (m, 1H, C*H*CH=), 3.52 (d, *J*=7.2

Hz, 2H, CH_2OH), 3.80 (s, 3H, OCH_3), 5.95 (dd, *J*=15.6 Hz, *J*=0.8 Hz, 1H, =C*H*CO_2CH_3), 7.23 (dd, *J*=15.6 Hz, *J*=9.0 Hz, 1H, C*H*=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.7 (*C*H_2), 25.1 (*C*H_2), 25.5 (*C*H_2), 30.7 (*C*H_2), 29.7 (*C*HCH_2OH), 43.0 (*C*HCH=), 51.8 (O*C*H_3), 65.3 (*C*H_2OH), 121.9 (=*C*HCO_2CH_3), 150.4 (*C*H=$CHCO_2CH_3$), 167.4 (*C*O_2CH_3); **FTIR** (film) ν cm^{-1}; 3423 (O-H), 2928, 2858, 1707 (C=O), 1649 (C=C), 1437, 1375, 1271, 1238, 1172; **LRMS** (EI^+) *m/z:* 198 (M, 3%), 167 (M-OCH_3, 53%), 81 (95%), 67 (100%); **HRMS** (EI^+) *m/z:* Requires 198.12558 for $C_{11}H_{18}O_3$ (M), found 198.12538.

Methyl (*E*)-3-(2-formyl-cyclohexyl)-acrylate 134



$C_{11}H_{16}O_3$

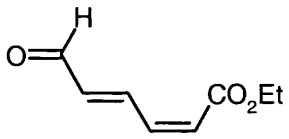
M= 196.11 $g.mol^{-1}$

To a stirred suspension of pyridinium chlorochromate (1.95 g, 9.1 mmol) and celite (2.1 g) in 15 mL of anhydrous dichloromethane, was added at room temperature and under a positive pressure of nitrogen, a solution of methyl (*E*)-*cis*-3-(2-hydroxymethyl-cyclohexyl)-acrylate **136** (1.2 g, 6.1 mmol) in 3 mL of dichloromethane. The reaction mixture was stirred for 2 h at room temperature and was then diluted with 50 mL of ether. The resulting suspension was filtered through a short pad of Florisil®, rinsed with several portions of ether and the solvent concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford aldehyde **134** (0.90 g, 76%) as a mixture of diastereoisomers (*cis:trans* 6:1) as a colourless oil.

Rf (P.E./EtOAc, 8:2): 0.67; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.52-1.98 (m, 8H, CH_2, *cis* + *trans*), 2.28-2.37 (m, 1H, C*H*CHO, *trans*), 2.49-2.61 (m, 1H, C*H*CH=, *trans*), 2.64-2.67 (m, 1H, C*H*CHO, *cis*), 2.86-2.89 (m, 1H, C*H*CH=, *cis*), 3.79 (s, 3H,

OCH_3, *trans*), 3.80 (s, 3H, OCH_3, *cis*), 5.91 (dd, *J*=15.8 Hz, *J*=1.2 Hz, 1H, $=CHCO_2CH_3$, *trans*), 5.94 (dd, *J*=15.8 Hz, *J*=1.3 Hz, 1H, $=CHCO_2CH_3$, *cis*), 6.94 (dd, *J*=15.8 Hz, *J*=8.0 Hz, 1H, $CH=CHCO_2CH_3$, *trans*), 7.20 (dd, *J*=15.8 Hz, *J*=7.3 Hz, 1H, $CH=CHCO_2CH_3$, *cis*), 9.64 (d, *J*=2.3 Hz, 1H, CHO, *trans*), 9.73 (s, 1H, CHO, *cis*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 23.7 (CH_2, *cis*), 23.9 (CH_2, *cis*), 24.3 (CH_2, *cis*), 24.9 (CH_2, *trans*), 25.1 (CH_2, *trans*), 25.9 (CH_2, *trans*), 29.6 (CH_2, *cis*), 31.3 (CH_2, *trans*), 39.5 (CHCHO, *cis*), 40.5 (CHCHO, *trans*), 51.9 (OCH_3, *cis* + *trans*), 52.2 (CHCH=, *cis*), 54.2 (CHCH=, *trans*), 121.5 ($=CHCO_2CH_3$, *trans*), 122.0 ($=CHCO_2CH_3$, *cis*), 149.7 ($CH=CHCO_2CH_3$, *cis*), 151.0 ($CH=CHCO_2CH_3$, *trans*), 167.1 (CO_2CH_3, *cis* + *trans*), 203.6 (CHO, *trans*), 204.1 (CHO, *cis*); **FTIR** (film) ν cm^{-1}: 2937, 2858, 1719 (C=O), 1655 (C=C), 1437, 1277, 1175; **LRMS** (FAB^+) *m/z:* 197 (M+H, 15%), 181 (M-CH_3, 24%), 165 (M-OCH_3, 30%); **HRMS** (FAB^+) *m/z:* Requires 197.11776 for $C_{11}H_{17}O_3$ (M+H), found 197.11916.

Ethyl (2*Z*,4*E*)-6-oxo-2,4-hexadienoate 138b



$C_8H_{10}O_3$

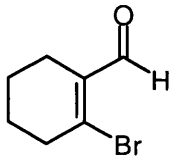
M= 154.16 $g.mol^{-1}$

A mixture of propenal (24 mg, 0.44 mmol), (*Z*)-ethyl 3-iodoacrylate (100 mg, 0.44 mmol), silver carbonate (120 mg, 0.44 mmol) and palladium acetate (5 mg, 0.022 mmol) in dry acetonitrile (4 mL), was stirred at room temperature for 3 days. After this time, the reaction mixture was filtered through a short pad of celite washing with ethyl acetate and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford aldehyde **138b** (37 mg, 56%) as a pale yellow oil.

Rf (P.E./EtOAc, 9:1): 0.25; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.26 (t, *J*=7.1 Hz, 3H, OCH_2CH_3), 4.18 (q, *J*=7.1 Hz, 2H, OCH_2CH_3), 5.98 (d, *J*=11.3 Hz, 1H,

=C*H*CO_2Et), 6.23 (dd, *J*=15.6 Hz, *J*=7.9 Hz, 1H, =C*H*CHO), 6.69 (t, *J*=11.3 Hz, 1H, C*H*=CHCO_2CH_3), 8.32 (dd, *J*=15.6 Hz, *J*=11.3 Hz, 1H, C*H*=CHCHO), 9.66 (d, *J*=7.9 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 13.9 (*C*H_3), 60.5 (O*C*H_2CH_3), 125.5 (=*C*HCO_2Et), 135.2 (*C*H=CHCO_2Et), 137.8 (=*C*HCHO), 146.0 (*C*H=CHCHO), 164.8 (*C*O_2Et), 193.8 (*C*HO); **FTIR** (film) ν cm^{-1}: 1715 (C=O), 1675, 1620 (C=C), 1580; **LRMS** (EI^+) *m/z:* 154 (M, 23%), 125 (M-Et, 100%); **HRMS** (EI^+) *m/z:* Requires 154.0630 for $C_8H_{10}O_3$ (M), found 154.0624.

2-Bromo-1-cyclohexenecarboxaldehyde 139[132b]



C_7H_9OBr

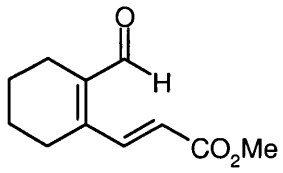
M= 189.06 $g.mol^{-1}$

A stirred solution of dimethylformamide (20.18 g, 276 mmol) in anhydrous dichloromethane (75 mL) was cooled in an ice bath while phosphorus tribromide (67.2 g, 248 mmol) was added dropwise over a 15 min period. The resulting yellow suspension was warmed to room temperature and stirred for a further 20 min. A solution of cyclohexanone (9.0 g, 92 mmol) in anhydrous dichloromethane (25 mL) was added dropwise over 10 min and stirring was continued for 12 h at room temperature. The dark-red solution was poured carefully into iced water (100 mL). Solid $NaHCO_3$ was added to neutralise the acids and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) afforded the desired compound **139** (7.0 g, 40%) as an orange oil.

Rf (P.E./EtOAc, 9:1): 0.76; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.81-1.90 (m, 4H, CH_2), 2.40-2.42 (m, 2H, CH_2C=), 2.85-2.89 (m, 2H, CH_2C=), 10.15 (s, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.5 (*C*H_2), 24.6 (*C*H_2), 25.4 (*C*H_2), 39.2

(CH_2), 135.7 (=CCHO), 144.0 (=CBr), 194.1 (CHO); **FTIR** (film) ν cm^{-1}: 1681 (C=O), 1621 (C=C); **LRMS** (EI^+) *m/z:* 190 (M+H, 10%), 111 (M-Br, 19%), 57 (100%); **HRMS** (EI^+) *m/z:* Requires 190.98945 for $C_7H_{10}OBr$ (M+H), found 190.98899.

Methyl (*E*)-3-(2-formyl-cyclohex-1-enyl)-acrylate 137b



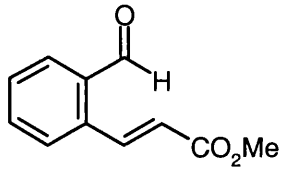
$C_{11}H_{14}O_3$

M= 194.10 $g.mol^{-1}$

A mixture of 2-bromo-cyclohexene-1-carboxaldehyde **139** (1.5 g, 7.9 mmol), methyl acrylate (0.81 g, 9.5 mmol), triethylamine (0.96 g, 9.5 mmol), palladium acetate (18 mg, 0.079 mmol) and triphenylphosphine (42 mg, 0.158 mmol), was heated at reflux under a positive pressure of nitrogen for 3 days. The heat was removed and the reaction mixture was diluted with ether and filtered. The solids were washed several times with small portions of ether, and the filtrate was concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) to afford aldehyde **137b** (0.85 g, 55%) as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.39; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.54-1.67 (m, 4H, CH_2), 2.29-2.36 (m, 4H, CH_2), 3.73 (s, 3H, OCH_3), 6.07 (d, *J*=15.6 Hz, 1H, =$CH$$CO_2CH_3$), 8.22 (d, *J*=15.6 Hz, 1H, CH=$CHCO_2CH_3$), 10.35 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.5 (CH_2), 22.0 (CH_2), 23.8 (CH_2), 27.3 (CH_2), 52.3 (OCH_3), 122.2 (=$C$$HCO_2CH_3$), 138.9 ($C$H=$CHCO_2CH_3$), 141.0 (=$C$CHO), 148.2 ($C$=CCHO), 167.2 ($CO_2CH_3$), 190.3 ($C$HO); **FTIR** (film) ν cm^{-1}: 2937, 2864, 1720 (C=O), 1668 (C=C), 1622, 1587, 1435, 1375, 1300, 1277, 1175; **LRMS** (EI^+) *m/z:* 195 (M+H, 8%), 165 (38%), 135 (100%); **HRMS** (EI^+) *m/z:* Requires 195.10210 for $C_{11}H_{15}O_3$ (M+H), found 195.10196.

Methyl (*E*)-3-(2'-formylphenyl)-propenoate 140[133]



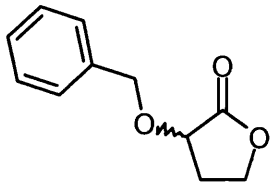
$C_{11}H_{10}O_3$

M= 190.19 g.mol^{-1}

Tetrabutylammonium bromide (0.56 g, 1.7 mmol), potassium carbonate (0.80 g, 5.8 mmol), palladium acetate (156 mg, 0.69 mmol) and methyl acrylate (2.97 g, 34.8 mmol) were stirred for 5 min under nitrogen, forming a dark orange solution. A solution of *o*-bromobenzaldehyde (1.28 g, 6.9 mmol) in 4 mL of degassed dimethylformamide was then added and the reaction was stirred at 70°C for 16 h. The resulting mixture was diluted with ethyl acetate and filtered through a short pad of celite. The filtrate was diluted with water and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (90:10) enabled *o*-bromobenzaldehyde to be removed from the crude mixture, with the desired aldehyde being isolated in 69% yield (based on recovered starting material).

Rf (P.E./EtOAc, 9:1): 0.32; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 3.85 (s, 3H, OCH_3), 6.40 (d, *J*=15.9 Hz, 1H, $=CHCO_2CH_3$), 7.56-7.91 (m, 4H, Ph), 8.55 (d, *J*=15.9 Hz, 1H, $CH=CHCO_2CH_3$), 10.31 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 52.3 (OCH_3), 123.2 ($=CHCO_2CH_3$), 128.4 (Ph), 130.3 (Ph), 132.7 (Ph), 134.2 (Ph), 134.3 (Ph), 137.0 (Ph), 141.6 ($CH=CHCO_2CH_3$), 167.0 (CO_2CH_3), 192.1 (CHO); **FTIR** (film) ν cm^{-1}: 1728 (C=O), 1699 (Ph), 1621 (Ph); **LRMS** (EI$^+$) *m/z:* 175 (M-CH_3, 3%), 131 (M-CO_2CH_3, 100%), 103 (32%), 77 (35%).

α-Benzyloxy-γ-butyrolactone 143[227]



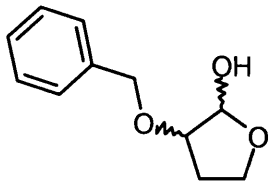
$C_{11}H_{12}O_3$

M= 192.08 g.mol^{-1}

A suspension of 60% sodium hydride dispersion in mineral oil (2.15 g, 54 mmol) and α-hydroxy-γ-butyrolactone (5.0 g, 49 mmol) in dry tetrahydrofuran (50 mL) was stirred at 0 -5°C for 0.5 h. Benzyl bromide (7.3 mL, 61.3 mmol) and tetrabutylammonium iodide (1.18 g, 4.9 mmol) were then added. The resulting suspension was stirred at ambient temperature for 3 h, and then a saturated $NaHCO_3$ solution (50 mL) was cautiously added. The aqueous layer was extracted with dichloromethane and the combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting brown oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) to afford the desired product **143** (5.70 g, 61%) as a colourless oil.

Rf (P.E./EtOAc, 6:4): 0.34; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 2.24-2.56 (m, 2H, CH_2CH_2O), 4.15-4.26 (m, 2H, OCH_2CH_2), 4.43 (t, *J*=8.0 Hz, 1H, OC*H*CH_2), 4.74 (d, *J*=12.0 Hz, 1H, PhCH_aH$_b$O), 4.95 (d, *J*=12.0 Hz, 1H, PhCH$_a$$H_b$O), 7.30-7.42 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 29.9 (*C*H_2), 65.5 (*C*H_2OCO), 72.2 (OCH_2Ph), 72.5 (O*C*H), 128.1 (Ph), 128.2 (Ph), 128.6 (Ph), 137.0 (Ph), 175.0 (*C*O_2R); **FTIR** (film) ν cm^{-1}: 1781 (C=O), 1175, 1142, 699; **LRMS** (ES$^+$) *m/z:* 210 (M+NH_4, 100%), 193 (M+H, 31%), **HRMS** (ES$^+$) *m/z:* Requires 193.0852 for $C_{11}H_{13}O_3$ (M+H), found 193.0860.

α-Benzyloxy-γ-butyrolactol 144[228]



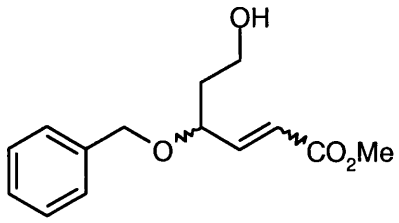
$C_{11}H_{14}O_3$

M= 194.08 g.mol^{-1}

DIBAL (1.22 M solution in toluene) (13.9 mL, 21 mmol) was added dropwise to a stirred solution of α-benzyloxy-γ-butyrolactone **143** (3.66 g, 19 mmol) in toluene (55 mL) at -75°C under positive nitrogen pressure. The resulting solution was stirred at -70°C for 3 h, and was then quenched by the addition of methanol (1.5 mL). The mixture was allowed to warm –10 -0°C, treated with 20% w/v aqueous solution of Rochelle's salt (50 mL) and the resulting mixture stirred at ambient temperature for 30 min. The biphasic mixture was separated, the aqueous layer extracted with toluene and the combined organic layers washed with water. The combined water washes were back extracted with toluene and the combined organics dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford a pale green oil of sufficient purity for further use (3.19 g, 87%).

Rf (P.E./EtOAc, 6:4): 0.27; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.96-2.28 (m, 2H, C*H*$_2$CH$_2$O), 2.49 (d, *J*=2.5 Hz, 1H, O*H*), 3.80-3.86 (m, 1H, BnOC*H*CH$_2$, *trans*), 4.00-4.12 (m, 3H, BnOC*H*CH$_2$, *cis* and C*H*$_2$O), 4.57 (s, 2H, PhC*H*$_2$O, *cis*), 4.63 (d, *J*=6.0 Hz, 2H, PhC*H*$_2$O, *trans*), 5.35 (dd, *J*=17.0 Hz, *J*=6.0 Hz, 1H, C*H*OH, *trans*), 5.45 (d, *J*=2.5 Hz, 1H, C*H*OH, *cis*), 7.25-7.40 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 29.9 (*C*H$_2$, *cis* + *trans*), 64.8 (*C*H$_2$O, *trans*), 67.0 (*C*H$_2$O, *cis*), 71.4 (O*C*H$_2$Ph, *cis*), 72.5 (O*C*H$_2$Ph, *trans*), 78.1 (O*C*H, *trans*), 83.4 (O*C*H, *cis*), 96.3 (HO*C*H, *trans*), 100.7 (HO*C*H, *cis*), 127.9 (Ph, *cis*), 128.1 (Ph, *trans*), 128.2 (Ph, *cis* + *trans*), 128.5 (Ph, *cis*), 128.6 (Ph, *trans*), 137.2 (Ph, *trans*), 137.9 (Ph, *cis*); **FTIR** (film) ν cm^{-1}: 3397 (O-H), 1071, 739, 699; **LRMS** (ES$^+$) *m/z:* 195 (M+H, 100%), 218 (M+NH$_4$, 67%), 177 (M-H$_2$O, 42%).

Methyl 6-hydroxy-4-benzyloxy-2-hexenoate 146



$C_{14}H_{18}O_4$

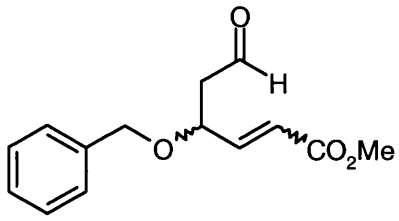
M= 250.28 g.mol^{-1}

A solution of α-benzyloxy-γ-butyrolactol **144** (1.8 g, 9.3 mmol) in toluene (10 mL) was added to a stirred suspension of carbomethoxymethyl triphenylphosphonium bromide (4.25 g, 10 mmol) and potassium *t*-butoxide (1.12 g, 10 mmol) in dry tetrahydrofuran (40 mL) which were premixed at 0°C for 30 min. The resulting suspension was heated at 80°C for 3 h, then cooled to ambient temperature, diluted with water (30 mL), and extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. Purification of the pale green oil by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) afforded the title compound as a mixture of isomers (1.89 g, 78%) in a *Z:E* 1:4.3 ratio as a colourless oil.

Rf (P.E./EtOAc, 6:4): 0.29; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.82-1.88 (m, 2H, C*H*$_2$CH$_2$OH), 3.73-3.79 (m, 5H, C*H*$_2$OH and OC*H*$_3$), 4.23 (q, *J*=7.0 Hz, 1H, BnOC*H*, *trans*), 4.41-4.57 (dd, *J*=11.0 Hz, *J*=6.0 Hz, 2H, PhC*H*$_2$O, *cis*), 4.31-4.65 (dd, *J*=11.0 Hz, *J*=6.0 Hz, 2H, PhC*H*$_2$O, *trans*), 5.19-5.25 (q, *J*=7.0 Hz, 1H, BnOC*H*, *cis*); 5.95 (d, *J*=12.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 6.05-6.10 (d, *J*=17.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 6.25 (dd, *J*=12.0 Hz, *J*=6.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.90 (dd, *J*=17.0 Hz, *J*=6.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*), 7.28-7.38 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 37.2 (*C*H$_2$CH$_2$OH, *trans*), 37.3 (*C*H$_2$CH$_2$OH, *cis*), 51.7 (O*C*H$_3$, *cis*), 51.8 (O*C*H$_3$, *trans*), 59.8 (*C*H$_2$OH, trans), 60.0 (*C*H$_2$OH, cis), 71.4 (*C*HOBn, *trans*), 71.7 (*C*HOBn, *cis*), 74.5 (PhCH$_2$O, *cis*), 76.7 (PhCH$_2$O, *trans*), 121.3 (=*C*HCO$_2$CH$_3$, *cis*), 122.0 (=*C*HCO$_2$CH$_3$, *trans*), 127.9 (Ph, *trans*), 128.0 (Ph, *cis*), 128.5 (Ph, *cis*), 128.6 (Ph, *trans*), 137.6 (Ph, *trans*), 137.7 (Ph, *cis*),

147.7 (*C*H=CHCO$_2$CH$_3$, *trans*), 150.9 (*C*H=CHCO$_2$CH$_3$, *cis*), 166.5 (*C*O$_2$CH$_3$, *trans*), 166.6 (*C*O$_2$CH$_3$, *cis*); **FTIR** (film) ν cm^{-1}: 3431 (O-H), 1730 (C=O), 738, 699; **LRMS** (ES$^+$) *m/z:* 268 (M+NH$_4$, 38%), 251 (M+H, 100%), 233 (17%), 210 (13%); **HRMS** (ES$^+$) *m/z:* Requires 268.1549 for $C_{14}H_{22}NO_4$ (M+NH$_4$), found 268.1549.

Methyl 6-oxo-4-benzyloxy-2-hexenoate 142



$C_{14}H_{16}O_4$

M= 248.11 g.mol^{-1}

To a stirred suspension of pyridinium chlorochromate (2.1 g, 9.6 mmol) in 10 mL of anhydrous dichloromethane, was added at room temperature and under a positive pressure of nitrogen, a solution of methyl 6-hydroxy-4-benzyloxy-2-hexenoate **146** (1.6 g, 6.4 mmol) in 10 mL of dichloromethane. The reaction mixture was stirred for 12 h at room temperature and the solvent removed under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) which allowed separation of *cis* and *trans* isomers as clear oils (1.08 g, 67%).

***Z* isomer (Z)-142**

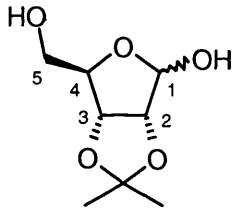
Rf (P.E./EtOAc, 8:2): 0.48; **^{1}H NMR** (CDCl$_3$, 400 MHz) δ ppm: 2.60-2.84 (m, 2H, C*H*$_2$CHO), 3.75 (s, 3H, OC*H*$_3$), 4.45-4.63 (dd, *J*=12.0 Hz, *J*=6.0 Hz, 2H, PhC*H*$_2$O), 5.50-5.63 (m, 1H, BnOC*H*CH$_2$); 6.00 (d, *J*=12.0 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.80-6.95 (m, 1H, C*H*=CHCO$_2$CH$_3$), 7.25-7.38 (m, 5H, Ph), 9.75 (s, 1H, C*H*O); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ ppm: 48.4 (*C*H$_2$CHO), 51.6 (O*C*H$_3$), 71.0 (*C*HOBn), 71.7 (Ph*C*H$_2$O), 121.5 (=*C*HCO$_2$CH$_3$), 127.9 (Ph), 128.4 (Ph), 137.7 (Ph), 149.7 (*C*H=CHCO$_2$CH$_3$), 166.1 (*C*O$_2$CH$_3$), 200.8 (*C*HO); **FTIR** (film) ν cm^{-1}: 2952, 1725

(C=O), 698; **LRMS** (ES^+) *m/z:* 514 ($2M+NH_4$, 43%), 266 ($M+NH_4$, 100%), 249 (M+H, 27%), 210 (14%); **HRMS** (ES^+) *m/z*: Requires 249.1116 for $C_{14}H_{17}O_4$ (M+H), found 249.1127.

***E* isomer (*E*)-142**

Rf (P.E./EtOAc, 8:2): 0.45; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 2.68-2.90 (m, 2H, CH_2CHO), 3.77 (s, 3H, OCH_3), 4.42-4.65 (dd, *J*=12.0 Hz, *J*=6.0 Hz, 2H, $PhCH_2O$), 5.50-5.63 (m, 1H, $BnOCHCH_2$); 6.15 (d, *J*=17.0 Hz, 1H, $=CHCO_2CH_3$), 6.85-6.98 (m, 1H, $CH=CHCO_2CH_3$), 7.21-7.45 (m, 5H, Ph), 9.78 (s, 1H, CHO); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 48.4 (CH_2CHO), 51.8 (OCH_3), 71.5 (CHOBn), 73.0 ($PhCH_2O$), 122.7 ($=CHCO_2CH_3$), 127.9 (Ph), 128.5 (Ph), 137.3 (Ph), 146.2 ($CH=CHCO_2CH_3$), 166.3 (CO_2CH_3), 199.0 (CHO).

2,3-*O*-isopropylidene-D-ribose 153[229a]



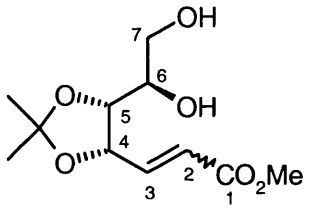
$C_8H_{14}O_5$

M= 190.19 g.mol^{-1}

2,2-Dimethoxypropane (61.50 mL, 0.5 mol) was added to a stirred suspension of (D)-(-)-ribose (50.0 g, 0.33 mmol) and *p*-toluenesulfonic acid (6.0 g, 0.033 mol) in acetone (1 L) at 0°C. After 1 h at room temperature, the reaction mixture was neutralised with an aqueous solution of K_2CO_3 (2 M). The organic layer was separated and the aqueous phase was extracted with EtOAc (6 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) to afford the desired product **153** (48.14 g, 76%) as a colourless oil.

Rf (EtOAc): 0.43; **^{1}H NMR** (DMSO, 400 MHz) δ ppm: 1.24 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.36-3.47 (m, 2H, H_5), 3.98 (dd, J=5.2 Hz, J=4.8 Hz, 1H, H_4), 4.43 (d, J=6.0 Hz, 1H, H_2), 4.68 (d, J=6.0 Hz, 1H, H_3), 5.16 (s, 1H, H_1); **^{13}C NMR** (DMSO, 100 MHz) δ ppm: 25.1 (*C*H_3), 26.8 (*C*H_3), 63.2 (*C*H_2), 82.3 (*C*H), 86.4 (*C*H), 86.8 (*C*H), 102.3 (O*C*OH), 111.5 (*C*$(CH_3)_2$); **FTIR** (film) ν cm^{-1}: 3366 (O-H), 2939, 2880, 1666 (C=O), 1383, 1300, 1211, 1043; **LRMS** (EI$^+$) *m/z:* 175 (M-CH_3, 55%), 173 (M-OH, 72%), 159 (M-CH_2OH, 20%), 85 (32%), 59 (100%); $[\alpha]^{24}_D$: -23.2° (*c* = 0.45, CH_2Cl_2), lit.,[229b]: -25.9° (*c* = 1.1, $CHCl_3$).

Methyl *cis*-2,3-dideoxy-4,5-*O*-isopropylidene-D-*ribo*-hept-2-enoate 154[230]



$C_{11}H_{18}O_6$

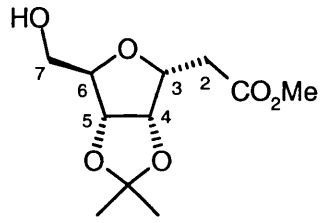
M= 246.25 g.mol^{-1}

To a stirred solution of lactol **153** (43 g, 226 mmol) in 430 mL of anhydrous dichloromethane was added carbomethoxymethylene triphenylphosphorane (83.2 g, 249 mmol) and the resulting mixture was stirred at room temperature under a nitrogen atmosphere for 5 h. The solvent was removed *in vacuo*. *t*-Butyl methyl ether (100 mL) was added and the mixture was stirred for an additional hour. The resulting mixture was filtered, the filtrate was washed with 25 mL of ether and the solvent was removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) to afford the alcohol **154** (33.4 g, 60%) as a mixture of diastereoisomers in a *E:Z* 1:6 ratio as a clear oil, together with methyl 2-(3,4-*O*-isopropylidene-α-D-ribofuranosyl)-acetate **157** which was obtained in 15% yield.

Rf (EtOAc): 0.36; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.38 (s, 3H, CH_3, *trans*), 1.39 (s, 3H, CH_3, *cis*), 1.50 (s, 3H, CH_3, *trans*), 1.51 (s, 3H, CH_3, *cis*), 3.47-3.83 (m,

3H, H_6 and H_7, *cis* + *trans*), 3.71 (s, 3H, OCH_3, *trans*), 3.77 (s, 3H, OCH_3, *cis*), 4.19 (t, *J*=8.0 Hz, 1H, H_5, *trans*), 4.35 (dd, *J*=8.3 Hz, *J*=6.4 Hz, 1H, H_5, *cis*), 4.88 (t, *J*=8.0 Hz, 1H, H_4, *trans*), 5.54 (dd, *J*=8.2 Hz, *J*=6.4 Hz, 1H, H_4, *cis*), 6.05 (d, *J*=12.0 Hz, 1H, H_2, *cis*), 6.19 (d, *J*=15.5 Hz, 1H, H_2, *trans*), 6.30 (dd, *J*=12.0 Hz, *J*=8.2 Hz, 1H, H_3, *cis*), 7.11 (dd, *J*=15.5 Hz, *J*=8.0 Hz, 1H, H_3, *trans*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 25.8 (*C*H_3, *trans*), 28.3 (*C*H_3, *trans*), 52.4 (*C*H_3O, *trans*), 64.7 (C_7, *trans*), 70.6 (O*C*H, *trans*), 75.2 (O*C*H, *trans*), 79.8 (O*C*H, *trans*), 110.0 (*C*$(CH_3)_2$, *trans*), 122.2 (C_2, *trans*), 146.8 (C_3, *trans*), 167.5 (C_1, *trans*); **FTIR** (film) ν cm^{-1}: 3495 (O-H), 1719 (C=O), 1647 (C=C); **LRMS** (EI^+) *m/z:* 246 (M, 5%), 231 (M-CH_3, 34%), 215 (M-OCH_3, 100%), 215 (M-CO_2CH_3, 67%); $[\alpha]^{24}_D$: -75° (c = 0.1, $CHCl_3$), lit.,[230]: -93° (c = 0.2, MeOH).

Methyl 3,6-anhydro-2-deoxy-4,5-*O*-isopropylidene–D-*allo*-heptonate 157[147]

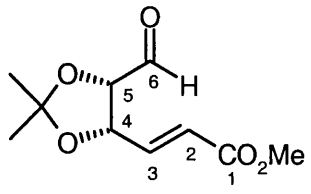


$C_{11}H_{18}O_6$

M= 246.25 $g.mol^{-1}$

Rf (EtOAc): 0.42; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.34 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.44-2.47 (m, 1H, O*H*), 2.63 (dd, *J*=16.0 Hz, *J*=6.8 Hz, 1H, H_2), 2.76 (dd, *J*=16.0 Hz, *J*=4.8 Hz, 1H, H_2), 3.63-3.69 (m, 1H, H_7), 3.71 (s, 3H, OCH_3), 3.80-3.83 (m, 1H, H_7), 4.08 (q, *J*=3.2 Hz, 1H, H_6), 4.26 (ddd, *J*=6.8 Hz, *J*=5.2 Hz, *J*=4.8 Hz, 1H, H_3), 4.54 (t, *J*=5.2 Hz, 1H, H_4), 4.72-4.75 (m, 1H, H_5); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 25.5 (*C*H_3), 27.4 (*C*H_3), 37.5 (C_2), 52.0 (O*C*H_3), 62.7 (C_7), 80.7 (C_3), 81.6 (C_5), 83.9 (C_4), 84.8 (C_6), 114.4 (*C*$(CH_3)_2$), 171.3 (*C*O_2CH_3); **FTIR** (film) ν cm^{-1}: 3469 (O-H), 2989, 2939, 1738 (C=O), 1439, 1383, 1259, 1213, 1078, 865; **LRMS** (ES^+) *m/z:* 515 (2M+Na, 26%), 269 (M+Na, 43%), 264 (M+NH_4, 100%), 247 (M+H, 92%); **HRMS** (ES^+) *m/z:* Requires 247.1169 for $C_{11}H_{19}O_6$ (M+H), found 247.1182; $[\alpha]^{24}_D$: +7.8° (c = 1.0, $CHCl_3$), lit.,[147]: +5.4° (c = 1.0, $CHCl_3$).

(4*S*,5*S*)-3-(5-Formyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-acrylic acid methyl ester 147b



$C_{10}H_{14}O_5$

M= 214.08 g.mol^{-1}

To a solution of alcohol **154** (13.0 g, 53 mmol) in dichloromethane (230 mL) at room temperature, was added sodium periodate (22.6 g, 106 mmol) with vigorous stirring, followed by the minimum volume of water required to effect solution. After 5 h, the organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40) to afford the desired product **147b** (5.08 g, 68%) as two separable diastereomers in a *E:Z* 1:6 ratio as colourless oils.

***Z* isomer (*Z*)-147b**

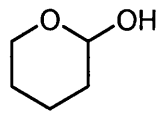
Rf (P.E./EtOAc, 6:4): 0.71; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.45 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.80 (dd, *J*=8.0 Hz, *J*=2.0 Hz, 1H, H_5), 5.82 (td, *J*=8.0 Hz, *J*=1.4 Hz, 1H, H_4), 5.99 (dd, *J*=12.0 Hz, *J*=1.4 Hz, 1H, H_2), 6.25 (dd, *J*=12.0 Hz, *J*=8.0 Hz, 1H, H_3), 9.49 (d, *J*=2.0 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 25.5 (*C*H_3), 27.6 (*C*H_3), 52.1 (O*C*H_3), 76.1 (C_5), 82.3 (C_4), 111.8 (*C*$(CH_3)_2$), 123.0 (C_2), 144.1 (C_3), 166.2 (C_1), 199.5 (C_6); **FTIR** (film) ν cm^{-1}: 1723 (C=O), 1659 (C=C); **LRMS** (EI$^+$) *m/z:* 214 (M, 20%), 185 (M-CHO, 35%), 127 (100%); **HRMS** (EI$^+$) *m/z:* Requires 214.08410 for $C_{10}H_{14}O_5$ (M), found 214.08389; $[\alpha]^{24}_D$: +92° (c = 0.85, $CHCl_3$).

***E* isomer (*E*)-147b**

Rf (P.E./EtOAc, 6:4): 0.65; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.46 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.52 (dd, *J*=8.0 Hz, *J*=2.0 Hz, 1H, H_5), 5.82

(m, 1H, H_4), 5.99 (dd, J=15.0 Hz, J=1.5 Hz, 1H, H_2), 6.84 (dd, J=15.0 Hz, J=8.0 Hz, 1H, H_3), 9.53 (d, J=2.0 Hz, 1H, C*H*O).

Tetrahydro-pyran-2-ol 179[155]



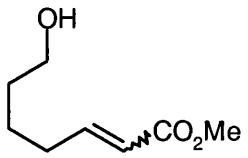
$C_5H_{10}O_2$

M= 102.13 g.mol^{-1}

In a 250 mL 3-necked flask were mixed water (75 mL), concentrated hydrochloric acid (6.25 mL) and 3,4-dihydropyran (25.0 g, 297 mmol). The mixture was stirred until the solution was homogenous and then stirred for a further 20 min. After the addition of a few drops of phenol-phthalein indicator, the acid was neutralised with 20% NaOH. The solution was extracted with ether (8 x 100 mL), the combined organic layers dried over $MgSO_4$ and concentrated *in vacuo*.
Distillation under reduced pressure (bp=120°C, 10 mmHg; lit.,[231] 70-81°C, 0.1 mmHg) afforded 2-hydroxy-tetrahydropyran (20.8 g, 69%) as a clear oil.

Rf (EtOAc): 0.55; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.41-1.47 (m, 4H, CH_2), 1.68-1.78 (m, 2H, CH_2CHOH), 3.45 (dt, J_{gem}=6.3 Hz, J_{cis}=4.2 Hz, 1H, CH_aH$_b$O), 3.94 (dt, J_{gem}=6.3 Hz, J_{trans}=2.0 Hz, 1H, CH$_a$$H_b$O), 4.50 (d, J=3.7 Hz, 1H, O*H*), 4.81 (dd, J_{cis}=2.6 Hz, J_{trans}=1.9, 1H, OC*H*OH); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 20.6 (*C*H$_2$), 25.7 (*C*H$_2$), 32.3 (*C*H$_2$), 64.2 (*C*H$_2$O), 94.8 (O*C*HO); **FTIR** (film) ν cm^{-1}: 3421 (O-H); **LRMS** (EI$^+$) *m/z*: 102 (M, 20%), 85 (M-OH, 31%), 56 (100%).

Methyl 7-hydroxo-2-heptenoate 180[232]



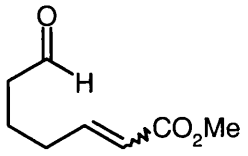
$C_8H_{14}O_3$

M= 158.19 g.mol^{-1}

To a solution of tetrahydropyran-2-ol **179** (4.0 g, 39.0 mmol) in dichloroethane (55 mL) was added carbomethoxymethylene triphenylphosphorane (13.1 g, 39.0 mmol). The resulting clear solution was heated at 60°C for 16 hours. The heat was removed and the solution was concentrated under reduced pressure. Diethyl ether was then added and the resulting white crystalline precipitate of $Ph_3P=O$ was removed by filtration and the filtrate concentrated *in vacuo.* The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (70:30) to yield the desired product (3.8 g, 62%) as a mixture of diastereomers in a *E:Z* 5.25:1 ratio. The product was isolated as a colourless liquid.

Rf (P.E./EtOAc, 6:4): 0.30; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.48-1.61 (m, 4H, C*H*$_2$, *trans* + *cis*), 2.21 (q, *J*=7.0 Hz, 2H, CH_2CH_2*H*$_2$CH=, *trans*), 2.65 (q, *J*=7.3 Hz, 2H, CH_2CH_2*H*$_2$CH=, *cis*), 3.62 (t, *J*=5.7 Hz, 2H, HOC*H*$_2$, *trans* + *cis*), 3.68 (s, 3H, OC*H*$_3$, *cis*), 3.69 (s, 3H, OC*H*$_3$, *trans*), 5.74 (d, *J*=11.5 Hz, 1H, CH=C*H*CO_2CH_3, *cis*), 5.80 (d, *J*=15.6 Hz, 1H, CH=C*H*CO_2CH_3, *trans*), 6.20 (dt, *J*=11.5 Hz, *J*=7.3 Hz, 1H, C*H*=$CHCO_2CH_3$, *cis*), 6.94 (dt, *J*=15.6 Hz, *J*=7.0 Hz, 1H, C*H*=$CHCO_2CH_3$, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 23.4 (*C*H$_2$, *trans*), 24.2 (*C*H$_2$, *cis*), 28.0 (*C*H$_2$, *cis*), 31.0 (*C*H$_2$, *trans*), 31.1 (*C*H$_2$, *cis*), 31.2 (*C*H$_2$, *trans*), 50.1 (O*C*H$_3$, *cis*), 50.5 (O*C*H$_3$, *trans*), 59.5 (*C*H$_2$OH, *cis*), 61.5 (*C*H$_2$OH, *trans*), 118.6 (CH=*C*HCO_2CH_3, *cis*), 120.3 (CH=*C*HCO_2CH_3, *trans*), 148.3 (*C*H=$CHCO_2CH_3$, *trans*), 149.4 (*C*H=$CHCO_2CH_3$, *cis*), 166.0 (*C*O$_2$CH$_3$, *trans*), 166.2 (*C*O$_2$CH$_3$, *trans*); **FTIR** (film) ν cm^{-1}: 3448 (O-H), 3054, 2986, 1722 (C=O), 1640 (C=C), 1422, 1265, 747, 705; **LRMS** (ES$^+$) *m/z*: 181 (M+Na, 17%), 159 (M+H, 100%); **HRMS** (ES$^+$) *m/z*: Requires 159.0997 for $C_8H_{15}O_3$ (M+H), found 159.1001.

Methyl 7-oxo-2-heptenoate 178[233]



$C_8H_{12}O_3$

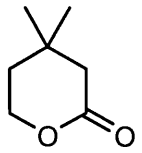
M= 156.18 g.mol^{-1}

A solution of methyl 6-hydroxy-2-heptenoate **180** (3.5 g, 22.0 mmol) in anhydrous dichloromethane (20 mL) was added in one portion to a stirred suspension of the oxidising agent pyridinium chlorochromate PCC (7.2 g, 33.0 mmol) and the buffering agent sodium acetate (0.54 g, 6.6 mmol) in anhydrous dichloromethane (16 mL). The resulting black solution was stirred for 4 h with careful monitoring by tlc. The reaction mixture was poured into diethyl ether and the black gum was extracted with additional ether until the gum had transformed into a granular solid. The combined organic layers were passed through a short pad of florisil® and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (60:40) to afford the desired product (2.2 g, 64%) as a mixture of diastereomers in a *E:Z* 5.25:1 ratio. The product was isolated as a colourless liquid.

Rf (P.E./EtOAc, 6:4): 0.51; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.68-1.78 (m, 2H, C*H*$_2$, *trans* + *cis*), 2.21 (qd, *J*=7.7 Hz, *J*=1.5 Hz, 2H, CH_2CH_2*H*$_2$CH=, *trans*), 2.43 (qd, *J*=7.7 Hz, *J*=1.6 Hz, 2H, CH_2CH_2*H*$_2$CH=, *cis*), 2.44 (td, *J*=7.9 Hz, *J*=1.3 Hz, 2H, C*H*$_2$CHO, *trans*), 2.64 (td, *J*=7.9 Hz, *J*=1.5 Hz, 2H, C*H*$_2$CHO, *cis*), 3.66 (s, 3H, OC*H*$_3$, *cis*), 3.70 (s, 3H, OC*H*$_3$, *trans*), 5.82 (dt, *J*=15.7 Hz, *J*=1.5 Hz, 1H, CH=C*H*CO_2CH_3, *trans*), 5.78 (dt, *J*=11.6 Hz, *J*=1.6 Hz, 1H, CH=C*H*CO_2CH_3, *cis*), 6.16 (dt, *J*=11.6 Hz, *J*=7.7 Hz, 1H, C*H*=$CHCO_2CH_3$, *cis*), 6.94 (dt, *J*=15.7 Hz, *J*=7.7 Hz, 1H, C*H*=$CHCO_2CH_3$, *trans*), 9.75 (t, *J*=1.5 Hz, 1H, C*H*O, *cis*), 9.78 (t, *J*=1.3 Hz, 1H, C*H*O, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 20.8 (*C*H$_2$, *trans*), 21.7 (*C*H$_2$, *cis*), 28.6 (*C*H$_2$, *cis*), 31.7 (*C*H$_2$, *trans*), 43.3 (*C*H$_2$, *trans*), 43.5 (*C*H$_2$, *cis*), 51.4 (O*C*H$_3$, *cis*), 51.8 (O*C*H$_3$, *trans*), 120.8 (CH=*C*HCO_2CH_3, *cis*), 122.3

(CH=*C*HCO$_2$CH$_3$, *trans*), 148.2 (*C*H=CHCO$_2$CH$_3$, *trans*), 149.5 (*C*H= CHCO$_2$CH$_3$, *cis*), 167.2 (*C*O$_2$CH$_3$, *trans*), 168.0 (*C*O$_2$CH$_3$, *cis*), 201.8 (*C*HO, *trans*), 202.3 (*C*HO, *cis*); **FTIR** (film) ν cm^{-1}: 3055, 2987, 1721 (C=O), 1641 (C=C), 1437, 1265, 739, 705; **LRMS** (ES$^+$) *m/z*: 174 (M+NH$_4$, 57%), 157 (M+H, 100%).

4,4-Dimethyl-tetrahydro-pyran-2-one 182[156]



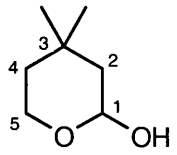
$C_7H_{12}O_2$

M= 128.08 g.mol^{-1}

To a cold (0°C) stirred suspension of sodium borohydride (2.5 g, 66 mmol) in anhydrous tetrahydrofuran (13 mL), was added, over 30 min, a solution of 3,3-dimethyl glutaric anhydride (7.0 g, 44 mmol) in dry tetrahydrofuran (35 mL). The resulting solution was allowed to warm to room temperature and stirred for 3.5 h. The solution was then cooled to 0°C and quenched by the addition of aqueous hydrochloric acid 6N. The organic layer was separated. The aqueous layer was extracted with ether (3 x 50 mL) and the combined organics dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford a clear oil of sufficient purity for further use (5.92 g, 83%).

Rf (P.E./EtOAc, 8:2): 0.41; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.13 (s, 6H, C*H*$_3$), 1.73 (t, *J*=6.1 Hz, 2H, C*H*$_2$CH$_2$O), 2.36 (s, 2H, C*H*$_2$CO$_2$R), 4.42 (t, *J*=6.1 Hz, 2H, C*H*$_2$O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 29.2 (*C*H$_3$), 30.2 (*C*(CH$_3$)$_2$), 36.3 (*C*H$_2$CH$_2$O), 44.6 (*C*H$_2$CO$_2$R), 67.1 (*C*H$_2$O), 177.3 (*C*O$_2$R); **FTIR** (film) ν cm^{-1}: 2960, 2874, 1733 (C=O), 1468, 1371, 1257, 1078; **LRMS** (ES$^+$) *m/z*: 279 (2M+Na, 8%), 257 (2M+H, 100%), 151 (M+Na, 9%), 129 (M+H, 82%); **HRMS** (ES$^+$) *m/z*: Requires 151.0738 for $C_7H_{12}O_2Na$ (M+Na), found 151.0735.

4,4-Dimethyl-tetrahydro-pyran-2-ol 183[156]



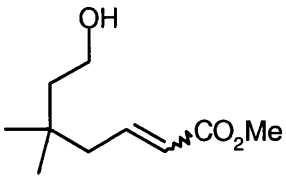
$C_7H_{14}O_2$

M= 130.08 g.mol^{-1}

To a stirred solution of lactone **182** (5.0 g, 36 mmol) in anhydrous diethyl ether (100 mL) at -20°C, was added dropwise a solution of DIBAL 1.22M in toluene (31 mL, 38 mmol) over 1 h. The resulting solution was stirred for a further 30 min and was then quenched by the addition of methanol (30 mL). The solution was allowed to warm to room temperature and was stirred overnight. The resulting suspension was diluted with 30% aqueous solution of Rochelle's salt (50 mL) and was stirred for 30 min. The organic layer was separated and washed with further 30% aqueous solution of Rochelle's salt. The combined aqueous phases were extracted with ether. The combined organics were dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure. Distillation of the crude oil under vacuum (bp=45-47°C/5 mmHg, lit.,[156] 40°C/<5 mmHg) afforded lactol **183** (2.86 g, 48%) of sufficient purity to be used in the next step without further purification as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.34; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.10 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.37-1.41 (m, 2H, H_{4eq} and H_{2eq}), 1.50-1.63 (m, 1H, H_{4ax}), 4.42 (m, 1H, H_{2ax}), 3.70-3.78 (m, 1H, H_{5eq}), 4.02 (dt, J=11.9 Hz, J=4.1 Hz, 1H, H_{5ax}), 5.02 (dd, J=8.2 Hz, J=2.5 Hz, 1H, H_1); **FTIR** (film) ν cm^{-1}: 3390 (O-H), 2951, 2870, 1556, 1385, 1197, 1078.

Methyl 5,5-dimethyl-7-hydroxy-2-heptenoate 184[156]



$C_{10}H_{18}O_3$

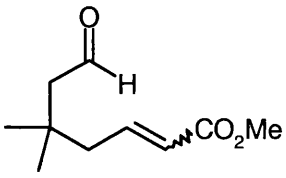
M= 186.13 g.mol^{-1}

To a stirred solution of lactol **183** (2.7 g, 18 mmol) in 150 mL of anhydrous acetonitrile was added carbomethoxymethylene triphenylphosphorane (8.9 g, 27 mmol) and the resulting mixture was heated at reflux under a nitrogen atmosphere for 2 days. The heat was removed and most of the solvent was concentrated *in vacuo*. Ether (25 mL) was added and the mixture was stirred for an additional 2 h. The resulting mixture was filtered and the filtrate washed with 15 mL of ether. The solvent was removed *in vacuo* and 20 mL of 70% ether in pentane was added. After stirring for a further 30 min, the suspension was filtered again and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the alcohol **184** (2.25 g, 60%) as a mixture of diastereoisomers in a *E:Z* 6:1 ratio as a pale yellow oil.

Rf (P.E./EtOAc, 8:2): 0.48; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.11 (s, 6H, C*H*$_3$, *trans*), 1.12 (s, 6H, C*H*$_3$, *cis*), 1.70 (t, *J*=7.2 Hz, 2H, C*H*$_2$CH$_2$OH, *trans*), 1.74 (t, *J*=7.0 Hz, 2H, C*H*$_2$CH$_2$OH, *cis*), 2.29 (d, *J*=7.8 Hz, 2H, C*H*$_2$CH=, *trans*), 2.79 (d, *J*=7.8 Hz, 2H, C*H*$_2$CH=, *cis*), 3.84-3.88 (m, 5H, C*H*$_2$OH and OC*H*$_3$, *cis* + *trans*), 5.98 (dt, *J*=15.6 Hz, *J*=1.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 6.02 (dt, *J*=11.1 Hz, *J*=1.0 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 6.46 (dt, *J*=11.1 Hz, *J*=7.8 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 7.14 (dt, *J*=15.6 Hz, *J*=7.8 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 27.7 (*C*H$_3$, *cis* + *trans*), 33.5 (*C*(CH$_3$)$_2$, *cis*), 33.6 (*C*(CH$_3$)$_2$, *trans*), 44.3 (*C*H$_2$CH$_2$OH, *cis*), 44.6 (*C*H$_2$CH$_2$OH, *trans*), 45.6 (*C*H$_2$CH=, *trans*), 46.4 (*C*H$_2$CH=, *cis*), 51.3 (O*C*H$_3$, *cis*), 51.7 (O*C*H$_3$, *trans*), 59.8 (*C*H$_2$OH, *trans*), 60.0 (*C*H$_2$OH, *cis*), 121.2 (=*C*HCO$_2$CH$_3$, *cis*), 123.6 (=*C*HCO$_2$CH$_3$, *trans*), 146.7

(*C*H=CHCO$_2$CH$_3$, *trans*), 147.5 (*C*H=CHCO$_2$CH$_3$, *cis*), 167.2 (*C*O$_2$CH$_3$, *cis* + *trans*); **FTIR** (film) ν cm^{-1}; 3460 (O-H), 3056, 2960, 1721 (C=O), 1655 (C=C), 1438, 1267, 1177, 738; **LRMS** (ES$^+$) *m/z:* 209 (M+Na, 16%), 187 (M+H, 34%), 155 (M-CH$_3$OH, 100%); **HRMS** (ES$^+$) *m/z:* Requires 187.1322 for C$_{10}$H$_{19}$O$_3$ (M+H), found 187.1328.

Methyl 5,5-dimethyl-7-oxo-2-heptenoate 181[156]



C$_{10}$H$_{16}$O$_3$

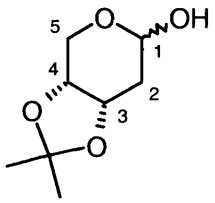
M= 184.11 g.mol^{-1}

To a stirred suspension of pyridinium chlorochromate (3.9 g, 18 mmol) and celite (4.1 g) in 30 mL of anhydrous dichloromethane, was added at room temperature and under a positive pressure of nitrogen, a solution of alcohol **184** (2.25 g, 12 mmol) in 6 mL of dichloromethane. The reaction mixture was stirred for 2 h at room temperature and was then diluted with 100 mL of ether. The resulting suspension was filtered through a short pad of Florisil®, rinsed with several portions of ether and the solvent concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford aldehyde **181** (1.12 g, 86%) as a mixture of diastereoisomers in a *E:Z* 6:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 8:2): 0.46; **^{1}H NMR** (CDCl$_3$, 300 MHz) δ ppm: 1.10 (s, 6H, C*H*$_3$, *trans*), 1.11 (s, 6H, C*H*$_3$, *cis*), 2.24 (d, *J*=7.9 Hz, 2H, C*H*$_2$CH=, *trans*), 2.30 (d, *J*=2.7 Hz, 2H, C*H*$_2$CHO, *trans*), 2.49 (d, *J*=2.2 Hz, 2H, C*H*$_2$CHO, *cis*), 2.96 (d, *J*=7.9 Hz, 2H, C*H*$_2$CH=, *cis*), 3.70 (s, 3H, OC*H*$_3$, *cis*), 3.73 (s, 3H, OC*H*$_3$, *trans*), 5.85 (d, *J*=15.5 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 5.91 (d, *J*=11.7 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 6.27 (dt, *J*=11.7 Hz, *J*=7.9 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.95 (dt, *J*=15.5 Hz, *J*=7.9 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*), 9.78 (t, *J*=2.2 Hz, 1H, C*H*O, *cis*), 9.82 (t, *J*=2.7

Hz, 1H, C*H*O, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 27.6 (*C*H_3, *cis*), 27.8 (*C*H_3, *trans*), 34.4 (*C*$(CH_3)_2$, *trans*), 34.5 (*C*$(CH_3)_2$, *cis*), 45.3 (*C*H_2CH=, *trans*), 46.0 (*C*H_2CH=, *cis*), 51.4 (O*C*H_3, *cis*), 51.8 (O*C*H_3, *trans*), 54.3 (*C*H_2CHO, *cis*), 54.8 (*C*H_2CHO, *trans*), 122.2 (=*C*HCO_2CH_3, *cis*), 124.5 (=*C*HCO_2CH_3, *trans*), 145.2 (*C*H=CHCO_2CH_3, *trans*), 145.9 (*C*H=CHCO_2CH_3, *cis*), 166.9 (*C*O_2CH_3, *cis* + *trans*), 202.6 (*C*HO, *trans*), 203.2 (*C*HO, *cis*); **FTIR** (film) ν cm^{-1}: 2980, 1731 (C=O), 1655 (C=C), 1390, 1371; **LRMS** (ES^+) *m/z:* 207 (M+Na, 12%), 185 (M+H, 33%), 153 (M-CH_3OH, 100%); **HRMS** (ES^+) *m/z:* Requires 185.1168 for $C_{10}H_{17}O_3$ (M+H), found 185.1175.

3,4-*O*-isopropylidene-2-deoxy-D-glucose 195[234]



$C_8H_{14}O_4$

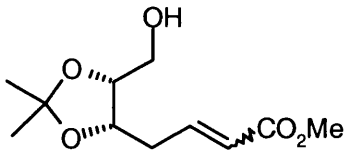
M= 174.19 $g.mol^{-1}$

To a solution of D-deoxy-ribose (5 g, 37 mmol) in dry dimethylformamide (25 mL) and dessicant ($CaSO_4$) was added 2-methoxypropene (2.67 g, 37 mmol) at 0°C, followed by a catalytic amount of *p*-toluenesulfonic acid. After 1 h at 0°C, an additional stoichiometric amount of reagent was added and stirring was continued for 2 h at 0°C. Sodium carbonate was then added to achieve a neutral pH and the mixture was stirred at room temperature for a further hour. The solids were filtered off and the filtrate concentrated under reduced pressure to afford the desired product (3.5 g, 54%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.38; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 1.32 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.75 (ddd, *J*=14.8 Hz, *J*=7.1 Hz, *J*=4.3 Hz, 1H, H_{2ax}), 2.20 (dt, *J*=14.8 Hz, *J*=4.3 Hz, 1H, H_{2eq}), 3.65 (dd, *J*=12.7 Hz, *J*=3.4 Hz, 1H, H_{5ax}), 3.92 (dd, *J*=12.7 Hz, *J*=3.4 Hz, 1H, H_{5eq}), 4.12 (dt, *J*=6.7 Hz, *J*=3.4 Hz, 1H, H_4), 4.45 (dt,

J=6.7 Hz, *J*=4.3 Hz, 1H, H_3), 5.21 (dt, *J*=7.1 Hz, *J*=4.3 Hz, 1H, H_1); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 25.8 (CH_3), 27.6 (CH_3), 32.6 (C_2), 62.5 (C_5), 70.8 (C_4), 72.0 (C_3), 91.4 (C_1), 109.1 ($C(CH_3)_2$); **FTIR** (film) ν cm^{-1}: 3412 (O-H), 2985, 2937, 1665 (C=O), 1457, 1381, 1245, 1216; **LRMS** (FAB^+) *m/z:* 175 (M+H, 33%), 157 (M-OH, 100%), 137 (52%); $[\alpha]^{24}_D$: -19.2° (*c* = 4.2, $CHCl_3$), lit.,[234]: -18.5° (*c* = 4.2, $CHCl_3$).

(4*S*,5*R*)-4-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester 196[234]



$C_{11}H_{18}O_5$

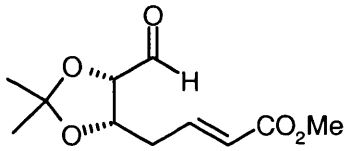
M= 230.25 $g.mol^{-1}$

A mixture of 3,4-*O*-isopropylidene-2-deoxy-D-glucose **195** (1.0 g, 5.74 mmol) and carbomethoxymethylene triphenylphosphorane (2.3 g, 6.9 mmol) in anhydrous tetrahydrofuran (50 mL) was heated at reflux with a catalytic amount of benzoic acid (50 mg) for 18 h. The heat was removed and the solution was concentrated under reduced pressure. Diethyl ether was then added and the resulting white crystalline precipitate of $Ph_3P=O$ was removed by filtration and the filtrate concentrated *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (60:40) to yield the desired product **196** (0.78 g, 59%) as a mixture of diastereomers in a *E:Z* 10:1 ratio. The product was isolated as a colourless liquid.

Rf (P.E./EtOAc, 6:4): 0.46; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.36 (s, 3H, CH_3, *cis* + *trans*), 1.48 (s, 3H, CH_3, *cis* + *trans*), 2.45-2.64 (m, 2H, $CH_2CH=$, *cis* + *trans*), 3.66 (d, *J*=5.5 Hz, 2H, CH_2OH, *cis* + *trans*), 3.71 (s, 3H, OCH_3, *cis*), 3.73 (s, 3H, OCH_3, *trans*), 4.18-4.33 (m, 2H, OCHCHO, *cis* + *trans*), 5.90 (dt, *J*=11.7 Hz, *J*=1.6 Hz, 1H, $=CHCO_2CH_3$, *cis*), 5.94 (dt, *J*=15.7 Hz, *J*=1.5 Hz, 1H, $=CHCO_2CH_3$, *trans*),

6.37 (ddd, *J*=11.7 Hz, *J*=7.8 Hz, *J*=6.7 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.98 (dt, *J*=15.7 Hz, *J*=6.9 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 25.7 (*C*H$_3$, *trans*), 25.8 (*C*H$_3$, *cis*), 28.3 (*C*H$_3$, *cis*), 28.4 (*C*H$_3$, *trans*), 29.7 (*C*H$_2$CH=, *cis*), 32.8 (*C*H$_2$CH=, *trans*), 51.5 (O*C*H$_3$, *cis*), 51.9 (O*C*H$_3$, *trans*), 61.8 (*C*H$_2$OH, *trans*), 62.0 (*C*H$_2$OH, *cis*), 75.8 (O*C*H, *trans*), 76.7 (O*C*H, *cis*), 77.9 (O*C*H, *trans*), 78.2 (O*C*H, *cis*), 108.9 (*C*(CH$_3$)$_2$, *cis* + *trans*), 121.4 (=*C*HCO$_2$CH$_3$, *cis*), 123.6 (=*C*HCO$_2$CH$_3$, *trans*), 145.2 (*C*H=CHCO$_2$CH$_3$, *trans*), 146.3 (*C*H=CHCO$_2$CH$_3$, *trans*), 167.0 (*C*O$_2$CH$_3$, *cis* + *trans*); **FTIR** (film) ν cm^{-1}: 3454 (O-H), 2985, 2940, 1736 (C=O), 1655 (C=C), 1456, 1377, 1201, 1103, 921; **LRMS** (FAB$^+$) *m/z:* 231 (M+H, 85%), 215 (M-H$_2$O, 100%), 173 (M+H-CO$_2$CH$_3$, 42%); $[\alpha]^{24}_D$: +22.2° (*c* = 2.7, $CHCl_3$), lit.,[234]: +21.8° (*c* = 2.7, $CHCl_3$).

(4*S*, 5*S*)-4-(5-Formyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester 185



$C_{11}H_{16}O_5$

M= 228.10 g.mol^{-1}

Procedure A

Oxalyl chloride (1.08 g, 8.58 mmol) was dissolved in dry dichloromethane (21 mL) and cooled to -60°C. A solution of dimethylsulfoxide (1.47 g, 18.7 mmol) in dry dichloromethane (9 mL) was added *via* canula at -60°C during 5 min. Stirring was continued at this temperature for 10 min, followed by the addition of a solution of alcohol **196** (1.8 g, 7.8 mmol) in anhydrous dichloromethane (18 mL). The reaction mixture was stirred for 15 min and triethylamine (3.9 g, 39 mmol) was added. The cooling bath was removed and water (30 mL) was added at room temperature. Stirring was continued for 10 min and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents were removed *in vacuo*. The

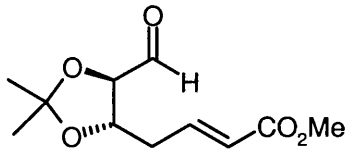
resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (70:30) to afford the aldehyde **185** (0.25 g, 14%) and its 5-epimer **197** (0.75 g, 42%) as colourless oils.

Procedure B

A solution of sulphur trioxide pyridine complex (3.11 g, 20 mmol) in anhydrous dimethylsulfoxide (17 mL) was added to a mixture of alcohol **196** (1.5 g, 6.51 mmol) and triethylamine (6.57 g, 65 mmol) in dry dichloromethane (20 mL) under nitrogen at 0°C. The reaction mixture was stirred for 5 h. During this period the temperature was raised to room temperature. Water was the added and the reaction mixture was acidified until pH=3 with aqueous hydrochloric acid 2M. The organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed twice with water, dried over anhydrous $MgSO_4$, filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (70:30) to afford the aldehyde **185** (0.15 g, 10%) and its 5-epimer **197** (0.45 g, 30%) as colourless oils.

Rf (P.E./EtOAc, 6:4): 0.54; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.46 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.39-2.55 (m, 2H, CH_2CH=), 3.73 (s, 3H, OCH_3), 4.36 (dd, *J*=7.2 Hz, *J*=2.9 Hz, 1H, C*H*CHO), 4.46-4.53 (m, 1H, OC*H*), 5.94 (dt, *J*=15.7 Hz, *J*=1.5 Hz, 1H, =C*H*CO_2CH_3), 6.96 (dt, *J*=15.7 Hz, *J*=6.9 Hz, 1H, C*H*=CHCO_2CH_3), 9.79 (d, *J*=2.9 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 25.6 (*C*H_3), 27.8 (*C*H_3), 33.0 (*C*H_2CH=), 51.9 (O*C*H_3), 77.2 (O*C*H), 82.0 (O*C*H), 111.4 (*C*$(CH_3)_2$), 124.3 (=*C*HCO_2CH_3), 143.8 (*C*H=CHCO_2CH_3), 166.8 (*C*O_2CH_3), 202.4 (*C*HO); **FTIR** (film) ν cm^{-1}: 2989, 2951, 1724 (C=O), 1659 (C=C), 1438, 1382, 1271, 1220, 1071; **LRMS** (FAB^+) *m/z:* 229 (M+H, 41%), 197 (M-OCH_3, 16%), 171 (M+H-CO_2CH_3, 100%); $[\alpha]^{24}_D$: -34° (*c* = 0.7, CH_2Cl_2).

(4*S*, 5*R*)-4-(5-Formyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester 197

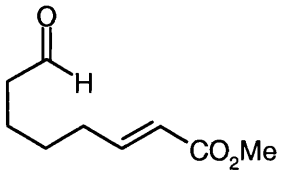


$C_{11}H_{16}O_5$

M= 228.10 g.mol^{-1}

Rf (P.E./EtOAc, 6:4): 0.46; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 1.38 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.48-2.51 (m, 1H, CH_2CH=), 3.70 (s, 3H, OCH_3), 3.95 (dd, *J*=7.4 Hz, *J*=2.0 Hz, 1H, C*H*CHO), 4.13 (dt, *J*=7.4 Hz, *J*=4.3 Hz, 1H, OC*H*), 5.92 (dt, *J*=15.7 Hz, *J*=1.5 Hz, 1H, =C*H*CO_2CH_3), 6.92 (dt, *J*=15.7 Hz, *J*=6.9 Hz, 1H, C*H*=$CHCO_2CH_3$), 9.70 (d, *J*=2.0 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 26.5 (*C*H_3), 27.2 (*C*H_3), 35.5 (*C*H_2CH=), 51.4 (O*C*H_3), 75.2 (O*C*H), 83.9 (O*C*H), 111.4 (*C*$(CH_3)_2$), 124.2 (=*C*HCO_2CH_3), 142.9 (*C*H=$CHCO_2CH_3$), 166.6 (*C*O_2CH_3), 200.9 (*C*HO); **LRMS** (FAB$^+$) *m/z:* 229 (M+H, 100%), 171 (M+H-CO_2CH_3, 59%); **HRMS** (FAB$^+$) *m/z*: Requires 229.10757 for $C_{11}H_{17}O_5$ (M+H), found 229.10669; $[\alpha]^{20}_D$: -16.8° (*c* = 1.5, $CHCl_3$).

Methyl (*E*)-8-oxo-2-octenoate 204[233]



$C_9H_{14}O_3$

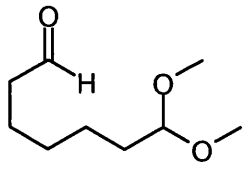
M= 170.20 g.mol^{-1}

To a stirred mixture of cyclohexene (2.5 g, 30.4 mmol) and aqueous ruthenium trichloride stock solution (160 mg, 0.78 mmol, 0.035 M) in 1,2-dichloroethane (120 mL) and distilled water (90 mL), was added, in portions, sodium periodate (9.8 g,

45.7 mmol) over a period of 5 min at room temperature. The colour turned from black to yellow immediately. The reaction was monitored by TLC. After completion in 3 h, the layers were separated. The aqueous layer was extracted with 1,2-dichloroethane (3 x 30 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate containing the crude adipaldehyde was directly used without further purification. A suspension of 60% sodium hydride dispersion in mineral oil (0.5 g, 12.2 mmol) in 25 mL of dry 1,2-dichloroethane under a positive nitrogen pressure, was stirred in an ice bath while trimethyl phosphonoacetate (2.2 g, 12.2 mmol) in 25 mL of dry 1,2-dichloroethane was added dropwise. After the addition was finished, the reaction mixture was stirred for further 1 h at 0°C. Then, the solution of crude adipaldehyde in 1,2-dichloroethane was added dropwise. The cold mixture was stirred for further 15 min after the addition. Then, it was slowly brought to reflux and stirred overnight. The clear organic layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the aldehyde **204** (2.9 g, 55%) as a single *E* isomer as a colourless oil.

Rf (P.E./EtOAc, 8:2): 0.66; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.38-1.46 (m, 2H, C*H*$_2$CH$_2$CH=), 1.55-1.62 (m, 2H, C*H*$_2$CH$_2$CHO), 2.17 (qd, *J*=7.1 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=), 2.39 (td, *J*=7.3 Hz, *J*=1.5 Hz, 2H, C*H*$_2$CHO), 3.66 (s, 3H, OC*H*$_3$), 5.76 (dt, *J*=15.7 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.87 (dt, *J*=15.7 Hz, *J*=7.1 Hz, 1H, C*H*=CHCO$_2$CH$_3$), 9.69 (t, *J*=1.5 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 21.9 (*C*H$_2$), 27.8 (*C*H$_2$), 32.2 (*C*H$_2$), 43.9 (*C*H$_2$), 51.8 (O*C*H$_3$), 121.8 (=*C*HCO$_2$CH$_3$), 149.0 (*C*H=CHCO$_2$CH$_3$), 167.4 (*C*O$_2$CH$_3$), 202.5 (*C*HO); **FTIR** (film) ν cm^{-1}: 2949, 2862, 2725, 1724, 1655, 1437, 1275; **LRMS** (ES$^+$) *m/z:* 188 (M+NH$_4$, 38%), 171 (M+H, 100%), 139 (19%).

7,7-Dimethoxy-heptanal 207[235]



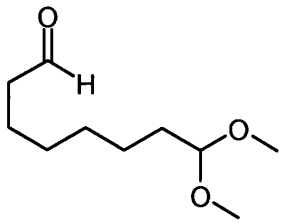
$C_9H_{18}O_3$

M= 174.12 g.mol^{-1}

A 500 mL, three necked, round-bottomed flask was charged with cycloheptene (10 g, 104 mmol), dichloromethane (330 mL) and methanol (70 mL). The flask was cooled to -78°C and ozone was bubbled through during 4 h until the solution turned blue. Nitrogen was passed through until the blue colour was discharged. *p*-Toluenesulfonic acid (1.97 g, 10.4 mmol, 10 mol%) was added and the solution allowed to warm to room temperature as it was stirred under nitrogen. Anhydrous $NaHCO_3$ (34.6 g, 416 mmol) was added and the mixture stirred for 15 min. Dimethyl sulfide (16 mL, 208 mmol) was then added and the reaction mixture was stirred overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to afford a clear oil of sufficient purity for further use (12.9 g, 71%).

Rf (P.E./EtOAc, 8:2): 0.81; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.06-1.31 (m, 4H, C*H*$_2$), 1.51-1.60 (m, 4H, C*H*$_2$), 2.33 (td, *J*=5.9 Hz, *J*=1.8 Hz, 2H, C*H*$_2$CHO), 3.23 (s, 6H, OC*H*$_3$), 4.27 (t, *J*=5.6 Hz, 1H, C*H*(OCH$_3$)$_2$), 9.69 (t, *J*=1.8 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.3 (*C*H$_2$), 25.0 (*C*H$_2$), 29.3 (*C*H$_2$), 34.1(*C*H$_2$), 44.1 (*C*H$_2$CHO), 53.1 (O*C*H$_3$), 104.9 (*C*H(OCH$_3$)$_2$), 202.8 (*C*HO); **FTIR** (film) ν cm^{-1}: 2939, 2861, 1737 (C=O), 1448, 1373, 1131, 1055, 951; **LRMS** (EI$^+$) *m/z:* 174 (M, 100%), 143 (M-OCH$_3$, 64%); **HRMS** (ES$^+$) *m/z*: Requires 174.1291 for $C_9H_{18}O_3$ (M), found 174.1290.

8,8-Dimethoxy-octanal 209[236]



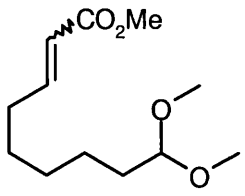
$C_{10}H_{20}O_3$

M= 188.14 g.mol^{-1}

A 500 mL, three necked, round-bottomed flask was charged with cyclooctene (10 g, 90 mmol), dichloromethane (330 mL) and methanol (70 mL). The flask was cooled to -78°C and ozone was bubbled through during 4 h until the solution turned blue. Nitrogen was passed through until the blue colour was discharged. *p*-Toluenesulfonic acid (1.7 g, 9 mmol, 10 mol%) was added and the solution allowed to warm to room temperature as it was stirred under nitrogen. Anhydrous $NaHCO_3$ (30 g, 360 mmol) was added and the mixture stirred for 15 min. Dimethyl sulfide (14 mL, 180 mmol) was added and the reaction mixture was stirred overnight. The solution was then extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to afford a clear oil of sufficient purity for further use (17.0 g, 100%).

Rf (P.E./EtOAc, 8:2): 0.82; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.24 (m, 6H, C*H*$_2$), 1.43-1.56 (m, 4H, C*H*$_2$), 2.31 (td, *J*=5.9 Hz, *J*=0.9 Hz, 2H, C*H*$_2$CHO), 3.21 (s, 6H, OC*H*$_3$), 4.24 (t, *J*=5.6 Hz, 1H, C*H*(OCH$_3$)$_2$), 9.66 (t, *J*=0.9 Hz, 1H, C*H*O); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.4 (*C*H$_2$), 24.7 (*C*H$_2$), 29.4 (*C*H$_2$), 29.5 (*C*H$_2$), 32.8 (*C*H$_2$), 44.2 (*C*H$_2$CHO), 53.0 (O*C*H$_3$), 104.9 (*C*H(OCH$_3$)$_2$), 203.0 (*C*HO); **FTIR** (film) ν cm^{-1}: 2940, 2859, 1737 (C=O), 1464, 1385, 1192, 1129, 1055, 945; **LRMS** (EI$^+$) *m/z:* 188 (M, 100%), 173 (M-CH$_3$, 26%), 157 (M-OCH$_3$, 47%); **HRMS** (ES$^+$) *m/z*: Requires 188.1417 for $C_{10}H_{20}O_3$ (M), found 188.1414.

Methyl 9,9-dimethoxy-2-nonenoate 208[235]



$C_{12}H_{22}O_4$

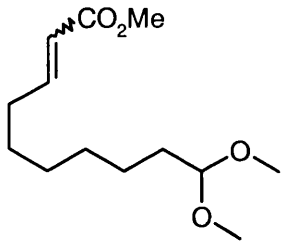
M= 230.15 g.mol^{-1}

A suspension of 60% sodium hydride dispersion in mineral oil (1.52 g, 38 mmol) in 40 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while trimethylphosphonoacetate (6.9 g, 38 mmol) in 40 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for a further 1 h at 0°C. Then, a solution of heptanal **207** (6.0 g, 35 mmol) in 60 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for 15 min, slowly brought to reflux and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the desired product (7.9 g, 100%) as a mixture of diastereomers in a *E:Z* 6:1 ratio as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.62; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.25-1.29 (m, 4H, CH_2, *trans* + *cis*), 1.38-1.42 (m, 2H, CH_2, *trans* + *cis*), 1.48-1.55 (m, 2H, CH_2, *trans* + *cis*), 2.12 (qd, *J*=7.0 Hz, *J*=1.4 Hz, 2H, CH_2CH=, *trans*), 2.57 (qd, *J*=7.2 Hz, *J*=1.7 Hz, 2H, CH_2CH=, *cis*), 3.22 (s, 6H, OCH_3, *cis*), 3.23 (s, 6H, OCH_3, *trans*), 3.59 (s, 3H, OCH_3, *cis*), 3.64 (s, 3H, OCH_3, *trans*), 4.27 (t, *J*=5.7 Hz, 1H, $CH(OCH_3)_2$, *trans* + *cis*), 5.69 (dt, *J*=11.7 Hz, *J*=1.7 Hz, 1H, $=CHCO_2CH_3$, *cis*), 5.74 (dt, *J*=15.6 Hz, *J*=1.4 Hz, 1H, $=CHCO_2CH_3$, *trans*), 6.14 (dt, *J*=11.7 Hz, *J*=7.2 Hz, 1H,

C*H*=CHCO$_2$CH$_3$, *cis*), 6.88 (dt, *J*=15.6 Hz, *J*=7.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 24.6 (*C*H$_2$, *trans*), 25.9 (*C*H$_2$, *cis*), 28.1 (*C*H$_2$, *cis*), 28.3 (*C*H$_2$, *trans*), 29.3 (*C*H$_2$, *cis*), 29.4 (*C*H$_2$, *trans*), 32.2 (*C*H$_2$, *trans* +*cis*), 32.7 (*C*H$_2$, *trans* + *cis*), 51.2 (O*C*H$_3$, *cis*), 51.6 (O*C*H$_3$, *trans*), 53.0 (O*C*H$_3$, *trans* + *cis*), 104.9 (*C*H(OCH$_3$)$_2$, *trans* + *cis*), 119.7 (=*C*HCO$_2$CH$_3$, *cis*), 121.3 (=*C*HCO$_2$CH$_3$, *trans*), 149.7 (*C*H=CHCO$_2$CH$_3$, *trans*), 140.7 (*C*H=CHCO$_2$CH$_3$, *cis*), 167.1 (*C*O$_2$CH$_3$, *cis*), 167.4 (*C*O$_2$CH$_3$, *trans*); **FTIR** (film) ν cm^{-1}: 1725 (C=O), 1657 (C=C); **LRMS** (EI$^+$) *m/z:* 230 (M, 100%), 199 (M-OCH$_3$, 64%); **HRMS** (ES$^+$) *m/z*: Requires 230.1518 for $C_{12}H_{22}O_4$ (M), found 174.1511.

Methyl 10,10-dimethoxy-2-decenoate 210



$C_{13}H_{24}O_4$

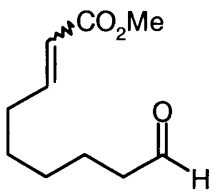
M= 244.32 g.mol^{-1}

A suspension of 60% sodium hydride dispersion in mineral oil (1.17 g, 29.2 mmol) in 30 mL of dry tetrahydrofuran under a positive nitrogen pressure was stirred in an ice bath while trimethylphosphonoacetate (5.32 g, 29.2 mmol) in 30 mL of dry tetrahydrofuran was added dropwise. The mixture becomes viscous near the end of the addition, but redissolved on continued stirring. After the addition was finished, the reaction mixture was stirred for a further 1 h at 0°C. Then, a solution of octanal **209** (5.0 g, 26.5 mmol) in 50 mL of dry tetrahydrofuran was added dropwise. The cold mixture was stirred for 15 min, slowly brought to reflux and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl. The clear ether layer was decanted from the oil. The remaining oil was dissolved in warm water and the upper organic layer was separated. The aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and the solvents were removed *in vacuo*. The resulting crude oil

was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the desired product (5.5 g, 84%) as a mixture of diastereomers in a *E:Z* 5.2:1 ratio as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.64; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.19 (m, 6H, C*H*$_2$, *trans* + *cis*), 1.37-1.41 (m, 2H, C*H*$_2$, *trans* + *cis*), 1.46-1.52 (m, 2H, C*H*$_2$, *trans* + *cis*), 2.12 (qd, *J*=7.0 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *trans*), 2.57 (qd, *J*=7.5 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *cis*), 3.24 (s, 6H, OC*H*$_3$, *trans* + *cis*), 3.63 (s, 3H, OC*H*$_3$, *cis*), 3.65 (s, 3H, OC*H*$_3$, *trans*), 4.27 (t, *J*=5.7 Hz, 1H, C*H*(OCH$_3$)$_2$, *trans* + *cis*), 5.69 (dt, *J*=11.5 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 5.76 (dt, *J*=15.6 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 6.15 (dt, *J*=11.5 Hz, *J*=7.5 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.89 (dt, *J*=15.6 Hz, *J*=7.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 24.8 (*C*H$_2$, *trans* + *cis*), 28.3 (*C*H$_2$, *trans*), 29.3 (*C*H$_2$, *cis*), 29.4 (*C*H$_2$, *trans*), 29.6 (*C*H$_2$, *trans*), 29.7 (*C*H$_2$, *cis*), 30.1 (*C*H$_2$, *cis*), 32.4 (*C*H$_2$, *trans* + *cis*), 32.5 (*C*H$_2$, *trans*), 34.4 (*C*H$_2$, *cis*), 51.3 (O*C*H$_3$, *cis*), 51.7 (O*C*H$_3$, *trans*), 53.0 (O*C*H$_3$, *trans* + *cis*), 105.0 (*C*H(OCH$_3$)$_2$, *trans* + *cis*), 119.6 (=*C*HCO$_2$CH$_3$, *cis*), 121.4 (=*C*HCO$_2$CH$_3$, *trans*), 150.0 (*C*H=CHCO$_2$CH$_3$, *trans*), 151.1 (*C*H=CHCO$_2$CH$_3$, *cis*), 167.4 (*C*O$_2$CH$_3$, *cis*), 167.5 (*C*O$_2$CH$_3$, *trans*); **FTIR** (film) ν cm^{-1}: 2931, 2857, 1727 (C=O), 1658 (C=C), 1437, 1271, 1128, 1055, 980; **LRMS** (EI$^+$) *m/z:* 267 (M +Na, 100%), 262 (M+NH$_4$, 10%), 244 (M+H, 20%), 213 (M-OCH$_3$, 29%); **HRMS** (ES$^+$) *m/z*: Requires 267.1583 for $C_{13}H_{24}O_4Na$ (M+Na), found 267.1572.

Methyl 9-oxo-2-nonenoate 205[237]



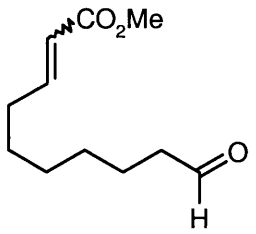
$C_{10}H_{16}O_3$

M= 184.23 $g.mol^{-1}$

To solution of ester **208** (1.0 g, 4.87 mmol) in tetrahydrofuran (30 mL) was added aqueous hydrochloric acid 2 M (15 mL) and the mixture was stirred at room temperature for 5 h. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography eluting with P.E. 30-40°C/EtOAc (85:15) afforded the product **205** (0.5 g, 56%) as a two distereomers in a *E:Z* 6:1 ratio as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.57; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.28-1.40 (m, 4H, C*H*$_2$, *trans* + *cis*), 1.55-1.60 (m, 2H, C*H*$_2$, *trans* + *cis*), 2.12 (qd, *J*=6.9 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *trans*), 2.35 (td, *J*=7.3 Hz, *J*=1.6 Hz, 2H, C*H*$_2$CHO, *trans* + *cis*), 2.64 (qd, *J*=7.0 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *cis*), 3.63 (s, 3H, OC*H*$_3$, *cis*), 3.65 (s, 3H, OC*H*$_3$, *trans*), 5.70 (dt, *J*=11.5 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 5.76 (dt, *J*=15.7 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 6.22 (dt, *J*=11.5 Hz, *J*=7.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.88 (dt, *J*=15.7 Hz, *J*=6.9 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*), 9.69 (t, *J*=1.6 Hz, 1H, C*H*O, *trans* + *cis*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.1 (*C*H$_2$, *trans*), 23.6 (*C*H$_2$, *cis*), 28.1 (*C*H$_2$, *trans*), 28.2 (*C*H$_2$, *cis*), 29.0 (*C*H$_2$, *trans*), 29.4 (*C*H$_2$, *cis*), 32.2 (*C*H$_2$, *trans*), 32.4 (*C*H$_2$, *cis*), 34.6 (*C*H$_2$, *cis*), 44.1 (*C*H$_2$, *trans*), 51.3 (O*C*H$_3$, *cis*), 51.7 (O*C*H$_3$, *trans*), 119.7 (=*C*HCO$_2$CH$_3$, *cis*), 121.5 (=*C*HCO$_2$CH$_3$, *trans*), 149.4 (*C*H=CHCO$_2$CH$_3$, *trans*), 151.0 (*C*H=CHCO$_2$CH$_3$, *cis*), 167.4 (*C*O$_2$CH$_3$, *trans* + *cis*), 202.6 (*C*HO, *trans* + *cis*); **FTIR** (film) ν cm^{-1}: 1724 (C=O), 1712 (C=O), 1658 (C=C); **LRMS** (EI$^+$) *m/z:* 185 (M+H, 49%), 153 (M-OCH$_3$, 48%), 113 (80%), 41 (100%).

Methyl 10-oxo-2-decenoate 206[238]



$C_{11}H_{18}O_3$

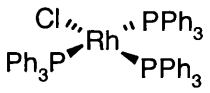
M= 198.25 g.mol^{-1}

To solution of ester **210** (4.5 g, 24 mmol) in tetrahydrofuran (100 mL) was added aqueous hydrochloric acid 2 M (50 mL) and the mixture was stirred at room temperature for 5 h. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. The resulting crude oil was purified by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20) to afford the desired product **206** (3.8 g, 80%) as a mixture of diastereomers in a *E:Z* 5.2:1 ratio as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.58; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.26-1.29 (m, 6H, C*H*$_2$, *trans* + *cis*), 1.54-1.59 (m, 2H, C*H*$_2$, *trans* + *cis*), 2.12 (qd, *J*=6.9 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *trans*), 2.35 (td, *J*=7.2 Hz, *J*=1.6 Hz, 2H, C*H*$_2$CHO, *trans* + *cis*), 2.58 (qd, *J*=7.0 Hz, *J*=1.4 Hz, 2H, C*H*$_2$CH=, *cis*), 3.63 (s, 3H, OC*H*$_3$, *cis*), 3.65 (s, 3H, OC*H*$_3$, *trans*), 5.69 (dt, *J*=11.6 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *cis*), 5.76 (dt, *J*=15.6 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$, *trans*), 6.14 (dt, *J*=11.6 Hz, *J*=7.0 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *cis*), 6.88 (dt, *J*=15.6 Hz, *J*=6.9 Hz, 1H, C*H*=CHCO$_2$CH$_3$, *trans*), 9.69 (t, *J*=1.6 Hz, 1H, C*H*O, *trans* + *cis*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 22.3 (*C*H$_2$, *trans*), 23.3 (*C*H$_2$, *cis*), 28.2 (*C*H$_2$, *trans*), 28.3 (*C*H$_2$, *cis*), 29.2 (*C*H$_2$, *trans*), 29.3 (*C*H$_2$, *trans* + *cis*), 29.5 (*C*H$_2$, *cis*), 32.4 (*C*H$_2$, *trans* + *cis*), 34.7 (*C*H$_2$, *cis*), 44.2 (*C*H$_2$, *trans*), 51.5 (O*C*H$_3$, *cis*), 51.7 (O*C*H$_3$, *trans*), 119.5 (=*C*HCO$_2$CH$_3$, *cis*), 121.4 (=*C*HCO$_2$CH$_3$, *trans*), 149.7 (*C*H=CHCO$_2$CH$_3$, *trans*), 150.0 (*C*H=CHCO$_2$CH$_3$, *cis*), 167.5 (*C*O$_2$CH$_3$, *trans* + *cis*), 202.8 (*C*HO, *trans* + *cis*); **FTIR** (film) ν cm^{-1}: 1725 (C=O), 1712 (C=O), 1659 (C=C); **LRMS** (EI$^+$) *m/z:* 199 (M+H, 100%), 167 (M-OCH$_3$, 90%), 139 (M-CO$_2$CH$_3$, 42%).

III.3 Cyclisation studies

Chlorotris(triphenylphosphine) rhodium (I) 158[148]



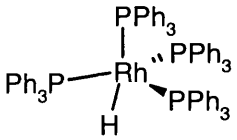
$C_{54}H_{45}ClP_3Rh$

M= 925.18 g.mol^{-1}

Rhodium chloride trihydrate (0.54 g, 2.6 mmol) was dissolved in degassed ethanol (20 mL). A solution of triphenylphosphine (3.25 g, 15.6 mmol) in hot, degassed ethanol (90 mL) was added and the flask purged with nitrogen. The solution was refluxed for 3 h and the crystalline product was collected from the hot solution on a sintered-glass filter. The precipitate was washed with small portions of anhydrous ether and dried under vacuum to afford the catalyst **158** (1.64 g, 67%) as deep red crystals (mp= 150°C; lit.,[148] 156°C).

LRMS (FAB$^+$) *m/z:* 889 (M-Cl, 12%), 627 ($Rh(PPh_3)_2$, 21%), 136 (100%); **Anal**: Calc. for $C_{54}H_{45}P_3RhCl$: C, 70.10; H, 4.90; Cl, 3.83; P, 10.04. Found: C, 69.78; H, 4.99; Cl, 3.62; P, 10.34.

Hydridotetrakis(triphenylphosphine) rhodium (I) 159[149a]



$C_{72}H_{61}P_4Rh$

M= 1153.01 g.mol^{-1}

Hydrated rhodium trichloride (0.5 g, 2.4 mmol) in warm degassed ethanol (35 mL) and sodium borohydride (0.45 g, 12 mmol) in warm degassed ethanol (35 mL) were

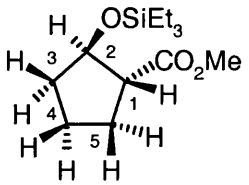
added rapidly and successively to a vigorously stirred solution of triphenylphosphine (5 g, 24 mmol) in boiling ethanol (150 mL). The mixture was heated under reflux for 10 min to ensure complete reaction, then cooled to room temperature, filtered, and the precipitate washed with water, ethanol and *n*-hexane. The resulting solid was dried under vacuum to give catalyst **159** (1.60 g, 54%) as yellow microcrystals (mp=147°C; lit.,[149a] 148°C).

FTIR (film) ν cm^{-1}: 2147 (Rh-H), 1582 (C=C); **LRMS** (FAB^+) *m/z:* 627 ($Rh(PPh_3)_2$, 5%), 557 (35%), 411 (80%), 369 (65%); **Anal**: Calc. for $C_{72}H_{61}P_4Rh$: C, 75.0; H, 5.35; Cl, 0.0; P, 10.75. Found: C, 75.32; H, 5.04; Cl, 0.0; P, 10.63.

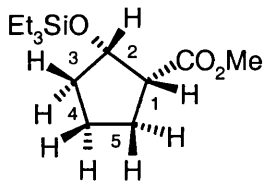
Typical procedure for the Rh(I) catalysed tandem hydrosilylation-aldol reaction:

Triethylsilane (2.1 equiv) was added slowly to a stirred solution of the 6-oxo-2-hexenoate derivative and the rhodium (I) catalyst (1 mol%) in anhydrous, degassed toluene (0.4 M in substrate) at ambient temperature. The resulting solution was heated for 16 h at 50°C and then cooled to room temperature. The reaction mixture was diluted with 2 M aqueous sodium hydroxide and extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography to afford the corresponding carbocycle as a mixture of *syn* and *anti* diastereomers.

Methyl 2-triethylsilyloxy-cyclopentanecarboxylate 83[80]



syn-**83**



anti-**83**

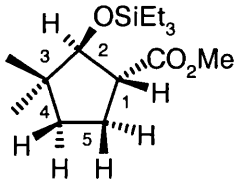
$C_{13}H_{26}O_3Si$

M= 258.17 $g.mol^{-1}$

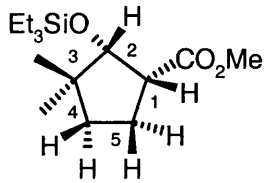
According to the general procedure, reaction of methyl (*E*)-6-oxo-2-hexenoate **78** (450 mg, 3.2 mmol), triethylsilane (770 mg, 6.7 mmol) and tetrakis(triphenylphosphine) rhodium hydride (30 mg, 0.032 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **83** (662 mg, 81%) as a mixture of diastereomers in a *syn:anti* 1:11 ratio as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **83** in 81% yield as a mixture of diastereomers in a *syn:anti* 3:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.69; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 0.48-0.72 (q, *J*=6.0 Hz, 6H, $OSiCH_2CH_3$, *syn* + *anti*), 0.98-1.02 (t, *J*=6.0 Hz, 9H, $OSiCH_2CH_3$, *syn* + *anti*), 1.49-2.05 (m, 6H, H_3, H_4, H_5, *syn* + *anti*), 2.70-2.81 (m, 1H, H_1, *syn* + *anti*), 3.67 (s, 3H, OCH_3, *syn*), 3.68 (s, 3H, OCH_3, *anti*), 4.40 (q, *J*=6.0 Hz, 1H, H_2, *anti*), 4.50 (q, *J*=4.0 Hz, 1H, H_2, *syn*); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 3.6 ($OSiCH_2CH_3$, *anti*), 3.8 ($OSiCH_2CH_3$, *syn*), 5.6 ($OSiCH_2CH_3$, *anti*), 5.7 ($OSiCH_2CH_3$, *syn*), 21.7 (C_4, *syn*), 22.7 (C_4, *anti*), 23.4 (C_5, *syn*), 28.1 (C_5, *anti*), 34.5 (C_3, *syn*), 35.5 (C_3, *anti*), 50.5 (C_1, *syn*), 50.6 (OCH_3, *syn*), 51.1 (OCH_3, *anti*), 53.1 (C_1, *anti*), 74.3 (C_2, *syn*), 78.3 (C_2, *anti*), 172.3 (CO_2CH_3, *syn*), 174.6 (CO_2CH_3, *anti*); **FTIR** (film) ν cm^{-1}: 2955, 2878, 1738, 1200, 1007; **LRMS** (FAB^+) *m/z*: 259 (M+H, 5%), 229 (M-Et, 10%), 115 (40%), 87 (100%); **HRMS** (FAB^+) *m/z*: Requires 259.1729 for $C_{13}H_{27}O_3Si$ (M+H), found 259.1720.

Methyl 3,3-dimethyl-2-triethylsilyloxy-cyclopentanecarboxylate 160



syn-**160**



anti-**160**

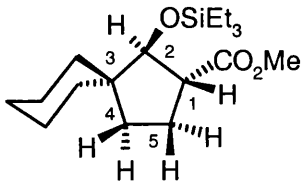
$C_{15}H_{30}O_3Si$

M= 286.20 $g.mol^{-1}$

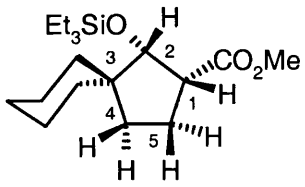
According to the general procedure, reaction of methyl (*E*)-5,5-dimethyl-6-oxo-2-hexenoate **102** (500 mg, 2.9 mmol), triethylsilane (720 mg, 6.2 mmol) and tetrakis(triphenylphosphine) rhodium hydride (34 mg, 0.029 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **160** (522 mg, 62%) as a mixture of diastereomers in a *syn:anti* 6.4:1 ratio as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **160** in 56% yield as a mixture of diastereomers in a *syn:anti* 1:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.63; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.55 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *syn*), 0.56 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *anti*), 0.87 (s, 3H, CH_3, *syn*), 0.92 (s, 3H, CH_3, *anti*), 0.93 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *syn*), 0.94 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *anti*), 0.97 (s, 3H, CH_3, *anti*), 0.98 (s, 3H, CH_3, *syn*), 1.50 (dd, *J*=7.4 Hz, *J*=8.4 Hz, 2H, H_4, *syn* + *anti*), 1.67-1.71 (dq, *J*=13.6 Hz, *J*=7.4 Hz, 1H, H_{5eq}, *syn*), 1.69-1.72 (m, 1H, H_{5eq}, *anti*), 1.97 (ddt, *J*=13.6 Hz, *J*=10.8 Hz, *J*=8.4 Hz, 1H, H_{5ax}, *syn*), 2.12-2.21 (m, 1H, H_{5ax}, *anti*), 2.73 (dt, *J*=10.8 Hz, *J*=7.4 Hz, 1H, H_1, *syn*), 2.96 (td, *J*=10.4 Hz, *J*=7.0 Hz, 1H, H_1, *anti*), 3.66 (s, 3H, OCH_3, *syn*), 3.67 (s, 3H, OCH_3, *anti*), 3.94 (d, *J*=10.4 Hz, 1H, H_2, *anti*), 3.94 (d, *J*=7.4 Hz, 1H, H_2, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.9 ($OSiCH_2CH_3$, *syn*), 5.0 ($OSiCH_2CH_3$, *anti*), 6.8 ($OSiCH_2CH_3$, *syn*), 6.9 ($OSiCH_2CH_3$, *anti*), 19.7 (C_5, *anti*), 21.1 (CH_3, *syn*), 22.9 (CH_3, *anti*), 24.7 (C_5, *syn*), 26.7 (CH_3, *syn*), 27.7 (CH_3, *anti*), 36.9 (C_4, *syn*), 37.0 (C_4, *anti*), 42.3 (C_3, *syn*), 43.7 (C_3, *anti*), 49.8 (C_1, *anti*), 50.8 (C_1, *syn*), 51.4 (OCH_3, *anti*), 51.5 (OCH_3, *syn*), 83.1 (C_2, *anti*), 83.5 (C_2, *syn*), 174.3 (CO_2CH_3, *anti*), 176.9 (CO_2CH_3, *syn*); **FTIR** (film) ν cm^{-1}: 1738; **LRMS** (FAB^+) *m/z*: 287 (M+H, 3%), 257 (M-Et, 10%), 255 (M-OCH_3, 5%), 155 (18%), 125 (60%), 95 (100%); **HRMS** (CI^+) *m/z*: Requires 287.20423 for $C_{15}H_{31}O_3Si$ (M+H), found 287.203.

Methyl 2-triethylsilyloxy-spiro[4.5]decane-carboxylate 161



syn-**161**



anti-**161**

$C_{18}H_{34}O_3Si$

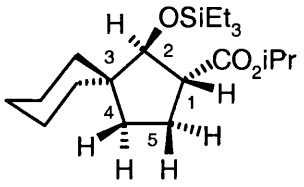
M= 326.22 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-4-(1-formyl-cyclohexyl)-2-butenoate **103a** (400 mg, 1.9 mmol), triethylsilane (470 mg, 4.0 mmol) and tris(triphenylphosphine) rhodium chloride (18 mg, 0.019 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **161** (333 mg, 54%) as a mixture of diastereomers in a *syn:anti* 2:1 ratio as a colourless oil.

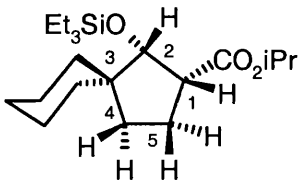
Rf (P.E./EtOAc, 9:1): 0.60; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.55-0.60 (q, *J*=7.8 Hz, 6H, OSiCH_2CH$_3$, *syn* + *anti*), 0.94 (t, *J*=7.8 Hz, 9H, OSiCH$_2$CH_3, *anti*), 0.95 (t, *J*=7.8 Hz, 9H, OSiCH$_2$CH_3, *syn*), 1.23-1.31 (m, 6H, CH_2, *syn* + *anti*), 1.44-1.49 (m, 1H, H_{4eq}, *syn* + *anti*), 1.53-1.58 (m, 4H, CH_2, *syn* + *anti*), 1.62-1.65 (m, 1H, H_{4ax}, *syn* + *anti*), 1.69-1.74 (m, 1H, H_{5eq}, *syn*), 1.75-1.81 (m, 1H, H_{5eq}, *anti*), 1.89-1.97 (m, 1H, H_{5ax}, *anti*), 2.12-2.20 (m, 1H, H_{5ax}, *syn*), 2.74 (td, *J*=10.4 Hz, *J*=7.9 Hz, 1H, H_1, *anti*), 2.99 (td, *J*=9.0 Hz, *J*=5.3 Hz, 1H, H_1, *syn*), 3.64 (s, 3H, OCH_3, *syn*), 3.65 (s, 3H, OCH_3, *anti*), 3.90 (d, *J*=7.9 Hz, 1H, H_2, *anti*), 3.98 (d, *J*=5.3 Hz, 1H, H_2, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 5.4 (OSiCH_2CH$_3$, *anti*), 5.5 (OSiCH_2CH$_3$, *syn*), 7.0 (OSiCH$_2$$CH_3$, *anti*), 7.1 (OSiCH$_2$$CH_3$, *syn*), 22.8 ($CH_2$, Cy, *anti*), 23.3 ($CH_2$, Cy, *syn*), 23.7 ($CH_2$, Cy, *syn*), 23.9 ($C_5$, *syn*), 24.2 ($CH_2$, Cy, *anti*), 25.0 ($C_5$, *anti*), 26.8 ($CH_2$, Cy, *syn*), 26.9 ($CH_2$, Cy, *anti*), 30.0 ($CH_2$, Cy, *anti*), 31.9 ($C_4$, *anti*), 32.2 ($C_4$, *syn*), 32.3 ($CH_2$, Cy, *syn*), 36.4 ($CH_2$, Cy, *syn*), 36.6 ($CH_2$, Cy, *anti*), 46.2 ($C_3$, *anti*), 47.9 ($C_3$, *syn*), 49.7 ($C_1$, *syn*), 50.7 ($C_1$, *anti*), 51.4 (O$CH_3$, *syn*), 51.7 (O$CH_3$, *anti*), 83.9 ($C_2$, *syn*), 84.4 ($C_2$, *anti*), 175.7 ($CO_2CH_3$, *syn*), 178.8 ($CO_2CH_3$, *anti*); **FTIR** (film) ν cm^{-1}: 1738; **LRMS** (CI$^+$) *m/z:* 326 (M, 10%), 298 (100%), 195

(49%), 135 (54%); **HRMS** (CI^+) *m/z*: Requires 326.22771 for $C_{18}H_{34}O_3Si$ (M), found 326.22536.

<u>*iso*-Propyl 2-triethylsilyloxy-spiro[4.5]decane-carboxylate 162</u>



syn-**<u>162</u>**



anti-**<u>162</u>**

$C_{20}H_{38}O_3Si$

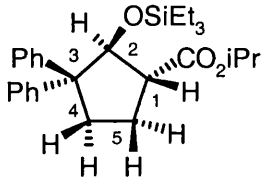
M= 354.26 g.mol^{-1}

According to the general procedure, reaction of *iso*-propyl (*E*)-4-(1-formyl-cyclohexyl)-2-butenoate **<u>103b</u>** (500 mg, 2.1 mmol), triethylsilane (510 mg, 4.4 mmol) and tetrakis(triphenylphosphine) rhodium hydride (24 mg, 0.021 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (95:5), silyl-protected cyclopentanol **<u>162</u>** (437 mg, 59%) as a mixture of diastereomers in a *syn:anti* 1:2 ratio as a colourless oil.

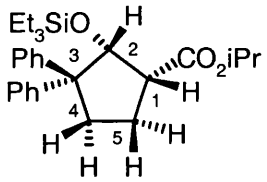
Rf (P.E./EtOAc, 9:1): 0.75; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.50-0.54 (q, *J*=7.8 Hz, 6H, OSiC*H*$_2$CH$_3$, *syn* + *anti*), 0.86-0.90 (t, *J*=7.8 Hz, 9H, OSiCH$_2$C*H*$_3$, *anti*), 0.95 (t, *J*=7.8 Hz, 9H, OSiCH$_2$C*H*$_3$, *syn*), 1.15-1.21 (m, 12H, C*H*$_2$, (C*H*$_3$)$_2$, *syn* + *anti*), 1.24-1.41 (m, 1H, *H*$_{4eq}$, *syn* + *anti*), 1.42-1.56 (m, 4H, C*H*$_2$, *syn* + *anti*), 1.57-1.61 (m, 1H, *H*$_{4ax}$, *syn* + *anti*), 1.64-1.71 (m, 1H, *H*$_{5eq}$, *syn* + *anti*), 1.85-1.93 (m, 1H, *H*$_{5ax}$, *anti*), 2.07-2.12 (m, 1H, *H*$_{5ax}$, *syn*), 2.60 (dt, *J*=10.4 Hz, *J*=7.3 Hz, 1H, *H*$_1$, *anti*), 2.84 (td, *J*=9.2 Hz, *J*=5.2 Hz, 1H, *H*$_1$, *syn*), 3.88 (d, *J*=7.3 Hz, 1H, *H*$_2$, *anti*), 3.89 (d, *J*=5.2 Hz, 1H, *H*$_2$, *syn*), 4.89 (m, 1H, OC*H*(CH$_3$)$_2$, *syn*), 4.91 (m, 1H, OC*H*(CH$_3$)$_2$, *anti*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.1 (OSi*C*H$_2$CH$_3$, *anti*), 4.2 (OSi*C*H$_2$CH$_3$, *syn*), 5.9 (OSiCH$_2$*C*H$_3$, *anti*), 6.0 (OSiCH$_2$*C*H$_3$, *syn*), 20.0 (*C*H$_3$, *anti*), 20.8 (*C*H$_3$, *syn*), 21.6 (*C*H$_2$, Cy, *anti*), 22.0 (*C*H$_2$, Cy, *syn*), 22.3 (*C*H$_2$, Cy, *syn*), 22.6 (*C*$_5$, *syn*), 22.7 (*C*H$_2$, Cy, *anti*), 24.1 (*C*$_5$, *anti*), 25.3 (*C*H$_2$, Cy, *syn*), 25.5 (*C*H$_2$, Cy, *anti*), 27.9 (*C*H$_2$, Cy, *anti*), 30.9 (*C*$_4$, *anti*), 31.1 (*C*$_4$, *syn*), 33.1 (*C*H$_2$, Cy, *syn*), 34.8

(CH_2, Cy, *anti*), 35.4 (CH_2, Cy, *syn*), 45.0 (C_3, *anti*), 46.2 (C_3, *syn*), 48.9 (C_1, *syn*), 50.0 (C_1, *anti*), 66.4 (O$CH(CH_3)_2$, *syn*), 66.5 (O$CH(CH_3)_2$, *anti*), 82.3 (C_2, *anti*), 82.4 (C_2, *syn*), 171.8 (CO_2*i*Pr, *syn*), 174.7 (CO_2*i*Pr, *anti*); **FTIR** (film) ν cm^{-1}: 2934, 2858, 1717, 1452, 1375, 1107, 908; **LRMS** (CI^+) *m/z:* 355 (M+H, 80%), 313 (18%), 283 (39%), 223 (100%); **HRMS** (CI^+) *m/z: R*equires 355.26683 for $C_{20}H_{39}O_3Si$ (M+H), found 355.26676.

<u>*iso*-Propyl 3,3-diphenyl-2-triethylsilyloxy-cyclopentanecarboxylate 163</u>



syn-**<u>163</u>**



anti-**<u>163</u>**

$C_{27}H_{38}O_3Si$

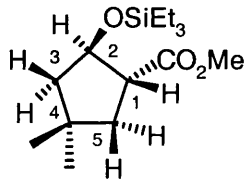
M= 438.26 $g.mol^{-1}$

According to the general procedure, reaction of *iso*-propyl (*E*)-5,5-diphenyl-6-oxo-2-hexenoate **<u>104</u>** (700 mg, 2.2 mmol), triethylsilane (530 mg, 4.6 mmol) and tetrakis(triphenylphosphine) rhodium hydride (25 mg, 0.022 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **<u>163</u>** (647 mg, 68%) as a mixture of diastereomers in a *syn:anti* 1:2.5 ratio as a colourless oil.

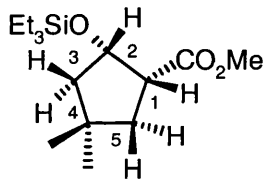
Rf (P.E./EtOAc, 9:1): 0.81; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.09-0.26 (q, *J*=7.8 Hz, 6H, OSiCH_2CH_3, *syn* + *anti*), 0.56 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$, *syn*), 0.59 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$, *anti*), 1.02 (d, *J*=6.3 Hz, 3H, CH_3, *anti*), 1.03 (d, *J*=6.3 Hz, 3H, CH_3, *syn*), 1.05 (d, *J*=6.3 Hz, 3H, CH_3, *anti*), 1.06 (d, *J*=6.3 Hz, 3H, CH_3, *syn*), 1.42-1.48 (m, 1H, H_{5eq}, *syn*), 1.49-1.54 (m, 1H, H_{5eq}, *anti*), 1.79-1.86 (m, 1H, H_{5ax}, *anti*), 2.11-2.16 (m, 1H, H_{5ax}, *syn*), 2.17 (dt, *J*=12.9 Hz, *J*=7.7 Hz, 1H, H_{4eq}, *anti*), 2.27 (ddd, *J*=12.9 Hz, *J*=7.7 Hz, *J*=5.9 Hz, 1H, H_{4ax}, *anti*), 2.29-2.32 (m, 1H, H_{4eq}, *syn*), 2.68 (ddd, *J*=12.0 Hz, *J*=11.0 Hz, *J*=9.2 Hz, 1H, H_{4ax}, *syn*), 2.70 (dt, *J*=11.0 Hz, *J*=6.3 Hz, 1H, H_1, *anti*), 2.89 (ddd, *J*=11.0 Hz, *J*=7.4 Hz, *J*=3.7 Hz, 1H,

H_1, *syn*), 4.74-4.82 (m, 1H, OC*H*$(CH_3)_2$, *syn* + *anti*), 4.85 (d, *J*=6.3 Hz, 1H, H_2, *anti*), 5.13 (d, *J*=3.7 Hz, 1H, H_2, *syn*), 6.93-7.19 (m, 10H, Ph, *syn* + *anti*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 5.2 (OSi*C*H_2CH_3, *anti*), 5.4 (OSi*C*H_2CH_3, *syn*), 7.2 (OSiCH_2*C*H_3, *anti*), 7.4 (OSiCH_2*C*H_3, *syn*), 22.2 (*C*H_3, *anti*), 22.3 (*C*H_3, *syn*), 22.5 (C_4, *syn*), 25.7 (C_4, *anti*), 32.8 (C_5, *syn*), 35.5 (C_5, *anti*), 50.2 (C_1, *syn*), 51.7 (C_1, *anti*), 59.5 (C_3, *anti*), 61.7 (C_3, *syn*), 68.2 (O*C*H$(CH_3)_2$, *syn*), 68.3 (O*C*H$(CH_3)_2$, *anti*), 81.2 (C_2, *syn*), 82.1 (C_2, *anti*), 126.1 (Ph, *syn* + *anti*), 126.4 (Ph, *syn* + *anti*), 126.9 (Ph, *syn*), 127.8 (Ph, *anti*), 127.9 (Ph, *anti*), 128.0 (Ph, *anti*), 128.4 (Ph, *syn*), 128.6 (Ph, *syn*), 128.9 (Ph, *syn*), 129.8 (Ph, *anti*), 145.1 (Ph, *anti*), 145.8 (Ph, *syn*), 146.6 (Ph, *syn*), 146.8 (Ph, *anti*), 172.6 (*C*O_2*i*Pr, *syn*), 175.2 (*C*O_2*i*Pr, *anti*); **FTIR** (film) ν cm^{-1}: 3059, 3028, 2955, 2912, 2876, 1728, 1661, 1651, 1599, 1495, 1447, 1373, 1265, 1109; **LRMS** (FAB^+) *m/z:* 439 (M+H, 33%), 409 (M-Et, 42%), 367 (25%), 349 (38%), 219 (77%); **HRMS** (FAB^+) *m/z:* Requires 439.26680 for $C_{27}H_{39}O_3Si$ (M+H), found 439.26640; **Crystal data for $C_{27}H_{38}O_3Si$:** M= 438.66, triclinic, *a*=8.6086(11), *b*= 8.9819(12), *c*=17.411(2) Å, *U*= 1285.6(3) $Å^3$, *T*= 293K, space group *P 1*, *Z*= 2, *&*(Mo-K_α) 0.115 mm^{-1}, 11181 reflections measured, 5848 unique F^2 values used in refinement (R_{int}= 0.0210). R_1[4707 with $F^2>2\sigma$]= 0.0543, wR_2(all data)= 0.1570 (see tabulation in appendices).

Methyl 4,4-dimethyl-2-triethylsilyloxy-cyclopentanecarboxylate 164



syn-**164**



anti-**164**

$C_{15}H_{30}O_3Si$

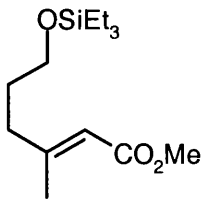
M= 286.20 $g.mol^{-1}$

According to the general procedure, reaction of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (500 mg, 2.9 mmol), triethylsilane (720 mg, 6.2 mmol) and tetrakis(triphenylphosphine) rhodium hydride (34 mg, 0.029 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-

40°C/EtOAc (90:10), silyl-protected cyclopentanol **164** (513 mg, 61%) as a mixture of diastereomers in a *syn:anti* 1:11 ratio as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **164** in 93% yield as a mixture of diastereomers in a *syn:anti* 2.2:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.59; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.50-0.56 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *syn* + *anti*), 0.88-0.93 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *syn* + *anti*), 0.95 (s, 3H, CH_3, *syn*), 1.05 (s, 3H, CH_3, *anti*), 1.06 (s, 3H, CH_3, *anti*), 1.13 (s, 3H, CH_3, *syn*), 1.45 (dd, *J*=12.9 Hz, *J*=7.2 Hz, 1H, H_{3ax}, *anti*), 1.54 (dd, *J*=12.9 Hz, *J*=7.7 Hz, 1H, H_{5eq}, *syn*), 1.56 (dd, *J*=13.3 Hz, *J*=3.7 Hz, 1H, H_{3eq}, *syn*), 1.58 (dd, *J*=12.9 Hz, *J*=10.0 Hz, 1H, H_{5ax}, *anti*), 1.71 (dd, *J*=13.3 Hz, *J*=5.7 Hz, 1H, H_{3ax}, *syn*), 1.77 (dd, *J*=12.9 Hz, *J*=7.2 Hz, 1H, H_{3eq}, *anti*), 1.79 (dd, *J*=12.9 Hz, *J*=8.9 Hz, 1H, H_{5eq}, *anti*), 2.09 (dd, *J*=12.9 Hz, *J*=11.0 Hz, 1H, H_{5ax}, *syn*), 2.83 (ddd, *J*=10.0 Hz, *J*=8.9 Hz, *J*=7.2 Hz, 1H, H_1, *anti*), 2.93 (ddd, *J*=11.0 Hz, *J*=7.7 Hz, *J*=5.7 Hz, 1H, H_1, *syn*), 3.63 (s, 3H, OCH_3, *syn*), 3.65 (s, 3H, OCH_3, *anti*), 4.45 (q, *J*=7.2 Hz, 1H, H_2, *anti*), 4.53 (td, *J*=5.7 Hz, *J*=3.7 Hz, 1H, H_2, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.4 ($OSiCH_2CH_3$, *syn*), 4.6 ($OSiCH_2CH_3$, *anti*), 6.4 ($OSiCH_2CH_3$, *syn*), 6.7 ($OSiCH_2CH_3$, *anti*), 27.3 (CH_3, *syn*), 30.3 (CH_3, *anti*), 36.6 (C_4, *syn*), 37.2 (C_4, *anti*), 40.6 (CH_2, *syn*), 43.0 (CH_2, *anti*), 50.1 (CH_2, *anti*), 50.5 (CH_2, *syn*), 50.8 (C_1, *syn*), 51.2 (OCH_3, *syn*), 51.5 (C_1, *anti*), 53.2 (OCH_3, *anti*), 75.4 (C_2, *syn*), 76.5 (C_2, *anti*), 173.1 (CO_2CH_3, *syn*), 175.9 (CO_2CH_3, *anti*); **FTIR** (film) ν cm^{-1}: 2955, 2876, 1740, 1460, 1435, 1171; **LRMS** (FAB^+) *m/z:* 287 (M+H, 3%), 257 (M-Et, 10%), 255 (M-OCH_3, 5%), 155 (18%), 125 (60%), 95 (100%); **HRMS** (CI^+) *m/z*: Requires 287.20423 for $C_{15}H_{31}O_3Si$ (M+H), found 287.20397.

Methyl (*E*)-3-methyl-6-triethylsilanyloxy-hex-2-enoate 165



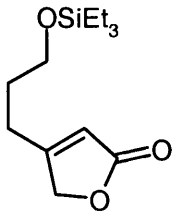
$C_{14}H_{28}O_3Si$

M= 272.18 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-3-methyl-6-oxo-2-hexenoate **127** (500 mg, 3.2 mmol), triethylsilane (780 mg, 6.7 mmol) and tetrakis(triphenylphosphine) rhodium hydride (37 mg, 0.032 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected hexenoate **165** (340 mg, 39%) as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave silyl-protected hexenoate **165** in 35% yield as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.70; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.52 (q, *J*=7.8 Hz, 6H, $OSiC\mathit{H}_2CH_3$), 0.89 (t, *J*=7.8 Hz, 9H, $OSiCH_2C\mathit{H}_3$), 1.60-1.65 (m, 2H, $C\mathit{H}_2CH_2OSi$), 2.09 (d, *J*=1.2 Hz, 3H, $C\mathit{H}_3$), 2.14 (td, *J*=7.8 Hz, *J*=1.1 Hz, 2H, $CH_2C\mathit{H}_2C$=), 3.52 (t, *J*=6.5 Hz, 2H, $C\mathit{H}_2OSi$), 3.61 (s, 3H, $OC\mathit{H}_3$), 5.61-5.64 (m, 1H, $=C\mathit{H}CO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 3.5 ($OSi\mathit{C}H_2CH_3$), 5.7 ($OSiCH_2\mathit{C}H_3$), 17.8 ($\mathit{C}H_3$), 29.7 ($\mathit{C}H_2CH_2OSi$), 36.3 ($CH_2\mathit{C}H_2C$=), 49.7 ($O\mathit{C}H_3$), 61.1 ($\mathit{C}H_2OSi$), 114.2 ($=\mathit{C}HCO_2CH_3$), 159.0 (C=$CHCO_2CH_3$), 166.2 ($\mathit{C}O_2CH_3$); **FTIR** (film) ν cm^{-1}: 2876, 1728, 1651, 1435, 1360, 1101; **LRMS** (DCI$^+$) *m/z:* 273 (M+H, 100%), 258 (5%), 243 (34%), 132 (28); **HRMS** (DCI$^+$) *m/z:* Requires 273.18858 for $C_{14}H_{29}O_3Si$ (M+H), found 273.18821.

4-(3-Triethylsilanyloxy-propyl)-5*H*-furan-2-one 166



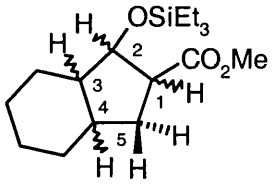
$C_{13}H_{24}O_3Si$

M= 256.15 g.mol^{-1}

According to the general procedure, reaction of 3-(5-oxo-2,5-dihydrofuran-3-yl)propionaldehyde **129** (120 mg, 8.6 mmol), triethylsilane (290 mg, 1.8 mmol) and tris(triphenylphosphine) rhodium chloride (8 mg, 8.6 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected furanone **166** (94 mg, 43%) as a colourless oil.

Rf (EtOAc): 0.62; **^{1}H NMR** (CD_2Cl_2, 300 MHz) δ ppm: 0.49 (q, *J*=7.8 Hz, 6H, OSiC*H*$_2$CH$_3$), 0.88 (t, *J*=7.8 Hz, 9H, OSiCH$_2$C*H*$_3$), 1.70-1.75 (m, 2H, C*H*$_2$CH$_2$OSi), 2.42 (td, *J*=7.9 Hz, *J*=1.8 Hz, 2H, CH$_2$C*H*$_2$C=), 3.58 (t, *J*=7.8 Hz, 2H, C*H*$_2$OSi), 4.67 (d, *J*=1.8 Hz, 2H, =CC*H*$_2$O), 5.71-5.76 (m, 1H, =C*H*CO$_2$R); **^{13}C NMR** (CD_2Cl_2, 75.5 MHz) δ ppm: 3.2 (OSi*C*H$_2$CH$_3$), 5.7 (OSiCH$_2$*C*H$_3$), 24.4 (*C*H$_2$CH$_2$OSi), 29.6 (CH$_2$*C*H$_2$C=), 60.8 (*C*H$_2$OSi), 72.4 (O*C*H$_2$C=), 114.3 (=*C*HCO$_2$R), 170.0 (*C*=CHCO$_2$R), 173.1 (*C*O$_2$R); **FTIR** (film) ν cm^{-1}: 2957, 2876, 1747, 1655, 1456, 1414, 1379, 1238, 1074; **LRMS** (DCI$^+$) *m/z:* 257 (M+H, 81%), 227 (M-Et, 47%), 197 (12%), 115 (15%); **HRMS** (DCI$^+$) *m/z:* Requires 257.15728 for $C_{13}H_{25}O_3Si$ (M+H), found 257.15669.

Methyl 1-Triethylsilanyloxy-octahydro-indene-2-carboxylate 167



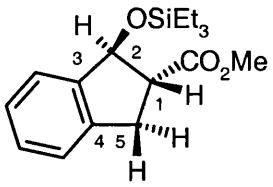
$C_{17}H_{32}O_3Si$

M= 312.21 g.mol^{-1}

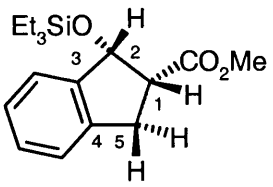
According to the general procedure, reaction of methyl (*E*)-3-(2-formyl-cyclohexyl)-acrylate **134** (400 mg, 2.0 mmol), triethylsilane (500 mg, 4.3 mmol) and tetrakis(triphenylphosphine) rhodium hydride (24 mg, 0.02 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **167** (983 mg, 81%) as a complex mixture of diastereomers as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.80; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.55-0.58 (q, *J*=7.8 Hz, 6H, $OSiCH_2CH_3$), 0.90-0.97 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$), 1.05-2.34 (m, 12H, CH_2, H_3, H_4 and H_5), 2.58-3.10 (m, 1H, H_1), 3.64-3.68 (s, 3H, OCH_3), 3.73-4.39 (m, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.4-3.9 ($OSiCH_2CH_3$), 5.7-5.8 ($OSiCH_2CH_3$), 19.9-33.5 (CH_2), 33.9-52.3 (CH, OCH_3), 75.6 (C_2), 77.7 (C_2), 78.2 (C_2), 78.3 (C_2), 78.5 (C_2), 80.2 (C_2), 172.9 (CO_2CH_3), 173.2 (CO_2CH_3), 173.6 (CO_2CH_3), 175.7 (CO_2CH_3), 176.2 (CO_2CH_3), 176.4 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3053, 2930, 2878, 2855, 1732, 1435, 1265; **LRMS** (FAB$^+$) *m/z:* 313 (M+H, 8%), 283 (M-Et, 100%), 267 (5%), 251 (31%), 221 (34%), 207 (25%); **HRMS** (FAB$^+$) *m/z:* Requires 313.21988 for $C_{17}H_{33}O_3Si$ (M+H), found 313.21948.

Methyl 2-triethylsilyloxy-3,4-phenyl-cyclopentane carboxylate 168[80]



syn-**168**



anti-**168**

$C_{17}H_{26}O_3Si$

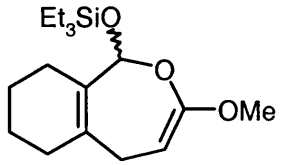
M= 306.17 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-3-(2'-formylphenyl)-propenoate **140** (250 mg, 1.3 mmol), triethylsilane (320 mg, 2.8 mmol) and tetrakis(triphenylphosphine) rhodium hydride (15 mg, 0.013 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **168** (278 mg, 69%) as a mixture of diastereomers in a *syn:anti* 1:20 ratio as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **168** in 61% yield as a mixture of diastereomers in a *syn:anti* 1.5:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.79; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.62 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *syn* + *anti*), 0.91 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *syn* + *anti*), 2.88 (dd, *J*=11.2 Hz, *J*=7.8 Hz, 1H, H_{5eq}, *syn*), 2.98 (dd, *J*=15.0 Hz, *J*=8.5 Hz, 1H, H_{5eq}, *anti*), 3.11 (dt, *J*=8.5 Hz, *J*=6.7 Hz, 1H, H_1, *anti*), 3.19 (dd, *J*=15.0 Hz, *J*=8.5 Hz, 1H, H_{5ax}, *anti*), 3.28 (dt, *J*=7.8 Hz, *J*=6.2 Hz, 1H, H_1, *syn*), 3.47 (dd, *J*=11.2 Hz, *J*=7.8 Hz, 1H, H_{5ax}, *syn*), 3.68 (s, 3H, OCH_3, *anti*), 3.73 (s, 3H, OCH_3, *syn*), 5.34 (d, *J*=6.2 Hz, 1H, H_2, *syn*), 5.51 (d, *J*=6.7 Hz, 1H, H_2, *anti*), 7.13-7.64 (m, 4H, Ph, *syn* + *anti*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.0 ($OSiCH_2CH_3$, *anti*), 5.7 ($OSiCH_2CH_3$, *anti*), 33.2 (C_5, *anti*), 50.6 (OCH_3, *anti*), 53.6 (C_1, *anti*), 78.2 (C_2, *anti*), 123.0 (Ph, *anti*), 123.4 (Ph, *anti*), 126.1 (Ph, *anti*), 127.5 (Ph, *anti*), 138.6 (Ph, *anti*), 142.9 (Ph, *anti*), 174.0 (CO_2CH_3, *anti*); **FTIR** (film) ν cm^{-1}: 2955, 2877, 1731, 1637, 1437, 1351, 909; **LRMS** (ES$^+$) *m/z:* 324 (M+NH_4, 100%), 307 (M+H, 44%),

246 (61%), 175 (93%); **HRMS** (ES^+) *m/z:* Requires 307.1729 for $C_{17}H_{27}O_3Si$ (M+H), found 307.1735.

Triethyl-(3-methoxy-1,5,6,7,8,9-hexahydro-benzo[c]oxepin-1-yloxy)-silane 169



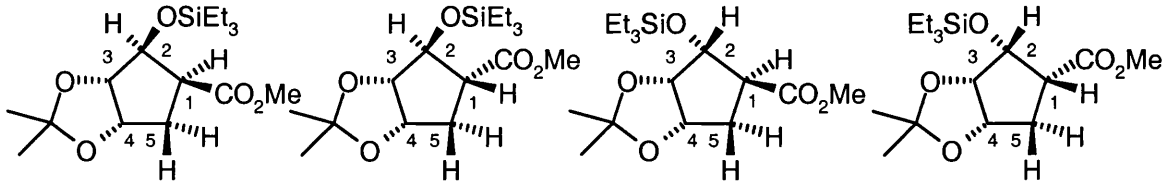
$C_{17}H_{30}O_3Si$

M= 310.20 $g.mol^{-1}$

According to the general procedure, reaction of methyl (*E*)-3-(2-formyl-cyclohex-1-enyl)-acrylate **137b** (300 mg, 1.6 mmol), triethylsilane (380 mg, 3.3 mmol) and tetrakis(triphenylphosphine) rhodium hydride (18 mg, 0.016 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected hexahydro-benzo[c]oxepin **169** (422 mg, 88%) as an orange oil.

Rf (P.E./EtOAc, 9:1): 0.57; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.56 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$), 0.88 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$), 1.51-1.54 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.90-1.94 (m, 2H, CH_2CH_2C=), 2.08-2.11 (m, 2H, CH_2CH_2C=), 2.95 (d, *J*=6.6 Hz, 2H, $=CCH_2CH$=), 3.59 (s, 3H, OCH_3), 5.35 (t, *J*=6.6 Hz, 1H, CH_2CH=), 6.02 (s, 1H, OCHOSi); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 4.8 ($OSiCH_2CH_3$), 6.8 ($OSiCH_2CH_3$), 28.5 (CH_2), 28.8 (CH_2), 31.9 (CH_2), 35.3 (CH_2), 37.3 ($=CCH_2CH$=), 51.8 (OCH_3), 116.2 (CH=C(O)OCH_3), 119.4 (CH_2C=CCH_2), 132.4 (OCHOSi), 138.4 (CH_2C=CCH_2), 174.1 (=C(O)OCH_3); **FTIR** (film) ν cm^{-1}: 2934, 2878, 1736, 1439, 1265, 1173; **LRMS** (ES^+) *m/z:* 328 ($M+NH_4$, 18%), 311 (M+H, 100%), 246 (11%); **HRMS** (ES^+) *m/z:* Requires 311.2042 for $C_{17}H_{31}O_3Si$ (M+H), found 311.2439.

Methyl 2-triethylsilyloxy-3,4-isopropylidene-dioxy-cyclopentane carboxylate 170[80]



170a **170b** **170c** **170d**

$C_{16}H_{31}O_5Si$

M= 330.19 g.mol^{-1}

According to the general procedure, reaction of methyl (4R, 5S)-6-oxo-4,5-isopropylidenedioxy-2-hexenoate **147b** (4.0 g, 19 mmol), triethylsilane (4.6 g, 39 mmol) and tetrakis(triphenylphosphine) rhodium hydride (220 mg, 0.19 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **170** (4.95 g, 81%) as four diastereomers in a **170a**:**170b**:**170c**:**170d** 5.4:4:2:1 ratio, three of which were isolated in a pure form as colourless oils. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **170** in 65% yield as a mixture of diastereomers in a **170a**:**170b**:**170c**:**170d** 2:5.4:2:1 ratio as a colourless oil.

(1*S*, 2*S*, 3*S*, 4*S*) isomer 170a

Rf (P.E./EtOAc, 9:1): 0.63; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.51 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.86 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.21 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.89 (dd, *J*=13.8 Hz, *J*=6.3 Hz, 1H, H_{5eq}), 2.24 (ddd, *J*=13.8 Hz, *J*=10.7 Hz, *J*=5.4 Hz, 1H, H_{5ax}), 3.02 (ddd, *J*=10.7 Hz, *J*=6.3 Hz, *J*=4.0 Hz, 1H, H_1), 3.60 (s, 3H, OCH_3), 4.20 (d, *J*=5.4 Hz, 1H, H_3), 4.28 (d, *J*=4.0 Hz, 1H, H_2), 4.67 (t, *J*=5.4 Hz, 1H, H_4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.7 ($OSiCH_2CH_3$), 5.7 ($OSiCH_2CH_3$), 22.8 (CH_3), 25.1 (CH_3), 30.8 (C_5), 46.2 (C_1), 50.4 (OCH_3), 76.8 (C_2), 78.2 (C_4), 84.9 (C_3), 108.9 ($OC(CH_3)_2$), 171.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 2936, 2878, 1733 (C=O), 1439, 1376, 1262, 902; **LRMS** (FAB$^+$) *m/z:* 331 (M+H, 20%), 301 (M-Et, 100%), 241 (15%), 211 (10%), 187 (10%); **HRMS** (FAB$^+$) *m/z:* Requires

331.19406 for $C_{16}H_{31}O_5Si$ (M+H), found 331.19408; $[\alpha]^{20}_D$: -20.7° (*c* = 0.50, $CHCl_3$/MeOH 9:1).

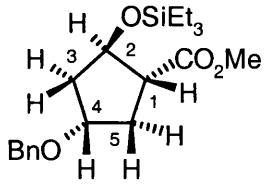
(1*R*, 2*S*, 3*S*, 4*S*) isomer 170b

***R*f** (P.E./EtOAc, 9:1): 0.59; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.54 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.88 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.19 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.14 (ddd, *J*=14.2 Hz, *J*=8.2 Hz, *J*=5.9 Hz, 1H, H_{5ax}), 2.25 (ddd, *J*=14.2 Hz, *J*=3.5 Hz, *J*=2.1 Hz, 1H, H_{5eq}), 2.67 (dt, *J*=8.2 Hz, *J*=3.5 Hz, 1H, H_1), 3.61 (s, 3H, OCH_3), 4.25 (d, *J*=5.9 Hz, 1H, H_3), 4.54 (d, *J*=3.5 Hz, 1H, H_2), 4.64 (td, *J*=5.9 Hz, *J*=2.1 Hz, 1H, H_4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.6 ($OSiCH_2CH_3$), 5.7 ($OSiCH_2CH_3$), 23.1 (CH_3), 24.8 (CH_3), 31.5 (C_5), 50.4 (C_1), 50.7 (OCH_3), 77.9 (C_2), 78.7 (C_4), 86.1 (C_3), 109.8 ($OC(CH_3)_2$), 171.7 (CO_2CH_3); $[\alpha]^{20}_D$: -7.1° (*c* = 0.43, CH_2Cl_2).

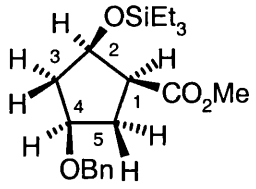
(1*S*, 2*R*, 3*S*, 4*S*) isomer 170c

***R*f** (P.E./EtOAc, 9:1): 0.56; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.56 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.88 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.22 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.65 (ddd, *J*=14.0 Hz, *J*=12.4 Hz, *J*=5.2 Hz, 1H, H_{5ax}), 1.89 (dd, *J*=14.0 Hz, *J*=6.4 Hz, 1H, H_{5eq}), 2.95 (ddd, *J*=12.4 Hz, *J*=10.1 Hz, *J*=6.4 Hz, 1H, H_1), 3.62 (s, 3H, OCH_3), 3.96 (dd, *J*=10.1 Hz, *J*=5.2 Hz, 1H, H_2), 4.29 (t, *J*=5.2 Hz, 1H, H_3), 4.50 (d, *J*=5.2 Hz, 1H, H_4); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.6 ($OSiCH_2CH_3$), 5.6 ($OSiCH_2CH_3$), 23.1 (CH_3), 25.1 (CH_3), 31.7 (C_5), 45.6 (C_1), 50.7 (OCH_3), 76.4 (OCH), 76.6 (OCH), 78.4 (OCH), 109.1 ($OC(CH_3)_2$), 177.1 (CO_2CH_3); $[\alpha]^{20}_D$: +38° (*c* = 0.50, CH_2Cl_2).

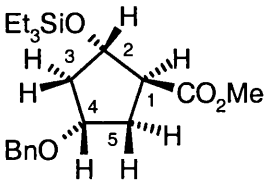
Methyl 2-triethylsilyloxy-4-benzyloxy-cyclopentane carboxylate 171[80]



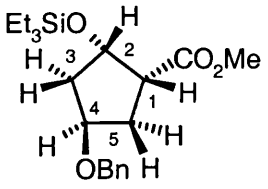
171a



171b



171c



171d

$C_{20}H_{32}O_4Si$

M= 364.20 g.mol^{-1}

According to the general procedure, reaction of methyl 6-oxo-4-benzyloxy-2-hexenoate **142** (250 mg, 1 mmol), triethylsilane (250 mg, 2.1 mmol) and tetrakis(triphenylphosphine) rhodium hydride (12 mg, 0.01 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclopentanol **171** (263 mg, 72%) as four diastereomers in a **171a**:**171b**: **171c**:**171d** 1.2:1:1.2:1.7 ratio, three of which were isolated in a pure form as colourless oils. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave cyclopentanol **171** in 81% yield as a mixture of diastereomers in a **171a**:**171b**:**171c**:**171d** 1.5:1:1:1.7 ratio as a colourless oil.

Isomer 171a

Rf (P.E./EtOAc, 9:1): 0.68; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.54 (q, *J*=7.7 Hz, 6H, OSiC*H*$_2$CH$_3$), 0.90 (t, *J*=7.7 Hz, 9H, OSiCH$_2$C*H*$_3$), 1.71 (ddd, *J*=13.6 Hz, *J*=7.0 Hz, *J*=6.6 Hz, 1H, H_{3eq}), 1.93 (ddd, *J*=13.3 Hz, *J*=9.9 Hz, *J*=6.5 Hz, 1H, H_{5eq}), 2.09 (ddd, *J*=13.3 Hz, *J*=8.1 Hz, *J*=3.6 Hz, 1H, H_{5ax}); 2.31 (ddd, *J*=13.6 Hz, *J*=7.2 Hz, *J*=6.7 Hz, 1H, H_{3ax}), 2.92 (ddd, *J*=9.9 Hz, *J*=8.1 Hz, *J*=7.8 Hz, 1H, H_1), 3.64 (s, 3H, OC*H*$_3$), 3.95 (m, 1H, H_4), 4.29 (ddd, *J*=7.8 Hz, *J*=7.2 Hz, *J*=7.0 Hz, 1H, H_2), 4.42 (s, 2H, ArC*H*$_2$O), 7.29-7.42 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.6 (OSi*C*H$_2$CH$_3$), 6.7 (OSiCH$_2$*C*H$_3$), 34.6 (*C*H$_2$), 42.0 (*C*H$_2$), 51.1 (O*C*H$_3$), 51.7 (C_1), 70.7 (O*C*H$_2$Ph), 74.5 (C_4), 76.9 (C_2), 127.5 (Ph), 127.6 (Ph), 128.4 (Ph), 138.5 (Ph), 175.6 (*C*O$_2$CH$_3$); **FTIR** (film) ν cm^{-1}: 2953, 2912, 2876, 1739 (C=O), 1496 (C=C), 1455, 1436, 1354, 1116, 1058, 736, 697; **LRMS** (ES$^+$) *m/z:* 382 (M+NH$_4$, 72%), 365

(M+H, 100%), 251 (10%); **HRMS** (ES^+) *m/z:* Requires 382.2414 for $C_{20}H_{36}NO_4Si$ ($M+NH_4$), found 382.2404.

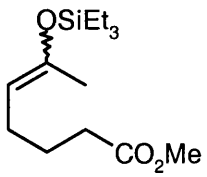
Isomer 171c

Rf (P.E./EtOAc, 9:1): 0.64; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.52 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.89 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.91-2.03 (m, 3H, H_{5eq} and H_3), 2.37 (ddd, *J*=13.8 Hz, *J*=8.9 Hz, *J*=6.7 Hz, 1H, H_{5ax}), 3.05 (ddd, *J*=9.3 Hz, *J*=8.9 Hz, *J*=5.8 Hz, 1H, H_1), 3.63 (s, 3H, OCH_3), 4.19 (m, 1H, H_4), 4.44 (d, *J*=11.9 Hz, 1H, $ArCH_aH_bO$), 4.46 (d, *J*=11.9 Hz, 1H, $ArCH_aH_bO$), 4.58 (td, *J*=9.3 Hz, *J*=5.4 Hz, 1H, H_2), 7.27-7.34 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.6 ($OSiCH_2CH_3$), 6.6 ($OSiCH_2CH_3$), 32.1 (CH_2), 42.7 (CH_2), 59.1 (C_1), 51.3 (OCH_3), 70.9 (OCH_2Ph), 73.9 (OCH), 78.5 (OCH), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.4 (Ph), 172.9 (CO_2CH_3).

Isomer 171d

Rf (P.E./EtOAc, 9:1): 0.60; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.52 (q, *J*=7.7 Hz, 6H, $OSiCH_2CH_3$), 0.89 (t, *J*=7.7 Hz, 9H, $OSiCH_2CH_3$), 1.78 (ddd, *J*=13.7 Hz, *J*=7.0 Hz, *J*=3.6 Hz, 1H, H_{3eq}), 2.15 (ddd, *J*=13.7 Hz, *J*=9.9 Hz, *J*=5.7 Hz, 1H, H_{3ax}), 2.09 (td, *J*=12.7 Hz, *J*=7.2 Hz, 1H, H_{5ax}), 2.26 (dt, *J*=12.7 Hz, *J*=7.5 Hz, 1H, H_{5eq}), 2.67 (ddd, *J*=12.7 Hz, *J*=7.5 Hz, *J*=5.7 Hz, 1H, H_1), 3.60 (s, 3H, OCH_3), 3.91 (m, 1H, H_4), 4.37 (td, *J*=5.7 Hz, *J*=3.6 Hz, 1H, H_2), 4.44 (d, *J*=11.9 Hz, 1H, $ArCH_aH_bO$), 4.46 (d, *J*=11.9 Hz, 1H, $ArCH_aH_bO$), 7.27-7.31 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.6 ($OSiCH_2CH_3$), 6.6 ($OSiCH_2CH_3$), 32.1 (CH_2), 41.5 (CH_2), 49.3 (C_1), 51.3 (OCH_3), 71.0 (OCH_2Ph), 72.3 (OCH), 77.1 (OCH), 127.3 (Ph), 127.5 (Ph), 128.2 (Ph), 139.0 (Ph), 172.2 (CO_2CH_3).

Methyl 6-triethylsilanyloxy-5-heptenoate 172



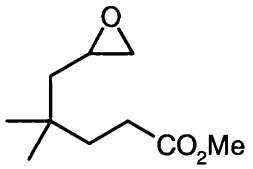
$C_{14}H_{28}O_3Si$

M= 272.18 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-6-oxo-2-heptenoate **127** (500 mg, 3.2 mmol), triethylsilane (781 mg, 6.7 mmol) and tris(triphenylphosphine) rhodium chloride (30 mg, 0.032 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected heptanoate **172** (724 mg, 83%) as a mixture of *E* and *Z* isomers in *E:Z* 1:5 ratio as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium hydride gave heptanoate **172** in 61% yield as a mixture of *E* and *Z* isomers in *E:Z* 1:5 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.69; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.99 (t, *J*=8.0 Hz, 9H, $OSiCH_2CH_3$, *Z* + *E*), 1.62-1.65 (m, 2H, $CH_2CH_2CH_2$, *Z* + *E*), 1.71 (d, *J*=1.0 Hz, 3H, CH_3, *E*), 1.77 (d, *J*=1.1 Hz, 3H, CH_3, *Z*), 1.95 (q, *J*=7.5 Hz, 2H, CH_2CH_2CH=, *E*), 2.02 (q, *J*=7.2 Hz, 2H, CH_2CH_2CH=, *Z*), 2.29 (t, *J*=7.5 Hz, 2H, $CH_2CO_2CH_3$, *Z* + *E*), 3.65 (s, 3H, OCH_3, *Z*), 3.66 (s, 3H, OCH_3, *E*), 4.33 (tq, *J*=7.2 Hz, *J*=1.1 Hz, 1H, CH=C(OSi)CH_3, *Z*), 4.60 (tq, *J*=7.5 Hz, *J*=1.0 Hz, 1H, CH=C(OSi)CH_3, *E*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm:4.9 ($OSiCH_2CH_3$, *Z*), 5.0 ($OSiCH_2CH_3$, *E*), 6.4 ($OSiCH_2CH_3$, *Z*), 6.5 ($OSiCH_2CH_3$, *E*), 17.6 (CH_3, *E*), 22.6 (CH_3, *Z*), 24.6 (CH_2CH_2C=, *Z*), 25.6 ($CH_2CH_2CH_2$, *Z* + *E*), 26.5 (CH_2CH_2C=, *E*), 33.3 ($CH_2CO_2CH_3$, *E*), 33.7 ($CH_2CO_2CH_3$, *Z*), 51.3 (OCH_3, *Z*), 51.4 (OCH_3, *E*), 106.4 (*C*H=C(OSi)CH_3, *E*), 107.0 (*C*H=C(OSi)CH_3, *Z*), 147.5 (CH=*C*(OSi)CH_3, *Z*), 148.7 (CH=*C*(OSi)CH_3, *E*), 174.2 (CO_2CH_3, *E*), 174.3 (CO_2CH_3, *Z*); **FTIR** (film) ν cm^{-1}: 3053, 2955, 2914, 2878, 1732, 1670, 1437, 1362, 1265; **LRMS** (CI$^+$) *m/z:* 273 (M+H, 51%), 243 (M-Et, 24%), 103 (100%); **HRMS** (CI$^+$) *m/z:* Requires 273.18858 for $C_{14}H_{29}O_3Si$ (M+H), found 273.18830.

Methyl 4,4-dimethyl-5-oxiranyl-pentanoate 173



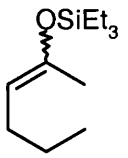
$C_{10}H_{18}O_3$

M= 186.13 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-4,4-dimethyl-5-oxiranyl-2-pentenoate **132** (60 mg, 0.33 mmol), triethylsilane (80 mg, 0.68 mmol) and tetrakis(triphenylphosphine) rhodium hydride (3.8 mg, 3.3 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), pentanoate **173** (36 mg, 60%) as a colourless oil. Repetition of the above experiment, but using tris(triphenylphosphine) rhodium chloride gave pentanoate **173** in 68% yield as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.28; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.91 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 1.34-1.36 (m, 2H, CH_2CHOCH_2), 1.56-1.66 (m, 2H, CH_2CH_2CO_2CH_3); 2.20-2.27 (m, 2H, CH_2CH_2CO_2CH_3); 2.35 (dd, *J*=5.0 Hz, *J*=2.7 Hz, 1H, CH_aHO), 2.69 (dd, *J*=5.0 Hz, *J*=4.1 Hz, 1H, CHH_bO), 2.89-2.90 (m, 1H, C*H*O), 3.59 (s, 3H, OCH_3); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 26.8 (*C*H_3), 26.9 (*C*H_3), 29.3 (*C*H_2CH_2CO_2CH_3); 32.8 (*C*H_2CO_2CH_3); 36.6 (*C*$(CH_3)_2$), 44.4 (*C*H_2), 46.7 (*C*H_2O), 49.2 (*C*HO), 51.6 (O*C*H_3), 174.5 (*C*O_2CH_3); **FTIR** (film) ν cm^{-1}: 2958, 2924, 2850, 1730, 1463, 1436, 1264, 1172; **LRMS** (ES$^+$) *m/z:* 187 (M+H, 100%), 204 (M+NH_4, 25%); **HRMS** (ES$^+$) *m/z:* Requires 187.1320 for $C_{10}H_{19}O_3$ (M+H), found 187.1328.

Triethyl-(1-methyl-pent-1-enyloxy)-silane 174



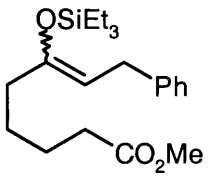
$C_{12}H_{26}OSi$

M= 214.18 g.mol^{-1}

According to the general procedure, reaction of 5-hexen-2-one (250 mg, 2.54 mmol), triethylsilane (622 mg, 5.4 mmol) and tris(triphenylphosphine) rhodium chloride (24 mg, 0.025 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-enol ether **175** (496 mg, 91%) as a mixture of *E* and *Z* isomers in *E:Z* 1:3 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.70; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.61-0.68 (q, *J*=8.1 Hz, 6H, OSiC*H*$_2$CH$_3$, *Z* + *E*), 0.86 (t, *J*=7.4 Hz, 3H, CH$_2$C*H*$_3$, *E*), 0.87 (t, *J*=7.4 Hz, 3H, CH$_2$C*H*$_3$, *Z*), 0.93-0.97 (t, *J*=8.1 Hz, 9H, OSiCH$_2$C*H*$_3$, *Z* + *E*), 1.27-1.34 (m, 2H, CH$_2$C*H*$_2$CH$_3$, *Z* + *E*), 1.71 (d, *J*=0.7 Hz, 3H, C*H*$_3$, *E*), 1.77 (d, *J*=1.1 Hz, 3H, C*H*$_3$, *Z*), 1.87 (q, *J*=7.2 Hz, 2H, CH$_2$C*H*$_2$CH=, *E*), 1.97 (q, *J*=7.3 Hz, 2H, CH$_2$C*H*$_2$CH=, *Z*), 4.37 (tq, *J*=7.3 Hz, *J*=1.1 Hz, 1H, C*H*=C(OSi)CH$_3$, *Z*), 4.63 (tq, *J*=7.2 Hz, *J*=0.7 Hz, 1H, C*H*=C(OSi)CH$_3$, *E*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.9 (OSi*C*H$_2$CH$_3$, *Z*), 5.0 (OSi*C*H$_2$CH$_3$, *E*), 6.4 (OSiCH$_2$*C*H$_3$, *Z*), 6.6 (OSiCH$_2$*C*H$_3$, *E*), 13.6 (*C*H$_3$, *E*), 13.9 (*C*H$_3$, *Z*), 17.6 (*C*H$_3$C=, *E*), 22.7 (*C*H$_3$C=, *Z*), 23.0 (CH$_2$*C*H$_2$CH$_2$, *Z*), 23.6 (CH$_2$*C*H$_2$CH$_2$, *E*), 27.4 (CH$_2$*C*H$_2$C=, *Z*), 29.3 (CH$_2$*C*H$_2$C=, *E*), 107.7 (*C*H=C(OSi)CH$_3$, *E*), 108.4 (*C*H=C(OSi)CH$_3$, *Z*), 146.6 (CH=*C*(OSi)CH$_3$, *Z*), 147.8 (CH=*C*(OSi)CH$_3$, *E*); **FTIR** (film) ν cm^{-1}: 2957, 2878, 1670, 1460, 1240; **LRMS** (CI$^+$) *m/z:* 215 (M+H, 21%), 185 (M-Et, 41%), 157 (14%), 115 (68%); **HRMS** (CI$^+$) *m/z:* Requires 215.18310 for $C_{12}H_{27}OSi$ (M+H), found 215.18272.

Methyl 7-phenyl-6-triethylsilanyloxy-6-heptenoate 175



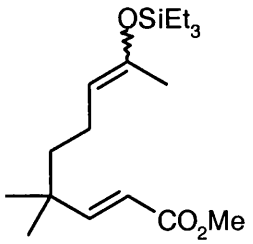
$C_{21}H_{34}O_3Si$

M= 362.23 g.mol^{-1}

According to the general procedure, reaction of methyl (2*E*, 7*E*)-6-oxo-8-phenyl-2,7-octadienoate **105** (100 mg, 0.4 mmol), triethylsilane (105 mg, 0.9 mmol) and tris(triphenylphosphine) rhodium chloride (5 mg, 4 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-enol ether **175** (110 mg, 74%) as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.76; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.60 (q, *J*=7.8 Hz, 6H, $OSiCH_2CH_3$), 0.90 (t, *J*=7.8 Hz, 9H, $OSiCH_2CH_3$), 1.40-1.62 (m, 4H, $CH_2CH_2CH_2CH_2$), 1.96-2.02 (m, 2H, $CH_2C(OSiEt_3)$=), 2.24 (t, *J*=7.2 Hz, 2H, $CH_2CO_2CH_3$), 3.31 (d, *J*=7.1 Hz, 1H, =$CHCH_2$Ph), 3.59 (s, 3H, OCH_3), 4.55 (t, *J*=7.1 Hz, 1H, =$CHCH_2$Ph), 7.09-7.28 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 5.7 ($OSiCH_2CH_3$), 7.2 ($OSiCH_2CH_3$), 27.0 (CH_2), 31.9 (CH_2), 34.6 (CH_2), 36.7 (CH_2), 51.9 (OCH_3), 54.8 (CH_2Ph), 107.0 (=$CHCH_2$Ph), 128.6 (Ph), 128.7 (Ph), 129.0 (Ph), 132.6 (Ph), 151.1 ($C(OSiEt_3)$=CH), 167.1 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3051, 2930, 2876, 1736, 1435, 1264, 1016; **LRMS** (CI$^+$) *m/z:* 363 (M+1, 30%), 348 (M+H-CH_3, 28%), 332 (M+H-OCH_3, 19%), 232 (M+H-$OSiEt_3$, 14%); **HRMS** (CI$^+$) *m/z:* Requires 363.23553 for $C_{21}H_{35}O_3Si$ (M+H), found 363.23519.

Methyl (2*E*)-4,4-dimethyl-triethylsilanyloxy-nona-2,7-dienoate 176



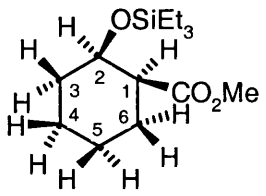
$C_{18}H_{34}O_3Si$

M= 326.23 g.mol^{-1}

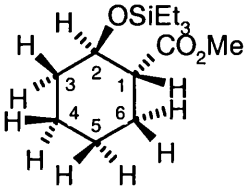
According to the general procedure, reaction of methyl (*E*)-4,4-dimethyl-8-oxo-2,6-nonadienoate **126** (100 mg, 0.5 mmol), triethylsilane (122 mg, 1.0 mmol) and tetrakis(triphenylphosphine) rhodium hydride (6.3 mg, 5 µmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-enol ether **176** (141 mg, 91%) as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.79; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.56 (q, *J*=7.9 Hz, 6H, OSiC*H*$_2$CH$_3$), 0.89 (t, *J*=7.9 Hz, 9H, OSiCH$_2$C*H*$_3$), 0.99 (s, 6H, C(C*H*$_3$)$_2$), 1.25-1.32 (m, 2H, C*H*$_2$CH$_2$CH=), 1.70 (s, 3H, C*H*$_3$C(OSiEt$_3$)=CH), 1.79-1.80 (m, 2H, C*H*$_2$CH=), 3.68 (s, 3H, OC*H*$_3$), 4.24 (t, *J*=6.6 Hz, 1H, CH$_2$C*H*=), 6.65 (d, *J*=15.8 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.84 (d, *J*=15.8 Hz, 1H, C*H*=CHCO$_2$CH$_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 6.0 (OSi*C*H$_2$CH$_3$), 7.1 (OSiCH$_2$*C*H$_3$), 21.0 (*C*H$_2$CH$_2$CH=), 23.1 (CH=C*C*H$_3$), 26.6 (C(*C*H$_3$)$_2$), 37.2 (*C*(CH$_3$)$_2$), 42.6 (*C*H$_2$CH=), 51.8 (O*C*H$_3$), 108.5 (=*C*HCH$_2$), 117.7 (=*C*HCO$_2$CH$_3$), 147.2 (*C*H=CHCO$_2$CH$_3$), 159.0 (CH=*C*(CH$_3$)OSiEt$_3$), 167.5 (*C*O$_2$CH$_3$); **FTIR** (film) ν cm^{-1}: 2959, 2914, 2877, 1717, 1651, 1465, 1437, 1380, 902; **LRMS** (FAB$^+$) *m/z:* 327 (M+H, 100%), 297 (M-Et, 60%), 253 (M-2Et-CH$_3$, 34%), 225 (21%), 185 (79%); **HRMS** (CI$^+$) *m/z:* Requires 327.23553 for $C_{18}H_{35}O_3Si$ (M+H), found 327.23496.

Methyl 2-triethylsilyloxy-cyclohexanecarboxylate 198



syn-**198**



anti-**198**

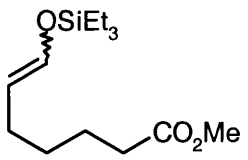
$C_{14}H_{28}O_3Si$

M= 272.18 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-7-oxo-2-heptenoate **178** (500 mg, 3.2 mmol), triethylsilane (781 mg, 6.7 mmol) and tetrakis(triphenylphosphine) rhodium hydride (37 mg, 0.032 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cyclohexanol **198** (567 mg, 65%) as a mixture of diastereomers in a *syn:anti* 1:3 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.55; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.50-0.57 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *syn* + *anti*), 0.89-0.92 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *syn* + *anti*), 1.15-1.90 (m, 8H, H_3, H_4, H_5, H_6, *syn* + *anti*), 2.27-2.30 (m, 1H, H_1, *syn*), 2.30-2.34 (ddd, *J*=9.7 Hz, *J*=9.2 Hz, *J*=3.5 Hz, 1H, H_1, *anti*), 3.63 (s, 3H, OCH_3, *syn*), 3.64 (s, 3H, OCH_3, *anti*), 3.77 (dt, *J*=9.7 Hz, *J*=4.3 Hz, 1H, H_2, *anti*), 3.96-4.00 (m, 1H, H_2, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.4 ($OSiCH_2CH_3$, *syn*), 4.9 ($OSiCH_2CH_3$, *anti*), 6.5 ($OSiCH_2CH_3$, *syn*), 6.8 ($OSiCH_2CH_3$, *anti*), 19.7 (CH_2, *syn*), 22.0 (CH_2, *syn*), 24.3 (CH_2, *anti*), 24.4 (CH_2, *anti*), 24.5 (CH_2, *syn*), 28.6 (CH_2, *anti*), 33.6 (CH_2, *syn*), 35.2 (CH_2, *anti*), 48.4 (C_1, *syn*), 51.2 (OCH_3, *syn*), 51.3 (OCH_3, *anti*), 52.5 (C_1, *anti*), 68.2 (C_2, *syn*), 72.2 (C_2, *anti*), 174.3 (CO_2CH_3, *syn*), 175.6 (CO_2CH_3, *anti*); **FTIR** (film) ν cm^{-1}: 2937, 2876, 1740, 1435, 1173; **LRMS** (CI$^+$) *m/z:* 272 (M, 14%), 243 (M-Et, 35%), 175 (10%), 57 (100%); **HRMS** (CI$^+$) *m/z:* Requires 272.18076 for $C_{14}H_{28}O_3Si$ (M), found 272.17809.

Methyl 7-triethylsilanyloxy-6-heptenoate 199



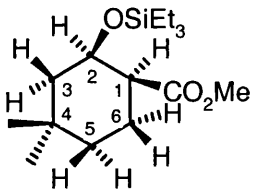
$C_{14}H_{28}O_3Si$

M= 272.18 g.mol^{-1}

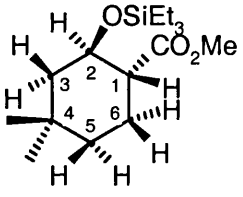
According to the general procedure, reaction of methyl (*E*)-7-oxo-2-heptenoate **178** (100 mg, 0.64 mmol), triethylsilane (160 mg, 1.34 mmol) and tris(triphenylphosphine) rhodium chloride (6 mg, 6.4 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected heptenoate **199** (115 mg, 66%) as a mixture of *E* and *Z* isomers in *E:Z* 4.6:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.70; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.53-0.67 (q, *J*=7.9 Hz, 6H, OSiC*H*$_2$CH$_3$, *cis* + *trans*), 0.88-0.98 (t, *J*=7.9 Hz, 9H, OSiCH$_2$C*H*$_3$, *cis* + *trans*), 1.27-1.40 (m, 2H, C*H*$_2$CH$_2$CH=, *cis* + *trans*), 1.56-1.68 (m, 2H, C*H*$_2$CH$_2$CO$_2$CH$_3$, *cis* + *trans*), 1.83-1.92 (qd, *J*=7.4 Hz, *J*=1.0 Hz, 2H, C*H*$_2$CH=, *trans*), 2.05-2.11 (qd, *J*=7.2 Hz, *J*=1.3 Hz, 2H, C*H*$_2$CH=, *cis*), 2.25-2.35 (m, 2H, C*H*$_2$CO$_2$CH$_3$, *cis* + *trans*), 3.65 (s, 3H, OC*H*$_3$, *cis* + *trans*), 4.41 (q, *J*=7.2 Hz, 1H, =C*H*CH$_2$, *cis*), 4.96 (dt, *J*=12.0 Hz, *J*=7.4 Hz, 1H, =C*H*CH$_2$, *trans*), 6.21 (d, *J*=7.2 Hz, 1H, =C*H*OSi, *cis*), 6.24 (d, *J*=12.0 Hz, 1H, =C*H*OSi, *trans*); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 4.4 (OSi*C*H$_2$CH$_3$, *cis*), 5.4 (OSi*C*H$_2$CH$_3$, *trans*), 6.9 (OSiCH$_2$*C*H$_3$, *cis*), 7.1 (OSiCH$_2$*C*H$_3$, *trans*), 23.5 (*C*H$_2$), 24.7 (*C*H$_2$), 24.9 (*C*H$_2$), 27.3 (*C*H$_2$), 29.5 (*C*H$_2$), 30.3 (*C*H$_2$), 34.3 (*C*H$_2$), 34.4 (*C*H$_2$), 51.7 (O*C*H$_3$, *cis* + *trans*), 110.4 (=*C*HCH$_2$, *cis*), 111.3 (=*C*HCH$_2$, *trans*), 139.0 (=*C*HOSi, *cis*), 140.6 (=*C*HOSi, *trans*), 174.3 (*C*O$_2$CH$_3$, *cis*), 174.6 (*C*O$_2$CH$_3$, *trans*); **FTIR** (film) ν cm^{-1}: 2937, 2877, 1732, 1652, 1436, 907; **LRMS** (CI$^+$) *m/z:* 273 (M+H, 25%), 243 (M-Et, 19%), 211 (12%); 175 (60%); **HRMS** (CI$^+$) *m/z:* Requires 273.18858 for $C_{14}H_{29}O_3Si$ (M+H), found 273.18832.

Methyl 4,4-dimethyl-2-triethylsilyloxy-cyclohexanecarboxylate 200



syn-**200**



anti-**200**

$C_{16}H_{32}O_3Si$

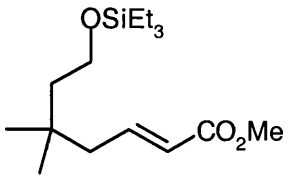
M= 300.22 g.mol^{-1}

According to the general procedure, reaction of methyl 4,4-dimethyl-7-oxo-2-heptenoate **181** (500 mg, 2.7 mmol), triethylsilane (660 mg, 5.7 mmol) and tetrakis(triphenylphosphine) rhodium hydride (32 mg, 0.027 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (95:5), silyl-protected cyclohexanol **200** (301 mg, 37%) as a mixture of diastereomers in a *syn:anti* 1:1 ratio as a colourless oil, together with the reduced product **201** which was obtained in 35% yield.

Rf (P.E./EtOAc, 9:1): 0.79; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.42-0.49 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$, *syn* + *anti*), 0.80 (s, 3H, CH_3), 0.84-0.89 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$, *syn* + *anti*), 0.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.05-1.58 (m, 5H, H_3, H_{6eq} and H_5, *syn* + *anti*), 1.87-1.95 (m, 1H, H_{6ax}, *syn*), 2.16 (ddd, *J*=12.6 Hz, *J*=10.1 Hz, *J*=4.1 Hz, 1H, H_{1ax}, *anti*), 2.33 (dt, *J*=10.1 Hz, *J*=3.7 Hz, 1H, H_{1ax}, *syn*), 3.58 (s, 3H, OCH_3, *syn*), 3.60 (s, 3H, OCH_3, *anti*), 3.93 (ddd, *J*=11.2 Hz, *J*=10.1 Hz, *J*=4.4 Hz, 1H, H_{2ax}, *anti*), 4.25 (q, *J*=3.7 Hz, 1H, H_{2eq}, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.8 ($OSiCH_2CH_3$), 4.0 ($OSiCH_2CH_3$), 5.4 ($OSiCH_2CH_3$), 5.6 ($OSiCH_2CH_3$), 24.0 (CH_2), 24.1 (CH_3), 27.5 (CH_3), 27.6 (CH_3), 31.1 (CH_3), 28.7 (CH_2), 29.2 ($C(CH_3)_2$), 31.8 ($C(CH_3)_2$), 36.5 (CH_2), 44.0 (CH_2), 44.2 (CH_2), 47.1 (CH_2), 47.1 (C_1), 50.1 (OCH_3), 50.4 (OCH_3), 51.8 (C_1), 67.9 (C_2), 68.5 (C_2), 173.1 (CO_2CH_3), 174.9 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3053, 2959, 2876, 1713 (C=O), 1421, 1265; **LRMS** (FAB$^+$) *m/z:* 301 (M+H, 54%), 271 (M-Et, 10%),

199 (100%); **HRMS** (FAB$^+$) *m/z:* Requires 301.21988 for $C_{16}H_{33}O_3Si$ (M+H), found 301.21991.

Methyl 5,5-dimethyl-7-triethylsilanyloxy-2-heptenoate 201

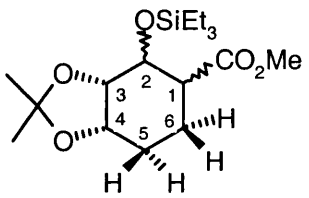


$C_{16}H_{32}O_3$

M= 272.23 g.mol^{-1}

Rf (P.E./EtOAc, 9:1): 0.75; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.59 (q, *J*=7.9 Hz, 6H, $OSiCH_2CH_3$), 0.94 (t, *J*=7.9 Hz, 9H, $OSiCH_2CH_3$), 1.00 (s, 6H, CH_3), 1.52 (t, *J*=7.4 Hz, 2H, CH_2CH_2OSi), 2.13 (dd, *J*=7.9 Hz, *J*=1.3 Hz, 2H, CH_2CH=), 3.63 (t, *J*=7.4 Hz, 1H, CHOSi), 3.72 (s, 3H, OCH_3), 5.78 (dt, *J*=15.5 Hz, *J*=1.3 Hz, 1H, =$CHCO_2CH_3$), 6.92 (dt, *J*=15.5 Hz, *J*=7.9 Hz, 1H, CH=$CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 4.4 ($OSiCH_2CH_3$), 6.7 ($OSiCH_2CH_3$), 27.8 (CH_3), 34.2 ($C(CH_3)_2$), 41.9 (CH_2), 45.2 (CH_2), 51.3 (OCH_3), 59.4 (CH_2OSi), 123.0 (=$CHCO_2CH_3$), 146.7 (CH=$CHCO_2CH_3$), 166.8 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 2980, 1730 (C=O), 1652 (C=C), 1390, 1371, 1100; **LRMS** (EI$^+$) *m/z:* 272 (M, 12%), 257 (M-CH_3, 100%), 243 (M-Et, 56%); **HRMS** (EI$^+$) *m/z:* Requires 272.23513 for $C_{16}H_{32}O_3$ (M), found 272.23555.

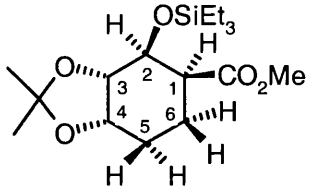
Methyl 2-triethylsilyloxy-3,4-isopropylidene-dioxy-cyclohexanecarboxylate 202



$C_{17}H_{32}O_5Si$

M= 344.20 g.mol^{-1}

According to the general procedure, reaction of methyl (5*S*, 6*S*)-7-oxo-5,6-isopropylidenedioxy-2-heptenoate **185** (100 mg, 0.43 mmol), triethylsilane (110 mg, 0.91 mmol) and tetrakis(triphenylphosphine) rhodium hydride (5 mg, 4.3 μmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (95:5), silyl-protected cyclohexanol **202** (70 mg, 47%) as a complex mixture of diastereomers, one of which was isolated in pure form as a colourless oil.

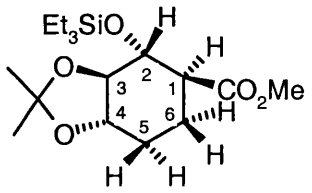


202a

(1*S*, 2*S*, 3*S*, 4*S*) isomer 202a

Rf (P.E./EtOAc, 9:1): 0.63; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.48-0.53 (q, *J*=8.0 Hz, 6H, $OSiCH_2CH_3$), 0.86 (t, *J*=8.0 Hz, 9H, $OSiCH_2CH_3$), 1.28 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.61-1.68 (m, 1H, H_{5ax}), 1.68-1.74 (m, 1H, H_{6ax}), 1.80-1.87 (m, 1H, H_{6eq}), 1.89-1.95 (m, 1H, H_{5eq}), 2.71 (ddd, *J*=8.9 Hz, *J*=5.7 Hz, *J*=3.5 Hz, 1H, H_{1ax}), 3.60 (s, 3H, OCH_3), 4.00 (dd, *J*=5.8 Hz, *J*=3.5 Hz, 1H, H_{3eq}), 4.22 (t, *J*=3.5 Hz, 1H, H_{2eq}), 4.24 (dt, *J*=10.9 Hz, *J*=5.8 Hz, 1H, H_{4ax}); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.8 ($OSiCH_2CH_3$), 5.8 ($OSiCH_2CH_3$), 16.8 (C_6), 23.5 (C_5), 24.6 (CH_3), 26.8 (CH_3), 41.7 (C_1), 50.4 (OCH_3), 69.5 (C_2), 72.0 (C_4), 76.5 (C_3), 107.3 ($C(CH_3)_2$), 172.9 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 2938, 2876, 1741 (C=O), 1437, 1370, 1095; **LRMS** (FAB^+) *m/z:* 345 (M+H, 14%), 315 (M-Et, 68%), 287 (17%), 257 (36%), 87 (100%); **HRMS** (FAB^+) *m/z:* Requires 345.2097 for $C_{17}H_{33}O_5Si$ (M+H), found 345.2095; $[\alpha]^{20}_D$: -4.0° (*c* = 2.75, $CHCl_3$).

Methyl (1*S*, 2*R*, 3*R*, 4*S*)-2-triethylsilyloxy-3,4-isopropylidene-dioxy-cyclohexane-carboxylate 203



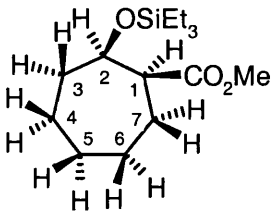
$C_{17}H_{32}O_5Si$

M= 344.2 0g.mol^{-1}

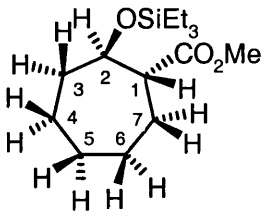
According to the general procedure, reaction of methyl (5*S*, 6*R*)-7-oxo-5,6-isopropylidenedioxy-2-heptenoate **197** (400 mg, 1.75 mmol), triethylsilane (430 mg, 3.7 mmol) and tetrakis(triphenylphosphine) rhodium hydride (20 mg, 0.018 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (95:5), silyl-protected cyclohexanol **203** (246 mg, 41%) as a single diastereomer as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.58; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.55-0.60 (q, *J*=7.9 Hz, 6H, OSiCH_2CH$_3$), 0.92 (t, *J*=7.9 Hz, 9H, OSiCH$_2$CH_3), 1.39 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.49-1.51 (m, 1H, H_{5ax}), 1.52-1.54 (m, 1H, H_{6ax}), 1.94-1.97 (m, 1H, H_{6eq}), 2.04-2.08 (m, 1H, H_{5eq}), 2.43 (ddd, *J*=12.5 Hz, *J*=9.5 Hz, *J*=4.5 Hz, 1H, H_{1ax}), 3.22 (t, *J*=9.5 Hz, 1H, H_{3ax}), 3.36 (ddd, *J*=11.3 Hz, *J*=9.5 Hz, *J*=3.9 Hz, 1H, H_{4ax}), 3.68 (s, 3H, OCH_3), 4.00 (t, *J*=9.5 Hz, 1H, H_{2ax}); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 5.2 (OSiCH_2CH$_3$), 7.1 (OSiCH$_2$$CH_3$), 27.1 ($CH_3$), 27.3 ($CH_3$), 26.3 ($C_5$), 27.5 ($C_6$), 51.4 ($C_1$), 52.2 (O$CH_3$), 73.4 ($C_2$), 77.3 ($C_4$), 84.2 ($C_3$), 110.1 ($C$(CH$_3$)$_2$), 174.8 ($CO_2CH_3$); **FTIR** (film) ν cm^{-1}: 2937, 2877, 1742 (C=O), 1437, 1370, 1096, 730; **LRMS** (FAB$^+$) *m/z:* 345 (M+H, 18%), 315 (M-Et, 61%), 287 (30%), 257 (38%), 87 (100%); **HRMS** (FAB$^+$) *m/z:* Requires 345.2097 for $C_{17}H_{33}O_5Si$ (M+H), found 345.2096, $[\alpha]^{20}_D$: +3.5° (*c* = 3.5, $CHCl_3$).

Methyl 2-triethylsilyloxy-cycloheptanecarboxylate 211



syn-**X**



anti-**X**

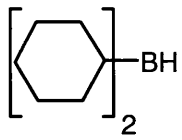
$C_{15}H_{30}O_3Si$

M= 286.20 g.mol^{-1}

According to the general procedure, reaction of methyl (*E*)-8-oxo-2-octenoate **204** (380 mg, 2.2 mmol), triethylsilane (540 mg, 4.6 mmol) and tetrakis(triphenylphosphine) rhodium hydride (26 mg, 0.022 mmol, 1 mol%) afforded, after purification by column chromatography eluting with P.E. 30-40°C/EtOAc (90:10), silyl-protected cycloheptanol **211** (435 mg, 68%) as a mixture of diastereomers in a *syn:anti* 2.5:1 ratio as a colourless oil.

Rf (P.E./EtOAc, 9:1): 0.55; **^{1}H NMR** ($CDCl_3$, 500 MHz) δ ppm: 0.54 (q, *J*=7.9 Hz, 6H, OSiC*H*$_2$CH$_3$, *syn* + *anti*), 0.92 (t, *J*=7.9 Hz, 9H, OSiCH$_2$C*H*$_3$, *anti*), 0.93 (t, *J*=7.9 Hz, 9H, OSiCH$_2$C*H*$_3$, *syn*), 1.34-1.88 (m, 10H, *H*$_3$, *H*$_4$, *H*$_5$, *H*$_6$, *H*$_7$, *syn* + *anti*), 2.50-2.55 (m, 1H, *H*$_1$, *syn* + *anti*), 3.65 (s, 3H, OC*H*$_3$, *syn*), 3.66 (s, 3H, OC*H*$_3$, *anti*), 4.00 (dt, *J*=8.3 Hz, *J*=3.6 Hz, 1H, *H*$_1$, *anti*), 4.00 (dt, *J*=6.8 Hz, *J*=3.4 Hz, 1H, C*H*OSi, *syn*); **^{13}C NMR** ($CDCl_3$, 125 MHz) δ ppm: 3.9 (OSi*C*H$_2$CH$_3$, *syn*), 4.0 (OSi*C*H$_2$CH$_3$, *anti*), 5.7 (OSiCH$_2$*C*H$_3$, *anti*), 5.8 (OSiCH$_2$*C*H$_3$, *syn*), 21.0 (*C*H$_2$, *anti*), 21.3 (*C*H$_2$, *syn*), 22.3 (*C*H$_2$, *syn*), 25.1 (*C*H$_2$, *anti*), 25.6 (*C*H$_2$, *syn*), 26.3 (*C*H$_2$, *anti*), 26.8 (*C*H$_2$, *anti*), 27.4 (*C*H$_2$, *syn*), 35.1 (*C*H$_2$, *syn*), 35.6 (*C*H$_2$, *anti*), 50.3 (O*C*H$_3$, *syn*), 50.8 (O*C*H$_3$, *anti*), 50.9 (*C*$_1$, *syn*), 53.6 (*C*$_1$, *anti*), 70.7 (*C*$_2$, *syn*), 73.7 (*C*$_2$, *anti*), 174.1 (*C*O$_2$CH$_3$, *syn*), 175.4 (*C*O$_2$CH$_3$, *anti*); **FTIR** (film) ν cm^{-1}: 2937, 2878, 1734, 1458, 1437, 1007, 908; **LRMS** (FAB$^+$) *m/z:* 287 (M+H, 18%), 257 (M-Et, 100%), 115 (45%), 87 (69%); **HRMS** (FAB$^+$) *m/z:* Requires 287.20420 for $C_{15}H_{31}O_3Si$ (M+H), found 287.20413.

Dicyclohexylborane 212[179]

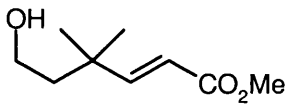


$C_{12}H_{23}B$

M= 178.11 g.mol^{-1}

A solution of cyclohexene (4.1 g, 50.0 mmol) in 20 mL of dry tetrahydrofuran was maintained under a positive pressure of nitrogen at 0°C. Borane-methyl sulfide complex 2 M in tetrahydrofuran (12.5 mL, 25.0 mmol) was added over a period of 15 min, followed by additional 7 mL of tetrahydrofuran. The solution was stirred for 3 h at 0°C. After evaporation of the volatile compounds under *vacuo*, the white solid was washed with cold ether (20 mL) and the supernatant solution was decanted by using a double-ended needle. Dicyclohexylborane was obtained (3.2 g, 72%) as a white solid and kept under nitrogen at 0°C.

Methyl (*E*)-4,4-dimethyl-6-hydroxo-2-hexenoate 214



$C_9H_{16}O_3$

M= 172.20 g.mol^{-1}

Procedure A

To a stirred solution of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (0.15 g, 0.8 mmol) in anhydrous tetrahydrofuran (3 mL) at -20°C under a positive pressure of nitrogen, was added tris(triphenylphosphine) rhodium (I) chloride (16 mg, 1.8.10^{-2} mmol, 2 mol%). Dicyclohexylborane **212** (0.31 g, 1.8 mmol) was added and the suspension stirred at -20°C for 16 hours. Water was added to quench the reaction, and the solution stirred for 30 min at room temperature. The reaction mixture was

extracted with ether, the combined organic layers were dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Purification was carried out by preparative t.l.c. eluting with P.E. 40-60°C/EtOAc (60:40), to give alcohol **214** (124 mg, 82%) as a clear oil.

Procedure B

To a stirred solution of methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (200 mg, 0.94 mmol) in anhydrous tetrahydrofuran (5 mL) at -20°C under a positive pressure of nitrogen, was added tris(triphenylphosphine) rhodium (I) chloride (17 mg, $1.9.10^{-2}$ mmol, 2 mol%). Catecholborane (0.23 g, 1.88 mmol) was added and the suspension stirred at -20°C for 20 hours. The reaction mixture was quenched by the addition of 3 mL of pH=7.0 phosphate buffer. After stirring 1 h at room temperature, the reaction mixture was extracted with diethyl ether and the organic extracts were dried over $MgSO_4$ and filtered. After evaporation of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford alcohol **214** (127 mg, 63%) as a clear oil.

Procedure C

A suspension of chloro(1,5-cyclooctadiene) rhodium(I) dimer (14 mg, 0.029 mmol) and BINAP (40 mg, 0.064 mmol) in anhydrous 1,2-dichloroethane (0.4 mL) was heated at 50°C for 2 h. After cooling down to room temperature, a solution of catecholborane (170 mg, 1.42 mmol) in dichloroethane (0.15 mL) was added and stirred for 30 min. Then, methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (300 mg, 1.42 mmol) in anhydrous dichloroethane (0.5 mL) was added dropwise and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was quenched with a solution of HCl 4N and extracted with dichloromethane. The organic extracts were washed with further HCl 4N, then with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford alcohol **214** (185 mg, 61%) as a clear oil.

Procedure D

To a mixture of anhydrous $CoCl_2$ (18 mg, 0.14 mmol) and 1,3-dimethyl-2-imidazolidinone (53 mg, 0.46 mmol) in dry acetonitrile (2 mL), was added at room

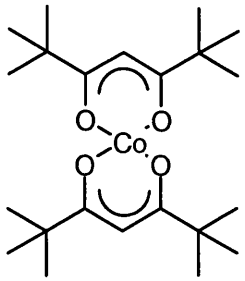
temperature under nitrogen methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (159 mg, 0.93 mmol) and then trichlorosilane (250 mg, 1.84 mmol). The resulting mixture was refluxed at 70°C for 24 h. The reaction mixture was allowed to cool to room temperature and the solid formed in the reaction was filtered through a short pad of Florisil and washed with pentane:acetonitrile (20:10). Purification was carried out by preparative t.l.c. eluting with P.E. 40-60°C/EtOAc (60:40) to give alcohol **214** (79 mg, 49%) as a clear oil.

Procedure E

To a stirred solution of phenylsilane (190 mg, 1.76 mmol) in anhydrous 1,2-dichloroethane (3.3 mL), was added at room temperature under nitrogen, bis(dipivaloylmethanido)cobalt(II) **216** (31 mg, 0.073 mmol, 5 mol%). After stirring for 30 min, methyl (*E*)-4,4-dimethyl-6-oxo-2-hexenoate **122** (250 mg, 1.47 mmol) in 1,2-dichloroethane (3 mL) was added and the mixture was stirred at 50°C for 24 h. At this point, only starting material was present as showed by t.l.c. The reaction mixture was heated at reflux for further 24 h. Then, methanol was added and the resulting solution was washed with 10% aqueous HCl and extracted with dichloromethane. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford alcohol **214** (217 mg, 86%) as a clear oil.

Rf (P.E./EtOAc, 7:3):0.17; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 1.20 (s, 6H, $C(CH_3)_2$), 1.90 (t, *J*=6.9 Hz, 2H, CH_2CH_2OH), 3.59 (t, *J*=6.9 Hz, 2H, CH_2OH), 3.67 (s, 3H, OCH_3), 5.66 (d, *J*=16.0 Hz, 1H, $CH=CHCO_2CH_3$), 6.9 (d, *J*=16.0 Hz, 1H, $CH=CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 27.1 ($C(CH_3)_2$), 36.2 ($C(CH_3)_2$), 45.0 (CH_2), 51.8 (OCH_3), 60.0 (CH_2OH), 117.9 ($=CHCO_2CH_3$), 158.2 ($CH=CHCO_2CH_3$), 167.8 (CO_2CH_3); **FTIR** (film) ν cm^{-1}: 3381 (O-H), 1730 (C=O), 1651 (C=C); **LRMS** (ES^+) *m/z:* 173 (M+H, 100%), 345 (2M+H, 77%); **HRMS** (ES^+) *m/z:* Requires 173.1173 for $C_9H_{17}O_3$ (M+H), found 173.1178.

Bis(dipivaloylmethanido)cobalt(II) 216[181]



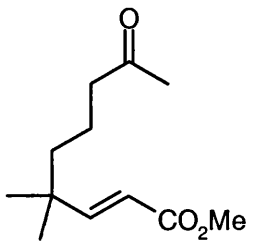
$C_{22}H_{38}O_4Co$

M= 425.45 $g.mol^{-1}$

A solution of 2,2,6,6-tetramethylheptane-3,5-dione (5.0 g, 27 mmol) and cobalt nitrate hexahydrate (3.9 g, 14 mmol) in 25 mL of methanol was boiled for 2-3 min under nitrogen and then stirred during the dropwise addition of sodium hydroxide (1.1 g, 27 mmol) in 7.5 mL of water. A red-pink precipitate formed immediately, but the reaction mixture was refluxed and stirred for 2h. The methanol was then distilled off in a stream of nitrogen, leaving a red solid in a small amount of water. Warm petroleum ether was added and the precipitate dissolved to give a magenta solution. This was separated from the aqueous layer, filtered, and nearly all the petroleum ether was distilled off and replaced by diethyl ether. The quantity of diethyl ether was adjusted to give a solution, which appeared to be saturated at the boiling point. This solution was then cooled in an ice bath for 1 h, and the reddish pink crystals were separated by filtration in a nitrogen atmosphere and quickly transferred to a desiccator. The colour grew paler with drying. The pale pink powder was easily sublimed at 110°C under vacuum, giving ruby-red crystals (2.7 g, 24%), mp (sealed tube): 139-140°C (lit.,[181] 142°C).

LRMS (FAB+) *m/z*: 426 (M+H, 95%), 242 (100%); **Anal**: Calc. for $C_{22}H_{38}O_4Co$: C, 62.10; H, 9.02. Found: C, 62.09; H, 8.92%.

Methyl (*E*)-4,4-dimethyl-8-oxo-2-nonenoate 217[233]

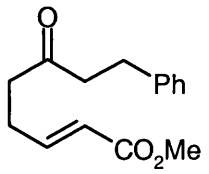


$C_{12}H_{20}O_3$
M= 212.13 g.mol^{-1}

To a stirred solution of phenylsilane (240 mg, 2.28 mmol) in anhydrous 1,2-dichloroethane (5 mL), was added at room temperature under nitrogen, bis(dipivaloylmethanido)cobalt(II) **216** (20 mg, 0.048 mmol, 5 mol%). After stirring for 30 min, methyl (*E*)-4,4-dimethyl-8-oxo-2,6-nonadienoate **126** (200 mg, 0.95 mmol) in 1,2-dichloroethane (2 mL) was added and the mixture was stirred at 50°C for 24 h. The reaction mixture was quenched with methanol, washed with 10% aqueous HCl and extracted with dichloromethane. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford ketone **217** (80 mg, 40%) as a yellow oil.

***R*$_f$** (P.E. /EtOAc, 9:1): 0.70; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 0.99 (s, 6H, $C(CH_3)_2$), 1.16-1.46 (m, 4H, CH_2), 2.05 (s, 3H, CH_3CO), 2.31 (t, *J*=7.3 Hz, 2H, CH_2COCH_3), 3.66 (s, 3H, OCH_3), 5.67 (d, *J*=16.0 Hz, 1H, $=CHCO_2CH_3$), 6.85 (d, *J*=16.0 Hz, 1H, $CH=CHCO_2CH_3$); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 18.0 (CH_2), 25.2 ($C(CH_3)_2$), 28.9 ($COCH_3$), 40.6 ($C(CH_3)_2$), 43.4 (CH_2), 47.1 (CH_2), 50.4 (OCH_3), 116.8 ($=CHCO_2CH_3$), 160.0 ($CH=CHCO_2CH_3$), 166.5 (CO_2CH_3), 207.5 ($COCH_3$); **FTIR** (film) ν cm^{-1}: 2971, 1728 (C=O), 1655 (C=C), 1437, 1367, 1280, 1175.

Methyl (*E*)-6-oxo-8-phenyl-2-octenoate 218



$C_{15}H_{18}O_3$

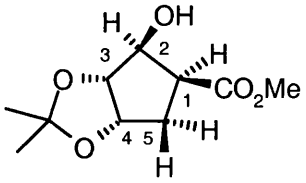
M= 246.13 g.mol^{-1}

To a stirred solution of phenylsilane (106 mg, 0.98 mmol) in anhydrous 1,2-dichloroethane (2 mL), was added at room temperature under nitrogen, bis(dipivaloylmethanido)cobalt(II) **216** (8.7 mg, 0.02 mmol, 5 mol%). After stirring for 30 min, methyl (2*E*, 7*E*)-6-oxo-8-phenyl-2,7-octadienoate **105** (100 mg, 0.4 mmol) in 1,2-dichloroethane (1 mL) was added and the mixture was stirred at 50°C for 24 h. The reaction mixture was quenched with methanol, washed with 10% aqueous HCl and extracted with dichloromethane. The organic extracts were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography eluting with P.E. 40-60°C/EtOAc (90:10) to afford ketone **218** (51 mg, 51%) as a clear oil.

Rf (P.E./EtOAc, 8:2): 0.40; **^{1}H NMR** ($CDCl_3$, 300 MHz) δ ppm: 2.43-2.55 (m, 4H, C*H*$_2$), 2.70 (t, *J*=7.5 Hz, 2H, C*H*$_2$CO), 2.88 (t, *J*=7.6 Hz, 2H, C*H*$_2$CO), 3.71 (s, 3H, OC*H*$_3$), 5.80 (dt, *J*=15.7 Hz, *J*=1.4 Hz, 1H, =C*H*CO$_2$CH$_3$), 6.90 (dt, *J*=15.7 Hz, *J*=6.7 Hz, 1H, C*H*=CHCO$_2$CH$_3$), 7.15-7.34 (m, 5H, Ph); **^{13}C NMR** ($CDCl_3$, 75.5 MHz) δ ppm: 26.3 (*C*H$_2$CH=), 30.2 (*C*H$_2$Ph), 41.2 (*C*H$_2$CO), 44.7 (*C*H$_2$CO), 51.8 (O*C*H$_3$), 122.1 (=*C*HCO$_2$CH$_3$), 126.5 (Ph), 128.7 (Ph), 128.9 (Ph), 141.2 (Ph), 147.8 (*C*H=CHCO$_2$CH$_3$), 167.2 (*C*O$_2$CH$_3$), 208.3 (*C*O); **FTIR** (film) ν cm^{-1}: 2953, 1724 (C=O), 1658 (C=C), 1437, 1276, 1206, 1156; **LRMS** (ES$^+$) *m/z:* 269 (M+Na, 22%), 247 (M+H, 62%), 215 (M-OCH$_3$, 100%); **HRMS** (FAB$^+$) *m/z:* Requires 247.1333 for $C_{15}H_{19}O_3$ (M+H), found 247.1334.

III.4 Synthesis of the carbocyclic moiety of (-)-carbovir and abacavir

Methyl (1*S*, 2*S*, 3*S*, 4*S*)-2-hydroxy-3,4-isopropylidene-dioxy-cyclopentane carboxylate 245



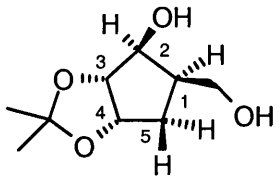
$C_{10}H_{16}O_5$

M= 216.22 g.mol^{-1}

To a solution of methyl (1*S*, 2*S*, 3*S*, 4*S*)-2-triethylsilyloxy-3,4-isopropylidenedioxy-cyclopentane carboxylate **171a** (300 mg, 0.9 mmol) in anhydrous tetrahydrofuran (3 mL), was added dropwise tetrabutylammonium fluoride 1.0 M in tetrahydrofuran (2 mL, 2.0 mmol) and the reaction mixture was stirred at room temperature for 1 h. After diluting with water, the resulting solution was extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (80:20), afforded cyclopentanol **245** (190 mg, 97%) as a white solid (mp= 102-104°C).

Rf (P.E./EtOAc, 6:4): 0.49; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.29 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.09-2.24 (m, 2H, H_5), 3.08 (ddd, *J*=12.0 Hz, *J*=8.0 Hz, *J*=4.0 Hz, 1H, H_1), 3.74 (s, 3H, OCH_3), 4.30 (d, *J*=8.0 Hz, 1H, H_2), 4.44 (d, *J*=5.6 Hz, 1H, H_3), 4.78 (t, *J*=5.6 Hz, 1H, H_4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 23.7 (*C*H_3), 26.1 (*C*H_3), 33.4 (C_5), 44.9 (C_1), 52.1 (O*C*H_3), 76.1 (C_2), 79.2 (C_3), 84.9 (C_4), 109.4 (*C*$(CH_3)_2$), 174.9 (*C*O_2CH_3); **FTIR** (film) ν cm^{-1}: 3463 (O-H), 2988, 2936, 1730 (C=O), 1440, 1375, 1269, 1211, 1028; **LRMS** (ES$^+$) *m/z:* 239 (M+Na, 100%), 217 (M+H, 20%); **HRMS** (ES$^+$) *m/z:* Requires 239.0892 for $C_{10}H_{16}O_5Na$ (M+Na), found 239.0895; $[\alpha]^{20}_D$: -21.2° (*c* = 0.40, $CHCl_3$/MeOH 9:1).

(1*R*, 2*S*, 3*S*, 4*S*)-2-Hydroxy-1-(hydroxymethyl)-3,4-isopropylidene-dioxy-cyclopentane 246[239]



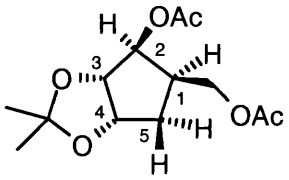
$C_9H_{16}O_4$

M= 188.22 g.mol^{-1}

To a solution of cyclopentanol **245** (170 mg, 0.79 mmol) in anhydrous tetrahydrofuran (10 mL) was added lithium aluminium hydride 1.0 M in ether (1.73 mL, 1.73 mmol) at 0°C under a nitrogen atmosphere. After 2 h, the reaction was quenched with 3.5 mL of 10% aqueous NaOH solution. EtOAc was added and the layers were separated. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (50:50), afforded the desired product **246** (127 mg, 86%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.21; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.30 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.77 (dd, *J*=13.6 Hz, *J*=6.4 Hz, 1H, H_{5eq}), 2.02 (td, *J*=13.6 Hz, *J*=5.2 Hz, 1H, H_{5ax}), 2.31-2.38 (m, 1H, H_1), 2.52 (s, 1H, O*H*), 3.13 (s, 1H, O*H*), 3.83 (dd, *J*=11.0 Hz, *J*=6.0 Hz, 1H, CH_aH_bOH), 4.03 (dd, *J*=11.0 Hz, *J*=3.6 Hz, 1H, CH_aH_bOH), 4.22 (d, *J*=5.2 Hz, 1H, H_3), 4.37 (d, *J*=5.6 Hz, 1H, H_2), 4.78 (t, *J*=5.62Hz, 1H, H_4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 23.8 (CH_3), 26.1 (CH_3), 31.6 (C_5), 41.4 (C_1), 61.8 (CH_2OH), 78.0 (C_3), 79.7 (C_4), 86.3 (C_2), 109.7 ($C(CH_3)_2$); **FTIR** (film) ν cm^{-1}: 3411 (O-H), 2987, 2935, 1376, 1265, 1210, 1029; **LRMS** (ES$^+$) *m/z:* 211 (M+Na, 100%), 189 (M+H, 14%); **HRMS** (ES$^+$) *m/z:* Requires 211.0946 for $C_9H_{16}O_4Na$ (M+Na), found 211.0946; $[\alpha]^{20}_D$: -21.7° (*c* = 1.60, $CHCl_3$/MeOH 9:1), lit.,[239]: -18.8° (*c* = 1.60, $CHCl_3$/MeOH 9:1).

(1*R*, 2*S*, 3*S*, 4*S*)-2-Acetoxy-1-(acetoxymethyl)-3,4-isopropylidene-dioxy-cyclopentane 247



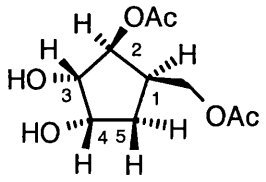
$C_{13}H_{20}O_6$

M= 272.13 g.mol^{-1}

To a solution of diol **246** (280 mg, 1.49 mmol) in anhydrous dichloromethane (10 mL) was added triethylamine (0.45 mL, 3.28 mmol) at 0°C under a nitrogen atmosphere. Acetic anhydride (0.42 mL, 4.47 mmol) was then added dropwise followed by a catalytic amount of 4,4-dimethyl-amino-pyridine (19.6 mg, 0.15 mmol). After 2 h, the reaction was quenched with 5% aqueous HCl and the layers were separated. The aqueous phase was extracted with dichloromethane and the combined organic extracts were washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40), afforded the desired product **247** (400 mg, 99%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.63; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.21 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.63 (td, *J*=13.6 Hz, *J*=5.2 Hz, 1H, H_{5ax}), 1.90 (dd, *J*=13.6 Hz, *J*=6.4 Hz, 1H, H_{5eq}), 1.98 (s, 6H, COCH_3), 2.59-2.65 (m, 1H, H_1), 4.01 (dd, *J*=11.0 Hz, *J*=3.6 Hz, 1H, C$H_a$$H_b$OAc), 4.08 (dd, *J*=11.0 Hz, *J*=6.0 Hz, 1H, C$H_a$$H_b$OAc), 4.33 (d, *J*=5.2 Hz, 1H, H_3), 4.67 (t, *J*=5.2 Hz, 1H, H_4), 5.05 (d, *J*=5.6 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 20.9 (2xCH_3), 23.8 (CH_3), 26.0 (CH_3), 33.7 (C_5), 38.6 (C_1), 62.1 (CH_2O), 77.4 (C_2), 79.2 (C_4), 84.2 (C_3), 110.4 ($C(CH_3)_2$), 170.0 ($OCOCH_3$), 171.0 ($OCOCH_3$); **FTIR** (film) ν cm^{-1}: 2984, 2938, 1746 (C=O), 1439, 1373, 1254, 1159, 1037; **LRMS** (ES$^+$) *m/z:* 295 (M+Na, 65%), 273 (M+H, 39%), 213 (M-OAc, 100%); **HRMS** (ES$^+$) *m/z:* Requires 273.1342 for $C_{13}H_{21}O_6$ (M+H), found 273.1338; $[\alpha]^{20}_D$: -20.0° (*c* = 0.65, CH_2Cl_2).

(1*R*, 2*S*, 3*S*, 4*S*)-2-Acetoxy-1-(acetoxymethyl)-3,4-dihydroxy-cyclopentane 244



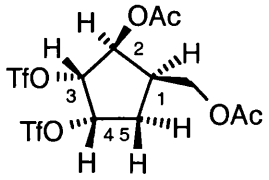
$C_{10}H_{16}O_6$

M= 232.10 g.mol^{-1}

Diacetate **247** (390 mg, 1.43 mmol) was dissolved in trifluoroacetic acid (180 µL) and water (20 µL) at 0°C under a nitrogen atmosphere. After 30 min, the reaction mixture was concentrated under reduced pressure. Ethyl acetate was then added and the mixture was washed three times with 5% aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (50:50), afforded the desired diol **244** (306 mg, 92%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.18; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.75 (ddd, *J*=14.4 Hz, *J*=9.6 Hz, *J*=4.4 Hz, 1H, H_{5ax}), 2.01 (ddd, *J*=14.4 Hz, *J*=8.4 Hz, *J*=1.6 Hz, 1H, H_{5eq}), 2.05 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.70 (br, 1H, O*H*), 2.89-2.95 (m, 1H, H_1), 3.55 (br, 1H, O*H*), 4.00 (t, *J*=4.4 Hz, 1H, H_3), 4.08 (dd, *J*=11.2 Hz, *J*=6.4 Hz, 1H, CH_aH_bOAc), 4.15 (dd, *J*=11.2 Hz, *J*=6.8 Hz, 1H, CH_aH_bOAc), 4.22 (t, *J*=4.4 Hz, 1H, H_4), 5.01 (dd, *J*=8.0 Hz, *J*=4.4 Hz, 1H, H_2); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 21.0 (2xCH_3), 33.7 (C_5), 36.7 (C_1), 63.3 (CH_2OAc), 70.9 (C_4), 79.3 (C_3), 81.1 (C_2), 171.0 ($OCOCH_3$), 172.4 ($OCOCH_3$); **FTIR** (film) ν cm^{-1}: 3419 (O-H), 2940, 1735 (C=O), 1435, 1370, 1246, 1099, 1039; **LRMS** (ES$^+$) *m/z:* 233 (M+H, 100%), 173 (M-OAc, 53%); **HRMS** (ES$^+$) *m/z:* Requires 233.1035 for $C_{10}H_{17}O_6$ (M+H), found 233.1025; $[\alpha]^{20}_D$: -23.0° (*c* = 0.50, CH_2Cl_2).

(1*R*, 2*S*, 3*R*, 4*S*)-2-Acetoxy-1-(acetoxymethyl)-2,3-bis-trifluoromethanesulfonyl-cyclopentane 248



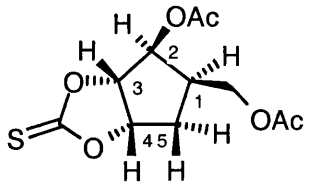
$C_{12}H_{14}F_6O_{10}S_2$

M= 496.25 g.mol^{-1}

To a solution of diol **244** (35 mg, 0.15mmol) in anhydrous dichloromethane (5 mL) was added pyridine (0.45 mL, 3.28 mmol) at 0°C under a nitrogen atmosphere. Triflic anhydride (120 mg, 0.45 mmol) was then added dropwise followed by a catalytic amount of 4,4-dimethyl-amino-pyridine (1.8 mg, 0.015 mmol). After 2 h, the reaction was quenched with 5% aqueous HCl and the layers were separated. The aqueous phase was extracted with dichloromethane and the combined organic extracts were washed with aqueous saturated $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to afford the desired crude product **248** (70 mg, 94%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.18; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 2.00 (ddd, *J*=14.4 Hz, *J*=9.6 Hz, *J*=4.4 Hz, 1H, H_{5ax}), 2.05 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.51 (ddd, *J*=14.4 Hz, *J*=8.4 Hz, *J*=1.6 Hz, 1H, H_{5eq}), 2.92-2.96 (m, 1H, H_1), 4.08 (dd, *J*=11.2 Hz, *J*=6.4 Hz, 1H, CH_aH_bOAc), 4.15 (dd, *J*=11.2 Hz, *J*=6.8 Hz, 1H, CH_aH_bOAc), 5.14 (t, *J*=4.4 Hz, 1H, H_3), 5.40 (t, *J*=4.4 Hz, 1H, H_4), 5.61 (dd, *J*=8.0 Hz, *J*=4.4 Hz, 1H, H_2).

(1*R*, 2*S*, 3*R*, 4*S*)-2-Acetoxy-1-(acetoxymethyl)-3,4-di-*O*-thionocarbonyl cyclopentane 249



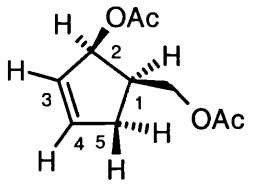
$C_{11}H_{14}O_6S$

M= 274.05 g.mol^{-1}

To a solution of diol **244** (70 mg, 0.30 mmol) in dry toluene (12 mL) was added pyridine (178 mg, 2.26 mmol) at 0°C under a nitrogen atmosphere. Pentafluorophenylchlorothionoformate (159 mg, 0.60 mmol) was added followed by a catalytic amount of 4-dimethylaminopyridine (3.6 mg, 0.03 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with 5% aqueous HCl and the layers were separated. The organic phase was washed with a saturated aqueous solution of $NaHCO_3$, and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography eluting with P.E. 30-40°C/EtOAc (60:40), afforded the desired thiocarbonate **249** (64 mg, 78%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.31; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 1.97 (ddd, *J*=14.4 Hz, *J*=9.6 Hz, *J*=4.4 Hz, 1H, H_{5ax}), 2.06 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.37 (dd, *J*=14.4 Hz, *J*=8.4 Hz, 1H, H_{5eq}), 2.61-2.67 (m, 1H, H_1), 4.11 (dd, *J*=11.2 Hz, *J*=7.2 Hz, 1H, CH_aH_bOAc), 4.19 (dd, *J*=11.2 Hz, *J*=8.4 Hz, 1H, CH_aH_bOAc), 5.09 (d, *J*=6.7 Hz, 1H, H_2), 5.40-5.44 (m, 2H, H_3 and H_4); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 21.0 ($2xCH_3$), 34.1 (C_5), 38.8 (C_1), 60.9 (CH_2OAc), 75.4 (C_3 or C_4), 85.5 (C_3 or C_4), 87.8 (C_2), 169.2 ($OCOCH_3$), 170.7 ($OCOCH_3$), 190.4 (*C*=S); **FTIR** (film) ν cm^{-1}: 2962, 1747 (C=O), 1469, 1351 (C=S), 1222, 1020; **LRMS** (ES$^+$) *m/z:* 275 (M+H, 100%); 214 (8%); **HRMS** (ES$^+$) *m/z:* Requires 275.0592 for $C_{11}H_{15}O_6S$ (M+H), found 275.0589; $[\alpha]^{20}_D$: -21.0° (*c* = 0.65, CH_2Cl_2).

(1*R*, 2*R*)-2-Acetoxy-1-acetoxymethyl-3-cyclopentene 47[37]



$C_{10}H_{14}O_4$

M= 198.25 g.mol^{-1}

To a solution of thiocarbonate **249** (55 mg, 0.24 mmol) in dry tetrahydrofuran (1 mL) was added 1,3-dimethyl-2-phenyl-1,3-diazaphospholidine (140 mg, 0.71 mmol), and the reaction mixture was stirred at 40°C for 4 h. The reaction was quenched with 5% aqueous HCl and the layers were separated. After concentration of the solvent under reduced pressure, the crude oil was purified by flash column chromatography eluting first with DCM and then P.E. 30-40°C/EtOAc (60:40), to afford the desired cyclopentene **47** (26 mg, 65%) as a clear oil.

Rf (P.E./EtOAc, 6:4): 0.68; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 2.02 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.22-2.29 (m, 1H, H_5), 2.46-2.53 (m, 1H, H_5), 2.68-2.73 (m, 1H, H_1), 4.14 (dd, *J*=11.2 Hz, *J*=7.2 Hz, 1H, CH_aH_bOAc), 4.22 (dd, *J*=11.2 Hz, *J*=8.4 Hz, 1H, CH_aH_bOAc), 5.74 (dd, *J*=7.2 Hz, *J*=2.0 Hz, 1H, H_2), 5.84-5.86 (m, 1H, H_4), 6.09-6.11 (m, 1H, H_3); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 21.0 (CH_3), 21.1 (CH_3), 34.7 (C_5), 39.5 (C_1), 63.4 (CH_2OAc), 78.1 (C_2), 129.4 (C_4), 136.8 (C_3), 170.7 ($OCOCH_3$), 171.1 ($OCOCH_3$); **FTIR** (film) ν cm^{-1}: 2925, 1736 (C=O), 1438, 1370, 1234, 1035; **LRMS** (ES$^+$) *m/z:* 199 (M+H, 100%); 216 ($M+NH_4$, 57%); **HRMS** (ES$^+$) *m/z:* Requires 199.09702 for $C_{10}H_{15}O_4$ (M+H), found 199.09712; $[\alpha]^{20}_D$: -181° (*c* = 0.45, CH_2Cl_2), lit.,[37]: -178.0° (*c* = 0.45, CH_2Cl_2).

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Appendices

Table I Crystal data and structure refinement for *syn*-**163**.

Chemical formula	$C_{27}H_{38}O_3Si$	
Formula weight	438.66	
Temperature	293(2) K	
Radiation, wavelength	MoKα, 0.71073 Å	
Crystal system, space group	triclinic, P $\bar{1}$	
Unit cell parameters	a = 8.6086(11) Å	α = 104.964(2)°
	b = 8.9819(12) Å	β = 98.181(2)°
	c = 17.411(2) Å	γ = 90.803(2)°
Cell volume	1285.6(3) Å^3	
Z	2	
Calculated density	1.133 g/cm^3	
Absorption coefficient μ	0.115 mm^{-1}	
F(000)	476	
Crystal colour and size	colourless, 0.45 × 0.28 × 0.21 mm^3	
Data collection method	Bruker SMART APEX diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.35 to 28.25°	
Index ranges	h −11 to 11, k −11 to 11, l −22 to 22	
Completeness to θ = 26.00°	97.6 %	
Reflections collected	11181	
Independent reflections	5848 (R_{int} = 0.0210)	
Reflections with $F^2>2\sigma$	4707	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.9499 and 0.9762	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0947, 0.1014	
Data / restraints / parameters	5848 / 0 / 280	
Final R indices [$F^2>2\sigma$]	R1 = 0.0543, wR2 = 0.1478	
R indices (all data)	R1 = 0.0651, wR2 = 0.1570	
Goodness-of-fit on F^2	1.034	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.387 and −0.191 e Å^{-3}	

Table II Atomic coordinates and equivalent isotropic displacement parameters ($Å^2$) for *syn*-**163**. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
Si(1)	0.13861(5)	0.92107(5)	0.21591(3)	0.04442(15)
O(1)	0.31595(12)	0.86999(11)	0.24337(6)	0.0413(3)
O(2)	0.47788(14)	0.72755(12)	0.08172(6)	0.0478(3)
O(3)	0.60028(18)	0.95248(14)	0.15257(8)	0.0616(4)
C(1)	0.39458(16)	0.73319(15)	0.24322(8)	0.0335(3)
C(2)	0.55787(17)	0.75446(17)	0.21926(8)	0.0380(3)
C(3)	0.65884(19)	0.8475(2)	0.29748(10)	0.0491(4)
C(4)	0.55751(18)	0.85862(17)	0.36407(9)	0.0403(3)
C(5)	0.43559(16)	0.72111(15)	0.33110(8)	0.0335(3)
C(6)	0.54985(18)	0.82621(17)	0.14969(9)	0.0409(3)
C(7)	0.4705(2)	0.7747(2)	0.00692(10)	0.0551(4)
C(8)	0.6234(3)	0.7467(4)	−0.02414(14)	0.0873(8)
C(9)	0.3355(3)	0.6803(3)	−0.05015(12)	0.0781(6)
C(10)	0.1626(3)	1.0359(3)	0.14285(13)	0.0689(6)
C(11)	0.0205(4)	1.1218(4)	0.1195(2)	0.1139(11)
C(12)	−0.0059(2)	0.7532(3)	0.17177(13)	0.0692(5)
C(13)	0.0268(3)	0.6433(4)	0.09522(18)	0.1072(10)
C(14)	0.0696(2)	1.0487(2)	0.30630(12)	0.0635(5)
C(15)	0.1820(4)	1.1834(3)	0.35161(16)	0.0966(9)
C(16)	0.29019(17)	0.73030(16)	0.37261(8)	0.0375(3)
C(17)	0.1698(2)	0.6180(2)	0.34293(11)	0.0520(4)
C(18)	0.0362(2)	0.6214(3)	0.37928(13)	0.0646(5)
C(19)	0.0231(2)	0.7378(3)	0.44719(12)	0.0669(6)
C(20)	0.1421(2)	0.8480(2)	0.47830(11)	0.0592(5)
C(21)	0.2749(2)	0.84515(19)	0.44160(9)	0.0466(4)
C(22)	0.51395(17)	0.57125(16)	0.33757(8)	0.0369(3)
C(23)	0.5859(2)	0.56147(19)	0.41309(10)	0.0469(4)
C(24)	0.6577(2)	0.4314(2)	0.42387(12)	0.0592(5)
C(25)	0.6594(3)	0.3055(2)	0.35864(13)	0.0664(5)
C(26)	0.5871(3)	0.3099(2)	0.28457(12)	0.0647(5)
C(27)	0.5137(2)	0.44152(18)	0.27349(10)	0.0501(4)

Table III Bond lengths [Å] and angles [°] for *syn*-**163**

Si(1)–O(1)	1.6416(11)	Si(1)–C(10)	1.8630(19)
Si(1)–C(12)	1.868(2)	Si(1)–C(14)	1.8700(19)
O(1)–C(1)	1.4106(17)	O(2)–C(6)	1.3431(19)
O(2)–C(7)	1.4634(19)	O(3)–C(6)	1.1949(19)
C(1)–C(2)	1.5451(19)	C(1)–C(5)	1.5526(19)
C(2)–C(6)	1.506(2)	C(2)–C(3)	1.538(2)
C(3)–C(4)	1.532(2)	C(4)–C(5)	1.544(2)
C(5)–C(16)	1.5249(19)	C(5)–C(22)	1.5368(19)
C(7)–C(8)	1.493(3)	C(7)–C(9)	1.505(3)
C(10)–C(11)	1.518(3)	C(12)–C(13)	1.505(3)
C(14)–C(15)	1.510(3)	C(16)–C(17)	1.381(2)
C(16)–C(21)	1.391(2)	C(17)–C(18)	1.386(2)
C(18)–C(19)	1.381(3)	C(19)–C(20)	1.364(3)
C(20)–C(21)	1.384(2)	C(22)–C(27)	1.389(2)
C(22)–C(23)	1.396(2)	C(23)–C(24)	1.372(2)
C(24)–C(25)	1.383(3)	C(25)–C(26)	1.360(3)
C(26)–C(27)	1.392(2)		

O(1)–Si(1)–C(10)	105.21(8)	O(1)–Si(1)–C(12)	113.12(8)
C(10)–Si(1)–C(12)	112.04(11)	O(1)–Si(1)–C(14)	108.33(8)
C(10)–Si(1)–C(14)	109.00(10)	C(12)–Si(1)–C(14)	109.00(10)
C(1)–O(1)–Si(1)	138.42(10)	C(6)–O(2)–C(7)	117.71(13)
O(1)–C(1)–C(2)	107.31(11)	O(1)–C(1)–C(5)	109.02(10)
C(2)–C(1)–C(5)	102.86(11)	C(6)–C(2)–C(3)	115.05(13)
C(6)–C(2)–C(1)	112.39(12)	C(3)–C(2)–C(1)	104.54(11)
C(4)–C(3)–C(2)	106.11(12)	C(3)–C(4)–C(5)	104.69(11)
C(16)–C(5)–C(22)	107.36(11)	C(16)–C(5)–C(4)	115.81(11)
C(22)–C(5)–C(4)	109.45(12)	C(16)–C(5)–C(1)	111.73(11)
C(22)–C(5)–C(1)	113.38(10)	C(4)–C(5)–C(1)	99.15(11)
O(3)–C(6)–O(2)	123.37(15)	O(3)–C(6)–C(2)	126.05(15)
O(2)–C(6)–C(2)	110.58(12)	O(2)–C(7)–C(8)	109.23(17)
O(2)–C(7)–C(9)	106.19(15)	C(8)–C(7)–C(9)	112.32(17)
C(11)–C(10)–Si(1)	115.75(16)	C(13)–C(12)–Si(1)	115.95(17)
C(15)–C(14)–Si(1)	114.55(15)	C(17)–C(16)–C(21)	117.71(14)
C(17)–C(16)–C(5)	119.53(13)	C(21)–C(16)–C(5)	122.72(14)
C(16)–C(17)–C(18)	121.36(17)	C(19)–C(18)–C(17)	119.74(19)
C(20)–C(19)–C(18)	119.76(16)	C(19)–C(20)–C(21)	120.41(17)
C(20)–C(21)–C(16)	121.00(17)	C(27)–C(22)–C(23)	117.21(14)
C(27)–C(22)–C(5)	124.37(13)	C(23)–C(22)–C(5)	118.39(12)
C(24)–C(23)–C(22)	121.88(15)	C(23)–C(24)–C(25)	119.68(17)
C(26)–C(25)–C(24)	119.91(16)	C(25)–C(26)–C(27)	120.53(16)
C(22)–C(27)–C(26)	120.74(16)		

Table IV Anisotropic displacement parameters ($Å^2$) for *syn*-**163**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ...+ 2hka^*b^*U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	0.0364(2)	0.0542(3)	0.0495(3)	0.0232(2)	0.01028(18)	0.01143(19)
O(1)	0.0366(5)	0.0415(5)	0.0493(6)	0.0171(4)	0.0078(4)	0.0085(4)
O(2)	0.0629(7)	0.0473(6)	0.0371(6)	0.0162(5)	0.0117(5)	–0.0001(5)
O(3)	0.0843(9)	0.0452(6)	0.0584(8)	0.0150(5)	0.0200(7)	–0.0073(6)
C(1)	0.0343(7)	0.0343(6)	0.0321(7)	0.0081(5)	0.0064(5)	0.0030(5)
C(2)	0.0364(7)	0.0411(7)	0.0380(7)	0.0101(6)	0.0113(6)	0.0060(6)
C(3)	0.0376(8)	0.0610(10)	0.0468(9)	0.0114(7)	0.0062(7)	–0.0035(7)
C(4)	0.0406(8)	0.0391(7)	0.0371(7)	0.0039(6)	0.0042(6)	0.0012(6)
C(5)	0.0352(7)	0.0351(6)	0.0294(6)	0.0056(5)	0.0070(5)	0.0053(5)
C(6)	0.0436(8)	0.0401(7)	0.0424(8)	0.0109(6)	0.0173(6)	0.0072(6)
C(7)	0.0756(12)	0.0559(10)	0.0424(9)	0.0225(7)	0.0187(8)	0.0103(9)
C(8)	0.0759(15)	0.138(2)	0.0583(13)	0.0367(14)	0.0242(11)	–0.0021(15)
C(9)	0.0725(14)	0.1164(19)	0.0485(11)	0.0291(12)	0.0056(10)	0.0102(13)
C(10)	0.0637(12)	0.0944(15)	0.0691(12)	0.0511(11)	0.0208(10)	0.0276(11)
C(11)	0.101(2)	0.153(3)	0.132(2)	0.106(2)	0.0309(18)	0.059(2)
C(12)	0.0465(10)	0.0917(15)	0.0698(13)	0.0242(11)	0.0047(9)	0.0021(10)
C(13)	0.0746(17)	0.129(2)	0.0915(19)	–0.0110(17)	–0.0004(14)	–0.0085(16)
C(14)	0.0600(11)	0.0748(12)	0.0721(12)	0.0348(10)	0.0332(9)	0.0301(10)
C(15)	0.133(2)	0.0672(14)	0.0916(18)	0.0063(13)	0.0503(18)	0.0161(15)
C(16)	0.0398(7)	0.0418(7)	0.0351(7)	0.0146(6)	0.0109(6)	0.0108(6)
C(17)	0.0510(10)	0.0543(9)	0.0532(10)	0.0143(8)	0.0157(8)	0.0013(8)
C(18)	0.0484(10)	0.0797(13)	0.0756(13)	0.0334(11)	0.0183(9)	–0.0023(9)
C(19)	0.0536(11)	0.1012(16)	0.0661(12)	0.0442(11)	0.0329(9)	0.0280(11)
C(20)	0.0627(11)	0.0778(12)	0.0457(9)	0.0216(9)	0.0241(8)	0.0314(10)
C(21)	0.0501(9)	0.0540(9)	0.0369(8)	0.0108(7)	0.0114(6)	0.0155(7)
C(22)	0.0387(7)	0.0379(7)	0.0356(7)	0.0100(6)	0.0095(6)	0.0054(6)
C(23)	0.0527(9)	0.0507(9)	0.0385(8)	0.0127(7)	0.0085(7)	0.0110(7)
C(24)	0.0642(12)	0.0651(11)	0.0551(10)	0.0287(9)	0.0065(8)	0.0178(9)
C(25)	0.0801(14)	0.0529(10)	0.0772(13)	0.0313(9)	0.0197(11)	0.0290(10)
C(26)	0.0948(15)	0.0395(9)	0.0603(11)	0.0077(8)	0.0222(10)	0.0183(9)
C(27)	0.0688(11)	0.0396(8)	0.0402(8)	0.0070(6)	0.0084(7)	0.0100(7)

Table V. Hydrogen coordinates and isotropic displacement parameters ($Å^2$) for *syn*-**163**.

	x	y	z	U
H(1A)	0.3345	0.6415	0.2079	0.040
H(2A)	0.6010	0.6525	0.2033	0.046
H(3A)	0.7541	0.7955	0.3086	0.059
H(3B)	0.6876	0.9496	0.2933	0.059
H(4A)	0.5060	0.9556	0.3746	0.048
H(4B)	0.6209	0.8506	0.4134	0.048
H(7A)	0.4500	0.8846	0.0171	0.066
H(8A)	0.7056	0.8102	0.0136	0.131
H(8B)	0.6169	0.7717	–0.0748	0.131
H(8C)	0.6459	0.6400	–0.0312	0.131
H(9A)	0.2398	0.7025	–0.0280	0.117
H(9B)	0.3537	0.5726	–0.0580	0.117
H(9C)	0.3269	0.7058	–0.1008	0.117
H(10A)	0.2506	1.1103	0.1656	0.083
H(10B)	0.1897	0.9668	0.0944	0.083
H(11A)	0.0449	1.1783	0.0824	0.171
H(11B)	–0.0067	1.1923	0.1667	0.171
H(11C)	–0.0665	1.0493	0.0945	0.171
H(12A)	–0.0102	0.6956	0.2116	0.083
H(12B)	–0.1090	0.7924	0.1615	0.083
H(13A)	–0.0540	0.5619	0.0774	0.161
H(13B)	0.1268	0.6000	0.1049	0.161
H(13C)	0.0287	0.6978	0.0546	0.161
H(14A)	–0.0302	1.0882	0.2893	0.076
H(14B)	0.0513	0.9869	0.3427	0.076
H(15A)	0.1383	1.2431	0.3969	0.145
H(15B)	0.1988	1.2471	0.3166	0.145
H(15C)	0.2803	1.1458	0.3701	0.145
H(17A)	0.1785	0.5386	0.2976	0.062
H(18A)	–0.0443	0.5455	0.3580	0.078
H(19A)	–0.0665	0.7410	0.4716	0.080
H(20A)	0.1340	0.9256	0.5245	0.071
H(21A)	0.3550	0.9212	0.4634	0.056
H(23A)	0.5851	0.6455	0.4574	0.056
H(24A)	0.7050	0.4280	0.4748	0.071
H(25A)	0.7100	0.2179	0.3654	0.080
H(26A)	0.5867	0.2243	0.2410	0.078
H(27A)	0.4639	0.4426	0.2226	0.060

Table VI Torsion angles [°] for *syn*-**163**.

C(10)–Si(1)–O(1)–C(1)	−122.12(15)	C(12)–Si(1)–O(1)–C(1)	0.49(17)
C(14)–Si(1)–O(1)–C(1)	121.44(15)	Si(1)–O(1)–C(1)–C(2)	139.46(12)
Si(1)–O(1)–C(1)–C(5)	−109.81(14)	O(1)–C(1)–C(2)–C(6)	−43.91(15)
C(5)–C(1)–C(2)–C(6)	−158.83(11)	O(1)–C(1)–C(2)–C(3)	81.53(14)
C(5)–C(1)–C(2)–C(3)	−33.38(14)	C(6)–C(2)–C(3)–C(4)	130.42(14)
C(1)–C(2)–C(3)–C(4)	6.66(16)	C(2)–C(3)–C(4)–C(5)	22.78(16)
C(3)–C(4)–C(5)–C(16)	−162.14(13)	C(3)–C(4)–C(5)–C(22)	76.37(14)
C(3)–C(4)–C(5)–C(1)	−42.51(14)	O(1)–C(1)–C(5)–C(16)	55.39(15)
C(2)–C(1)–C(5)–C(16)	169.07(11)	O(1)–C(1)–C(5)–C(22)	176.87(11)
C(2)–C(1)–C(5)–C(22)	−69.46(14)	O(1)–C(1)–C(5)–C(4)	−67.22(13)
C(2)–C(1)–C(5)–C(4)	46.46(12)	C(7)–O(2)–C(6)–O(3)	4.0(2)
C(7)–O(2)–C(6)–C(2)	−175.54(13)	C(3)–C(2)–C(6)–O(3)	−8.1(2)
C(1)–C(2)–C(6)–O(3)	111.42(18)	C(3)–C(2)–C(6)–O(2)	171.47(12)
C(1)–C(2)–C(6)–O(2)	−69.05(15)	C(6)–O(2)–C(7)–C(8)	80.7(2)
C(6)–O(2)–C(7)–C(9)	−157.99(15)	O(1)–Si(1)–C(10)–C(11)	−169.3(2)
C(12)–Si(1)–C(10)–C(11)	67.4(2)	C(14)–Si(1)–C(10)–C(11)	−53.3(2)
O(1)–Si(1)–C(12)–C(13)	−63.0(2)	C(10)–Si(1)–C(12)–C(13)	55.7(2)
C(14)–Si(1)–C(12)–C(13)	176.4(2)	O(1)–Si(1)–C(14)–C(15)	52.26(18)
C(10)–Si(1)–C(14)–C(15)	−61.71(19)	C(12)–Si(1)–C(14)–C(15)	175.73(17)
C(22)–C(5)–C(16)–C(17)	−62.36(17)	C(4)–C(5)–C(16)–C(17)	175.04(14)
C(1)–C(5)–C(16)–C(17)	62.53(17)	C(22)–C(5)–C(16)–C(21)	115.38(15)
C(4)–C(5)–C(16)–C(21)	−7.2(2)	C(1)–C(5)–C(16)–C(21)	−119.72(15)
C(21)–C(16)–C(17)–C(18)	1.6(3)	C(5)–C(16)–C(17)–C(18)	179.44(16)
C(16)–C(17)–C(18)–C(19)	−0.8(3)	C(17)–C(18)–C(19)–C(20)	−0.4(3)
C(18)–C(19)–C(20)–C(21)	0.9(3)	C(19)–C(20)–C(21)–C(16)	−0.1(3)
C(17)–C(16)–C(21)–C(20)	−1.1(2)	C(5)–C(16)–C(21)–C(20)	−178.88(15)
C(16)–C(5)–C(22)–C(27)	108.17(17)	C(4)–C(5)–C(22)–C(27)	−125.37(16)
C(1)–C(5)–C(22)–C(27)	−15.7(2)	C(16)–C(5)–C(22)–C(23)	−69.49(17)
C(4)–C(5)–C(22)–C(23)	56.96(17)	C(1)–C(5)–C(22)–C(23)	166.62(13)
C(27)–C(22)–C(23)–C(24)	1.9(3)	C(5)–C(22)–C(23)–C(24)	179.71(16)
C(22)–C(23)–C(24)–C(25)	−0.2(3)	C(23)–C(24)–C(25)–C(26)	−1.4(3)
C(24)–C(25)–C(26)–C(27)	1.2(3)	C(23)–C(22)–C(27)–C(26)	−2.1(3)
C(5)–C(22)–C(27)–C(26)	−179.75(16)	C(25)–C(26)–C(27)–C(22)	0.6(3)

Figure I Structure of *syn*-**163**.