Methodological Studies Directed Towards

the Synthesis of

Diastereo- and Enantio-pure Cyclopropanes.

A thesis submitted in fulfillment

of the requirements of the

Degree of Doctor of Philosophy.

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Abstract.

The development of a new synthetic pathway for the formation of a diverse range of diastereo- and enantio-pure cyclopropanes (**16**), derived from *trans* γ-hydroxy enones (**17**) is presented.

The proposal required generation of optically pure *trans* γ-hydroxy enones (**17**), which were initially targeted from the deprotection of *trans* γ-*tert*-butyldimethylsilyloxy enones (**44/45**). The chiral pool of natural products was exploited to introduce optical purity and the silyloxy enones (**44/45**) were provided in excellent yields. However, the target hydroxy enones (**17**) were not afforded by this approach, as discussed in Chapter 2.

Chapter 3 presents the results obtained from the synthesis of the hydrochlorin adducts (**56/57**). Removal of the conjugation within the silyloxy enones (**44/45**), prior to cleavage of the silyl group was expected to enable generation of the *trans* γ-hydroxy enones (**17**), whilst this was not the case the results were, nonetheless, interesting.

Chapter 4 presents a more successful strategy to reach the target *trans* γ-hydroxy enones (**17**), through the use of the readily available α-hydroxy aldehyde sub-unit, and a variety of *trans* enones (**17**) were synthesised. The diastereoselective synthesis of disubstituted cyclopropanes (**16**) verified that thermal reaction techniques could be employed to effect the conversion of *trans* enones (**67**) to cyclopropanes (**16**) using stabilised phosphorus ylides, as outlined in Chapter 4.

Subsequent transformation of the optically pure enones (**17**) afforded functionalised cyclopropanes (**16**) in high diastereomeric excess and outstanding enantiomeric excess of ≥ 98%, as presented in Chapter 5. Optimisation of the cyclopropanation was accomplished through the incorporation of a sensitised photoisomerisation step, resulting in a dramatic increase in cyclopropane (**16**) yield and reduced reaction times. These results, along with a study on the effect of the triplet sensitiser employed are presented in Chapter 6.

The potential of this new technique was highlighted by the synthesis of a sugar derived cyclopropane (**92**), Chapter 7. The absolute configuration of the six chiral centres present within this adduct were established from an X-ray crystal structure, enabling prediction of the absolute configuration about the cyclopropyl ring of all future cyclopropane products.

Declaration.

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge it contains no material published or written by another person, except where due reference has been made.

I give my consent to this copy of my thesis being available for loan and photocopying when deposited in the University Library.

Francine Palmer

December 2000.

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Abbreviations.

Adamantyl	Ad
Accurate mass calculated	Acc. Mass Calc.
Analysis calculated	Anal. Calc.
Benzyl (Phenyl methyl)	Bn
tert-Butyl (2,2-dimethylpropane)	*t*-Bu
tert-Butyldimethylsilyl	TBDMS
Correlated Spectroscopy	COSY
Tetracyanoethylene	TCNE
2-Dimensional	2-D
Diastereomeric excess	de
9,10-Dicyanoanthracene	DCA
Di-isobutylaluminium hydride	DIBAL-H
Enantiomeric excess	ee
Ethyl acetate	EtOAc
Gas chromatography-mass spectrometry	GCMS
Ground state	S_0
Heteronuclear Multiple Bond Connectivity	HMBC
Heteronuclear Multiple Quantum Coherence	HMQC
Mass to charge ratio	m/z
Mn	$(1R,2S,5R)$-Menthol
Singlet excited state	S_1
Sulfoxide, piperidine and carbonyl	SPAC
Tetrabutylammonium fluoride	TBAF
Tetrahydrofuran	THF
Thin layer chromatography	TLC
Trifluoroacetic acid	TFA
Triplet energy	E_T
Triplet excited state	T_1

1   Introduction.

1.1   Biological significance of the cyclopropyl motif.

Much of the research devoted towards developing new cyclopropanation techniques has been facilitated by the existence of diversely functionalised cyclopropyl containing compounds found in both natural and non-natural products. As a basic structural feature, the strained cyclopropyl unit has attracted a great deal of interest since many such compounds exhibit impressive biological activity.[1]

Additionally, cyclopropanes can undergo a variety of transformations to provide many useful synthetic intermediates (for both cyclic and acyclic classes of compounds),[2,3] and are generated transiently in primary and secondary metabolisms of humans, plants and microorganisms.[1]

One well known class of cyclopropyl natural products is the pyrethroid group of insecticides, which have been the focus of many investigations.[4,5] As photodegradable low mammalian-toxic insecticides, the pyrethroids are extremely commercially important.[6] The basic structural backbone of this class of compounds includes a tetra-substituted cyclopropane with *gem*-dimethyl substitution and *trans* geometry about the three membered ring. Figure 1 shows one such pyrethroid synthon.
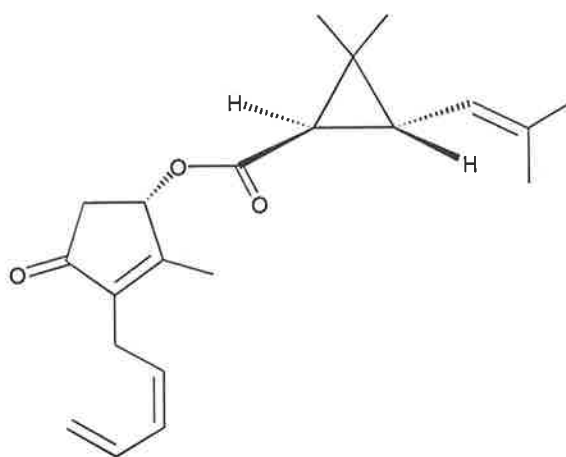
Figure 1. An example from the pyrethroid family.

The recently discovered polycyclopropanated fatty amides FR-900848[7,8] and U-106305[9] (Figure 2) show unusually specific biological activity and unprecedented structure. FR-900848 is a chiral nucleoside and potent anti-fungal agent with an aliphatic side chain containing five (four adjacent) cyclopropyl units.[8] Analogously, U-106305 contains six disubstituted cyclopropane rings and has potential application in the prevention of arteriosclerosis due to its inhibitory effect on cholesterol ester transfer proteins.[10]

FR - 900848

U -106305
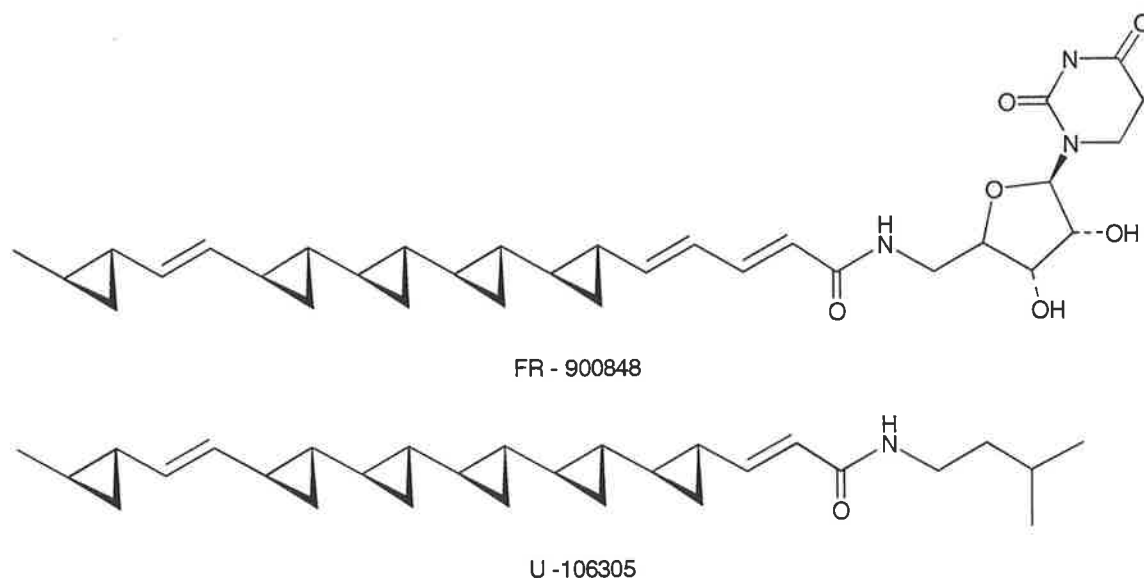
Figure 2. Two recently discovered polycyclopropanated fatty amides.

Further bioactive cyclopropyl substrates include phylpa (DNA polymerase inhibitor),[11] the curacins A-C (antimitotic agents)[12] and the ambruticins (anti-fungal/anti-bacterial agents)[13] family of compounds, displayed in Figure 3.

Whilst the above examples are not exhaustive, they do serve to display an overview of the diverse activity and structure associated with an extensive array of cyclopropyl containing compounds.

There is a strong relationship between the absolute stereochemistry and biological activity of cyclopropane analogues. As a result, the development of efficient procedures for stereo- and enantioselective syntheses of the substituted cyclopropyl subunit have been investigated by a large number of chemists.
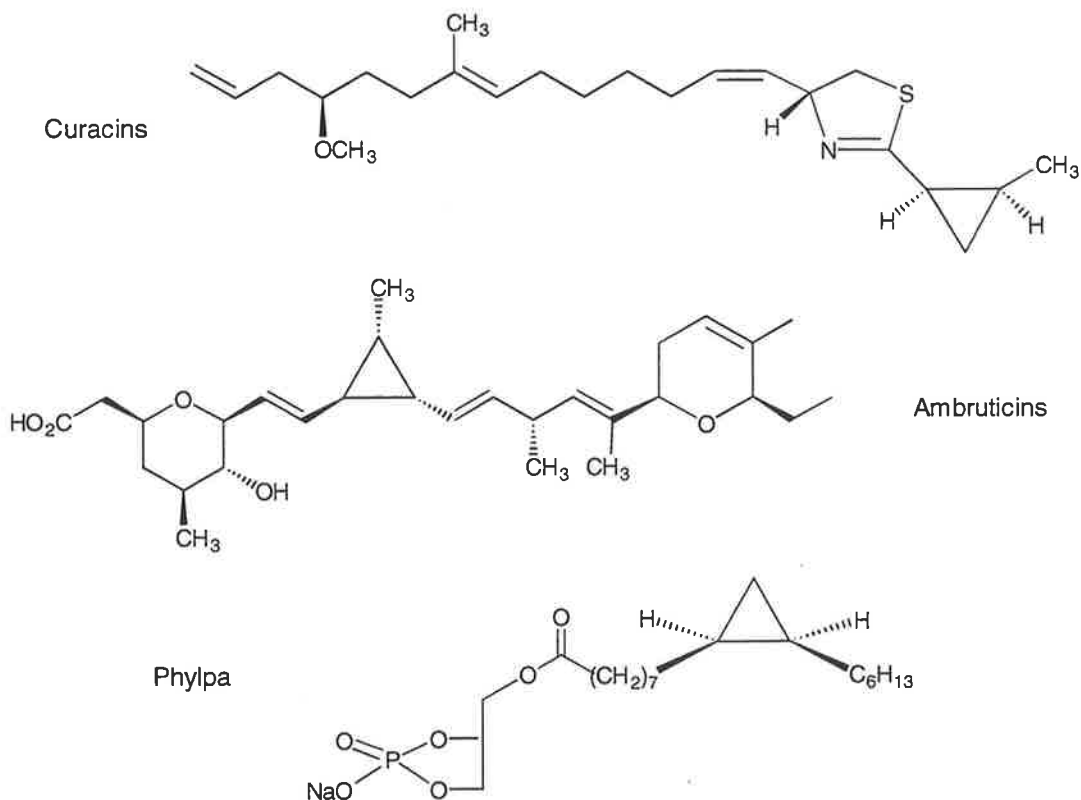
Figure 3. The DNA polymerase inhibitor phylpa and an example from each of the curacin and ambruticin family of compounds.

1.2   Current strategies for cyclopropane construction.

There are several standard reaction procedures reported in the literature for the synthesis of cyclopropane derivatives. Notable examples include cyclopropane formation by; 1) carbene addition to carbon-carbon double bonds ($1\pi + 2\pi$ cycloaddition),[14] 2) Simmons-Smith procedure incorporating the use of a Zn-Cu couple,[15,16] 3) Michael addition with sulfur[17] and phosphorus ylides[18,19] to α,β-enones, and 4) metal-complexed intermediates from diazo compounds,[20] among others. Whilst a diverse range of cyclopropyl containing derivatives can be produced by employing these methods, the product and reaction efficiencies vary considerably depending upon solvents, stability, steric and electronic factors.

1) Cyclopropanation by free carbene addition to an alkene is typically a stereoselective *syn* cycloaddition reaction. Stereospecificity is reliant on the geometry of the precursor alkene i.e. product stereochemistry correlates with precursor olefin geometry, Scheme 1.[14,21]
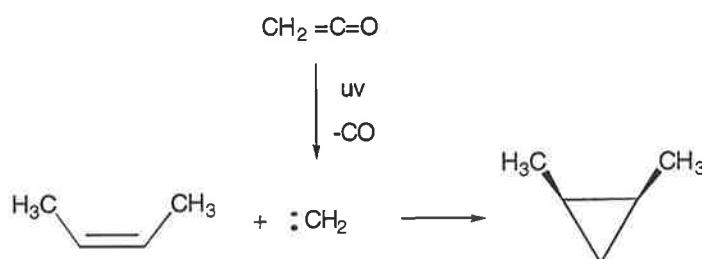
Scheme 1

One limitation to this methodology is the potential for a reduction in product yield as a result of competing insertion reactions of the highly reactive carbene.

The analogous free dihalocarbene addition has been employed by Banwell and co-workers to produce an enantiomerically pure cyclopropane.[22] Enantio-purity was incorporated into the precursor *cis* 1,2-dihydrocatecol (**1**) through the enzyme controlled, microbial oxidation of the mono-substituted aromatic substrate (**2**), Scheme 2. The optically pure bis(*tert*-butyldimethylsilyl) ether of (**1**) was treated with dibromocarbene to afford the cyclopropyl adduct (**3**). Conversion of (**3**) to the trimethylated species and subsequent ozonolytic cleavage of the double bond provided the monochiral open-chain cyclopropane (**4**).

Whilst the product (**4**) was obtained in a good enantiomeric excess, reliant upon the initial asymmetric microbial oxidation, this methodology is still susceptible to potential complications associated with the use of a free carbene.
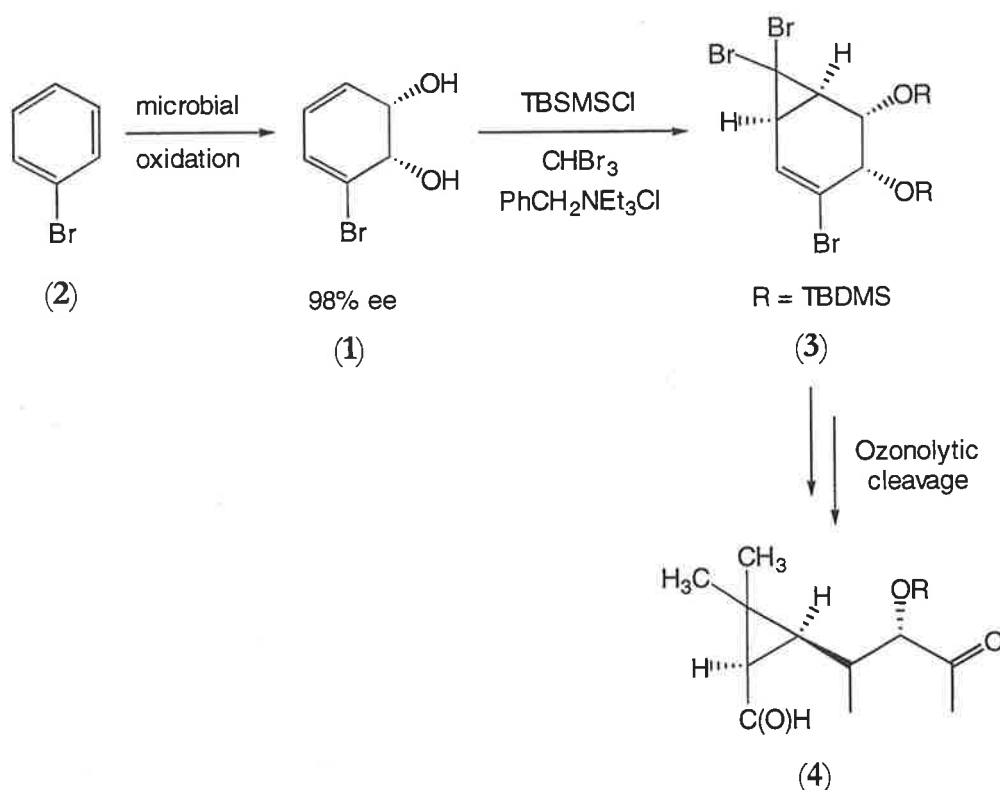
Scheme 2

2) The well known Simmons-Smith procedure[15,16] is analogous to the carbene addition reaction[14] mentioned above with the exception that it does not involve a free carbene, but rather a carbenoid intermediate. The metal-complexed carbenoid reagent delivers methylene to the less encumbered face of the double bond, without competing insertion.

Cycloaddition is influenced by both steric and electronic effects whereby internal functionality can 'assist and direct' the cyclopropanation.[23] The implications of this can be double sided as the example in Scheme 3 depicts. The *cis* allylic alcohol (5a) reaction with the carbenoid is highly stereoselective, yet the isomeric *trans* substrate (5b) shows no diastereoselection, providing a mixture of epimeric alcohols.[24]

This stereoselectivity difference is partially due to the directing effect of the neighbouring oxygen atom. Figure 4 displays how coordination of the zinc reagent with the hydroxyl group directs the addition of methylene to the neighbouring alkene.[25]
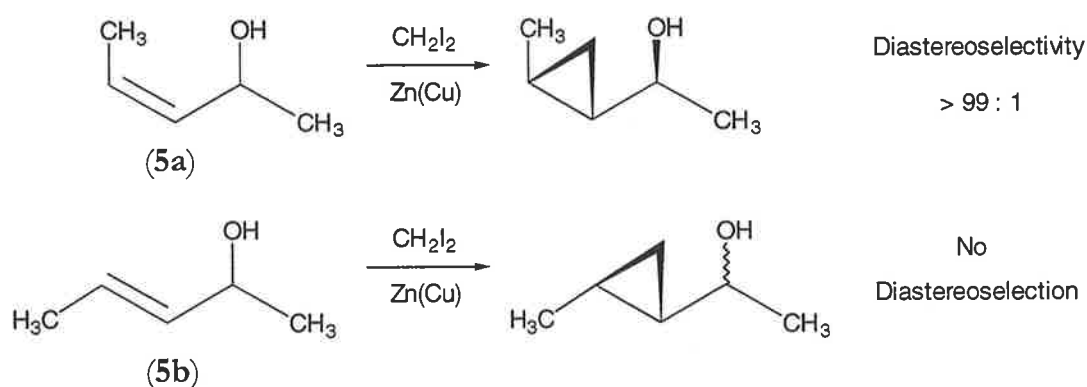
Scheme 3
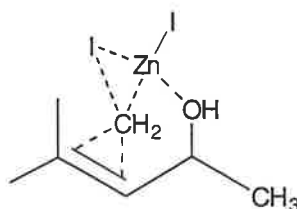
Figure 4. The three-centred transition structure showing the coordination between
the oxygen, the (iodomethyl)zinc iodide and the alkene in a Simmons-Smith reaction.

An additional influence on stereoselectivity can be explained by analogy with the epoxidation model proposed by Chautemps and Pierre.[26,27] The three possible transition states for cyclopropanation show the carbon-carbon double bond is eclipsed, whilst also constituting a part of the complexation with the hydroxyl group and the zinc reagent, Figure 5.[24]

In the case of (5a), where the methyl group is present in the β-*cis* position on the double bond, transition state (III) is the most favourable because of the comparatively small H atom eclipsing the double bond. As transition state (III) leads to the *erythro* cyclopropyl product, diastereoselectivity is observed. However, for (5b), where the methyl group is in the β-*trans* position, the fastest cyclopropanation involves transition state (II).[27] 'Attack' by the coordinated zinc reagent can occur from either face (a) or (b) and therefore no diastereoselectivity is observed, Figure 5.
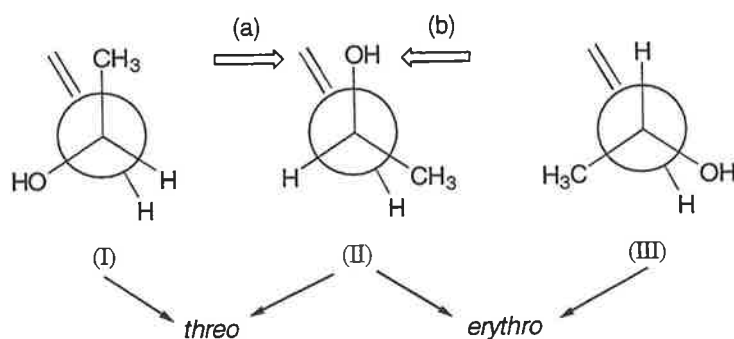
Figure 5. Transition state conformers for the Simmons-Smith reaction with an allylic alcohol, leading to either the *threo-* or *erythro*-cyclopropyl derivative as indicated. The assignment of *erythro* was designated for where the configuration of the functional and contiguous carbon atoms are specified by the same letter (*R,R* or *S,S*).[24]

Reported studies into asymmetric versions of the Simmons-Smith protocol typically involve the use of optically active alkene substrates containing chiral auxiliaries.[2,3] Mash and co-workers[28] have reported one such example with reasonable diastereoselection in products (**6a** and **6b**) obtained in a combined yield of 84%, Scheme 4. Subsequent hydrolysis of recrystallised and separated (**6a**) or (**6b**) could then provide cyclopropyl products with good enantiomeric purity.
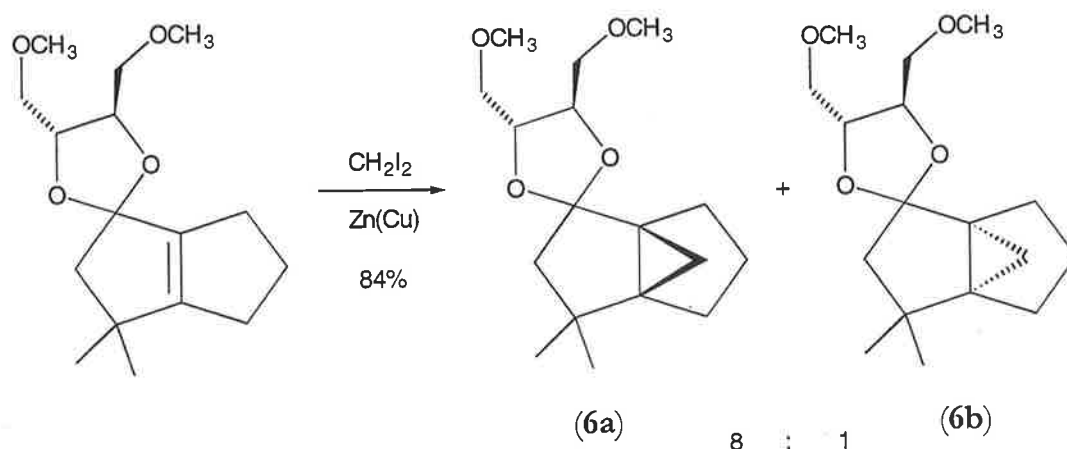
Scheme 4

3) Ylide cyclopropanation is one of the earliest developed and extensively studied reactions within ylide chemistry.[29] Phosphorus ylides have been employed for ylide cyclopropanation reactions,[30,31] yet sulfur ylides (typically sulfonium, sulfoxonium and sulfoximine) have received the most attention.[17,29,32-36] Cyclopropanation predominates

with systems that are normally susceptible to Michael addition, however, complications may arise as a result of ylide reactivity.[17] Depending on the substrate and ylide involved competition between direct addition to the electronegative group on the substrate and cyclopropanation may significantly reduce reaction efficiency.[17,29,32,35,37]

The introduction of chiral sulfur ylides has enabled the preparation of optically pure cyclopropanes. This area can be divided into two categories, reagent-controlled (chiral ylide) and substrate-controlled (chiral Michael acceptor).[29] An example of the former process reported by Trost and co-workers[38] employs the chiral sulfonium ylide (7) to afford asymmetric cyclopropanation of the α,β-unsaturated ester (8), Scheme 5.
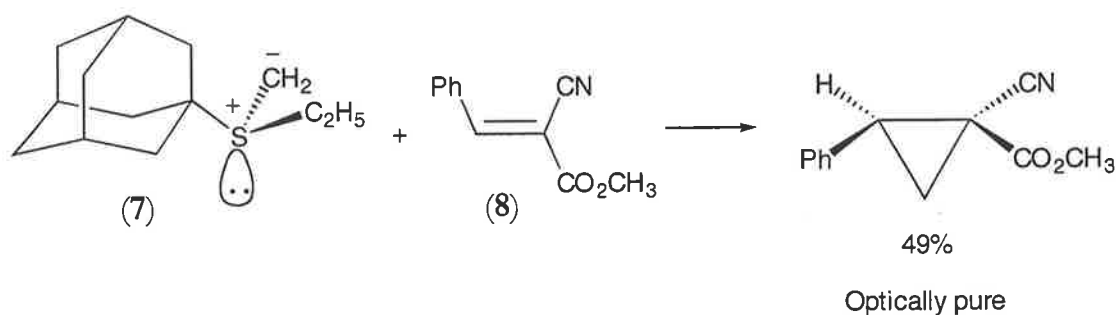
Scheme 5

Meyers *et al.*[39] have reported a substrate-controlled example wherein reaction of the chiral α,β-unsaturated bicyclic γ-lactam (9) ('Meyers' lactam') with dimethylsulfonium methylide, gave chiral cyclopropanes (10a) and (10b) in 65% overall yield and 98% diastereomeric excess (de), Scheme 6. Cyclopropane (10a) and/or (10b) could then be hydrolysed to provide the optically pure cyclopropyl keto ester (11).

These types of reactions yield optically pure cyclopropyl substrates with excellent enantioselectivities, yet typically provide relatively low yields of product. The choice of ylide employed is clearly both important and restricted in terms of potential side reactions, yields, and the substitution pattern desired about the cyclopropyl motif. To date, most studies have focused on substrate-controlled asymmetric cyclopropanations, yet more recent results with reagent- and auxiliary-controlled processes show potential for further development.[29]

100 : 1

65%

de 98%
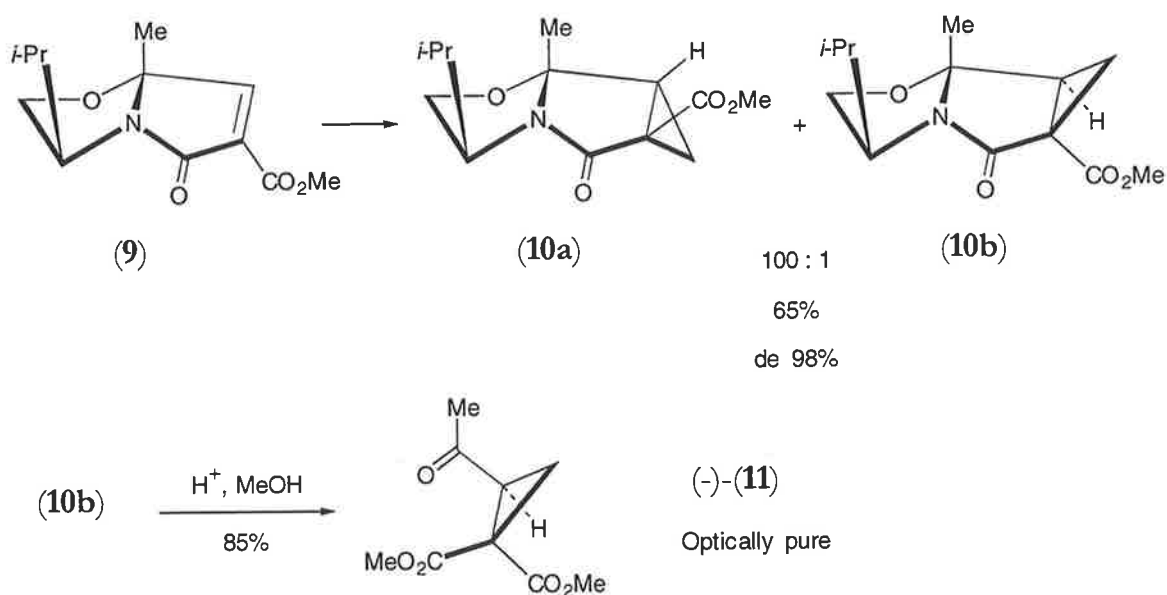
Scheme 6

4) Decomposition of diazo compounds in the presence of transition metals generates a carbene-like species, which gains stabilisation through interaction with the transition metal.[20] Transition metal compounds with a vacant coordination site, which renders the metal electrophilic and favours addition to the diazo carbon, have proved effective catalysts. Following the extrusion of dinitrogen from the diazo compound, a carbon-metal bond forms to afford the metal-carbenoid. The resulting metal-carbene complex reacts with alkenes to form cyclopropanes in a stereocontrolled manner directed by organic ligands attached to the metal center.[20,40-42]

Metal-catalysed decomposition of diazo compounds avoids potential side reactions (e.g. Wolff rearrangements,[43] C-H insertion and hydride migrations[44]) encountered from thermal or photochemical carbene generation.[44] Whilst a variety of systems have been employed for cyclopropanation, diazoacetates have been most extensively utilised.[44] Similarly, copper and rhodium have received the greatest attention as suitable metals, yet cobalt and ruthenium have also shown positive results.[41,42,45,46]

Since the first reported catalytic asymmetric cyclopropanation in 1966,[47] significant advances have been achieved. Enantiocontrol by catalytic diazo decomposition is now known to be influenced by a number of factors including ligand size and steric bulk,[48] chelate size of the metal complex,[48] and the ester functionality of the diazoacetate.[41,42]

Scheme 7 shows the synthesis of a disubstituted cyclopropane from diazoacetate (**12**) in the presence of the chiral copper complex (**13**).[20] Good enantiomeric excess (ee) was obtained yet only moderate diastereopurity.

trans / cis ratio		trans	cis
		ee %	
80 : 20		94	89
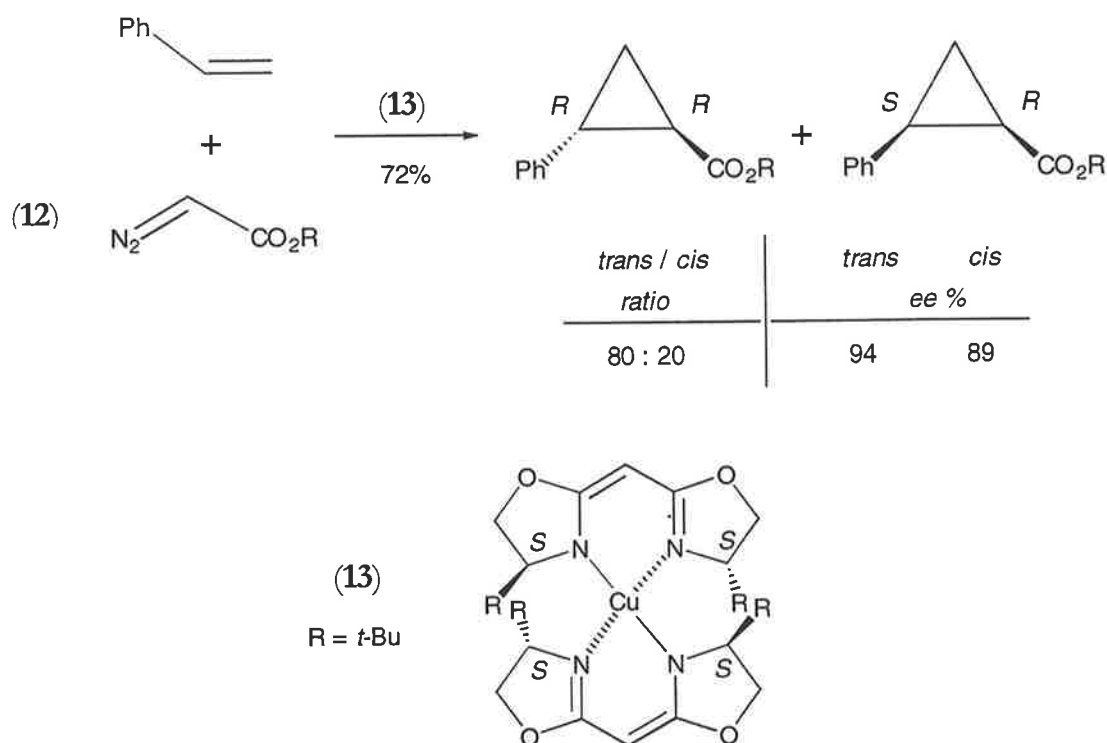
Scheme 7

A significant restriction of this cyclopropanation methodology is the competitive formation of a dimeric by-product, formed through reaction of the carbenoid with its diazo precursor.[44] It is further limited in the range of compatible functional groups relative to alternate techniques, catalyst sensitivity,[44] and the potentially explosive nature of diazo precursors.

Despite the individual merits of each of the cyclopropanation techniques discussed above, there is no single reported approach which directly accommodates for the formation of highly substituted cyclopropanes in good yields with high diastereomeric and/or enantiomeric excess. Of particular interest is the lack of methodologies that allow for the construction of cyclopropanes containing greater than di-substitution. Furthermore, these methods typically require the use of highly complex reagents, complicated reaction conditions and often must be carried out under strictly anhydrous conditions.

1.3   A new cyclopropanation methodology.

Taylor *et al.* recently reported a new and novel cyclopropanation methodology, which entails the construction of di- and trisubstituted cyclopropanes.[49] The methodology involves the treatment of 3,6-disubstituted 1,2-dioxines (**14**) with stabilised phosphorus ylides (**15**) yielding highly functionalised cyclopropanes (**16**) in excellent yields and diastereomeric excesses, typically of greater than 90% and 98% respectively, Scheme 8.

X and Y = combinations of H, aryl and alkyl
R^1 and R^2 = combinations of H, alkyl, keto and ester
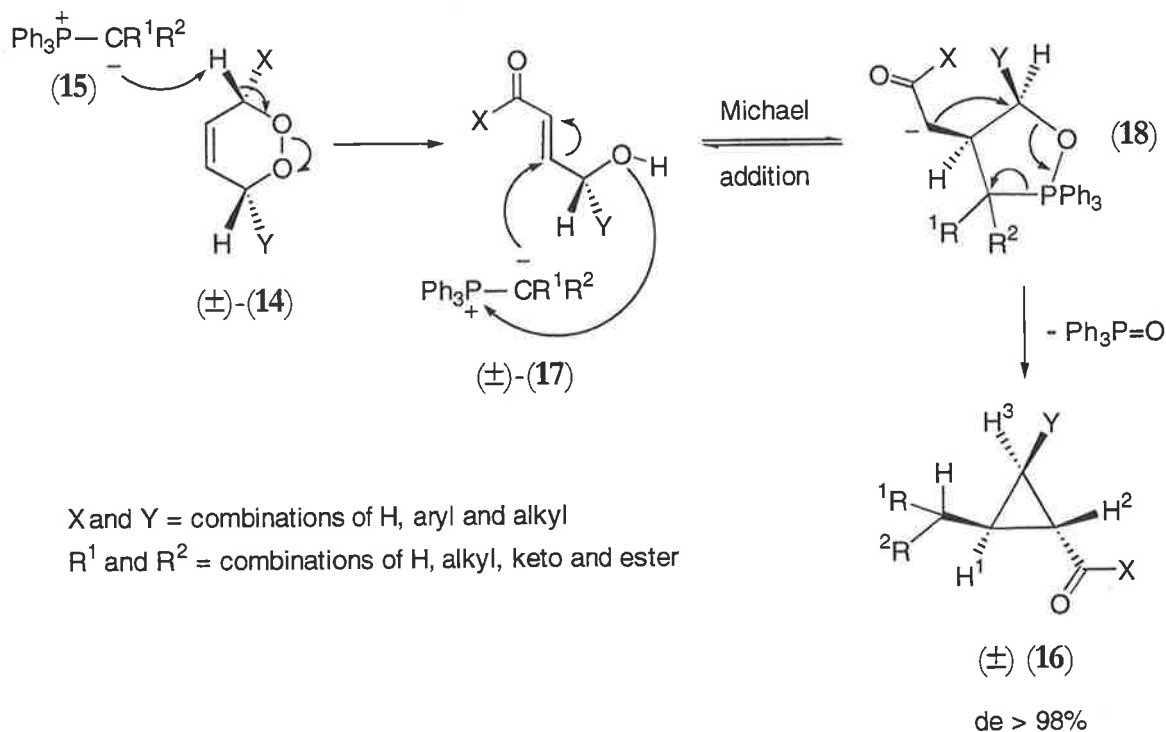
Scheme 8

A series of preliminary studies enabled the mechanism depicted in Scheme 8 to be proposed.[49] The ylide (**15**) initially acts as a weak base removing the α-proton from the dioxine (**14**), inducing cleavage of the O-O linkage. Subsequent ring opening and rearrangement leads to the formation of, what was proposed to be the key intermediate, *trans* γ-hydroxy enone (**17**). Michael addition of the ylide (**15**) to *trans* enone (**17**) generates the 5-membered $1,2\lambda^5$-oxaphospholane (**18**) intermediate, which subsequently collapses as intramolecular cyclisation of the enolate (**18**) expels triphenylphosphine oxide, and final proton transfer affords the observed cyclopropane (**16**).

A collection of functionalised cyclopropanes have been synthesised employing this technique with the major diastereomer obtained in each instance being the *trans* cyclopropane (**16a**), wherein H[1] and H[3] are in a *trans* orientation with respect to H[2]. The *syn* Michael addition of (**15**) onto (**17**), with regard to the hydroxyl moiety rationalises the *cis* stereochemistry observed between H[1] and H[3].

Studies revealed that a minor amount of the corresponding all *cis* isomer (**16b**) occasionally formed and that cyclopropane production was sometimes accompanied by the formation of trace amounts of 1,4-dicarbonyl products (**19**),[50] Scheme 9, *vide infra*.
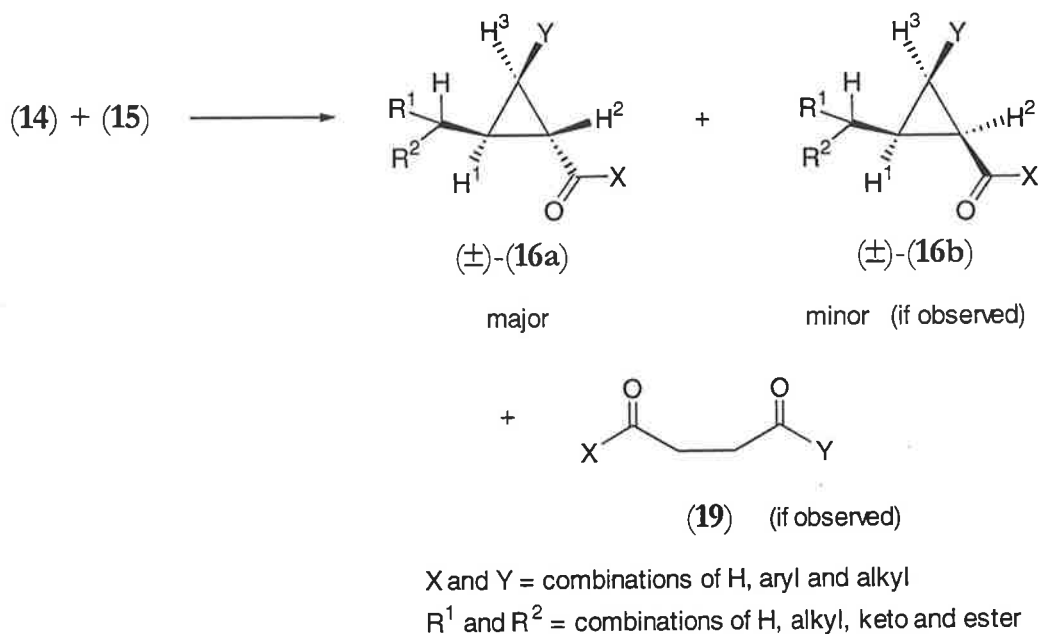
Scheme 9

The most important observation to come from the initial mechanistic investigations was that the *trans* γ-hydroxy enone (**17**) appeared to be a key intermediate in the reaction manifold. This was confirmed most conclusively from ^{1}H nuclear magnetic resonance (NMR) studies, which indicated formation of (**17**) as a transient species in the reaction pathway. Experimental evidence seemed to confirm this, as isolation and characterisation of the *trans* enone (**17**) was achieved. It was discovered that enone (**17**) decomposed on standing at ambient temperature, undergoing rearrangement to isomeric dicarbonyl (**19**) and furan (**20**) derivatives. Any uncertainty concerning the mechanistic significance of the

trans enone (**17**) was waylaid when it was shown to yield the same cyclopropyl products (**16**) as the precursor 1,2-dioxines (**14**).[49,51]
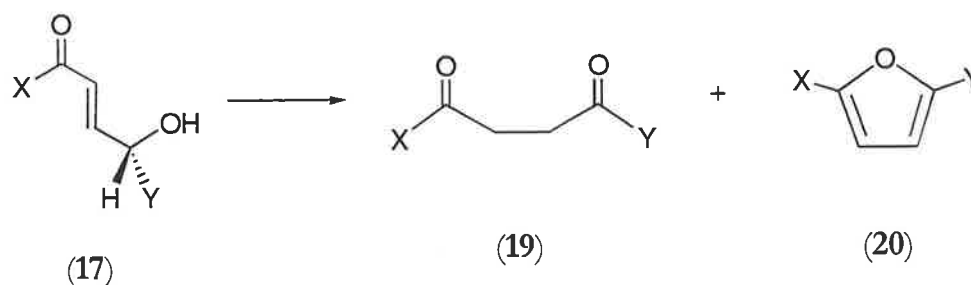
Scheme 10

This new discovery was not only exciting in terms of providing an alternate route to cyclopropanes, see Section 1.2, but additionally in its potential to greatly simplify the synthesis of several natural and non-natural cyclopropyl containing compounds, as highlighted earlier, Section 1.1. This new cyclopropanation technique makes it viable to construct the desired cyclic structure with predetermined substitution and known stereochemistry, and utilises simple, inexpensive and readily available starting materials.

As stated above, cyclopropanes formed by this approach were obtained in excellent diastereo-purity, however, enantiomerically pure products are not possible utilising this strategy. The precursor 1,2-dioxine (**14**) is generated by a [4π + 2π] cycloaddition reaction of a 1,3-butadiene (**21**) with singlet oxygen, Scheme 11. This cycloaddition is not enantioselective. Therefore, treatment of (**14**) with a ylide (**15**) will always result in racemic γ-hydroxy enone (**17**) formation, and accordingly racemic cyclopropanes (**16**).

X and Y = combinations of H, aryl and alkyl
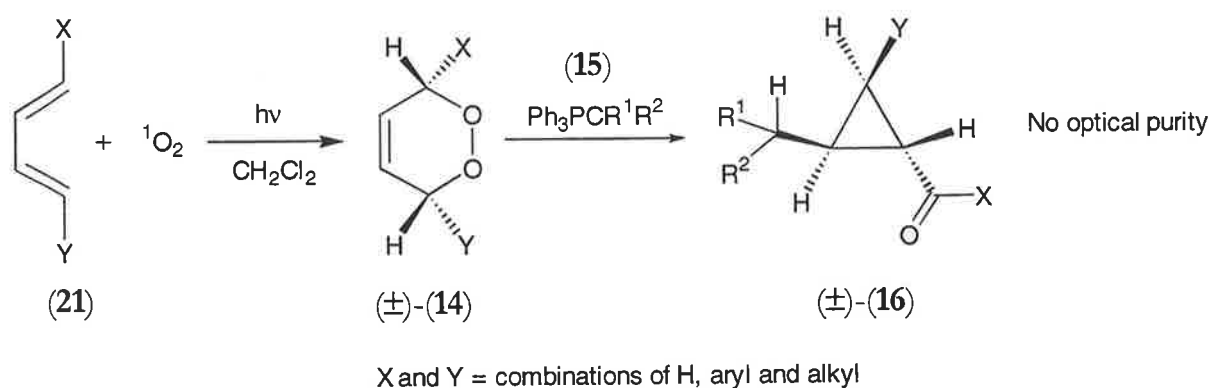
Scheme 11

Classical resolution techniques could be employed to afford cyclopropanes with optical purity, however, several factors discourage this approach. The ester functionality present in the proposed cyclopropane (**16**) should accommodate for the formation of diastereomers when treated with a chiral agent. Subsequent separation of the diastereomeric mixture must then be achieved by physical techniques and optimum results would be obtained with a crystalline product. As there are no means to predict whether the diastereomers will be crystalline or liquid in nature, this poses a potential disadvantage. In the later case, separation of the liquids by chromatography is a significant deterrent in terms of potential product loss (depending upon the separation between diastereomers), and both time and monetary expense. Most importantly, the optimum yield of the desired enantiomer can only be 50%.

Kinetic resolution would involve reaction of the substrate, to form one enantiomer or diastereomer of the product, with a chiral reagent at a faster rate than the opposite isomer. In this case, resolution is reliant on there being a significant energy difference between the two transition states. Like the classical technique, kinetic resolution (of cyclopropanes with no plane of symmetry) can produce at best 50% of the desired product.

There is also potential to construct enantiomerically pure cyclopropanes by treating the precursor 1,2-dioxines (**14**) with chiral ylides, or alternatively through the implementation of chiral auxiliary methods.[52] The choice of the chiral ylide or auxiliary employed would be highly sensitive to the reaction conditions and reagents involved, and could require extensive 'blind' experimentation to obtain positive results, if at all. The unattractive nature of the above resolution and enantioselective techniques made the investigation of an alternative approach for this new cyclopropanation methodology more appealing.

It was envisaged that the preparation of optically pure cyclopropanes could be efficiently accommodated for through a modification of this newly reported strategy. The C-4 chiral centre present in the proposed key intermediate, *trans* γ-hydroxy enone (**17**), provides the opportunity to incorporate enantio-purity into the product. It was rationalised that direct synthesis of optically pure *trans* enones (**17**) would allow for the generation of the corresponding optically pure cyclopropanes (**16**). Successful synthesis of enantiomerically

pure enones (**17**) would provide an alternate entry point into the reaction pathway (Scheme 8) whilst avoiding the use of precursor 1,2-dioxines (**14**).

1.4   Research objectives: synthesis of the *trans* γ-hydroxy enone.

Research has shown that although yields were reduced and reaction times extended, *trans* γ-hydroxy enones (**17**) did afford cyclopropanes (**16**) on treatment with stabilised phosphorus ylides (**15**).[49] Therefore, it was proposed to synthesise enantiomerically pure *trans* γ-hydroxy enones (**17**) for subsequent conversion to functionalised cyclopropanes with both high diastereomeric and enantiomeric excess, Scheme 12.
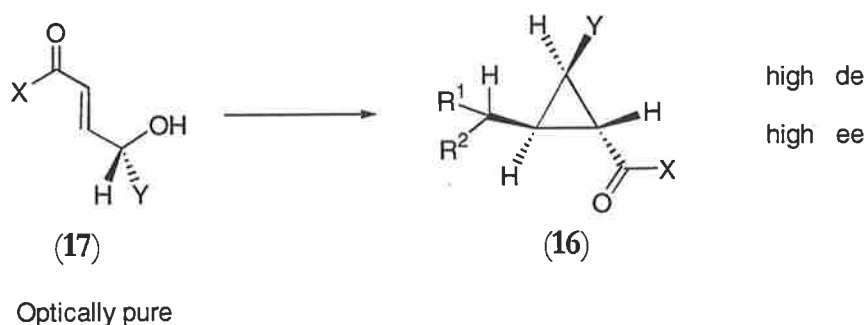
X and Y = combinations of H, aryl and alkyl
R^1 and R^2 = combinations of H, alkyl, keto and ester

Scheme 12. Research objectives: transformation of optically pure *trans* enones (**17**) into optically pure cyclopropanes (**16**).

In view of this goal, the initial focus of this research was the development of a generic and stereoselective procedure that would provide a diverse range of γ-hydroxy enone (**17**) analogues. Development of one general pathway to a number of functionalised enones (**17**) would not only allow for the synthesis of optically pure cyclopropyl analogues, but also provide an opportunity to study the effects of such functionality on the reaction outcome.

Therefore, an additional objective of this research was to investigate the effect of:
- increasing the steric bulk of the substituents ('X' and 'Y') at both termini of (**17**),

- electron withdrawing groups at the carbonyl terminus of (**17**), eg. ester versus keto substitution, and

- inductively withdrawing/donating groups at the hydroxyl terminus of (**17**).

In conjunction with this, the consequence of varying the cyclopropanation solvent was to be examined.

The effect of the above variations on enantio-purity will be closely examined, with the enantiomeric excess of each product to be determined through chiral shift NMR experiments. The use of a chiral shift reagent enables the *in situ* generation of a transient diastereomeric species, which can then be studied by either ^{1}H or ^{13}C NMR to accurately calculate the enantiomeric excess of the product.[53] It was expected this would enable determination of the ideal conditions and substitution pattern required to afford cyclopropanes in optimum yield, diastereo- and enantio-purity.

The outcome of the steric, electronic and solvent effect studies should provide greater insight into the significance of such factors on this new methodology. Further understanding of the reaction manifold will aid in promoting the application potential of this technique.

1.4.1   Literature approaches to γ-hydroxy-α,β-unsaturated carbonyl compounds.

In spite of the versatility of the γ-hydroxy enone synthon, γ-hydroxy-α,β-unsaturated carbonyl compounds have received limited attention in the past. A vast number of *in situ* applications are reported in the literature,[54] however, few techniques are reported for their synthesis and isolation in either racemic or optically active forms. Synthesis of γ-hydroxy-α,β-unsaturated carbonyl compounds has been achieved by utilising Sulfoxide, Piperidine And Carbonyl (SPAC) reactions,[54,55] α,β-epoxy diazomethylketone methodology[56,57] and Wittig olefination reactions with α-hydroxy aldehydes.[54]

SPAC reactions involve the treatment of aldehydes with kinetically resolved methyl sulfinyl acetates (**22**), Scheme 13, with resolution achieved using a crude preparation of lipase *Pseudomomas* K-10.[54] Burgess reported that good chemical and moderate optical yields were obtained with the provision that the aldehyde component is not vulnerable to self-condensation. Phenylacetaldehyde is one such component, which is susceptible to

self-condensation and   the γ-hydroxy-α,β-unsaturated carbonyl products (**23**, R' = phenyl) obtained were virtually racemic. Conversely, lactaldehyde provided the corresponding methyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (**23**, R'= methyl) in 71% yield with 64% ee.
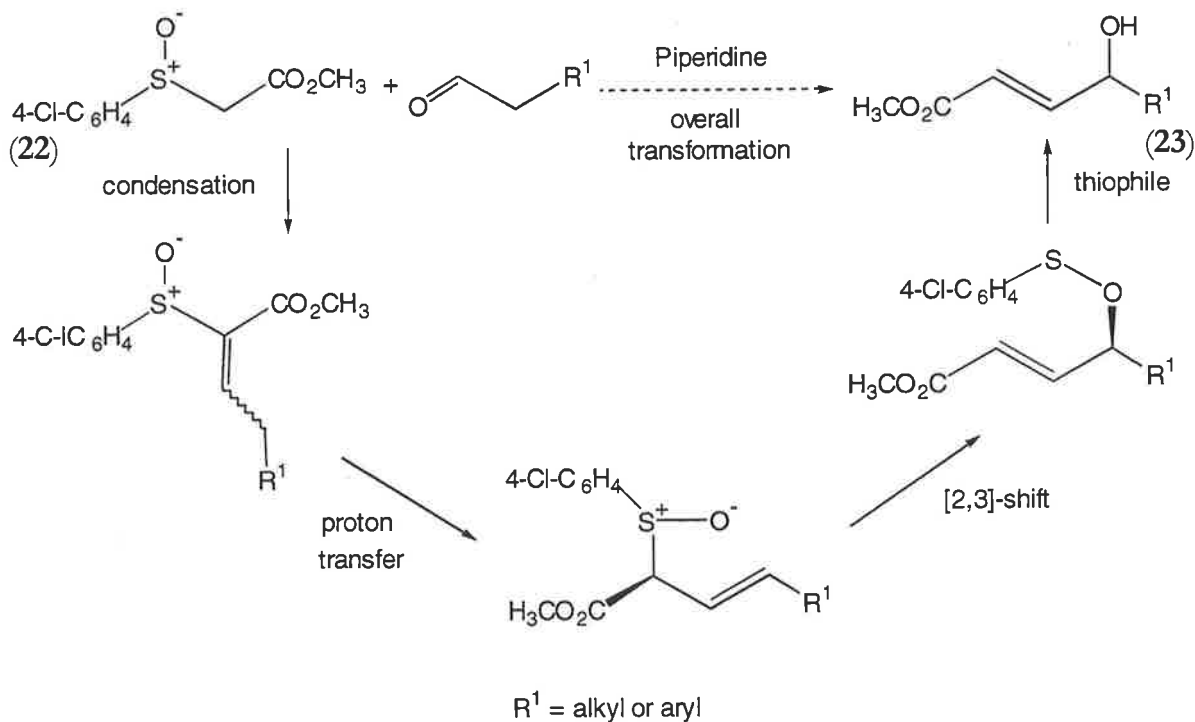
Scheme 13

Whilst the SPAC methodology is experimentally simple, it is only adequate for the generation of γ-hydroxy enesters due to the precursor sulfinylacetate species (**22**). This technique was dismissed for use in this study, as it does not satisfy the criterion of providing numerous analogues of (**17**) through one general synthetic route.

γ-Hydroxy α,β-unsaturated compounds have also been independently prepared by Woolsey [56] and van Haard,[57] using α,β-epoxy diazomethyl ketones. The irradiation of diazo adducts gave rise to a reactive ketene intermediate, which underwent epoxide ring opening to afford γ-hydroxy enesters, see Scheme 14.[56,57]

Both of these studies[56,57] were interested in extending the synthetic utility of diazo ketones. Whilst the authors were successful in meeting their objectives, the methodology shows only limited suitability to the current proposal. Products were typically obtained in

relatively good yields, however, only ester compounds were reported and more significantly no optical purity was obtained.

R = combinations of H, CH$_3$, C$_6$H$_5$.
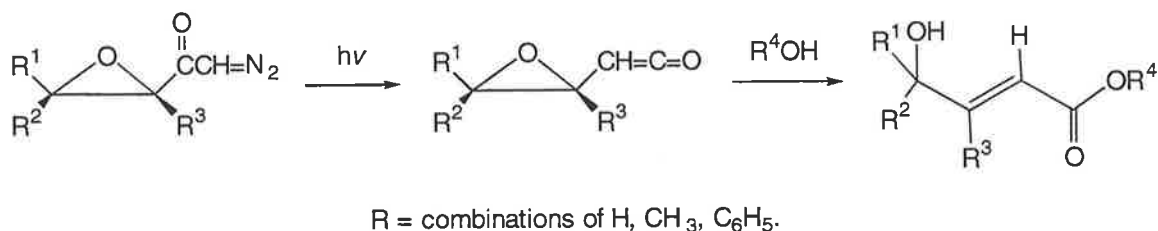
Scheme 14

As the current research is not concerned with studying the chemistry involved in the formation of hydroxymethine centres, it was concluded that the simplest and most practical route to provide a range of γ-hydroxy enones (17) was through a Wittig olefination reaction of α-hydroxy aldehydes with stabilised ylides. Of the small number of routes to γ-hydroxy-α,β-unsaturated carbonyl compounds cited in the literature, Wittig olefination is perhaps the most prevalent approach. However, while a Wittig reaction with stabilised phosphorus ylides stereoselectively yields the *trans* isomer as the major product, the reaction is not enantioselective. This limitation necessitates that the chiral centre be pre-existent in the precursor α-hydroxy aldehyde.

1.4.2   Literature approaches to the α-hydroxy aldehyde synthon.

The α-hydroxy carbonyl unit is wide spread in natural products and has frequently been employed as a convenient building block.[58] Accordingly, literature precedent for the construction of both racemic and enantiomerically pure α-hydroxy aldehydes is significantly greater than for the corresponding Wittig olefination products,[54] γ-hydroxy-α,β-unsaturated compounds.

A larger number of techniques are cited in the literature for the synthesis of optically pure tertiary α-hydroxy aldehydes than exists for the required secondary α-hydroxy aldehyde. The presence of a hydrogen α to the carbonyl group in the secondary aldehydes, which increases the likelihood of racemisation during synthesis, is perhaps the reason for the

apparent imbalance. Despite this, several procedures are known for the provision of optically pure secondary hydroxy aldehydes, a selection of which is summarised below.

A notable example is the catalytic asymmetric synthesis of protected α-hydroxy aldehydes (**25**) reported by Vettel *et al.* in 1997.[59] This study was interested in the synthesis of chiral non-natural α-hydroxy aldehydes involving the treatment of α,β-unsaturated aldehydes (**26**) with diorganozinc reagents (**27**) to provide allylic alcohols, followed by simple oxidative cleavage, Scheme 15.
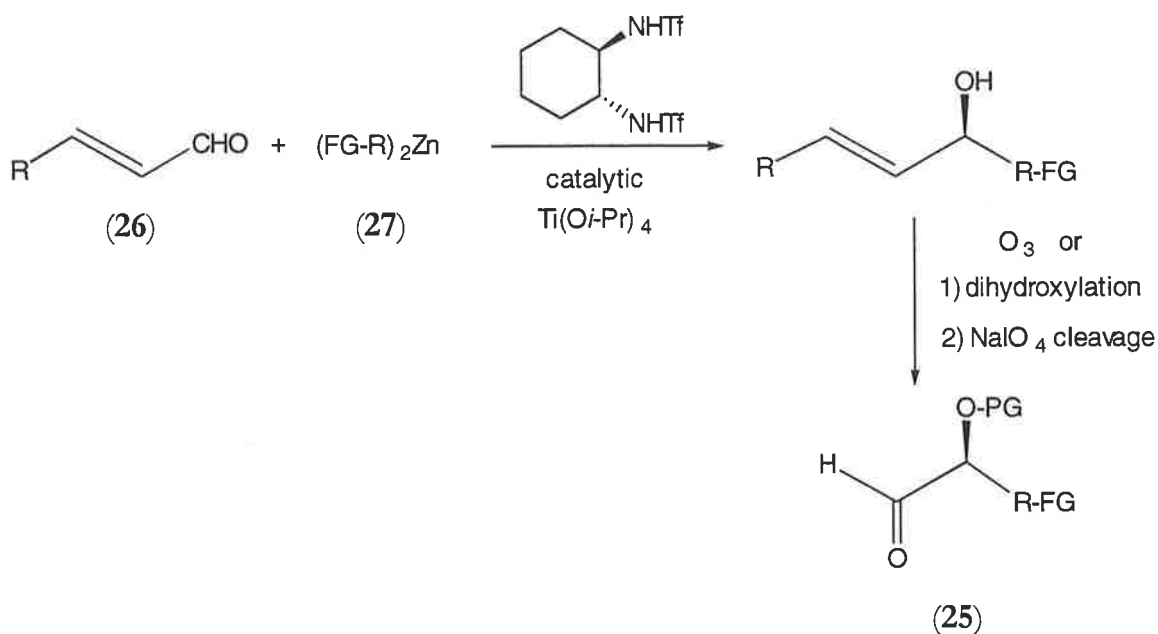
R = alkyl or aryl. PG = protecting group FG = functional group

Scheme 15

The chiral centre was introduced in the C-C bond formation step using asymmetric catalytic addition of organozincs. Almost complete retention of configuration was achieved through the conversion of the allylic alcohols to the corresponding α-alkoxy aldehydes (**25**). Moderate yields were obtained with product optical purity typically greater than 90% ee.[59]

Heathcock applied a similar methodology in the preparation of three analogous protected α-hydroxy aldehydes (**25**).[60] Ozonolysis of the   alkene ether yielded the desired *R*-enantiomer after preparative high-pressure liquid chromatography, with the best isolated

yield of 47% observed for the silyl-ether derivative (**25**), Scheme 16. This application was only reported for lactaldehyde derivatives, which were obtained in relatively poor yield, and no reference was made to the isolated yield of the opposite *S*-enantiomer.

R = *t*-BuMe$_2$Si , C$_6$H$_5$CH$_2$, C$_6$H$_5$CH$_2$OCH$_2$.
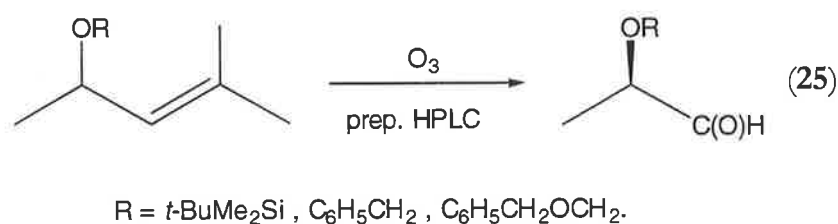
Scheme 16

The ozonolysis technique employed by Heathcock[60] was discarded as a potential method for the synthesis of the target enone synthon (**17**) as poor yields and restrictive purification procedures make this option impractical. On the other hand, this ozonolysis protocol in conjunction with diorganozinc reagents[59] has the potential to accommodate for this proposals requirements. In spite of this, it was believed that a simpler means of achieving the same result was possible.

The use of a Grignard reagent and the tributylstannane (**28**) to form the intermediate oxazolidine (**29**) was reported by Colombo and co-workers.[61] Under chelation control, the reaction is highly stereoselective yielding enantiomerically enriched O-protected α-hydroxy aldehydes (**25**) in a total of 7 synthetic steps. The aldehyde (**25**) was isolated, yet used without purification to afford the corresponding diol (**30**), Scheme 17. No mention is given of the enantiomeric excess of the aldehyde product (**25**), only the enantiomeric excess of the targeted masked diol (**30**) (>96% ee) was reported.

This methodology was described for alkyl, allyl and aryl substitution, nonetheless it was not considered for the current strategy due to the large number of synthetic steps required to reach the desired aldehyde target (**25**). The complex starting materials and the lack of data for the α-hydroxy aldehyde products isolated further detracted from adopting this method.

a) *n*-BuLi, THF, -78 $^\circ$C   b) DMF
c) TiCl$_4$ or MgBr$_2$, CH$_2$Cl$_2$, -78 $^\circ$C
d) RMgX or AllylSnBu$_3$ e) PhCOCl, Py
f) HCl/AcOEt, 0 $^\circ$C   g) THF/H$_2$O, r.t.

R = *n*-Bu, Ph, cyclohexyl or allyl.

ee > 96%

61-73%

Scheme 17

Diastereoselectivity
48 : 52 to 91 : 9

R = Ph, Me, allyl, *n*-butyl.

1) NaH, THF,
DMSO, BnCl

2) H$_2$SO$_4$,
dioxane

Pb(OAc)$_4$,
benzene

High ee

Yield 63 - 85%
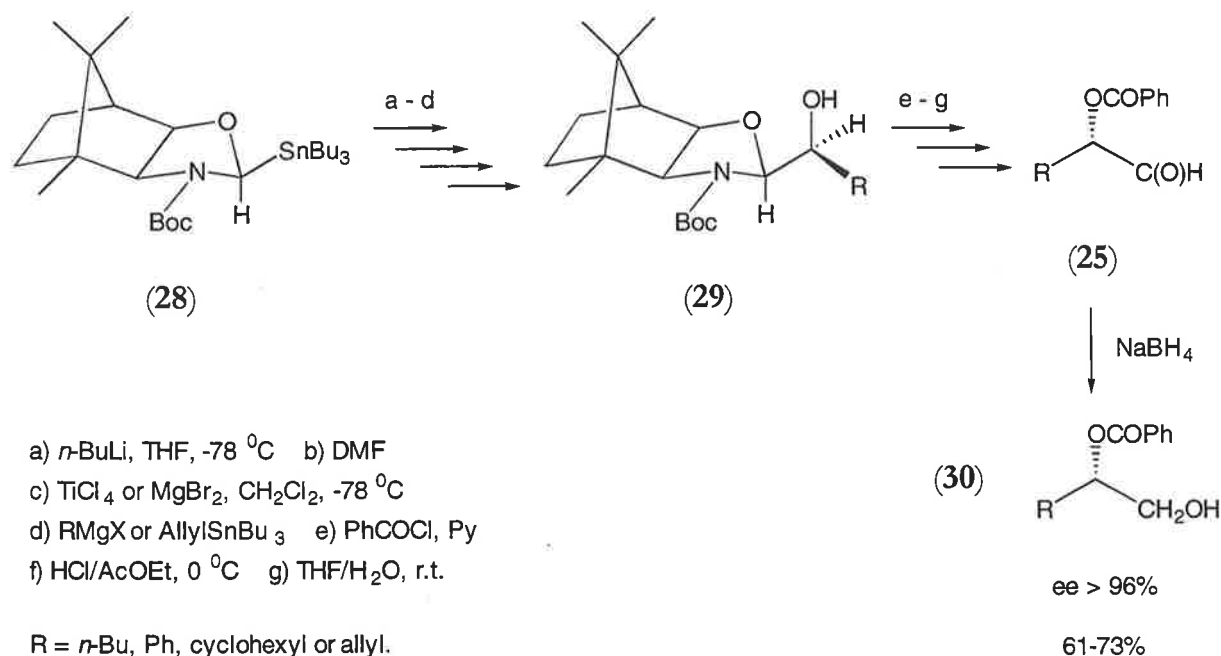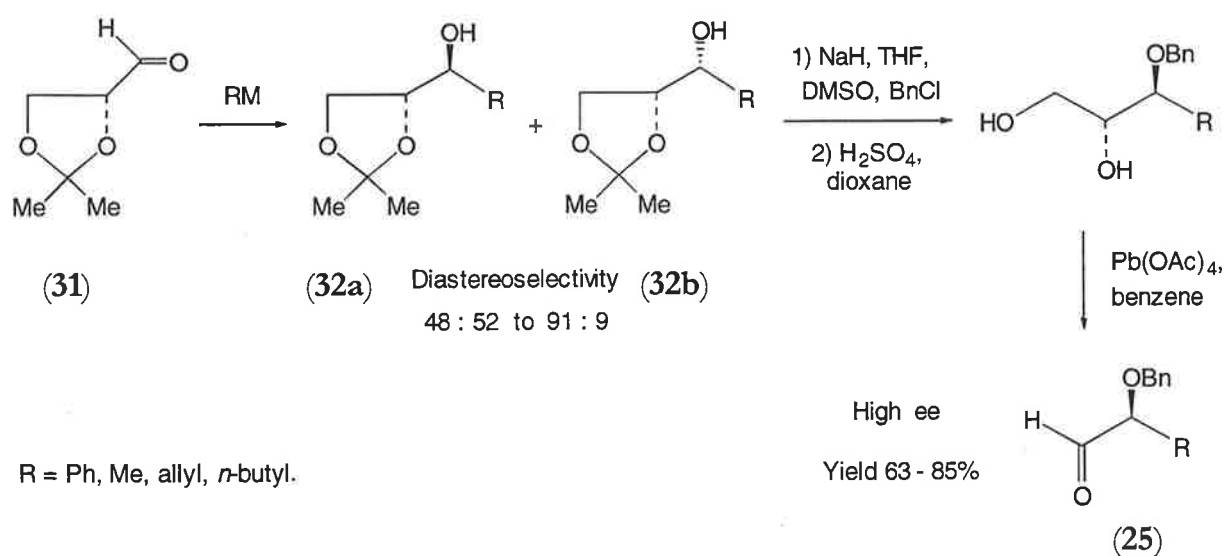
Scheme 18

Another example of an organometallic reaction, which furnishes secondary protected α-hydroxy aldehydes (**25**) is shown in Scheme 18. It requires four transformations from optically pure 2,3-isopropylidene glyceraldehyde (**31**) and the first step was achieved in an average yield of 60-80%.[62] However, the diastereoselectivity was quite sensitive to the

reagents and substitution involved. In order to obtain high enantiomeric excess in the final product the stereoisomers (**32a/32b**) must be separated, resulting in a significant decrease in the overall yield. This was not accounted for in the yields quoted for the protected hydroxy aldehydes (**25**), which were calculated over the final two steps in the reaction pathway.

One final example is the report of an additive Pummerer reaction of vinylic sulfoxides (**33**) that suggests an alternate means to reach the desired α-hydroxy aldehyde synthon.[63-65] Craig *et al.* reported the use of a trifluoroacetic anhydride mediated additive Pummerer reaction as an efficient method for the synthesis of protected α-hydroxy aldehydes (**25**) and α-hydroxy aryl ketones (**34**). The first step in this procedure generates an α,β-*bis*(trifluoroacetoxy)thioether in high yield, which when subsequently treated under basic methanolysis conditions gives monomeric and dimeric α-hydroxy species as shown in Scheme 19. The precursor disubstituted α,β-unsaturated sulfoxides (**33**) were prepared through a modified one-pot Wadsworth-Emmons procedure in high yield.[64]
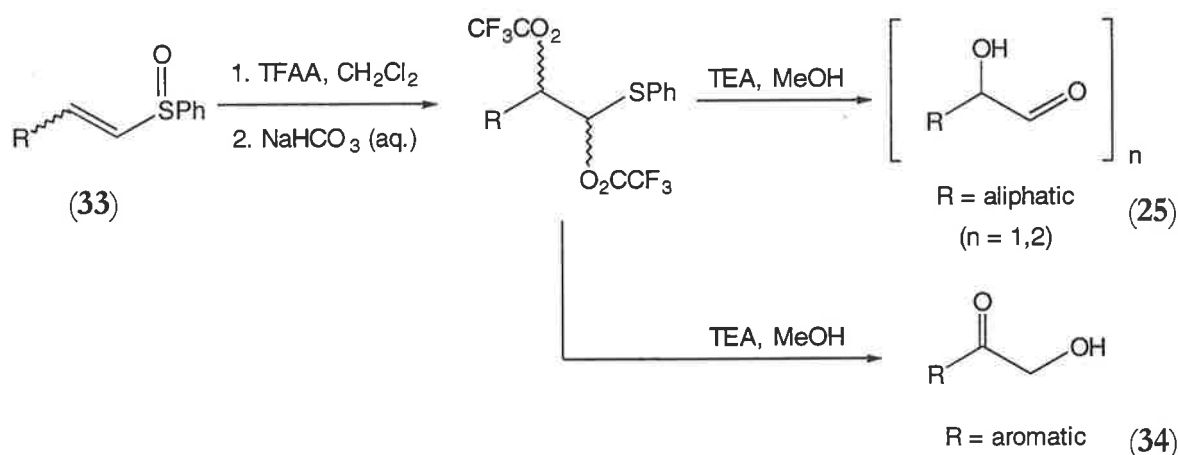
Scheme 19

Unfortunately, this procedure only accommodates for the synthesis of alkyl aldehydes. When aryl substituents were present solely monomeric α-hydroxy ketones (**34**) were formed. High yields were obtained for each of the carbonyl products, however, only optical enrichment was observed, insufficient for the need of this present study

The additive Pummerer procedure is capable of generating a wide selection of alkyl α-hydroxy aldehydes in good yields from relatively simple reaction conditions. It does not, however, provide the products in a high enough enantiomeric excess to meet successfully all of the synthetic criteria for this research proposal.

The five literature procedures discussed above by no means complete the list of available procedures, however, they do serve to impart an overview of the associated chemistry. Further procedures reported for the synthesis of racemic α-hydroxy aldehydes (25) include the use of 4-ethoxy-2-oxazolines and subsequent catalysed hydrolysis to directly generate the α-hydroxy aldehyde.[59,63-67] Alternately, a Michael reaction of an aldehyde with the 4-isopropyl-2-oxazolin-5-one anion followed by hydrolysis may be used.[68] These techniques will not be discussed in detail, as they are limited to the generation of racemic aldehyde derivatives only. Implementation of any of these techniques would require some form of resolution to be performed, an unattractive alternative for the current proposal.

Each of the above literature reviews provide further insight into the chemistry of the α-hydroxy aldehyde synthon; nevertheless the published results do not suggest such techniques alone would provide one clear route to a diverse range of products. Many of the reported procedures only allow for selective substitution or report that the aldehydes synthesised undergo self-condensation or polymerisation as a result of the reaction conditions employed.

1.5   Proposed synthetic pathway.

Rather than devising two separate strategies for the synthesis of both alkyl and aryl containing α-hydroxy aldehydes, as the literature suggests would be required, it was envisaged that optically pure hydroxy aldehydes could be obtained simply from the chiral pool of natural products. The wide variety of chiral esters commercially available is extensive (often in both enantiomeric forms), and their synthetic value has been exploited by many organic chemists.

Scheme 20 depicts the retrosynthetic pathway proposed to provide the targeted key intermediate enone (**17**). Conversion of ester (**35**) to the corresponding α-hydroxy aldehyde (**36**) will be achieved by simple chemical reduction of the ester functionality without loss of optical purity. Allowing a keto stabilised phosphorus ylide (**37**) to react with the generated aldehyde (**36**), under standard Wittig olefination conditions, should afford a range of *trans* enones (**17**). For specific synthetic details for the proposed transformations with protection of the hydroxyl moiety see Chapter 2, while Chapter 4 details the same strategy without hydroxyl protection.
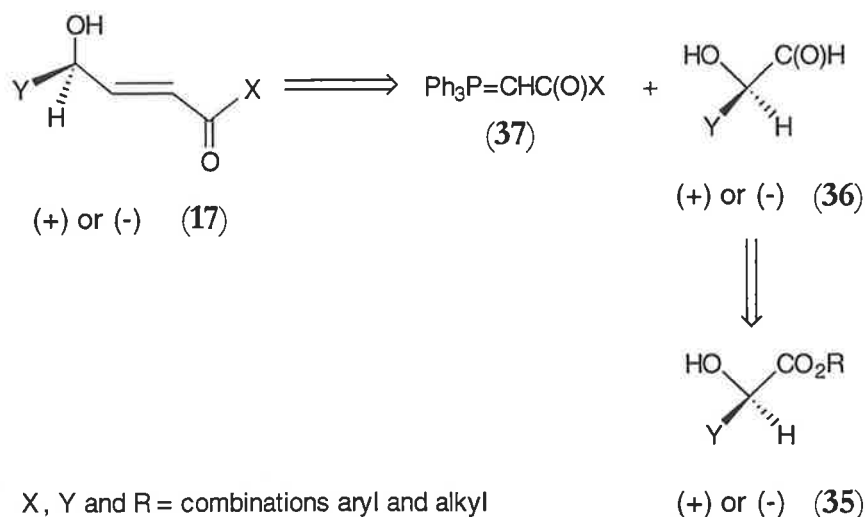
Scheme 20

When considering the time and financial costs involved in synthesising the same compounds with equivalent optical purity, this alternative is clearly the more viable option for the purposes of this research. This proposed synthetic scheme should allow a diverse collection of γ-hydroxy enones (**17**) to be synthesised from inexpensive starting materials whilst employing simple reaction conditions.

Successful synthesis of the targeted intermediate *trans* enones (**17**) would allow cyclopropanation reactions to be trialed, using stabilised phosphorus ylides (**15**) to provide a new collection of high diastereo- and enantiomerically pure cyclopropanes (**16**).

Application of this newly developed methodology to a variety of γ-hydroxy enone (**17**) derivatives should provide further insight into the mechanism of this cycloaddition

technique. It is believed that this will further establish the application and potential of this new cyclopropanation technique to many areas of synthetic organic chemistry. Additionally, this research will significantly increase the number of hydroxy enone analogues that have been synthesised and that are available for application to this and other research projects.

2   Towards the key intermediate: *trans* γ-hydroxy enone.

2.1   Proposed synthetic strategy.

Scheme 20 (Section 1.5) shows the retrosynthetic strategy for the generation of variously substituted *trans* γ-hydroxy enones (**17**). The experimental details for the proposed transformations suggested in that scheme will now be presented.

The first intended targets were designated as the mandelate and lactate derivatives with 'Y' equivalent to phenyl and methyl respectively, Figure 6. Previous results from 1,2-dioxine precursors (**14**) have indicated that a wide range of substituents (X and Y= H, alkyl, aryl etc.) can be accommodated in cyclopropane synthesis, on treatment with a stabilised ylide (**15**).[49] Accordingly, it was anticipated that equivalent substitution of the target enone (**17**) should afford analogous cyclopropyl products.

Where 'Y' represents a phenyl group, the starting material was envisaged to be the commercially available ethyl mandelate (**35**), which is available in racemic and both the R and S optically pure forms. Preliminary studies were to be performed employing the inexpensive racemate (**35**) and subsequently repeated with enantiomerically pure *S*-(+)-(**35a**) following optimisation of the methodology. Methyl substitution α to the hydroxyl grouping would be achieved through the transformation of *S*-(-)-ethyl lactate (**38a**) and *R*-(+)-methyl lactate (**38b**) purchased from the same supplier.

(**17**)   Y = Ph   (Mandelate derivative)   X = alkyl or aryl   (enone)

(**39**)   Y = CH$_3$ (Lactate derivative)   X = alkoxy   (enester)
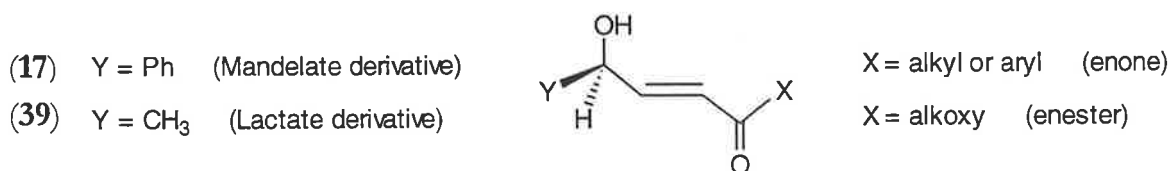
Figure 6. Target *trans* γ-hydroxy enone/enester (**17/39**) derived from the chiral pool mandelate (**35**) and lactate (**38**) esters.

Whilst the 'X' substituent of the 1,2-dioxine (**14**) has been investigated when equivalent to various alkyl and aryl groups, the effect of alternate functional groups at this position are unknown. Therefore, it was further proposed that the targeted intermediate (**17**) will

incorporate the functionality of an ester group at this position, in addition to derivatives exhibiting ketone functionality only, Figure 6.

The first proposed step in the retrosynthetic pathway (Scheme 20) would require reduction of the ester functionality of (**35**) to the corresponding α-hydroxy aldehyde (**36**). The choice of reducing agent is restricted to one in which the first reduction to yield the aldehyde is faster than further reduction, yielding the undesired alcohol derivative. Typically, a hydride reagent is employed for ester reduction, specifically for aldehyde formation, an aluminium hydride with decreased reducing capacity.[69] Di-isobutylaluminum hydride (DIBAL-H) is a characteristic reagent applied for this purpose,[69] and was selected as the reducing reagent to be applied.

The stability of the generated α-hydroxy aldehyde (**36**) was a further consideration in this approach,[54,63-65] as discussed in Sections 1.4.1 and 1.4.2. Protection of the hydroxyl functionality is a potential means of assisting product stability. It was proposed that protection of the hydroxyl group would be performed as the first synthetic transformation, providing the protected α-hydroxy esters (**40 and 41**), Scheme 21. This would allow for the generation of the protected α-hydroxy aldehydes (**42 and 43**), which it was perceived, would exhibit greater stability to self-condensation and dimerisation, see later for examples of aldehyde dimerisation in Chapters 4 and 5.

A wide number of protecting groups are available for the protection of free hydroxyl groups,[70-72] and the most commonly utilised are a) benzyl-, b) tetrahydropyranyl- (THP), and c) silyl- groups. Beyond its stability to a variety of reagents and reaction conditions, a principal factor in selecting a suitable protecting group is the reaction conditions required for its eventual removal. Cleavage of the protecting group would be executed following successful synthesis of the protected γ-hydroxy enones (**44 and 45**), Scheme 21. The following is a list of the conventional methods for the removal of common hydroxyl protecting groups, as well as justification for the protecting group choice:

     a) Use of a benzyl-protecting group was discounted due to the hydrogenation conditions required for cleavage to regenerate the alcohol. Hydrogenation would not only remove the benzyl substituent, but may also effect the loss of the alkene moiety.

b) Protection of the hydroxyl as a THP-ether would not require extreme conditions for either formation or destruction of the ether, however, as it contains a chiral centre its use would result in the formation of diastereomers. Diastereomeric mixtures are unfavourable in terms of inconvenience for NMR spectra interpretation and purification by chromatographic techniques.[70-72]

c) Silyl ethers are compatible with a wide range of organic reaction conditions, and are reportedly easily removed by a variety of reagents.[70-72] No problems were foreseen cleaving the silyl-group as the other functional groups present within the molecule are likely to be stable under these conditions.

(35)   Y = Ph

(38a) Y = CH$_3$, R = CH$_2$CH$_3$

(38b) Y = CH$_3$, R = CH$_3$

(40)   Y = Ph

(41a) Y = CH$_3$, R = CH$_2$CH$_3$

(41b) Y = CH$_3$, R = CH$_3$

(42)   Y = Ph

(43)   Y = CH$_3$

Wittig Olefination

Ph$_3$P=CHC(O)X

(37)

(17)   Y = Ph

(39)   Y = CH$_3$

(44)   Y = Ph

(45)   Y = CH$_3$

X = alkyl , aryl or alkoxy.

P = TBDMS
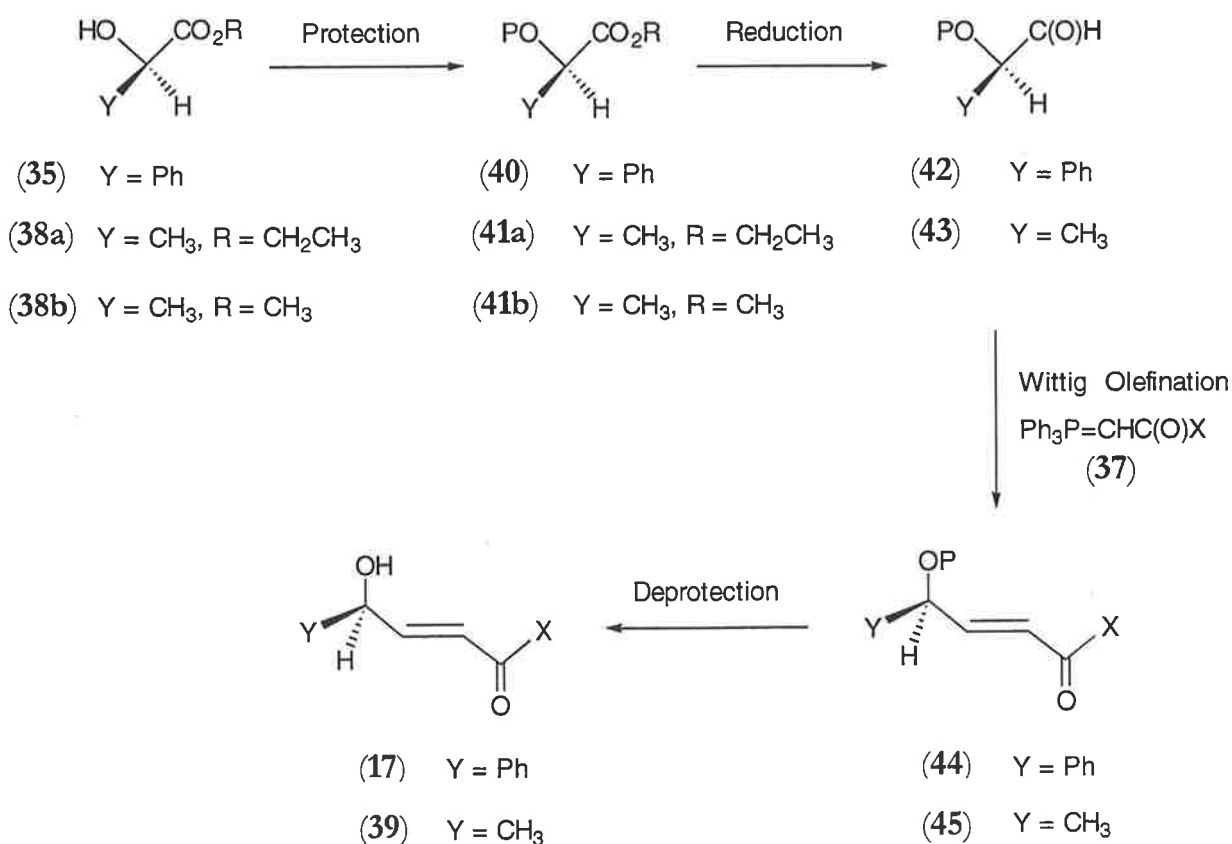
Scheme 21. Proposed synthetic procedure.

Consequently, due to the anticipated ease of incorporation and cleavage, and the stability of such ethers to an extensive range of reaction conditions, it was decided that the silyl-

protecting group would be the most suitable. Specifically, the *tert*-butyldimethylsilyl (TBDMS) protecting group was chosen for a number of reasons including;

- increased stability of the corresponding ether in comparison to trimethylsilyl ethers,
- derivatives are frequently crystalline making them easier to handle and purify, and are suitable for mass spectral analysis[73],
- incorporation of a large steric bulk into the molecule, *vide supra*, and
- cleavage can be effected in basic, acidic and/or close to neutral conditions.

While the main function of the protecting group would be to mask the free hydroxyl, it was hoped that use of the sterically bulky TBDMS-group would facilitate reduction of the ester functionality to the desired aldehyde. The combination of a sterically bulky hydride and a sterically hindered reduction site should provide optimum conditions for preventing over reduction to the resultant alcohol.[74] The incorporation of the bulky TBDMS-group should also increase the stereoselectivity of the following step in the proposed pathway, that of the Wittig olefination reaction.

Following production of the optically active α-silyloxy aldehyde (**42/43**), the next stage would be generation of the corresponding optically active γ-silyloxy enone (**44/45**). It was envisaged that standard reaction conditions would be employed for the Wittig transformation and that high stereoselectivity would be obtained. As the *trans* isomer is the thermodynamic product of Wittig reactions with stabilised ylides, the added bulk of a TBDMS-protecting group ought to further enhance selectivity for *E*-isomer formation, over the kinetic *Z*-isomer product.

As highlighted previously, the initial targets were with 'Y' equivalent to phenyl (**17**) and methyl (**39**). It is at this point in the synthesis where the number of analogues produced can be greatly expanded. The Wittig step entails reaction of an aldehyde with a stabilised phosphorus ylide (**37**), therefore, only ylide availability restricts the possible derivatives of protected enones or indeed enesters (**44/45**) that can be synthesised. In this way the 'X' substituent can be varied extensively depending on the ylide selected, hence accommodating for the generation of ketone and ester functionality in the key intermediate.

Finally, all that remains is the simple deprotection of the γ-silyloxy enones (**44/45**) to afford the target intermediate *trans* γ-hydroxy enone derivatives (**17/39**). It was anticipated that cleavage of the silyl-group would be accomplished under standard conditions. Desilylation is most commonly effected by the use of fluoride ion as a result of its affinity for silicon. This technique has been applied extensively in the literature for the deprotection of TBDMS-protected secondary hydroxyl groups,[70,71,75] and for this reason it was planned to employ analogous conditions to regenerate the parent alcohol (**17/39**).

Quantitative yields are generally obtained for the protection with, and deprotection of silyl groups, whilst standard DIBAL-H reductions and Wittig reactions typically provide products in good to high yields. Therefore, it was predicted that the final enone products (**17/39**) in this reaction pathway would be synthesised in a high overall yield from the starting ester (**35/38**).

2.2   Synthesis of protected γ-hydroxy enones.

In order to provide diversely substituted γ-hydroxy enones, a variety of stabilised phosphorus ylides needed to be available for utilisation in the Wittig olefination step. As the initial targets were restricted to two different substituent groups at the hydroxy terminus of the enone, methyl and phenyl, further derivatisation must be incorporated on formation of the alkene moiety. To accommodate for the formation of enone and enester functionality both keto and ester ylides must be accessible.

2.2.1. Ylide selection.

Methyl substitution (ie. 'X' = methyl, Figure 6) can easily be provided through the use of commercially available 1-triphenylphosphoranylidene-2-propanone (**37a**), first synthesised by Ramirez *et al.*[76] The analogous phenyl keto ylide (**37b**), 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, was synthesised in high yield from triphenylphosphine and 2-bromoacetophenone through a modification of Ramirez's procedure,[76] Scheme 22. The phosphonium salt (**37b'**) precipitated out of ether after heating under reflux overnight and was subsequently collected and treated with aqueous sodium carbonate over two

days, to afford conversion to ylide (**37b**). It is noted in the literature that sodium hydroxide could be employed as the base in this transformation providing the product in a much shorter reaction time, yet in a significantly reduced yield.[76]
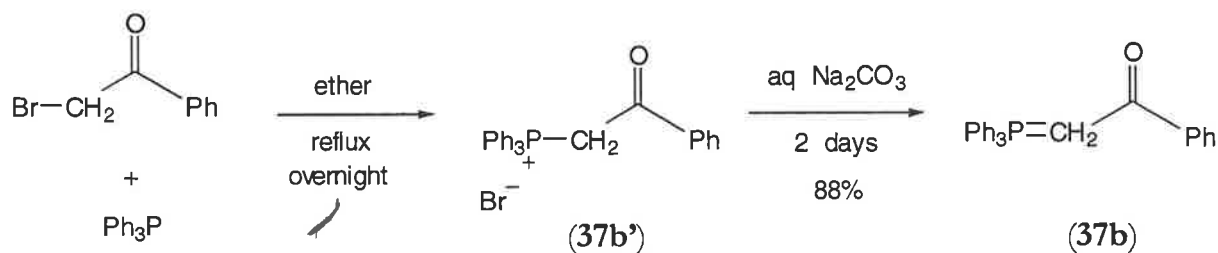
Scheme 22

This standard procedure was later employed for the synthesis of *tert*-butyl keto ylide (**37c**) and *para*-bromophenyl keto ylide (**37d**), substituting for the appropriate keto halide, 1-chloropinacolone and 4-bromo-phenacyl bromide respectively. In each instance ylide formation was confirmed by an upfield shift of the doublet signal for the methylene group protons in the ^{1}H NMR, Figure 7. Splitting of the methylene resonance was due to ^2J coupling with the neighbouring phosphorus. The chemical shifts and coupling constants were consistent with the conversion of a single bond into an electron withdrawing pπ-dπ bond.[53,77]
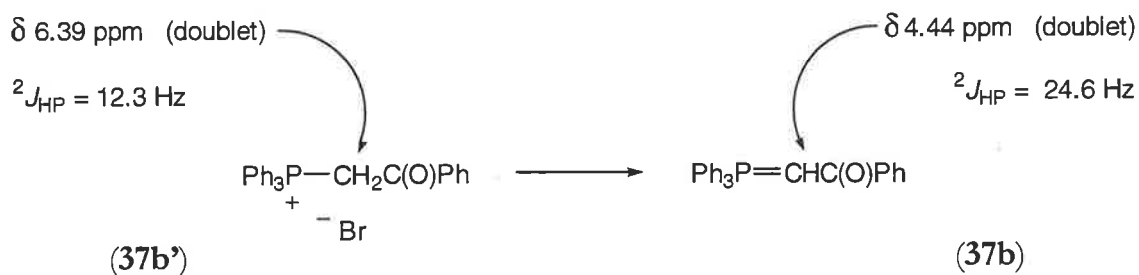
Figure 7. Chemical shift and coupling constants for the methylene group protons in the ylide salt (**37b'**) and ylide (**37b**), recorded at 300 MHz.

Methoxy substitution (i.e. 'X' = OCH_3, Figure 6) generated through utilisation of the commercially available methyl (triphenylphosphoranylidene)acetate (**37e**), would provide an enester analogue of (**17**).

It was anticipated that the use of the above ylides in combination with both the protected mandelaldehyde (**42**) and lactaldehyde (**43**) intermediates, under standard Wittig conditions, would provide a diverse array of the *trans* enone/enester targets (**17/39**), which could then be employed to trial the subsequent cyclopropanation step. It was envisaged that these derivatives would provide further insight into the versatility of the cyclopropanation reaction manifold.

2.2.2. Synthesis of protected enones derived from the mandelate ester.

As anticipated the initial alcohol protection[78] generating the α-TBDMSO-mandelate (**40**) was straightforward and was achieved in a quantitative yield. This allowed for trialing of the ensuing DIBAL-H reduction, which was initially achieved following a literature procedure for the reduction and Wittig olefination reactions performed sequentially in one pot,[31] Scheme 23.
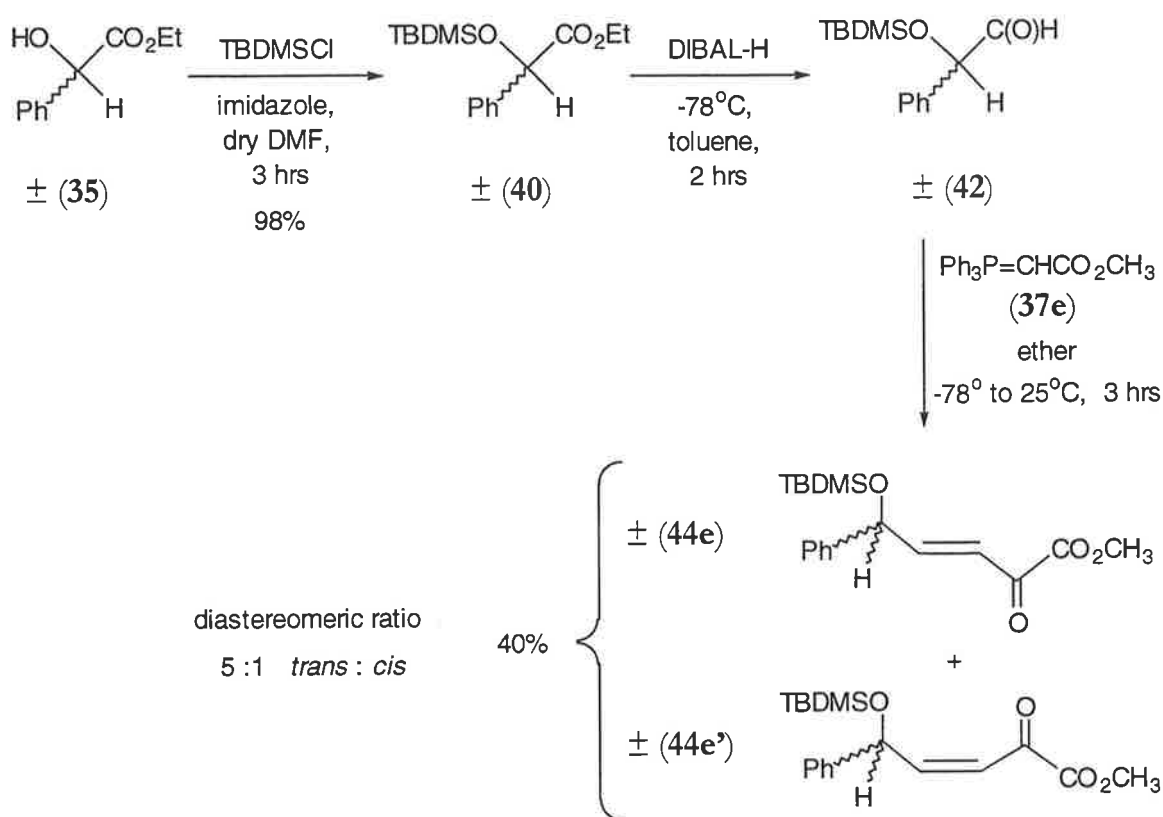
Scheme 23

Generation of racemic α-silyloxy mandelaldehyde (**42**) utilising DIBAL-H in hexanes at -78 °C was followed by the addition of a solution of methyl (triphenylphosphoranylidene) acetate (**37e**) in dry ether, Scheme 23. Analysis of the reaction products showed the formation of one major product along with a proportion of by-products. It was assumed that the major product was the desired *trans* alkene (**44e**), whilst the corresponding *cis* isomer (**44e'**) had formed as a minor product. In addition, unreduced starting material (**40**) and over reduction to the corresponding alcohol accommodated for the remaining impurities. Separation of the geometric isomers was achieved by column chromatography.

At this stage it was not conclusively known which isomer was the *cis* or the *trans*, as the corresponding ¹H NMR data did not provide definitive evidence, Table 1. Preliminary assignment of the major product as the *trans* alkene (**44e**) was justified by virtue of it being the more favoured thermodynamic product of the Wittig reaction. However, whilst the *cis* (**44e'**) vinylic coupling constant was smaller than that for the *trans* (**44e**), $J = 11.4$ Hz is relatively large for a *cis* alkene.[77] Additionally, each of the 'isomers' displayed a significant difference in chemical shift values for the three respective methine group protons. The most significant shift being for what was believed to be the C$\underline{H}$-OTBDMS proton signal, appearing at 6.57 ppm and well up field at 5.31 ppm for *cis* (**44e'**) and *trans* (**44e**) respectively, Table 1.

Table 1. 600 MHz ¹H NMR data for *E* (**44e**) and *Z* (**44e'**) with the exclusion of signals corresponding to the phenyl and TBDMS-protecting groups.

E (**44e**) δ (ppm)	Mult.	*J* (Hz)	Assign.	*Z* (**44e'**) δ (ppm)	Mult.	*J* (Hz)	Assign.
7.48-7.23	m	-	Ph	7.48-7.22	m	-	Ph
6.98	dd	4.8, 15.6	C$\underline{H}$=CH	6.57	d	9.0	C$\underline{H}$-O
6.12	d	15.6	CH=C$\underline{H}$	6.22	dd	9.0, 11.4	C$\underline{H}$=CH
5.31	d	3.0	C$\underline{H}$-O	5.72	d	11.4	CH=C$\underline{H}$
3.70	s	-	OC$\underline{H}_3$	3.76	s	-	OC$\underline{H}_3$

Nuclear Overhauser effect (NOE) difference spectroscopy provided conclusive evidence confirming the original assignment, as pictorially represented in Figure 8. For each compound the two vinylic and methoxy group protons were irradiated independently to observe any through space interactions between these groups. For the assigned *cis* enone (**44e'**) a strong enhancement between the neighbouring alkene protons was observed, as would be expected for such a structural conformation. Conversely, no interactions were observed for the analogous experiment on the isomeric *trans* enone (**44e**).
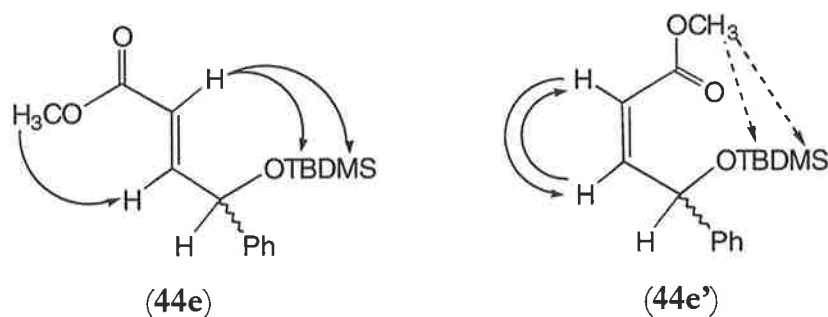
Figure 8. NOE difference spectral enhancements for *cis* and *trans* γ-silyloxy enones (**44e**).

The low combined product yield of 40%, high proportion of *cis* enone (**44e'**) and the significant by-product formation was undesirable. As such attempts to improve the selectivity for *trans* isomer (**44e**) formation were undertaken through modification of the literature procedure.

An analogous procedure was followed for the reduction of the protected mandelate ester (**40**) to aldehyde (**42**) with two exceptions. Firstly, DIBAL-H in toluene was employed, and secondly, the subsequent ylide (**37e**) addition was performed in a solution of methanol to assist solubility. These minor modifications did not improve the *cis:trans* ratio, rather caused further degeneration to 3:5. Despite this, the combined *cis/trans* yield was successfully raised to 79%.

Much greater efficiency was achieved by separating the two reactions into a two-pot procedure with product isolation at each stage. Intrinsically, this required the separate generation of mandelaldehyde (**42**), which was achieved in 92% by employing the previous method of ester reduction with DIBAL-H in toluene at -78°C for 3.5 hours. Work–up and isolation was aided by filtering the emulsion through a pad of kenite after

careful quenching with water and no further purification was required. The neat aldehyde (**42**) was stable for up to one week at room temperature and exhibited a typical ¹H NMR resonance at 9.51 ppm for the aldehyde proton.

Dissolution of O-protected mandelaldehyde (**42**) in dry dichloromethane (CH₂Cl₂), followed by stirring at ambient temperature for two hours in the presence of methyl (triphenylphosphoranylidene)acetate (**37e**), provided *trans* methyl 4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-4-phenylbut-2-enaote (**44e**) in a good isolated yield of 65%. Under these modified two-pot reaction conditions less than 5% of the *cis* O-protected enone (**44e'**) was observed in the crude product (determined by ¹H NMR analysis).

Whilst the one-pot methodology was experimentally convenient, the advantages of the two-pot modification were to increase the overall product yield as a result of ensuring complete ester reduction, decrease by-product formation, and to significantly reduce the amount of excess ylide otherwise required. The literature procedure required 1.3 equivalents of ylide, however, the modified two-pot procedure required only 1.05 equivalents. Moreover, it allowed for the synthesis of protected mandelaldehyde (**42**) on large scale, which could then be conveniently converted to various enones by separate reaction with the corresponding ylides. This two-pot methodology proved to be extremely successful, proceeding with much greater reaction efficiency and was employed for all future protected enone syntheses.

Employing the optimised two-pot procedure described for the synthesis of enester (**44e**), γ-silyloxy enones (**44a**) and (**44b**) were synthesised through treatment of the corresponding ylides, (**37a**) and (**37b**), with protected mandelaldehyde (**42**) in separate reaction vessels, Scheme 24. Stirring at room temperature under an inert atmosphere provided for enone formation in both examples. ¹H NMR spectroscopy revealed no *cis* isomer in the crude reaction mixture and no purification by chromatography was required. Simple work-up, involving washing the organic phase with water and brine, drying and removing triphenylphosphine oxide by precipitation from hexane, provided the analytically pure product.
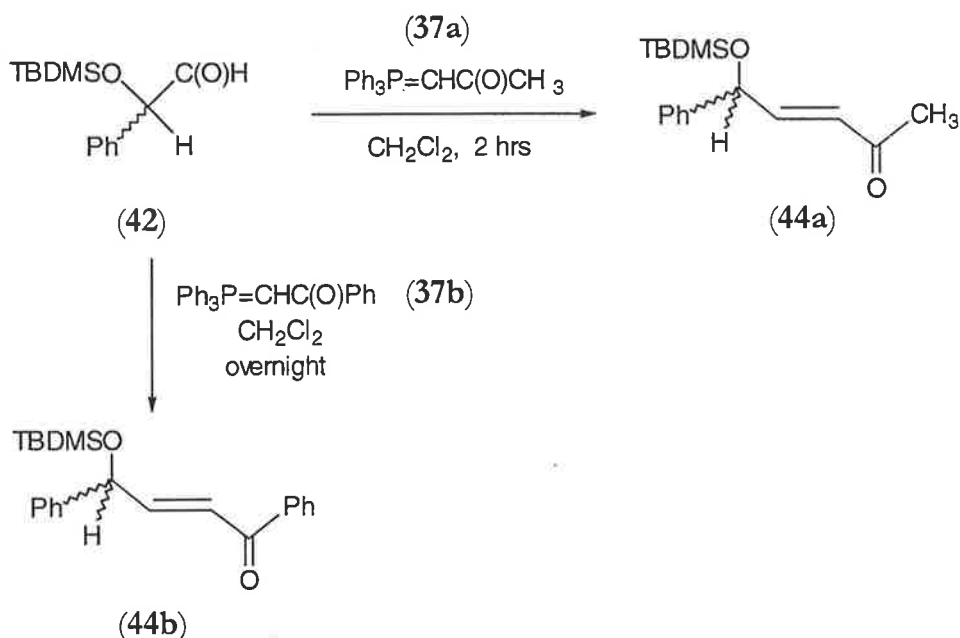
Scheme 24

E-4-*tert*-butyldimethylsilyloxy-1,4-diphenyl-but-2-ene-1-one (**44b**) was obtained in a high yield of 80%, while the methyl analogue (**44a**) was formed in an excellent 94%. The vinylic proton coupling constants were 15.3 and 15.7 Hz, for (**44b**) and (**44a**) respectively, consistent with *trans* geometry about the double bond.[77]

2.2.3. Synthesis of protected enones derived from the lactate ester.

S-(+)-Ethyl lactate (**38a**) was the chosen enantiomer for synthesis of the first lactate enone derivatives. The standard silylation procedure was followed for the generation of *S*-(-)-ethyl 2-silyloxypropanoate (**41a**) as reported in the literature, Scheme 25.[78] Reduction of (**41a**) to α-silyloxy aldehyde (**43a**) was achieved using a combination of two reported procedures,[65,78] involving treating an ethereal solution of ester (**41a**) with DIBAL-H in hexanes at −78 °C, Scheme 25. After an additional one hour stirring at ambient temperature, the reaction was quenched and worked-up under the conditions described in Section 2.2.2 for protected mandeladehyde (**42**). Pure α-silyloxy lactaldehyde (**43a**) was obtained in 81% after reduced pressure distillation. All spectral and physical data recorded for compounds (**41a**) and (**43a**) were consistent with the literature reported values.[65,78]
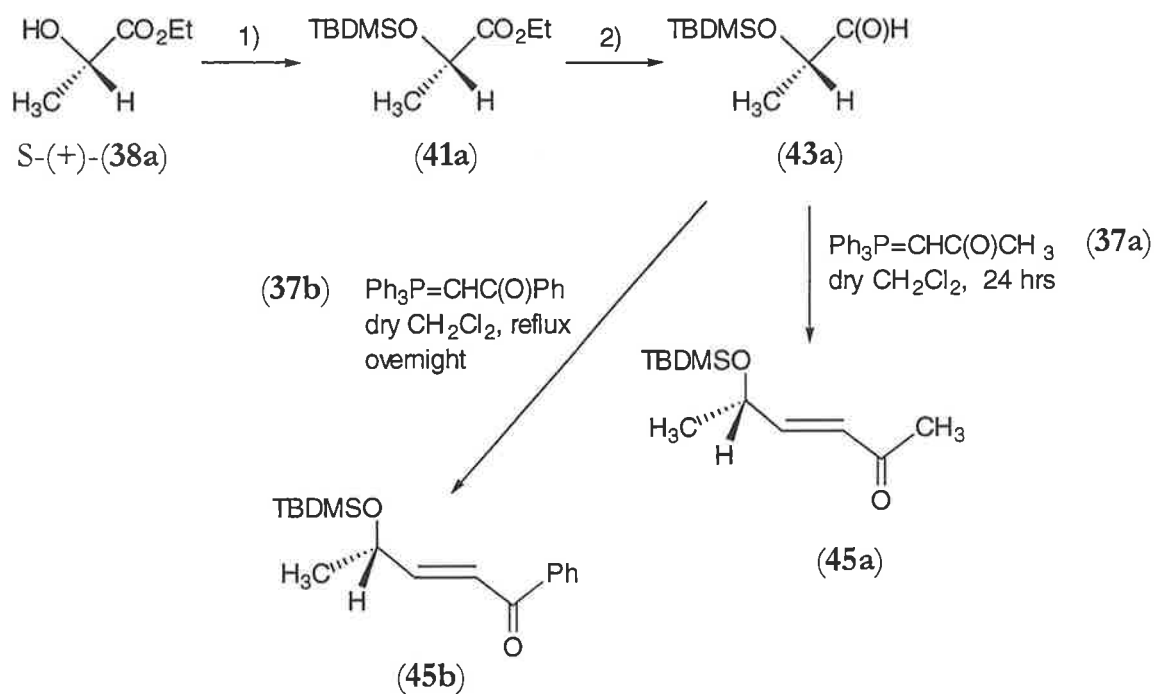
1) TBDMSCl, imidazole, DMF, 25 °C, 1.5 hrs, 98%;
2) DIBAL-H (1 M in hexanes), ether, -78 °C, 10 min,
   then MeOH/H$_2$O to 25 °C, 1 hr, 81%.

Scheme 25

Scheme 25 depicts the two enones (**45a-b**) synthesised from lactaldehyde (**43a**), which were generated utilising the reaction conditions listed therein. The Wittig reaction required stronger reaction conditions to reach completion, of either longer reaction time or heating under reflux, than was required with the previous mandelaldehyde (**42**) olefination, Scheme 24.

It was proposed that this may be due to the slightly decreased electrophilicity of the carbonyl centre in the lactaldehyde substrate (**43a**), when compared to mandelaldehyde (**42**) which contains an inductively electron withdrawing phenyl substituent, Figure 9. The methyl substituent present in lactaldehyde (**43a**) is intrinsically electron donating, hence providing a comparatively less attractive carbonyl site for 'attack' by the nucleophilic pole of the ylide.

Figure 9. Pictorial representation of the carbonyl carbon electrophilicity in aldehydes (42-3).

A difference in the nucleophilicity of the ylide employed is also apparent from the variation in reaction times for complete enone formation within the mandelaldehyde (42) and lactaldehyde (43a) series. Formation of phenyl keto enone (44b) required heating under reflux overnight, yet the methyl keto enone (44a) did not require addition heat, merely stirring for 24 hours at ambient temperature. As with aldehyde reactivity, the withdrawing/donating effects of the carbonyl substituent also affect ylide reactivity, Figure 10. Phenyl keto ylide (37b) contains a less nucleophilic carbon pole due to the inductive electron withdrawing effect of the attached phenyl group. However, the methyl keto ylide (37a) has no such electron withdrawal occurring and therefore contains a comparatively 'stronger' nucleophilic carbon pole able to 'attack' the reactant carbonyl species, effectually lowering the activation barrier.
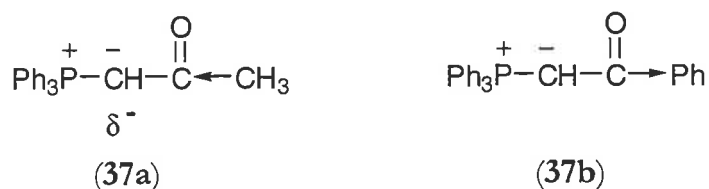
Figure 10. Pictorial representation of the carbon pole nucleophilicity in the keto ylides (37a-b).

E-5-*tert*-Butyldimethylsilyloxyhex-3-en-2-one (45a) and *E*-4-*tert*-butyldimethylsilyloxy-1-phenylpent-2-en-1-one (45b) were synthesised in high yields of 77% and 71% respectively, following purification by column chromatography. ^{1}H NMR spectroscopy displayed the characteristic signals of a doublet of doublets for CHC$\underline{H}$=CH, a doublet of doublets for CHCH=C$\underline{H}$, and a multiplet for CH$_3$C$\underline{H}$CH=CH, at 6.75, 6.23, 4.48 ppm for (45a). This same splitting pattern was recorded for (45b) with a dramatic shift (and order interchange) in the resonance of the two vinylic protons: a doublet of doublets for CHCH=C$\underline{H}$, a doublet of doublets for CHC$\underline{H}$=CH, and a multiplet for CH$_3$C$\underline{H}$CH=CH

at 7.12, 7.04, 4.58 ppm. Each displayed two carbonyl peaks in the infrared (IR) spectrum characteristic of α,β-unsaturated ketones; 1709 and 1682 cm^{-1} for (**45a**) and 1674 and 1628 cm^{-1} for (**45b**).[92]

Despite the literature suggestion that hydroxyl protection as a TBDMS-ether often affords crystalline products,[73] none of the synthesised enones (**44a-b, 44e, 45a-b**) were solid compounds, but rather colourless oils. Despite this, each protected enone derivative was stable to mass spectral analysis with either M^{+} or MH^{+} peaks providing structural evidence, albeit in low relative intensities.

2.3 Deprotection of synthesised γ-silyloxy enones.

With the successful synthesis of a number of *trans* γ-silyloxy enones (**44a-b/45a-b**) and one enester (**44e**), completed in excellent overall yields, the next step was simple deprotection of the silyl ethers to regenerate the parent alcohol functionality. It was envisaged this would be merely an exercise in experimental technique and that quantitative yields of the key intermediate *trans* γ-hydroxy enone/enester(s) (**17/39**) would be obtained.

Cleavage of the silyl-protecting group was to be accomplished utilising the standard deprotecting conditions incorporated into a large number of syntheses by a myriad of organic chemists.[70] Due to high product yields, the experimental ease of the technique and the general stability of other functional groups to the conditions, use of the free fluoride ion is the most common and effective means for regeneration of the alcohol from the corresponding protected ether. Typically this is achieved through the use of either tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), or alternatively, boron-trifluoride etherate (BF$_3$-Et$_2$O).[70,71,73,79] The affinity of fluoride ion for silicon is the driving force behind deprotection reactions employing these reagents.

2.3.1   Attempted deprotection of mandelate enone/enester derivatives.

2.3.1.1   Deprotection of methyl 4-*tert*-buytldimethylsilyloxy-4-phenylbut-2-enoate (44e).

trans γ-Silyloxy enester (**44e**) was selected as the first synthon to be deprotected as the demasked hydroxy enester (**17e**) is a known literature compound.[54] It was assumed that the deprotection step would proceed as successfully as the original hydroxyl protection and initial trials were performed using standard reagents and conditions.[71] TBAF was added to a solution of *trans* enester (**44e**) in THF at 0 °C and was deemed complete after one hour, determined by thin layer chromatography (TLC), Scheme 26.
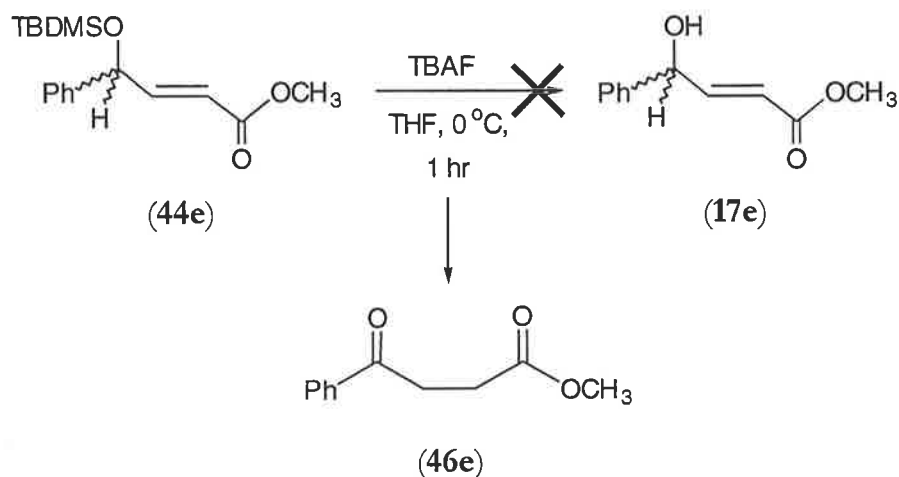
Scheme 26

Following aqueous work-up and concentration, the crude product was analysed by ^{1}H NMR spectroscopy. No vinylic protons were visible in the spectrum nor was the anticipated hydroxyl proton signal for (**17e**). Rather, the spectrum indicated that the sole product of the reaction was in fact the isomeric 1,4-dicarbonyl (**46e**) shown in Scheme 26. The two olefinic proton signals expected for the targeted enester (**17e**), instead appeared as two separate non-equivalent triplets at 2.78 ppm (protons of the (O)CC$\underline{H}_2$CH$_2$) and 3.34 ppm (protons of the CH$_2$C$\underline{H}_2$CO$_2$CH$_3$) for the asymmetric dicarbonyl (**46e**).

Rearrangement through a Kornblum-De La Mare type mechanism[80] accommodates for the observed dicarbonyl product (**46**) formed through isomerisation of the *E*-conjugate base (**47a**) to *Z*-(**47b**), and subsequent intramolecular cyclisation to hemiacetal (**48**).

Proton abstraction under basic conditions and further rearrangement results in ring opening and proton transfer to yield the dicarbonyl isomer (**46**). Scheme 27 shows a representation of the mechanism for the proposed rearrangement.
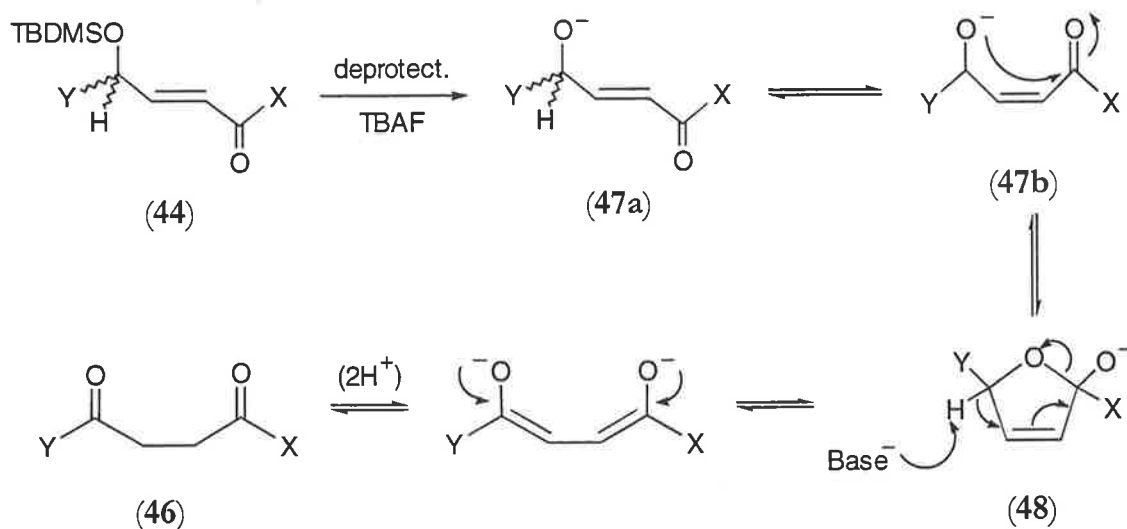
X and Y = combinations of aryl, alkyl and alkoxy.

Scheme 27

Removal of the α-proton from (**48**) can be effected by the free fluoride ion in solution or by the conjugate base (**47**), generated *in situ* on initial deprotection. Therefore, the problem appeared to be not only the basic deprotection conditions employed but also the alkoxide intermediate (**47**) formed as a transient species in the reaction manifold.

It is interesting to note that both the *cis* and *trans* isomers of the protected γ-silyloxy enester, (**44e**) and (**44e'**), were subjected to identical deprotection conditions and each afforded the same dicarbonyl product (**46e**), thus providing further support to the earlier assignment that the olefination products (**44e**) and (**44e'**) were indeed the *trans* and *cis* alkenes.

Despite the desired γ-hydroxy enester (**17e**) not being generated, the results did provide encouragement as the formation of dicarbonyl (**46e**) proved that deprotection had indeed occurred. With this in mind, alternative desilylation procedures were trialed in the hope of isolating the targeted γ-hydroxy enester (**17e**).

Clearly the optimum conditions, which would accommodate not only deprotection but also for the sensitivity of the intermediate alkoxide (**47**), were required. As deprotection was taking place, the balance needed to be tipped to favour the stability of the alkoxide (**47a**) directly following desilylation and prior to protonation, to yield the comparatively stable γ-hydroxy enester (**17e**). Table 2 displays examples of the reagents and reaction conditions trialed in attempt to meet these requirements.

Table 2. Reaction conditions and reagents trialed for deprotection of γ-silyloxy enester (**44e**).

	Reagent(s)	Temp. (°C)	Time (min)	γ-hydroxy enester (17e) (%)[a]	Ketoester (46e) (%)[a]	Unknown Alkene (%)[a]		
						(49a)	(49b)	(49c)
1	TBAF	0	60	-	100	-	-	-
2	TBAF	20	5	-	100	-	-	-
3	BF$_3$-Et$_2$O	20	15	-	7	27	37	-
4[b]	BF$_3$-Et$_2$O	-10	10	-	15	16	16	-
5	BF$_3$-Et$_2$O/ NH$_4$Cl	0	30	-	100	-	-	-
6[b]	TFA:H$_2$O	20	11 days	35	8	4	8	8
7[b]	TFA:H$_2$O	55	210	12	6	6	12	38
8[b]	TFA:H$_2$O excess	45	120	25	6	6	7	50

[a] Percentage yields were calculated from analysis of crude ^{1}H NMR spectra for entries 1-2, 5, 7-8, and from isolated samples for entries 3-4 and 6. [b] Starting protected enester (**44e**) was recovered or observed in the ^{1}H NMR spectrum.

None of the conditions trialed employing the typical deprotecting reagents TBAF or BF₃-Et₂O yielded the targeted *trans* γ-hydroxy enester (**17e**) by comparison with the known literature compound,[54] entries 1-5 in Table 2. With the exception of two attempts, the major product was the rearranged ketoester (**46e**).

Entry 5 in Table 2 shows one endeavour to prevent such decomposition by the inclusion of a proton source in the reaction mixture. It was hoped that in the presence of a readily available protonating agent, the alkoxide ion (**47a**) would be immediately protonated, thus

preventing any rearrangement through the Kornblum – De La Mare pathway. Despite the large excess of acid present in solution the only observed product was ketoester (**46e**).

Entries 3 and 4 mark the only occasions that significant amounts of the alternate alkene products (**49a-b**) were afforded. The identity of these products (**49a-b**) was unclear at this point despite extensive analytical analysis. It appeared that (**49a**) and (**49b**) were isomeric compounds both to each other and also to the targeted *trans* γ-hydroxy enester (**17e**). As would be anticipated for such isomers, both (**49a**) and (**49b**) exhibited a ¹H NMR spectrum with signals corresponding to two neighbouring olefinic protons, one proton adjacent to an electron withdrawing group, and three isolated and equivalent protons of a methyl group, Table 3.

Table 3. 300 MHz ¹H NMR data for *trans* γ-hydroxy enester (**17e**)[54] and alkenes (**49a-b**).

Assignment	E γ-hydroxy enone (**17e**) δ ppm (*J*, Hz)	Alkene (**49a**) δ ppm (*J*, Hz)	Alkene (**49b**) δ ppm (*J*, Hz)
Ph	7.39-7.29	7.38-7.25	7.38-7.24
C**H**=CH	7.06 (4.7, 15.8)	6.98 (5.6, 15.8)	6.92 (4.7, 15.7)
CH=C**H**	6.18 (2.0, 15.5)	6.13 (1.5, 15.6)	6.14 (2.1, 15.6)
C**H**-O	5.37 (1.7, 4.9)	5.07 (1.4, 5.6)	4.87 (1.8, 4.5)
OC**H**₃	3.73	3.74	3.72

The remarkable similarity between these three compounds is obvious from inspection of Table 3 and the assumption that these compounds were structural isomers was based on this similarity. Despite the *trans*-like high coupling constants between olefinic protons,[77] it is possible that perhaps one compound may be the *cis* enester. Whilst coupling constants in the range of 15-16 Hz are typically associated with a *trans* configuration, it is not unprecedented for a *cis* alkene to exhibit analogously high *J* values.[77] Clearly however, only one of the unknown products can be the opposing *cis* geometrical isomer. The spectral data for the unidentified products (**49a-b**) are discussed in further detail, *vide infra*.

More importantly, successful deprotection of γ-silyloxy enester (**44e**) had been achieved, yielding products other than the ketoester (**46e**). The trial now was to find the correct conditions to afford the targeted *trans* γ-hydroxy enester (**17e**).

Silyl group cleavage using a 9:1 mixture of TFA and H_2O[81] has been reported in the literature and was the next technique trialed, entries 6-8 in Table 3. The first attempt entailed stirring silyloxy enester (**44e**) at ambient temperature in the presence of TFA and following the reaction progress by TLC, entry 6. These conditions finally provided the *trans* γ-hydroxy enester (**17e**), albeit in a low yield of 35%. Nevertheless, it was progress much beyond any of the previous conditions employed.

A high proportion of by-product formation, including the formerly observed alkenes (**49a-b**) and ketoester (**46e**), accompanied the poor enester (**17e**) yield. The reduction in ketoester (**46e**) formation was a direct result of the acidic deprotection conditions, whilst the alkoxide derivative (**47**) was presumably responsible for the formation of ketoester (**46e**). These factors, along with the lengthy reaction time of 11 days, led to attempts to improve the reaction efficiency by altering the concentration, TFA equivalence and reaction temperature, entries 7-8. Unfortunately, no increased enone (**17e**) yield was recorded. The only major effect was that each variation increased the formation of a new alkene (**49c**).

Close analysis of the NMR data obtained for the new unknown alkene (**49c**), showed immense similarity to both the known *trans* hydroxy enester (**17e**) and the previous products (**49a-b**), isolated from the BF_3-Et_2O deprotections. The splitting pattern for the three methine protons of (**49c**) were essentially identical to that of aforementioned products (**17e** and **49a-b**). That is, the ^{1}H NMR spectrum for each (**17e** and **49a-c**) contains a signal for:

- C<u>H</u>O: as either a doublet of doublets with one *J* value between 5.6 and 4.5 Hz and a second smaller coupling constant 1.8 - 1.5 Hz, or, a broad doublet suggesting further coupling,

- CHC<u>H</u>=CH: as a doublet of doublets with a large vinylic coupling constant in the range of 15.8 to 15.6 Hz and a smaller constant of 5.6 - 4.7 Hz, and

- CHCH=C<u>H</u>: as a doublet of doublets with J = 15.9 – 15.5, and J = 2.1 – 1.4 Hz for the second splitting.

However, in this instance the resonance frequencies for the methine proton signals of (**49c**) were remarkably different. Both the similarities and differences between (**17e**) and (**49a-c**) are perhaps more clearly observed in Figure 11. Whilst the immense likeness of these four compounds (**17e** and **49a-c**) is further verified through consideration of their corresponding ^{13}C NMR spectrum, Figure 12.

γ-Hydroxy enester (**17e**)
600 MHz

Unknown (**49a**)
300 MHz

Unknown (**49b**)
300 MHz

Unknown (**49c**)
600 MHz
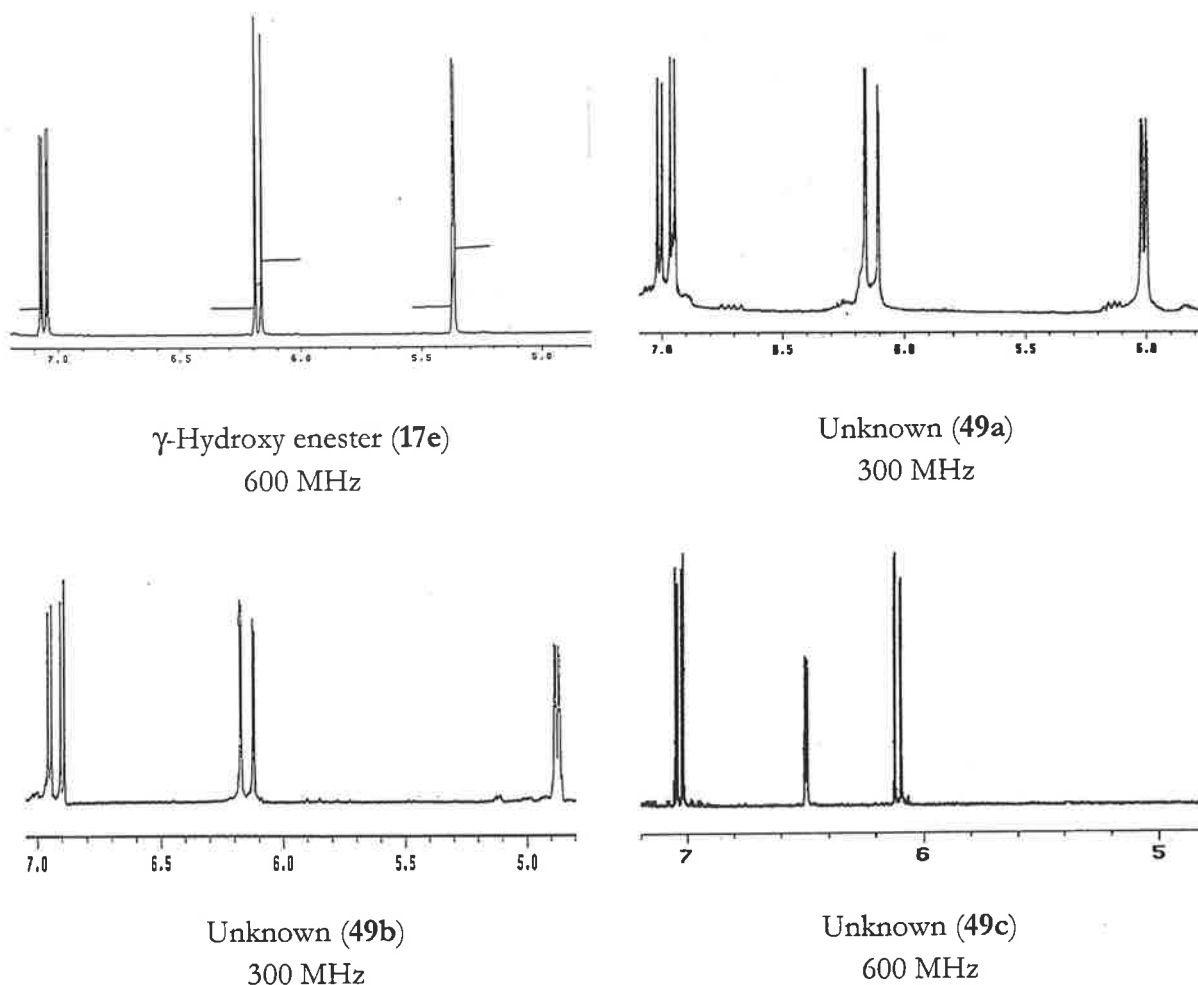
Figure 11. ^{1}H NMR spectra for the unidentified alkenes (**49a-c**) and the known γ-hydroxy enester (**17e**), displaying the three methine signals for each compound.

γ-Hydroxy enester (**17e**)
600 MHz

Unknown (**49a**)
300 MHz

Unknown (**49b**)
300 MHz

Unknown (**49c**)
600 MHz
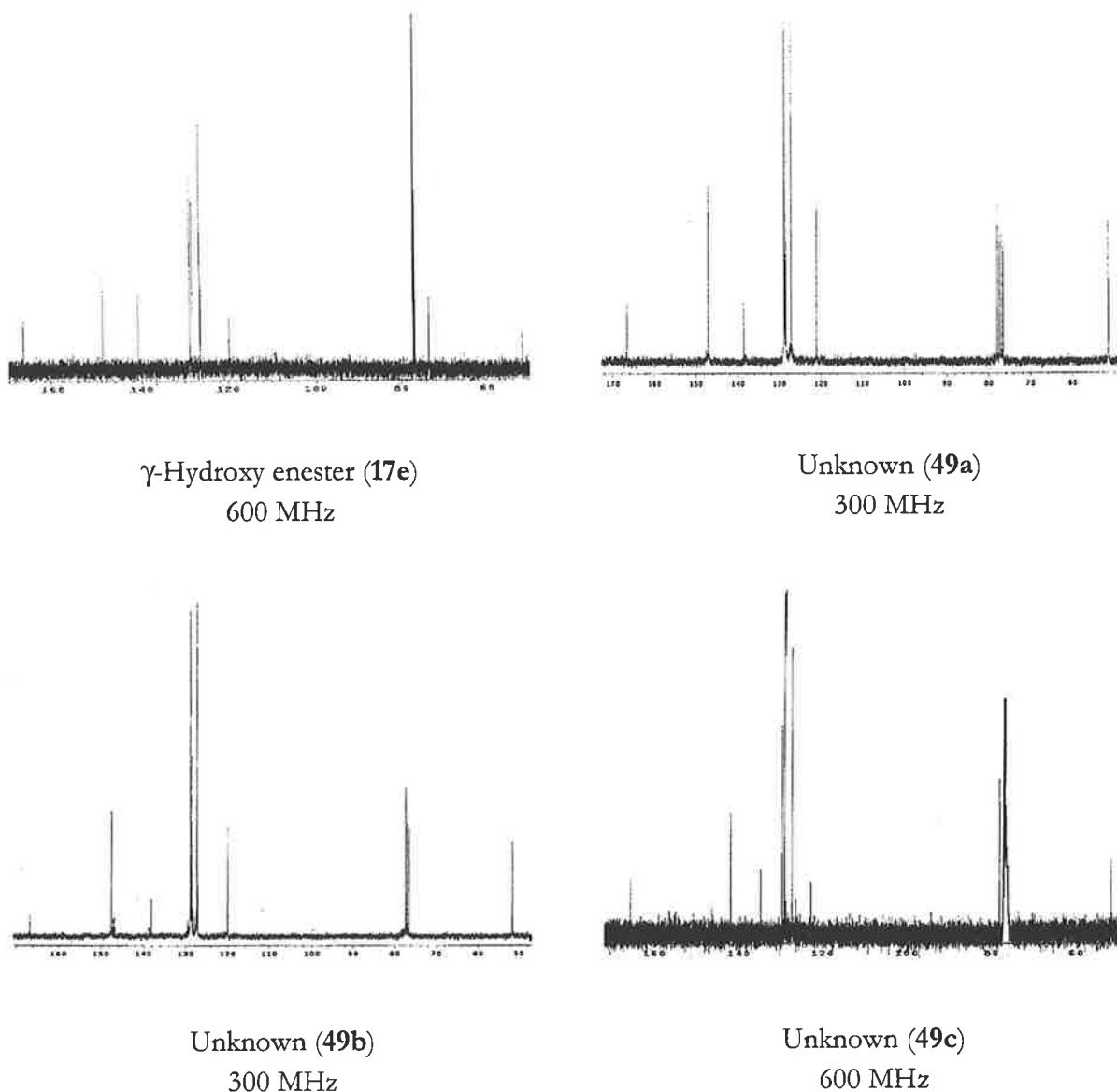
Figure 12. ^{13}C NMR spectra for the unknown alkenes (**49a-c**) and known γ-hydroxy enester (**17e**).

Figure 12 illustrates that each compound (**17e** and **49a-c**) exhibits the anticipated ^{13}C signals for a phenyl group (4 signals between *ca.* 140-125 ppm), a carbon-carbon double bond (2 signals between *ca.* 150-120 ppm) and a methoxy group (one signal at *ca.* 50 ppm). Only the γ-hydroxy enester (**17e**) and unknown (**49c**) display the expected ^{13}C signal corresponding to a carbon bearing an electron withdrawing group (e.g. OH) at approximately 75 ppm.

In summary, the synthetic proposal (Scheme 20) had been successful to the point of providing the targeted methyl (*E*)-4-hydroxy-4-phenylbut-2-enoate γ-hydroxy enester

(**17e**), yet the overall yield was considerably reduced by the disappointing results obtained in the deprotection step. At this stage the identity of the three unknown compounds (**49a-c**) are yet to be fully established. One important omission is that no hydroxyl signal was observed in their ¹H NMR spectrum, despite the suggestion of an attached electronegative element in the ¹H and/or ¹³C NMR. It is possible that the hydroxyl signal might have been masked in the ¹H NMR, although it is unlikely for all three unknown alkenes (**49a-c**). However, neither mass spectral nor microanalytical data supported any of the unknowns being the geometrical *cis* isomer as was supposed. Further analysis of these compounds (**49a-c**) would be required to progress further in their identification. Nevertheless, it was decided that such research was not warranted for this study due to their poor yields and since the target enester (**17e**) had been obtained.

It was hoped that moving on to the deprotection of generated silyloxy enones (**44a-b**) would be more productive due to the reduced nucleophilicity of the carbonyl group. The added electron withdrawing effect of the methoxy moiety of enester (**44e**) may have been facilitating the intramolecular cyclisation of alkoxide (**47b**), as depicted in Scheme 27. If this was indeed the case, cleavage of the silyl group from enone derivatives should proceed more readily without the detrimental rearrangement to the undesired diketone (**46**).

2.3.1.2   Deprotection of 5-*tert*-butlydimethylsilyloxy-5-phenylpent-3-en-2-one (**44a**).

With extreme interest in the outcome, deprotection of *trans* γ-silyloxy enone (**44a**) was attempted, following analogous procedures to those previous employed, *vide supra*. A summary of the results for the attempted deprotections is presented in Table 4. As TBAF afforded 100% of the rearranged 1,4-dicarbonyl (**46e**) in previous experiments, no attempt was made to deprotect enone (**44a**) with this reagent.

The results were extremely disappointing, as on no occasion was any of the target deprotected alcohol (**17a**) afforded. The only products obtained were the corresponding 1,4-diketone (**46a**) and/or two new alkene products (**50a** and **50b**). A number of conditions were trialed beyond that reported in Table 4, including varying the concentration and reaction temperature. Nevertheless, no modification resulted in any noteworthy change to the reaction outcome.

Table 4. A brief summary of results for the attempted deprotections of (**44a**).

| | Reagent[a] | Time | Diketone (**46a**) (%)[b] | Unknown Alkene (%)[b] | |
				(**50a**)	(**50b**)
1	BF_3-Et_2O	10 min	trace	16	15
2	TFA:H_2O	72 hrs	80	-	-

[a] Reactions were performed at ambient temperature. [b] Percentage yields were calculated from isolated products.

Characterisation of the two alkenes (**50a-b**) proved to be rather difficult due to their extremely close R_f values. Three sequential silica gel chromatography columns enabled less than 10 mg of each alkene to be isolated, in greater than 95% purity. These samples were used for the recording of IR spectra and gas chromatography-mass spectra (GC-MS), as well as for 2D-NMR studies. Analysis of the analytical data obtained suggested that neither (**50a**) nor (**50b**) was the targeted *trans* γ-hydroxy enone (**17a**).

Unknown (**50a**) 300 MHz

Unknown (**50b**) 300 MHz
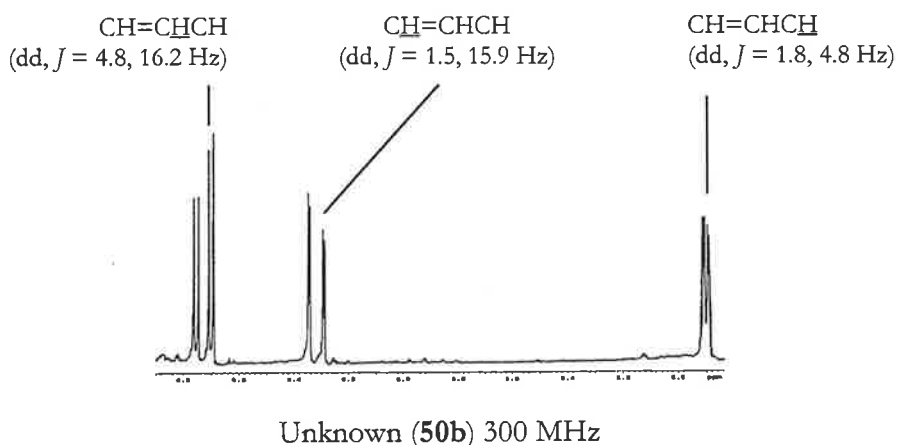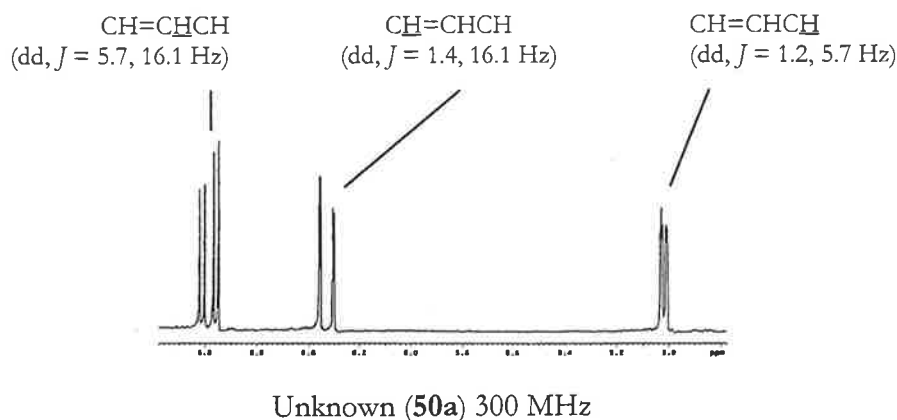
Figure 13. ^1H NMR spectra (δ 7.0-4.8 ppm) for the unknown alkenes (**50a-b**).

Neither compound (**50a** or **50b**) exhibited a recognisable mass peak by GC-MS or electron ionisation (EI) mass spectrometry. Yet, each displayed a peak at 159 of greater than 40% relative intensity, which could correspond to the loss of a hydroxyl group from the target enone (**17a**). Consideration of the chemical shift values, coupling constants (Figure 13) and 2D-NMR experimental results (Figure 14) suggests that both compounds (**50a-b**) contain two adjacent vinylic protons, one attached to a neighbouring methine group. An electronegative element appears to be attached to the said methine group, however, this was proven not to be the oxygen of a hydroxyl group by IR spectrometry which displayed no corresponding hydroxyl absorption.
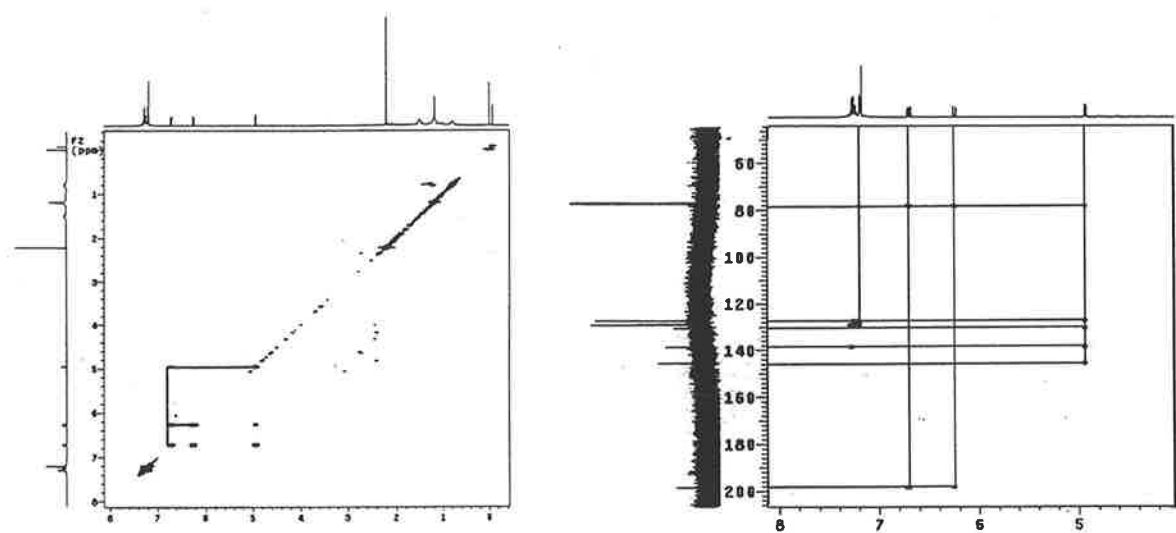
600 MHz COSY and HMBC (**50a**)
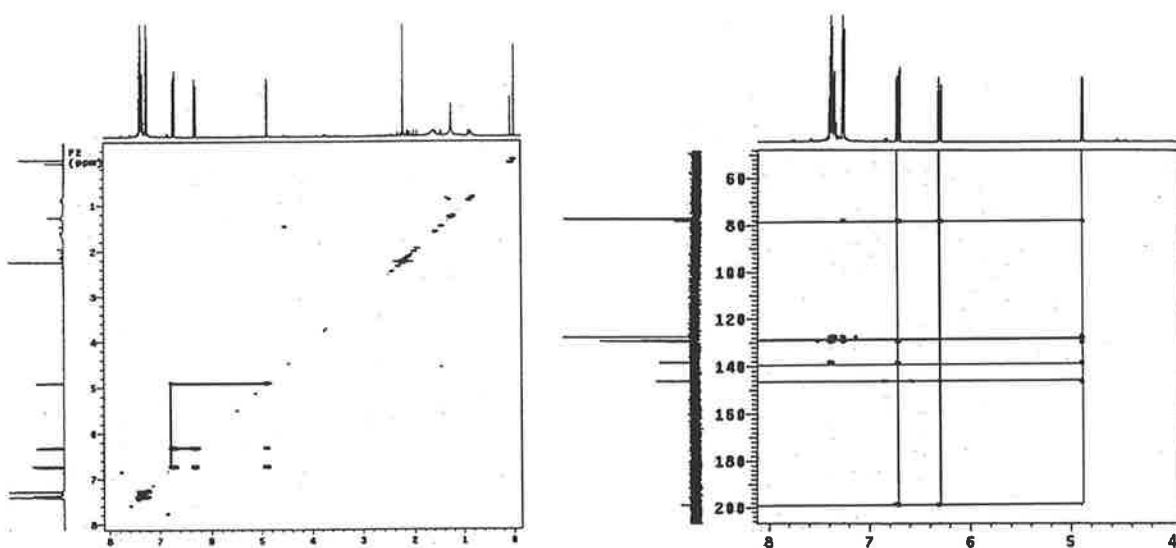
600 MHz COSY and HMBC (**50b**)

Figure 14. Heteronuclear Multiple Bond Connectivity (HMBC) and Correlated Spectroscopy (COSY) spectra for alkenes (**50a-b**), with the group connections indicated by linking lines.

For the above reasons, it was believed that neither of the isolated alkenes (**50a-b**) were the target γ-hydroxy enone (**17a**). Additionally, these somewhat ambiguous results are also the reason that the deprotection products (**50a-b**) remain unidentified. Further experimentation could be carried out, perhaps including a Bolstein test (a check for attached halogens) or isomerisation attempts with a light source. But, as it was almost 100% assured that neither (**50a** nor **50b**) were the desired enone (**17a**), it was decided it would be more efficient to continue with an alternate synthon.

2.3.1.3   Deprotection of 4-*tert*-butlydimethylsilyloxy-1,4-diphenylbut-2-en-1-one (**44b**).

Initially the same reagents and conditions were employed for the trialed deprotection of silyloxy diphenyl enone (**44b**), and the anticipated results were obtained, Table 5. Under the strong basic conditions of TBAF in THF, the sole product was diphenyl diketone (**46b**), entry 1. Due to the symmetry of the product (**46b**), the ^{1}H NMR spectrum displayed simply a split multiplet for the ten aromatic hydrogens, and one sharp singlet at 3.48 ppm, for the two equivalent methylene groups protons.[82]

Table 5. Reaction conditions and reagents trialed for deprotection of γ-TBDMSO-enone (**44b**).

	Reagent(s)[a]	Time	Diketone (**46b**) (%)[b]	Furan (**51b**) (%)[b]	Silyloxy enone (**44b**) (%)[b]
1	TBAF	15 min	100	-	-
2	TBAF/CH$_3$C(O)Cl	15 hrs	20	60	-
3	TBAF/CH$_3$C(O)Cl/ Ph$_3$P=CHCO$_2$CH$_3$	35 min	30	5	-
4	TBAF/Ph$_3$P=CHCO$_2$CH$_3$	24 hrs	90	-	5
5	TBAF/Ph$_3$P=CHCO$_2$CH$_3$/ Ph$_3$PCH$_2$CO$_2$CH$_3$$^{+-}$Br (**53**)	96 hrs	90	-	5
6	BF$_3$-Et$_2$O	12 min	50	25	-
7	BF$_3$-Et$_2$O/ Ph$_3$P=CHC(O)CH$_3$	72 hrs	trace	-	95
8	TFA:H$_2$O	30 min	trace	>90	-

[a] All reactions were performed at ambient temperature. [b] Percentage yields were calculated from analysis of crude ^{1}H NMR spectra for entries 1, 4-8, and from isolated samples for entries 2-3.

Conversely, a new product (**51b**) was obtained under the acidic cleavage conditions of TFA and water, entry 8. This new participant turned out to be the furan derivative (**51**), which was forming through a mechanism analogous to the Kornblum-De La Mare pathway.[80] Scheme 27 provided a mechanistic explanation for the formation of the observed dicarbonyl (**46**), indicating that under basic conditions the major product of desilylation and the subsequent rearrangement was (**46**). However, in an acidic environment, an alternate pathway is available whereby the position of equilibrium may be shifted towards the formation of the corresponding hemiacetal (**52**), Scheme 28.

Scheme 28 shows a mechanistic justification for the formation of the furan (**51**).[80,83] Deprotection with TFA proceeds by protonation of the oxygen prior to cleavage of the silyl group, which should accordingly generate the *trans* γ-hydroxy enone (**39**). The mechanism then assumes that some isomerisation of *trans* to *cis* enone takes places, the latter of which is known to exist in equilibrium with its hemiacetal (**48**). In an acidic medium, this species (**48**) can undergo further protonation to afford (**52**), which subsequently loses water to provide the observed furan product (**51**).
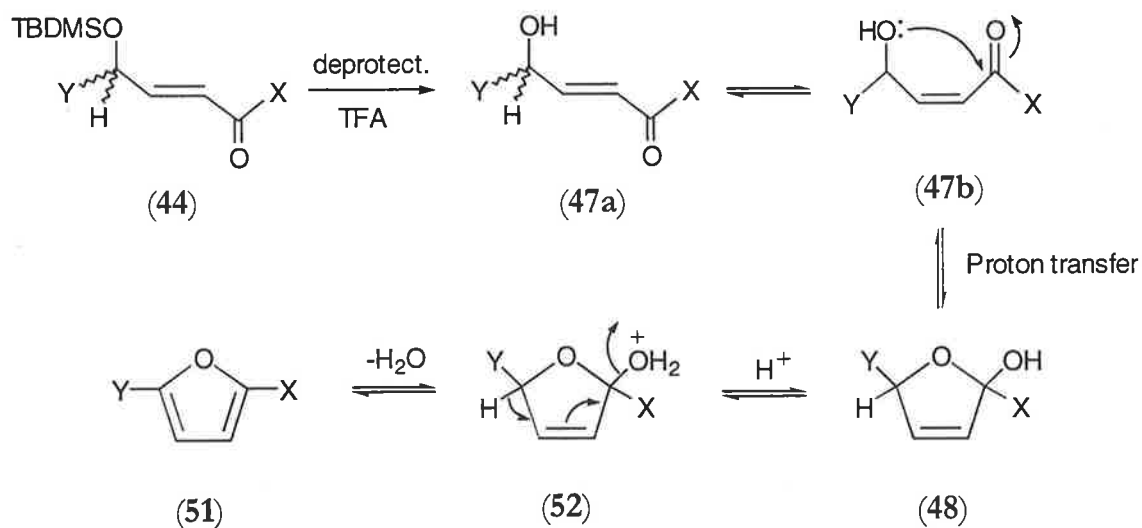
X and Y = combinations of H, aryl, alkyl and alkoxy

Scheme 28

Entry 2 of Table 5 involved treating the protected enone (**44b**) with TBAF in the presence of acetyl chloride. It was intended that the presence of an acylating agent would acylate the alkoxide (**47a**) prior to it rearranging to the diketone (**46b**). Unfortunately this

was not the case, as the major product was again the cyclised furan (**51b**). Clearly, the reagent chosen was not suitable for the delicate equilibrium balance. A minor amount of diketone (**46b**) was also produced, which was proposed to be a result of the 15 hour reaction time. The formation of any diketone under these conditions establishes the earlier proposal that the alkoxide (**47a**), itself a conjugate base, is able to deprotonate the enone (**17b**) allowing the Kornblum – De La Mare rearrangement[80] to take place.

It was hoped that these facile rearrangements (Scheme 27 and Scheme 28) could be prevented by the inclusion of a ylide in the reaction mixture. If the target γ-hydroxy enone (**17b**) was forming at all prior to deprotonation and intramolecular cyclisation, it was proposed that the enone intermediate (**17b**) could, in theory, be trapped by the ylide and undergo a Michael addition 'setting off' the cyclopropanation reaction desired. Enone (**42b**) was allowed to react with TBAF in the presence of excess methyl ester ylide (**37e**) and the reaction progress was followed by TLC, entry 4 in Table 5. Disappointingly, no cyclopropane was observed after 24 hours reaction time. The sole product was diketone (**46b**), presumably a result of both the extended reaction time and the basicity of the ester ylide (**37a**).[84]

These two theories were combined in an attempt to provide a source to trap the alkoxide (**47**) with either the acetyl chloride and/or the reactive ylide (**37e**), entry 3. This rather ambitious attempt was again thwarted, as the only products were diketone (**46b**) and furan (**51b**).

In a similar light, the ylide salt (2-methoxy-2-oxoethyl)(triphenyl)phosphonium bromide (**53**) was substituted as potential proton source. The ylide salt (**53**) is more acidic than the hydroxy enone (**17b**) and less acidic than previously employed TFA, and it was envisaged that the alkoxide (**47**) should be able to abstract a proton from the ylide salt (**53**) without the detrimental rearrangement to either (**46b**) or (**51b**). This should result in concomitant methyl ester ylide (**37e**) generation; nonetheless, extra ylide (**37e**) was included in the reaction mixture to increase the ylide concentration, therefore improving the chances of hydroxy enone (**17b**) encountering the ylide before decomposing. Some progress appeared to be made in slowing down the rearrangement, as consumption of the starting enone (**44b**) was greatly slowed, yet the only observed product was the persistent 1,4-

diketone (**46b**). It was apparent that the facile intramolecular rearrangement to hemiacetal (**48**) was much faster than any of the trialed counter measures could accommodate for.

BF$_3$-Et$_2$O was re-employed in the hope that the large BF$_3$-Et$_2$O may be able to stabilise the alkoxide (**47**) through coordination with the oxygen and, therefore, provide more time for protonation to yield enone (**17b**). Treatment of a solution of protected enone (**44b**) with BF$_3$-Et$_2$O for only 12 minutes saw complete consumption of the starting material and the formation of both by-products (**46b**) and (**51b**), entry 6. 1,4-Diketone (**46b**) was anticipated, however, the formation of furan (**51b**) was somewhat surprising, whilst also encouraging. It provided support to the proposal that boron complexation had stabilised the alkoxide (**47a**) to some degree, rendering it unavailable to act as a conjugate base and abstract a proton from the hemiacetal (**48**). Additionally, BF$_3$-Et$_2$O possesses Lewis acid properties, which may also account for the formation of furan (**51b**), although this effect was not evident in the deprotection of enone (**44a**) under analogous reaction conditions, entry 1 in Table 4. Unfortunately, this complexation effect only provided for rearrangement to the equally unwanted furan (**51b**).

With this in mind, the reaction was repeated in the presence of triphenylphosphoranylidene-2-propanone (**37a**), with the intention that the combined stabilising effect of the boron species and the immediately available ylide may provide the necessary conditions for cyclopropanation to occur, entry 7. In an effort to reduce the basicity of the reaction medium a keto ylide was used as it is less basic than the corresponding ester ylide, the weak basicity of stabilised ylides has been highlighted in the literature.[84] After three days reaction time only a trace of diketone (**46b**) was apparent with no other reaction taking place.

It is well noted at this stage that only three reagents had been employed for the attempted deprotections of (**44a-b/e**). Other techniques have been reported in the literature to afford cleavage of a silyl group.[70] The majority of these alternative reagents still incorporate the use of a fluoride ion or strong acid, conditions that are clearly not suitable for this current system.

Therefore, it was decided not to trial any additional methodologies on enones (**44a-b**) or enester (**44e**) as it was possible that another factor, not previously considered may have

been at play. That is, the problem may be associated with the electron withdrawing effect of the attached phenyl group. Potentially, this could be causing further destabilisation of the deprotonated γ-hydroxy enone (**47**). A similar phenomenon was observed in the decreased stability of phenyl substituted α-hydroxy aldehydes.[63] Therefore, it was decided to trial, and hopefully optimise, an efficient deprotection technique on the protected γ-silyloxy enones (**45a-b**) containing methyl substitution at the hydroxy terminus.

2.3.2   Attempted deprotection of lactate enone derivatives.

2.3.2.1   Deprotection of 5-*tert*-butlydimethylsilyloxyhex-3-en-2-one (**45a**).

In keeping with previous experiments, the lactate derived *trans* γ-silyloxy enone (**45a**) was treated with TBAF and BF$_3$-Et$_2$O under the conditions given in entries 1-2, Table 6. On both occasions the major product was the symmetrical diketone (**54a**). Interestingly, these reactions proceeded considerably slower than the equivalent reactions with mandelate derived enones (**44a-c**), as was evident by the large proportion of residual protected enone (**45a**). This slower cleavage of the silyl group was encouraging in that it may provide the opportunity to slow the reaction down long enough to allow hydroxy enone (**39a**) formation. As no intermediate to diketone (**54a**) was seen on repeated attempts with either TBAF or BF$_3$-Et$_2$O, these reagents were dismissed.

Table 6. Deprotection conditions trialed for the formation of γ-hydroxy enone (**39a**).

	Reagent(s)	Temp. (°C)	Time (min)	Diketone (54a) (%)[a]	Furan (55a) (%)[a]	Silyloxy enone (45a) (%)[a]
1[b]	TBAF	0	10	20	-	70
2	BF$_3$-Et$_2$O	20	120	10	-	80
3[b]	TFA:H$_2$O	20	120	trace	50	30
4	AcOH/aq THF	40	3 days	trace	trace	>90

[a] Percentage yields were calculated from analysis of crude ^{1}H NMR spectra. [b] Up to *ca.* 10% of a mixture of unidentified decomposition products was observed in the crude ^{1}H NMR spectra.

The reaction of (45a) with the TFA and water mixture was likewise a very slow reaction and was still incomplete after two hours at ambient temperature, entry 3. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated that the main product was furan (55a), present in approximately 50%. Despite the acidic conditions, a trace of diketone (54a) had formed over the reaction period. A mixture of unidentified decomposition products was also noted in the ^{1}H NMR spectrum, however, these were not recovered after column chromatography. It was accepted that none of these compounds were the targeted hydroxy enone (39a), due to the absence of any vinylic proton signals.

Since no 'true' success had been obtained with earlier attempts to trap the alkoxide (47) prior to its decomposition, with either acetyl chloride or ylide *in situ*, such trials were not repeated. The final endeavour to afford hydroxy enone (39a) utilised acetic acid in aqueous THF, employed as a weaker acid alternative to TFA, entry 4 in Table 6. According to the literature procedure,[71,85] a solution of silyloxy enone (45a) in THF and water (1:1) was treated with acetic acid and heated to 40°C. The reaction progress was followed for three days by TLC, at which time the major constituent was the starting enone (45a). No deprotected product was evident in the crude ^{1}H NMR spectrum, with only the trace amounts of diketone (54a) and furan (55a) evidence of any reaction occurring at all.

As with all previous attempts, deprotection was taking place yet rapid decomposition through the corresponding hemiacetal species (48) was triumphant with each attempt. Whilst cleavage of the TBDMS-group from the methyl substituted enone (45a) was considerably slower for each trial run, the lifetime of the alkoxide (47) had not been extended, hence none of the target *trans* γ-hydroxy enone (39a) had been produced.

2.3.2.2 Deprotection of 4-*tert*-butlydimethylsilyloxy-1-phenylpent-2-en-1-one (45b).

All hopes now resided with the only remaining enone, phenyl keto enone (45b). The first experiment with TBAF was expected to proceed similarly to that with methyl keto enone (45a) and to some extent this was true, entry 1 in Table 7. The reaction was only slightly faster (compared to entry 1 in Table 6) and the main component after 10 minutes was unreacted starting material (45b). As anticipated 1,4-diketone (46a) was formed, yet

surprisingly the furan (**55b**) was also obtained. This was the first occasion that TBAF had resulted in the generation of a furan derivative (**51** or **55**), without the assistance of an additional acid. One explanation for this result may be that water was present in the reaction mixture in a concentration high enough to facilitate loss of water with concomitant furan formation. Whilst the crude ^{1}H NMR spectrum did identify other products of the reaction, attempted isolation by column chromatography was unsuccessful. Since no alkene proton signals were observed in the spectrum, it is assured that none of these unidentified products were the target synthon (**39b**).

Table 7. Conditions and reagents employed for the deprotection of γ-silyloxy enone (**45b**)

	Reagent(s)	Temp. (°C)	Time (min)	Diketone (46a) (%)[a]	Furan (55b) (%)[a]	Silyloxy enone (45b) (%)[a]
1[b]	TBAF	0	10	5	5	50
2	BF$_3$-Et$_2$O	20	30	1	99	-
3	BF$_3$-Et$_2$O	0	45	-	100	-
4	TFA:H$_2$O	20	15 hrs	-	27	73
5[b]	PPTS	55	15 hrs	-	trace	40

[a] Percentage yields were calculated from analysis of crude ^{1}H NMR spectra for entries 2-4, and from isolated samples for entries 1 and 5. [b] Up to ca. 30% of a mixture of unidentified decomposition products was observed in the crude ^{1}H NMR spectra. PPTS = pyridinium *para*-toluenesulfonate

Enties 2 and 3 in Table 7, both utilised BF$_3$-Et$_2$O and provided interesting results. All former attempts with BF$_3$-Et$_2$O had provided the corresponding diketone (**46** or **54**) as the major product, and on only one occasion resulted in minor furan (**55**) formation, entry 6 in Table 5. Yet in this instance, the main product was the rearranged furan (**55b**), at both ambient temperature and at 0 °C. Unlike the analogous reaction with protected enone (**45a**), all starting enone (**45b**) was consumed within 45 minutes. The role of the BF$_3$-Et$_2$O reagent had clearly altered to the point that its Lewis acid nature was strongly overpowering the basic nature of the incorporated fluoride. It did not seem likely that reducing the temperature further would delay the decomposition to furan, hence the strongly acidic TFA conditions were attempted with hesitation.

Surprisingly, the same rapid decomposition to furan (**55b**) did not occur employing TFA and water, entry 4. Rather the reaction progress was slowed immensely, such that after 15 hours greater than 70% of the starting enone (**45b**) remained. Only a quarter of the reaction mixture consisted of the anticipated furan (**55b**).

In an effort to find middle ground between the rapid furanisation with BF₃-Et₂O, and the comparatively slow reaction with TFA:H₂O, an alternative reagent was employed. Pyridinium *para*-toluenesulfonate (PPTS) has been reported in the literature for the cleavage of a TBDMS-group in the presence of a *tert*-butyldiphenylsilyl (TBDPS) group.[72] The TBDPS-group is more stable than the TBDMS-group,[70] therefore it was proposed that PPTS should be strong enough to effect cleavage of the TBDMS-group, yet weak enough to decrease formation of furan (**55b**).

The proposal was accurate in that the formation of furan (**55b**) was greatly reduced, only a trace was visible in the crude reaction mixture after 15 hours at 55 °C. Unfortunately, the easy cleavage of the silyl group did not occur as proposed. Cleavage of the silyl group was slow with 40% of enone (**45b**) remaining after deliberate cessation of the reaction and more than 25% of the mixture consisted of unidentified decomposition products. The identity of these compounds was not achieved as they proved to be unstable to attempted isolation.

It remains unclear why no alkene products were obtained from either of the lactate derived enones (**45a-b**), akin to those formed (**49a-c** and **50a-b**) from the deprotection reactions involving the mandelate enones (**44a/c**).

It is worth mentioning at this point that all of the unidentified alkene compounds (**49a-c** and **50a-b**) were treated with either methyl (triphenylphosphoranylidene)acetate (**37e**) or the benzyl ester ylide (**37f**), at increasing ranges between ambient and elevated temperatures. None of the so treated alkenes afforded any cyclopropyl product. If any of the olefins (**49a-c** or **50a-b**) had been the target *trans* γ-hydroxy enone (**17**), it was expected that cyclopropanation would have resulted.

Additionally, each alkene was treated with triphenylphosphine in CH₂Cl₂ following a literature protocol that effects isomerisation of *cis* enones to *trans* enones.[86] No reaction

took place for any of the so treated alkenes (**49a-c** and **50a-b**), supporting the suggested *trans* geometry of each, as was indicated by the large vinylic coupling constants.

2.4   Summary of results.

All of the proposed transformations up to the final deprotection step had been accomplished with excellent efficiency, Scheme 21. Dishearteningly, only one of the synthesised γ-silyloxy enone/enester(s) (**44e**) had been successfully deprotected. The above results highlight the hitherto unknown difficulty in deprotection of *trans* γ-silyloxy enones under acid and/or base conditions, as may have been expected in hindsight.

3   The hydrochlorin adducts.

3.1   Removing the conjugation.

It was postulated that upon attempted deprotection, conjugation within the enone derivatives (**44/45**) was assisting the facile rearrangement to the corresponding 1,4-diketone (**51/54**) and/or furan (**50/55**) by-products. That is to say, that the major decomposition products were occurring through intramolecular cyclisation and subsequent rearrangement, facilitated by the conjugation within the system. Therefore, if the conjugation could be removed it may enable cleavage of the silyl group to be accomplished.

It was proposed to remove the carbon-carbon double bond prior to cleavage of the TBDMS-group. With the conjugation no longer present the detrimental rearrangement should be eliminated. Whilst considering the method to remove the alkene moiety, it was also necessary to consider how it would be reintroduced following successful deprotection of the silyl ether.

3.2   Synthesis of the hydrochlorin adducts.

Addition of hydrochloric acid (HCl) across the double bond would provide a means of achieving the desired objectives. Not only would HCl addition remove the conjugation, additionally it should provide a simple method for regenerating the double bond following deprotection, Scheme 29. Whilst the addition of HCl is known to be more difficult than other hydrogen halides,[87] it was selected as it should not effect other functionality within the compound.

HCl should add across the double bond with chloride attaching α to the silyloxy bearing carbon. This prediction was justified by the known ability of a silicon atom to stabilise a γ carbocation, as highlighted in the literature.[88-90] Further, Michael type alkenes are known to undergo hydrogen halide addition to provide the predicted orientation.[53] The hydrochlorin (**56/57**) produced should not be affected by standard deprotection

conditions, other than silyl-group cleavage to afford the hydroxy adduct (**58/59**). Base induced proton removal from (**58/59**) should result in elimination of chloride and regeneration of the carbon-carbon double bond. It was believed that these conditions would provide the target *trans* γ-hydroxy enone analogues (**17/39**) in good yields, and as the major product.

(**44**)   Y = Ph
(**45**)   Y = CH$_3$

(**56**)   Y = Ph
(**57**)   Y = CH$_3$

(**17**)   Y = Ph
(**39**)   Y = CH$_3$

(**58**)   Y = Ph
(**59**)   Y = CH$_3$
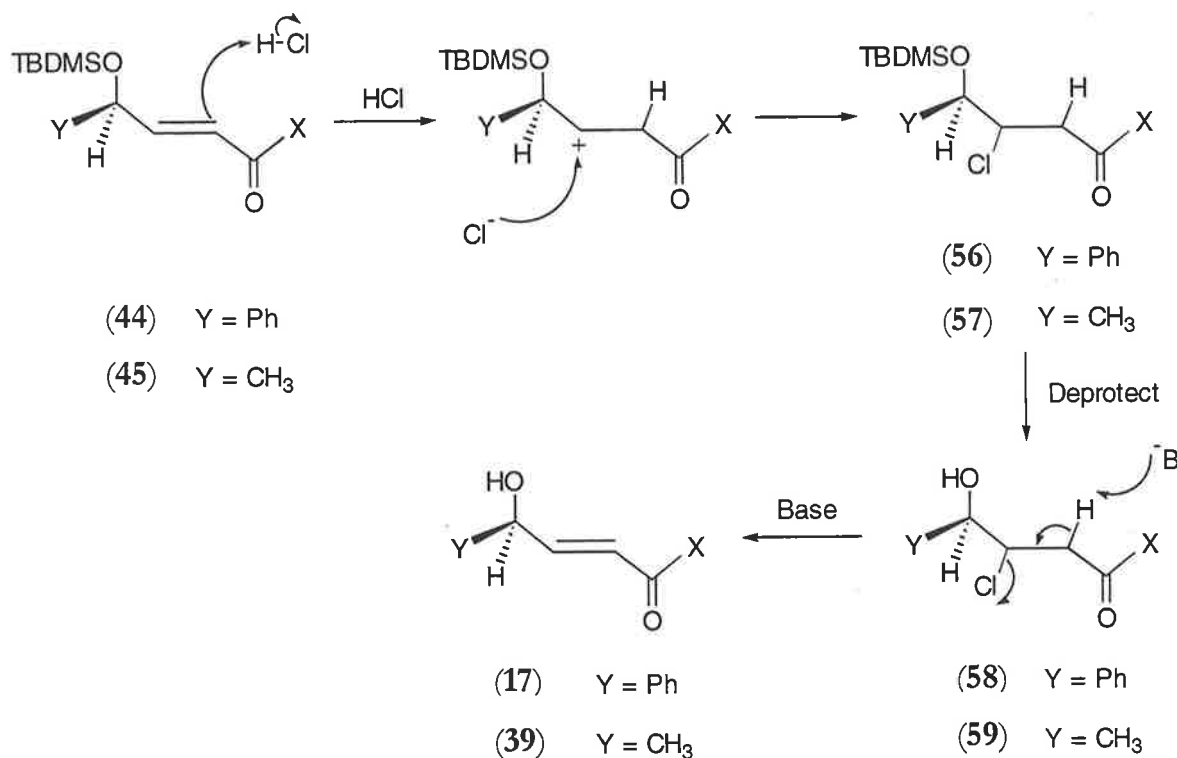
Where (a) X= CH$_3$
     (b) X= Ph
     (e) X= OCH$_3$

Scheme 29

3.2.1   Mandelate derivatives (**56a-b** and **56e**).

To a vigorously stirred solution of each γ-silyloxy enone/enester (**44a-b** and **44e**) in CH$_2$Cl$_2$, was added five equivalents of concentrated aqueous HCl at ambient temperature. As anticipated, HCl added cleanly across the double bond for enones (**44a-b**), however, the analogous reaction with enester (**44e**) did not provide the corresponding hydrochlorin adduct (**56e**), Table 8.

Table 8. Reaction conditions and results for the treatment of (**44a-b** and **44e**) with HCl.

	Silyloxy enone/enester X		Reaction Time (hrs)	Hydrochlorin % yield[a] (56)	
1	CH$_3$	(**44a**)	2	96	(**56a**)
2	Ph	(**44b**)	24	82	(**56b**)
3	OCH$_3$	(**44e**)	24	0	(**56e**)

[a] Percentage yields are quoted for products obtained in greater than 95% purity.

At first glance, interpretation of the highly complex ^{1}H NMR spectra for adducts (**56a-b**) was not obvious. However, after close analysis it was elucidated that a mixture of two diastereomers had formed. All attempts to purify and/or separate the diastereomeric oil mixture were unsuccessful. Decomposition of both (**56a**) and (**56b**) to unidentified mixtures resulted from trialed purification on both silica gel and florisil chromatography columns, hence the adducts were analysed as diastereomeric mixtures, as isolated in greater than 95% purity.

The formation of diastereoisomers was due to the fact that 'attack' by the chloride ion can occur from either face of the trigonal planar carbocation. This was evident from the essentially 1:1 diastereomeric ratio for both adducts (**56a-b**). Careful analysis of Figure 15 reveals that the ratio is not exactly 1:1, nonetheless, a more accurate ratio cannot be quoted due the error margin in measuring, and the closeness of, the relative integrations (51:49). Fortunately, the slight majority (ca. 2%) of one diastereomer over the other enables the assignment of each set of signals to one isomer.

The ^{1}H NMR spectrum for each hydrochlorin (**56a-b**) can be described as follows:

- an unresolved multiplet for the aromatic protons
- two diastereotopic doublets for TBDMSO-C<u>H</u>
- a complex multiplet for C<u>H</u>Cl
- two sets of two diastereotopic doublets of doublets for ClCHC<u>H</u>$_2$
- two diastereotopic singlets for O=CC<u>H</u>$_3$ ((**56a**) only), and
- three sets of two diastereotopic singlets for each of the C<u>H</u>$_3$ and C(C<u>H</u>$_3$)$_3$ groups in the TBDMS-group.
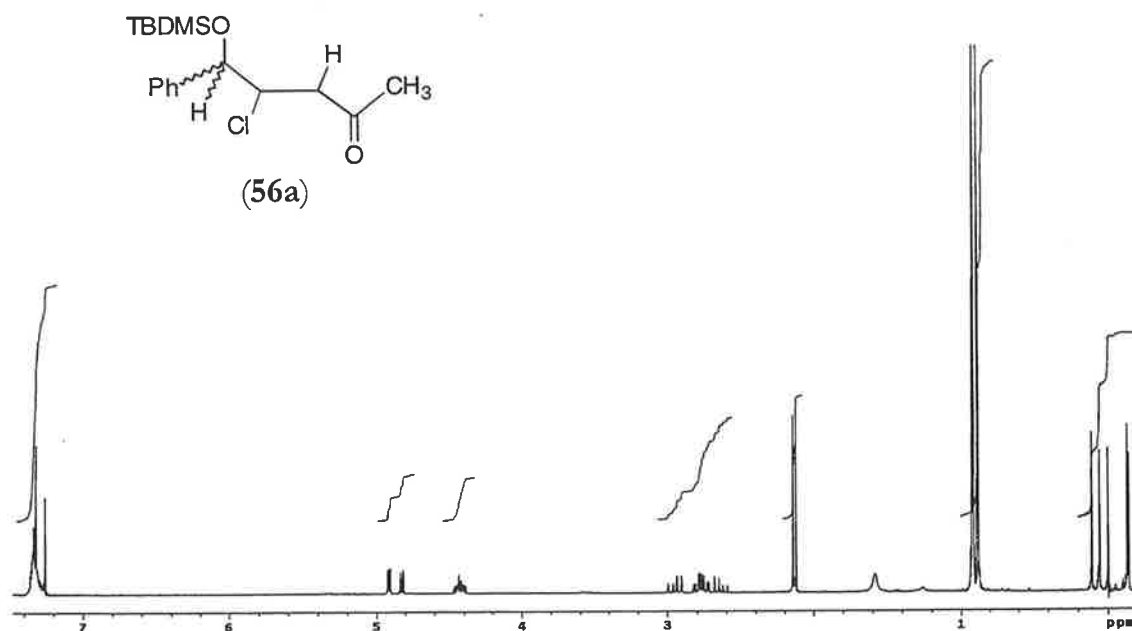
Figure 15. 300 MHz ^{1}H NMR spectrum for HCl adduct (**56a**).

The assignments for each of the above signals were determined through extensive two-dimensional NMR experimentation; COSY and HMBC spectroscopy providing convincing evidence, see Appendix. By far the most interesting feature of the ^{1}H NMR spectrum for each adduct (**56a-b**) was the four doublets of doublets resulting from the CH$_2$ group protons α to the carbonyl.

The addition of chloride to the β carbon with respect to the carbonyl group, generated a chiral center in the molecule. Therefore, each of the geminal hydrogens in the CH$_2$ group is non-equivalent to the other. Each proton resonates at a different frequency and is coupled to the other geminal hydrogen, in addition to the methine group bearing the chloride. Four separate doublets of doublets, or two sets of two doublets of doublets, are observed as two diastereomers are present, i.e. one diastereomer with the chloride to the front and one with the chloride to the back. Figure 16 shows this region of the spectrum for adduct (**56a**) in which each of the doublets of doublets is separated from one another making the assignment of the associated peaks relatively easy to determine.
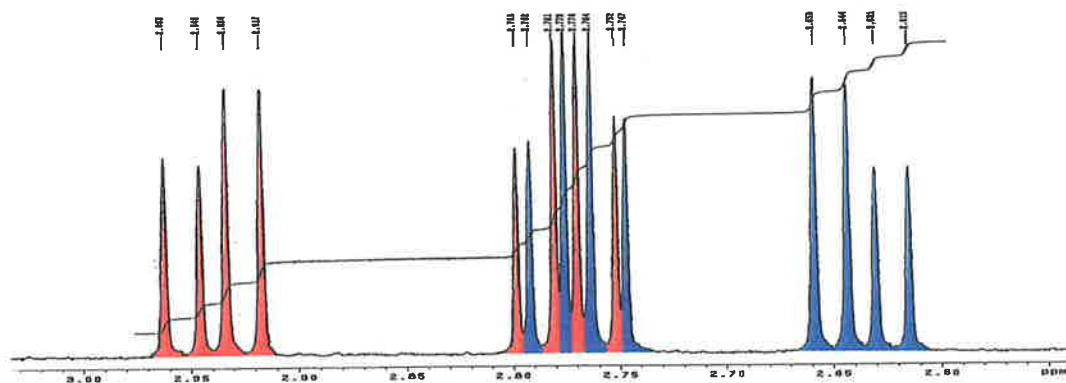
Figure 16. 600 MHz ^{1}H NMR of (**56a**) from 3.05 - 2.55 ppm.

The diphenyl adduct (**56b**) ^{1}H NMR spectrum exhibits the same splitting pattern, however, in this case the individual protons resonate at closer frequencies which further complicates the interpretation, Figure 17. Calculation of the associated coupling constants assisted in establishing the correct assignment of each signal as a doublet of doublets for each diastereomer.
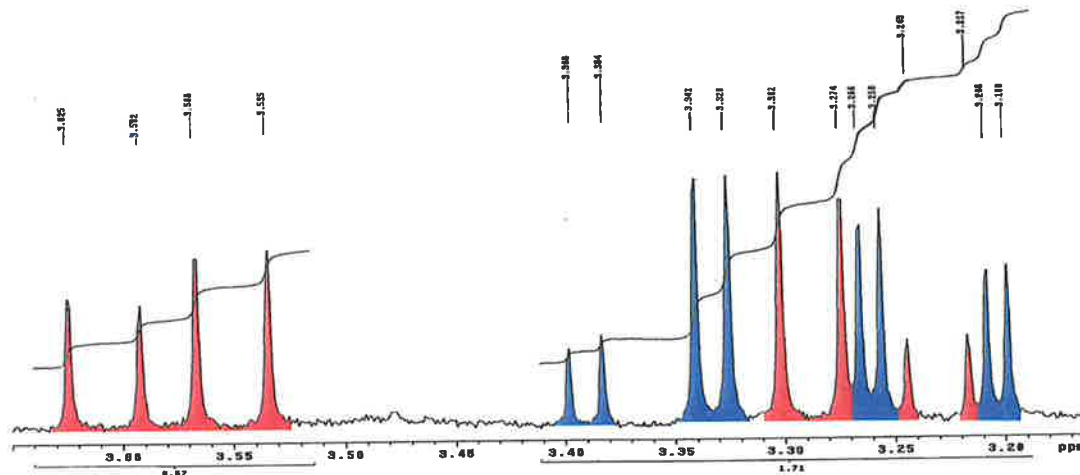
Figure 17. 300 MHz ^{1}H NMR of (**56b**) from 3.65 – 3.15 ppm.

Heteronuclear Multiple Quantum Coherence (HMQC) spectroscopy was used to confirm the compound structure and to assign the ^{13}C NMR signals to a specific diastereomer. Figure 18 displays an illustrative expansion of the HMQC spectrum that enabled these assignments to be made. From the slightly askew diastereomeric ratio in the ^{1}H NMR spectrum, the corresponding ^{13}C signals were determined, where reasonable separation was observed between signals and cross peaks.
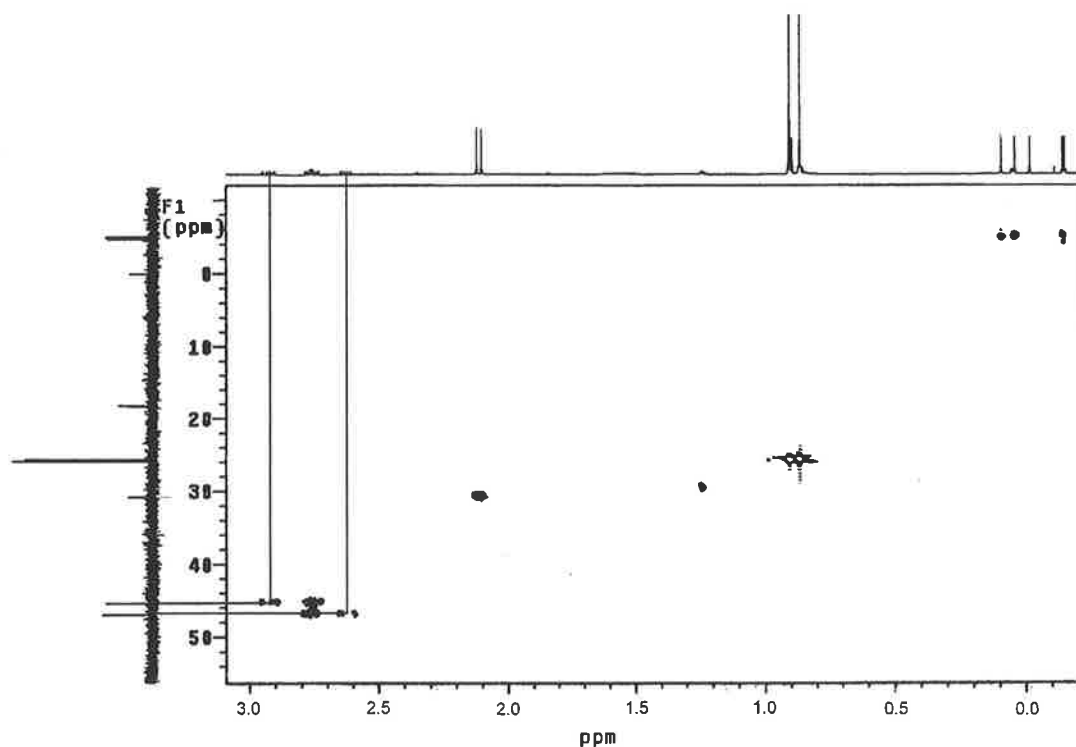
Figure 18. An expansion of the 600 MHz HMQC spectrum for hydrochlorin (**56a**).

For instance, the ^{1}H NMR signal (doublet of doublets) centered on 2.92 ppm corresponds to the ^{13}C signal at 45.3 ppm. Whilst the opposite diastereomer, with its doublet of doublets at 2.62 ppm in the ^{1}H NMR spectrum, has a ^{13}C resonance at 46.9 ppm, Figure 18. This was not always possible depending upon the proximity of signals in the respective spectrum. For quaternary carbons, HMBC spectroscopy was employed to assign the diastereomeric signals by correlation with the neighbouring proton bearing carbon.

This technique was applied for all of the hydrochlorin products synthesised, Sections 3.2.1 and 3.2.2. Where possible, each signal in both the ^{1}H and ^{13}C NMR spectrum has been assigned to one diastereomer out of the pair, denoted in the experimental section of

this thesis with an asterisk. Where the signals could not be conclusively assigned, no differentiation has been noted, e.g. in most cases the aromatic NMR signals could not be distinguished.

Entry 3 in Table 8 denotes the reaction of enester (**44e**) with concentrated HCl. As previously mentioned, this reaction did not provide any of the expected hydrochlorin product (**56e**). Total consumption of the starting enester was noted after 24 hours, at which time ^{1}H NMR disclosed that three distinct products had formed, Scheme 30. Surprisingly, one of these was in fact the deprotected *trans* γ-hydroxy enester (**17e**).[54] Apparently the aqueous acid environment provided suitable conditions for cleavage of the silyl group. In addition to hydroxy enester (**17e**), ketoester (**46e**) was also present.
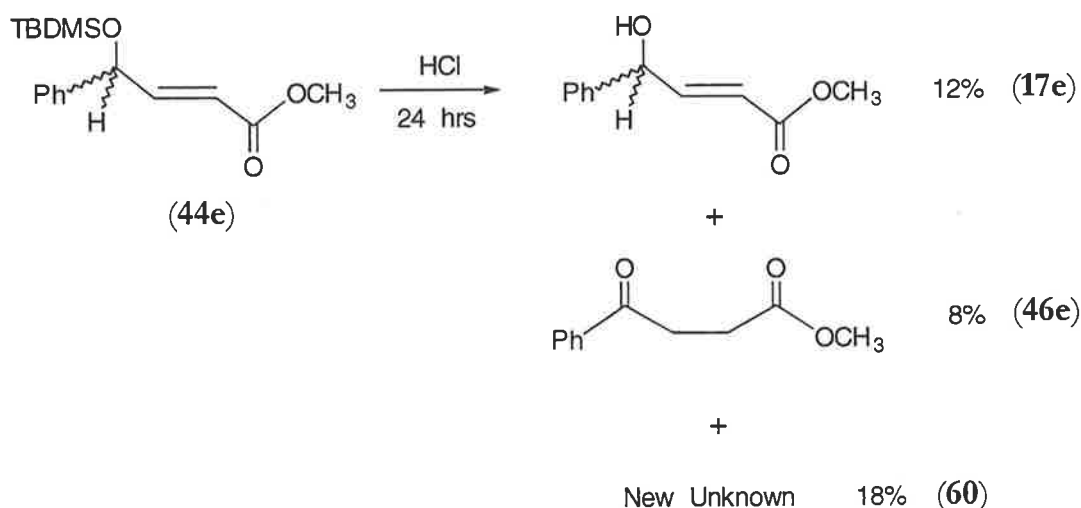
Scheme 30

The third product was yet another unknown alkene (**60**), which exhibited similar spectral data to the previous unidentified deprotection products (**49a-c**). Once again the ^{1}H NMR spectrum contained three doublets of doublets resonating at 7.15, 6.08 and 5.54 ppm and the vinylic coupling constants were consistent with a *trans* orientation about the double bond (15.4 Hz). The same structural configuration of X-CHCH=CH was indicated, where 'X' is equivalent to an electronegative element, Table 9. This configuration was established from consideration of the above information and from the analysis of two-dimensional NMR spectroscopy (COSY and HMQC spectra included in Appendix).

Table 9. 600 MHz ^{1}H NMR data for alkene (**60**), 'X' = electronegative element.

Assignment	δ (ppm)	Multiplicity	J (Hz)
Ph	7.42-7.34	m	-
C**H**=CH	7.15	dd	6.8, 15.4
CH=C**H**	6.08	dd	1.5, 15.4
C**H**-X	5.54	dd	1.5, 6.8
OC**H**$_3$	3.75	s	-

Gas chromatographic mass spectral analysis of the unknown (**60**) displayed two peaks at 213 and 211, with relative intensities of 7 and 12 respectively. These signals may correspond to the protonated molecular ion peaks (MH$^+$) for the isotopic chloride species i.e. X = chloride, Scheme 31. The natural isotopic abundance of chloride is 3:1 (^{35}Cl:^{37}Cl), however, the mass spectral results for (**60**) show a ratio of only 2:1. The low relative intensity of each of the mass peaks may account for the slight discrepancy in the observed isotopic ratio, as the margin of error in calculating these intensities may have resulted in inaccuracies. In the same mass spectrum the base peak occurred at 175, consistent with the loss of chloride. A proposed mechanism for the formation of (**60**) is outlined in Scheme 31.
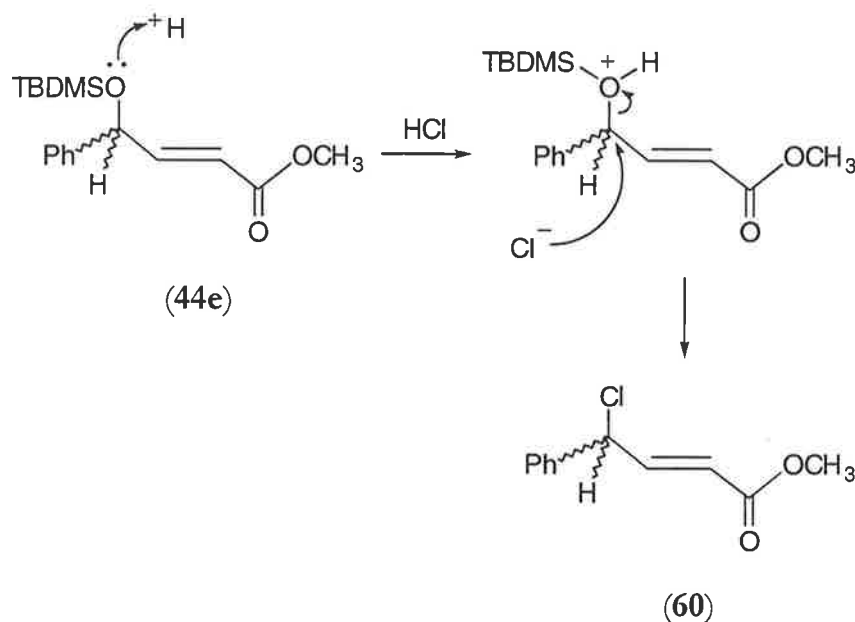
Scheme 31

This structural assignment was supported by the results obtained from the treatment of (**60**) with a stabilised phosphorus ylide, Scheme 32. Methyl ester ylide (**37e**) was added to a solution of the chloride adduct (**60**) in CH_2Cl_2, and the mixture was heated under reflux for 15 days. The crude ^1H NMR spectrum disclosed that some starting material (**60**) remained and that more than one product had formed. The major identifiable product was the known trisubstituted alkene (**61**), recovered in a 23% yield following isolation by column chromatography. Fry and Moore reported the ^1H NMR data for (**61**) in a carbon tetrachloride (CCl_4) solution, which was repeated for comparison to confirm the identity of (**61**).[91] However, the spectral data reported in the experimental section of this thesis is quoted for a deuterated chloroform solution in keeping with modern convention.
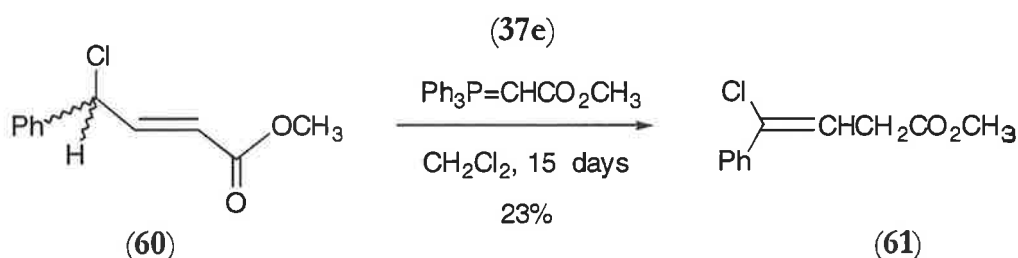
Scheme 32

Scheme 33 depicts a mechanistic proposal accounting for the formation of (**61**). The ylide (**37a**) acts as a base removing a proton from the chloride bearing carbon affording the resonance stabilised carbonionic intermediate (**62**). Subsequent reprotonation by the ylide salt provides the observed product (**61**).

Treatment of the silyloxy enone derivatives (**44a-b**) with HCl successfully afforded the desired hydrochlorin products (**56a-b**) in excellent yields. Under analogous conditions silyloxy enester (**44e**) did not provide any such adduct, yet directly provided the deprotected enester (**17e**), albeit in a low yield. The two hydrochlorin derivatives (**56a-b**) formed were to be employed for the proposed desilylation methodology discussed above.
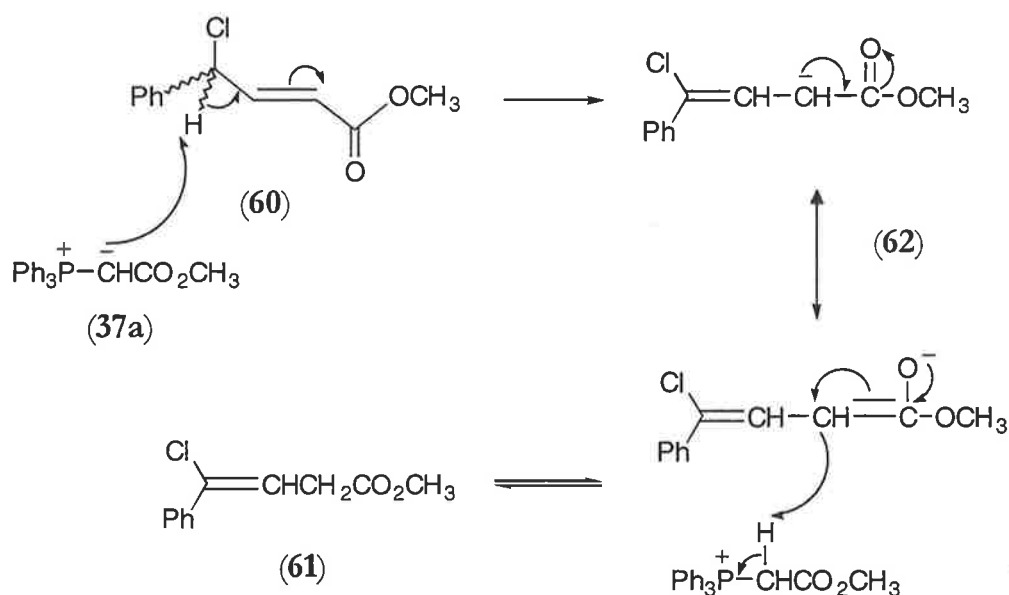
Scheme 33

3.2.2 Lactate derivatives (57a-b).

The lactate derived γ-silyloxy enones (**45a-b**) were subjected to the same reaction conditions as the mandelate enones (**44a-b** and **44e**), Scheme 34. This time the reactions with HCl were complete in reduced reaction times for both the methyl and phenyl keto adducts, Table 10. As anticipated the reactions were extremely fruitful in providing the corresponding hydrochlorin products (**57a-b**) in excellent yields. Through a simple aqueous work-up procedure, greater than 95% purity of product was obtained (from ^{1}H NMR analysis), and no further purification was necessary.

Scheme 34
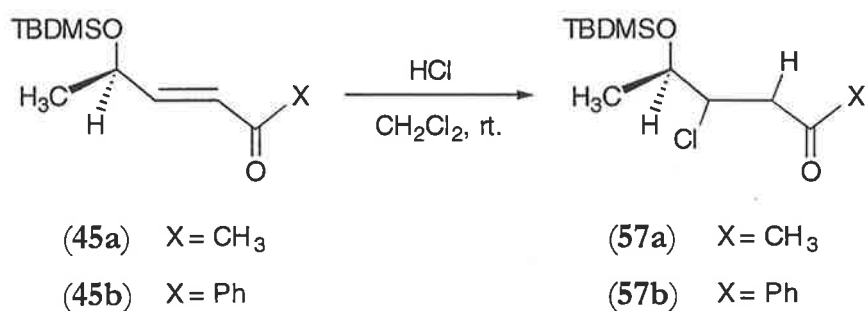
Table 10. Reaction conditions and results from the treatment of enones (**45a-b**) with HCl.

	Silyloxy enone/enester X	Reaction Time (hrs)	Hydrochlorin % yield [a] (57)	
1	CH$_3$ (**45a**)	1.25	92	(**57a**)
2	Ph (**45b**)	3	90	(**57b**)

[a] Percentage yields are quoted for product obtained in > 95% purity.

Again the ^{1}H NMR spectrum for both hydrochlorin adducts (**57a-b**) were highly complex, more so than the mandelate analogous (**56a-b**) due to the additional coupling of the terminal methyl group. The diastereomeric ratio of products of 1:1.5 for (**57a**) and 1:1.2 for (**57b**), indicates a slight preference for 'attack' from one face of the carbocation, not previously seen with the mandelate-derived adducts (**56a-b**). The facial selectivity can be pictorially represented as in Figure 19, whereby the position of the TBDMSO(CH$_3$)CH- substituent on the carbocation centre may hinder 'attack' from one face. Why this selectivity was observed for the lactate analogues (**57a-b**) and not for the mandelate analogues (**56a-b**) is unclear, but may be associated with the more similar size of the phenyl and TBDMS-groups.
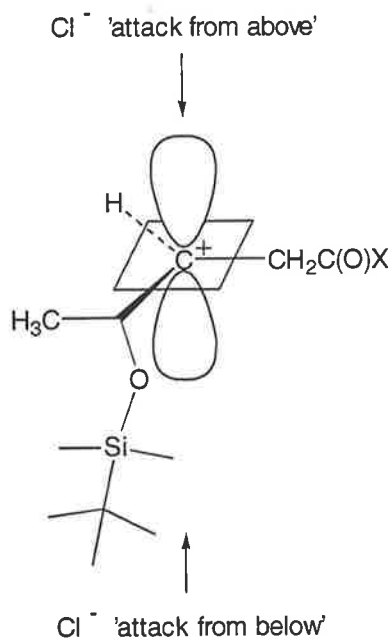
Figure 19. The vacant *p* orbital of the carbocation extends perpendicular to the plane of the carbon and the three attached groups, chloride ion 'attack' can occur from either face (above or below the plane).

The ^{1}H NMR spectrum for each adduct (**57a-b**) contains the following signals:

- an unresolved multiplet for the aromatic protons ((**57b**) only)
- two diastereotopic doublets of doublets of doublets for C<u>H</u>Cl
- two diastereotopic doublets of quartets for TBDMSO-C<u>H</u>
- two sets of two diastereotopic doublets of doublets for (**57a**) and an unresolved multiplet for (**57b**), due to ClCHC<u>H</u>$_2$
- two diastereotopic singlets for O=CC<u>H</u>$_3$ ((**57a**) only)
- two diastereotopic doublets for C<u>H</u>$_3$CH, and
- three sets of diastereotopic singlets for each of the C<u>H</u>$_3$ and C(C<u>H</u>$_3$)$_3$ groups in the TBDMS-group.

The NMR spectra were assigned by employing analogous techniques as detailed for the interpretation of (**56a-b**), Section 3.2.1. Similarly, an asterisk in the NMR data differentiates diastereomeric signals where possible.

The main difference between the previous hydrochlorin adducts (**56a-b**) and the new synthons (**57a-b**) are the proton signals for the hydrogen attached to the carbon bearing the protecting group. Coupling with the neighbouring methyl group results in the formation of a doublet of quartets. Considering hydrochlorin (**57b**), both diastereomers exhibit the same coupling with the methyl group protons (6.2 Hz), yet different coupling with the adjacent Cl-C-<u>H</u> proton (3.6 and 5.1 Hz), Figure 20. The effect of the position of the chloride atom is highlighted pictorially in Figure 21.

4.50 (J = 3.5, 4.7, 8.0 Hz) &
4.41 (J = 4.1, 5.0, 8.9 Hz)

2 x ddd

4.13 (J = 3.6, 6.2 Hz) &
4.06 (J = 5.1, 6.2 Hz)

2 x dq

multiplet
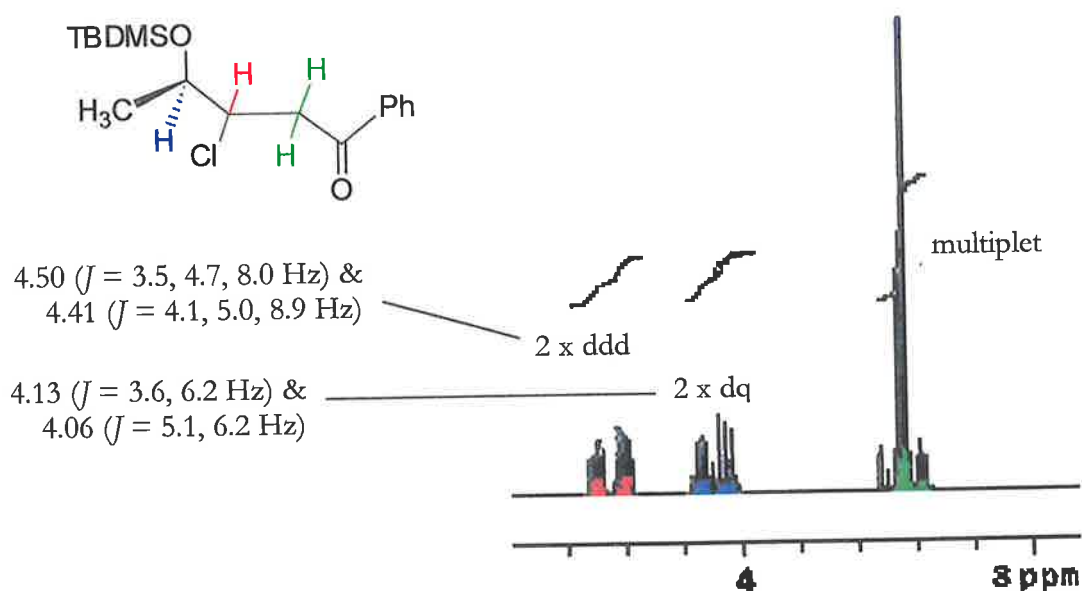
Figure 20. 600 MHz ^{1}H NMR spectrum for (**57b**) from 4.8 – 3.0 ppm.
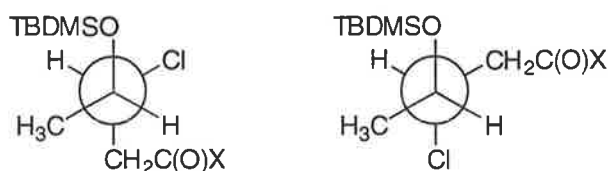
Figure 21. Fischer projection diagrams for the diasteromers of hydrochlorin adducts (**57a-b**) highlighting the orientation of the chloride atom in relation to adjacent protons.

The methine proton attached to the chloride bearing carbon was previously reported in the ^{1}H NMR spectrum of the mandelate analogues (**56a-b**) as an unresolved multiplet for both. These signals are now well resolved into two sets of diastereotopic doublets of doublets of doublets for the lactate derived hydrochlorins (**57a-b**), Figure 20. This splitting pattern was expected as a result of ^3J coupling with the three non-equivalent neighbouring protons. The reverse is true for the methylene group protons; whereas two sets of doublets of doublets were clearly resolved and separated for each stereoisomer of the mandelate adducts (**57a-b**), the corresponding signals resonated at very close frequencies for the lactate derivatives (**56a-b**). The signals are partially overlapping for the methyl keto hydrochlorin (**57a**), yet the splitting pattern is still discernible. However, for the phenyl analogue (**57b**) the signals lay on top of one another, hence the signal has been reported as an unresolved complex multiplet, Figure 20.

Not all of the hydrochlorins (**56a-b** and **57a-b**) synthesised exhibited a molecular ion peak in their respective mass spectrum, however, each displayed fragment ion peaks in the isotopic ratio expected for the chloride atom. All derivatives were unstable and decomposed over varying time periods. The only analogue stable enough to enable a high-resolution mass spectrum to be recorded was the first product synthesised, hydrochlorin (**56a**). All other samples decomposed prior to reaching the site of measurement in Tasmania.

Each adduct (**56a-b/57a-b**) did eventually decompose completely to either the corresponding furan (**51/55**) or 1,4-diketone (**46/54**). No pattern was apparent as to which by-product was produced on decomposition, and the duration varied from overnight for (**57a**) to 1 month for (**57b**). It is interesting that on decomposition each hydrochlorin not only eliminated HCl but also cleaved the TBDMS-group. The formation

of the furan (**51/55**) and dicarbonyl (**46/54**) by-products will be discussed in more detail in Section 3.3.

3.3   Attempted deprotection of the hydrochlorin adducts (**56a-b and 57a-b**).

With four hydrochlorin products (**56a-b/57a-b**) in hand, the next step was to complete their deprotection to afford the corresponding hydroxy analogues (**58a-b/59a-b**), Scheme 29. As outlined in Section 3.2, it was envisaged that this step would be achieved using standard silyl-group cleavage conditions. Following this, the final step in the revised pathway would be regeneration of the alkene moiety.

The three reagents chosen to effect deprotection were TBAF, BF_3-Et_2O and TFA in water. Each hydrochlorin was treated with the deprotecting reagent under the conditions previously described for the attempted desilylation of the silyloxy enones/enester (**44/45**), Section 2.3. An overview of the results for each of these experiments is presented below in Table 11 for the phenyl adducts (**56a-b**) (Scheme 35), and Table 12 for the methyl adducts (**57a-b**) (Scheme 36).

Table 11. A summary of results for the attempted deprotection of hydrochlorins (**56a-b**).

Hydrochlorin (**56a**)	Diketone (**46**)	Furan (**51**)	Alkene (%)[a]	Silyloxy enone (**44**)
TBAF	✓	-	✓ (**50a**) (60%)	-
BF_3-Et_2O	✓	-	-	-
TFA:H_2O	✓	✓	-	-
Hydrochlorin (56b)[b]				
TBAF	✓	✓	-	-
BF_3-Et_2O	-	✓	✓ (**17b**) (10%)	-

[a] Percentage yields were calculated from the analysis of ^1H NMR. [b] The deprotection of (**56b**) was not trialed with TFA:H_2O.
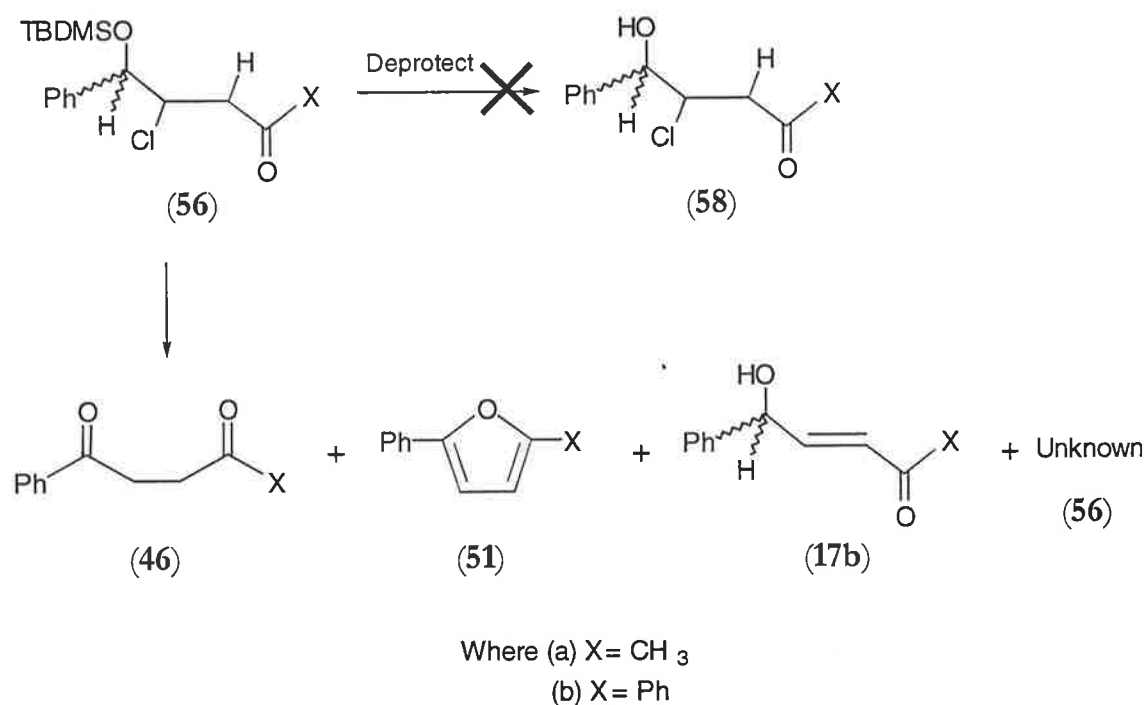
Scheme 35

Table 12. A summary of results for the attempted deprotection of hydrochlorins (**57a-b**).

Hydrochlorin (**57a**)	Diketone (**54**)	Furan (**55**)	Alkene (%)[a]	Silyloxy enone (**45**)
TBAF	-	-	-	✓ (**45a**)
BF$_3$-Et$_2$O	✓	-	-	-
TFA:H$_2$O	✓	-	-	✓ (**45a**)
Hydrochlorin (**57b**)				
TBAF	-	-	-	✓ (**45b**)
BF$_3$-Et$_2$O	✓	-	-	-
TFA:H$_2$O	✓	✓	-	-

[a] Percentage yields were calculated from the analysis of ^{1}H NMR.
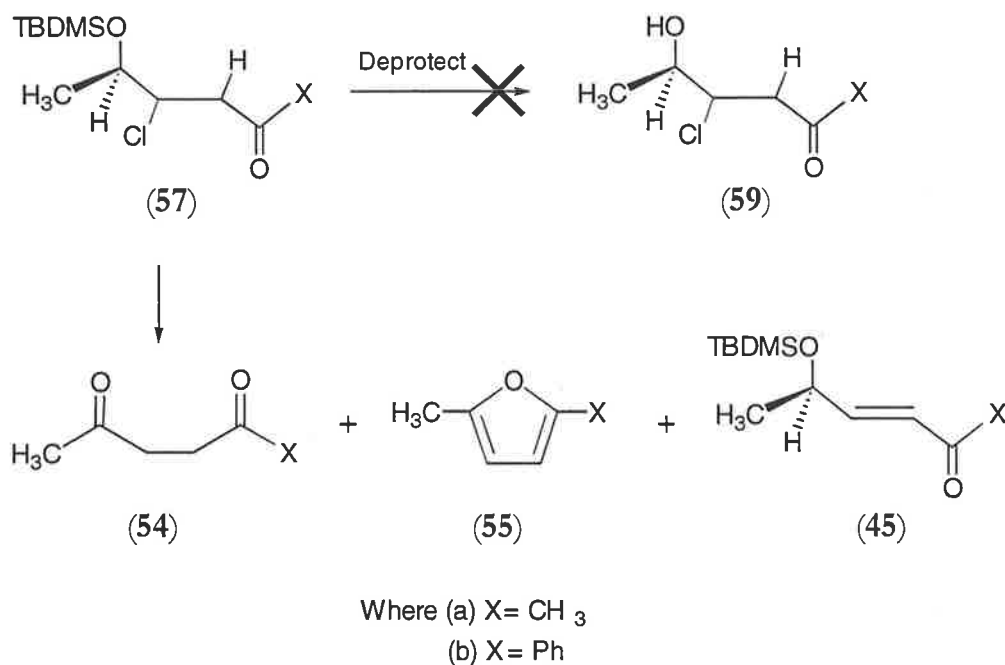
Scheme 36

Similarly to previous deprotection experiments with the protected enone/enester synthons (**44/45**), the predominating products of deprotection for the hydrochlorin adducts (**56/57**) were the rearranged 1,4-diketone (**46/54**) and furan (**51/55**) by-products. This outcome was extremely disappointing, as the sole purpose of synthesising the hydrochlorins was to avoid such rearrangement.

The observed by-product formation can be rationalised by two potential situations, depicted in Scheme 37 and Scheme 38. That desilylation had occurred was not in doubt, however, it was unclear whether cleavage of the silyl group or elimination is taking place first. Scheme 37 proposes that initially deprotection occurs, generating the intermediate alkoxide species (**63**) under the basic conditions of TBAF and BF_3-Et_2O. Intramolecular 'attack' of the alkoxide (**63**) then results in the elimination of chloride and the formation of epoxide (**64**). Subsequent ring opening of the so formed epoxide (**64**) is facilitated by an *in situ* base source (eg. the fluoride ion) and provides the alkene alkoxide (**47**), which it has been shown rearranges to both 1,4-diketone (**46/54**) and furan (**51/55**), Section 2.3.
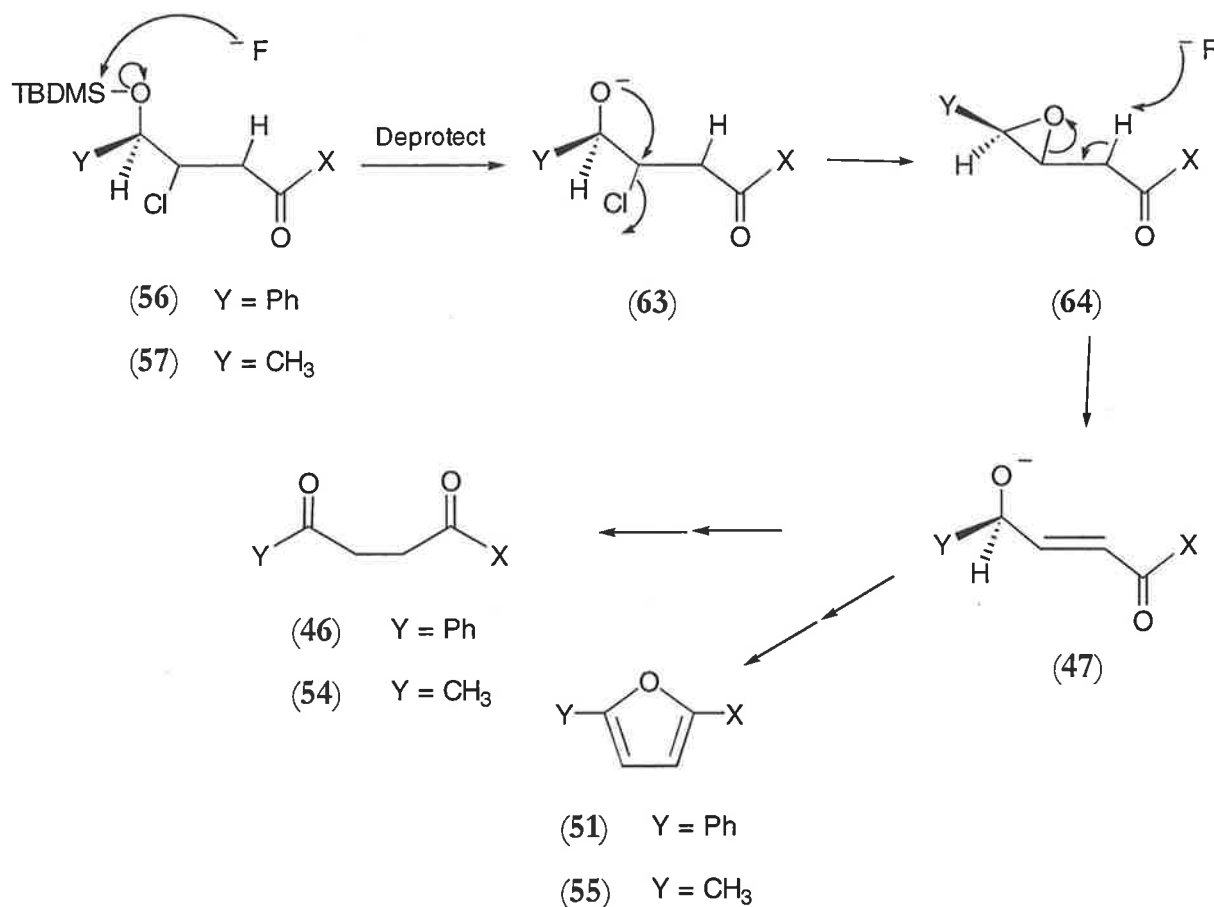
Scheme 37

Alternatively, elimination may be the first transformation as postulated in Scheme 38. Under basic deprotection conditions, removal of the α proton would cause elimination of chloride and regeneration of the γ-silyloxy enone (**44/45**). As has been demonstrated previously, treatment of (**44/45**) under these conditions does not afford the target γ-hydroxy enones (**17/39**), rather a mixture of compounds including the 1,4-diketone (**46/54**) and furan (**51/55**) by-products, Section 2.3.

How the rearrangement was transpiring is not all that important, suffice to say that all attempts to produce the deprotected hydrochlorin targets (**58/59**) were unsuccessful. Many variations in reaction conditions were trialed to no avail.
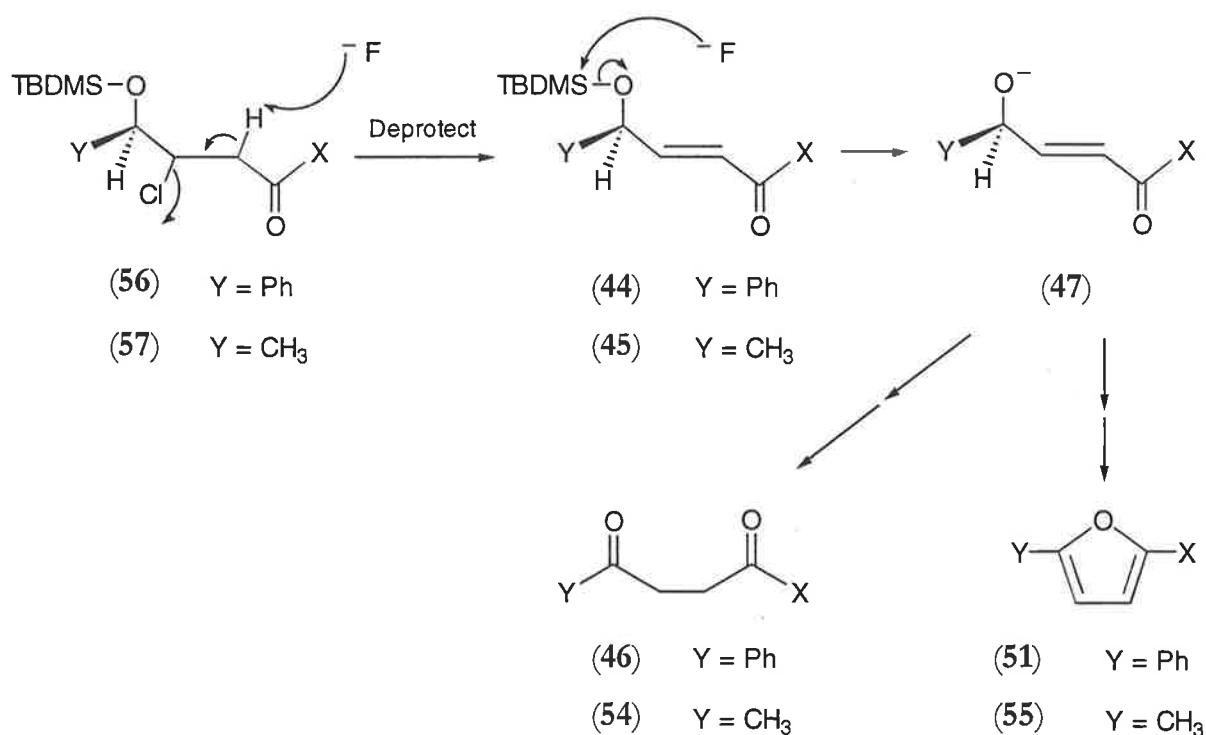
Scheme 38

Table 11 indicates that on two occasions an acyclic alkene product was obtained. The unidentified alkene (**50a**), previously isolated from the deprotection of silyloxy enone (**44a**), was observed in the crude ^{1}H NMR spectrum for the reaction of hydrochlorin (**56a**) with TBAF. Alkene (**50a**) was formed as the major product of this reaction accompanied by the formation of 1,4-diketone (**46a**).

The second alkene obtained resulted from the treatment of (**56b**) with BF$_3$-Et$_2$O, Table 11. Approximately 10% of the crude reaction mixture consisted of the unknown product and a very small sample was isolated in less than 50% purity (estimated by ^{1}H NMR). Significant decomposition occurred during purification attempts and a clean sample could not be obtained for characterisation. Consequently, the product was dismissed as yet another unidentified product. Later examination of the ^{1}H NMR spectrum confirmed that it was in fact the *trans* γ-hydroxy enone (**17b**), Chapter 5.

No unidentified alkene products were generated from deprotection of the lactate derived hydrochlorins (**57a-b**), Table 12. Surprisingly, treatment of both hydrochlorins (**57a-b**) with TBAF resulted in the formation of the formerly synthesised *trans* γ-silyloxy enones (**45a-b**), as the sole product. Protected enone (**45a**) was also a product under the TFA:H$_2$O deprotection conditions of (**57a**). The generation of the protected enone derivatives supports the proposal that elimination of HCl, regenerating the carbon-carbon double bond, was the first transformation to take place on at least some occasions, Scheme 38. Presumably, if these experiments were repeated with an increased excess of the basic deprotecting reagent the result would be removal of the TBDMS-group and rearrangement to furan (**51/55**) and/or 1,4-diketone (**46/54**).

On no occasions were any of the desired deprotected hydrochlorins (**58/59**) afforded. Concomitant deprotection and elimination was the prevalent result of the reactions trialed. A detailed account of the results obtained for the reactions summarised in Table 11 and Table 12 has not been included due to the unsuccessful outcome of this strategy. Accordingly, it was decided that inclusion of these reactions in the experimental section of this thesis was not warranted.

4   The formation of disubstituted cyclopropanes by a more successful strategy.

4.1   A new synthetic strategy.

At this stage the synthetic strategy proposed for the formation of the targeted *trans* γ-hydroxy enone intermediates (**17/39**) was reconsidered. It was clear that the problems already highlighted with deprotection of the γ-silyloxy enones (**44/45**) rendered that particular approach unsuitable. Whilst cleavage of the silyl group had been achieved, regeneration of the parent alcohol (**17/39**) had only been accomplished on one occasion, yielding the enester analogue (**17e**). A new strategy was required.

As has been discussed in earlier chapters, it was believed that conjugation within the enone derivatives and the *in situ* generation of alkoxide (**47**), were two of the primary factors causing the observed rearrangement and decomposition to by-products. In order to overcome this problem, an alternative approach needed to be considered whereby this situation could be avoided.

In Chapter 2 it was noted that the bulky TBDMS-group used to protect the hydroxyl moiety, aided both in the ester reduction and Wittig olefination transformations. There is, however, no requirement that the hydroxyl group be protected during the Wittig reaction. Therefore, there is potential to accomplish deprotection of the α-silyloxy aldehyde (**42/43**), to provide the corresponding α-hydroxy aldehyde (**36/65**), prior to reaction with a phosphorus ylide, Scheme 39.

This approach had not been considered previously due to the reported instability of α-hydroxy aldehyde synthons.[63] Craig and co-workers reported the synthesis of a variety of alkyl α-hydroxy aldehydes through an additive Pummerer procedure, as discussed in Chapter 1, Scheme 19.[63] Specifically, it was reported that the α-hydroxy aldehyde existed as a monomeric and dimeric mixture, inseparable by chromatographic techniques. In a side reaction, Craig successfully treated this mixture with the phosphorus ester ylide (**37e**) to effect a Wittig olefination reaction, implying that the mixture reacts in the same manner as the corresponding monomer. This provides a precedent for performing the

olefination on the deprotected aldehyde (**36/65**). However, it was reported in the same paper that aromatic α-hydroxy aldehydes could not be produced.

Where (a) X = CH$_3$
         (b) X = Ph, and
         R^1 / R^2 = combinations of H, alkyl, keto and ester
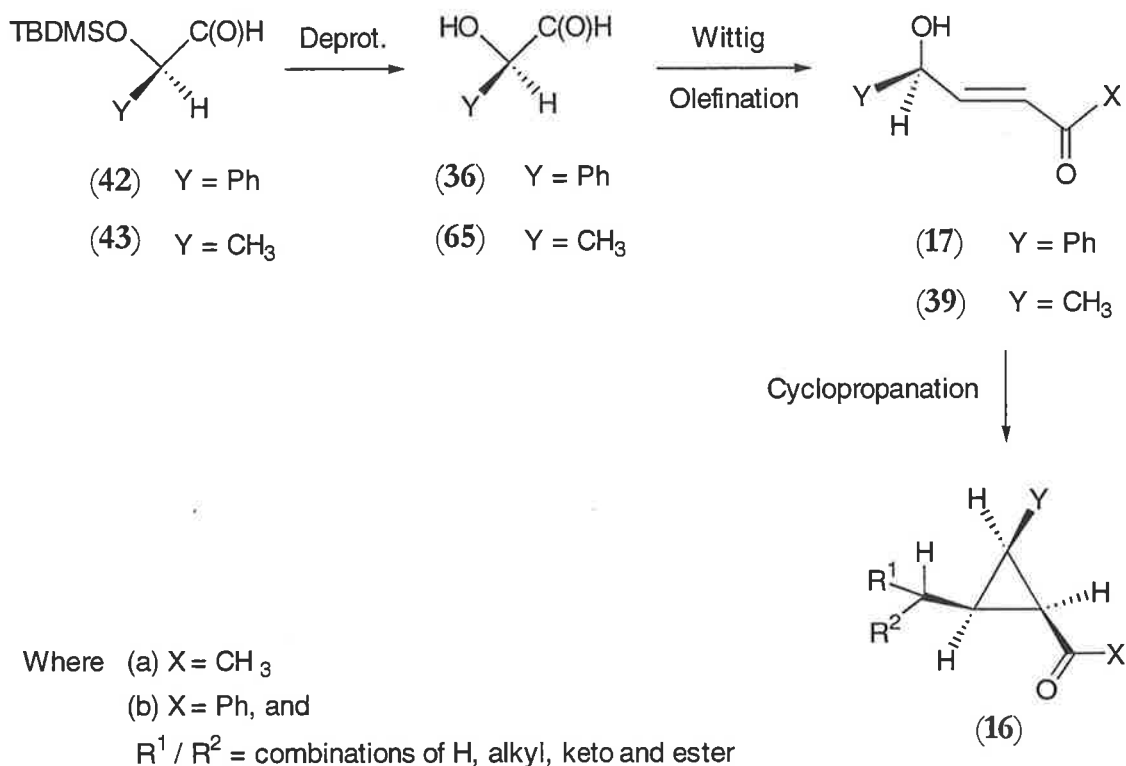
Scheme 39

Craig reported that when 'R' was equivalent to a phenyl group, the α-hydroxy ketone (**34**) was the sole product, Scheme 19. This was attributed to the greater thermodynamic stability of (**34**), resulting from conjugation of the carbonyl and the aromatic π-system.[63] Similar results have also been reported for phenylacetaldehyde, whereby the introduction of an aromatic substituent resulted in complications due to self-condensation of the aldehyde.[54]

Scheme 40 shows the suggested mechanism under basic conditions,[63] accounting for the rearrangement of hydroxy aldehyde (**36**) to the hydroxy ketone analogue (**34**). Removal of the acidic proton α to the carbonyl and the aromatic ring results in a rearrangement to afford the enolate, which subsequently rearranges to the final ketone product (**34**).
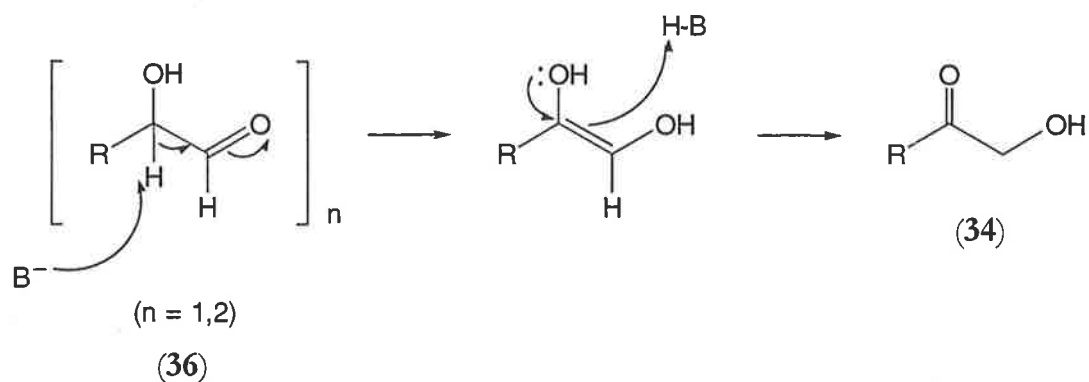
R = aromatic

Scheme 40

Formation of the free α-hydroxy aldehyde species had previously been discounted due to the above literature results indicating that two independent pathways would be required to provide both methyl and phenyl substituted γ-hydroxy enones (**17/39**). The development of one simple and divergent synthetic strategy to afford a variety of analogues had been one of the goals of this research. Despite this, it was re-proposed to attempt the synthesis of the target *trans* enones (**17/39**) via the intermediate α-hydroxy aldehydes (**36/65**).

Whilst Craig reported the reaction of the monomeric/dimeric mixture of (**65**) afforded the *trans* alkene on treatment with three equivalents of ester ylide (**37e**), the reaction had required heating under reflux in benzene.[63] Hence, the reaction conditions that would be required for the intended keto stabilised phosphorus ylides were uncertain. As such it was proposed to test this revised approach with the commercially available glycoaldehyde dimer (**66**). The analogous reactions would then be repeated with optically active α-hydroxy aldehyde derivatives, to provide the desired substitution.

For (**65**), where 'Y' = methyl, no problems were foreseen as (**65**) is a known literature compound. For (**36**), where 'Y' = phenyl, it was thought that an alternate procedure would be required, see Chapter 5 for how this literature predicted obstacle was successfully overcome.

4.2   Testing the new methodology – the glycoaldehyde dimer.

Successful synthesis of γ-hydroxy enones derived form the glycoaldehyde dimer (**66**) would encourage further application of the new proposal. The enones would be optically inactive, and subsequently, the cyclopropanes generated by this technique would only be diastereomerically pure racemates. Despite this, the methodology to provide cyclopropanes from *trans* γ-hydroxy enones would be established.

It was expected that the glycoaldehyde dimer (**66**) would react with stabilised ylides (**37**) in the same way as reported for lactaldehyde (**65**).[63] Glycoaldehyde (**66**) was added in two portions to warm dry CH$_2$Cl$_2$ to ensure complete dissolution, prior to the addition of 1.05 equivalents of a keto ylide (**37a-c** or **37e**), under a nitrogen atmosphere. The corresponding 'hydrogen' enones (**67a-c** and **67e**) were cleanly formed after heating the solution under reflux, Scheme 41.
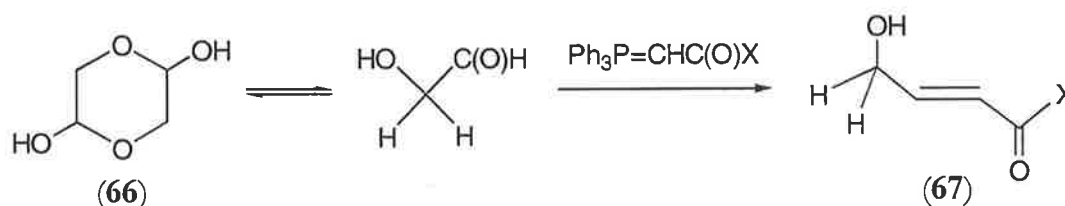
Where (a) X= CH$_3$
       (b) X= Ph
       (c) X= *t*-Bu
       (e) X= OCH$_3$

Scheme 41

After some initial experimentation it was observed that the rate of the reaction was dependant on the concentration of the dimer (**66**) in solution, as highlighted by the results presented in Table 13. Initially, attempts to reduce the 4 to 5 day reaction times were made by heating the solution at higher temperatures (e.g. heating under reflux in CHCl$_3$). Such conditions were not successful. However, decreasing the concentration of the glycoaldehyde dimer (**66**) actually increased the overall reaction rate. Reducing the concentration of the dimer (**66**) resulted in an increase in the concentration of the monomeric aldehyde (**66**), which is the reactive species in the Wittig reaction.

Interestingly, even a small change in concentration had a dramatic effect in the case of 'R' = Ph (**67b**), Entry 2 in Table 13.

Table 13. Comparison of concentration and reaction times for the formation of enones (**67a-b**).

	X	Enone	Concentrated		Dilute	
			Conc. (M)	Time (hr)	Conc. (M)	Time (hr)
1	CH₃	(**67a**)	0.37	96	0.13	4
2	Ph	(**67b**)	0.17	120	0.13	4

Provided that the concentration was maintained at 0.13 M, all of the enones (**67a-c** and **67e**) were synthesised within only four hours of heating under reflux. The experimental section of this thesis includes procedures for enone formation from dimer (**66**) under both concentrated and dilute conditions; not all reactions were repeated following the discovery of the concentration effect. Under the inert nitrogen atmosphere, the enones (**67a-c** and **67e**) were cleanly synthesised and were judged to be of greater than 90% purity by ^{1}H NMR spectroscopy.

Enones (**67a-c** and **67e**) were used without purification due to their instability, noted by their facile rearrangement to the isomeric dicarbonyl species (**68**) and an unidentified product mixture. The dicarbonyl (**68**) was not isolated, but identified by comparison with previous 1,4-diketone analogues (**46/54**). Additionally, the formation of (**68**) was later confirmed by its reaction with a stabilised ylide through a Wittig mechanism, see Chapter 6.

The *trans* γ-hydroxy enones (**67a-c** and **67e**) could only be partially purified prior to characterisation. The Wittig reaction by-product, triphenylphosphine oxide, was removed by precipitation from cold hexane and subsequent gravity filtration and the resultant oil was analysed in the crude state. This procedure was only employed for the procurement of samples for characterisation.

A CDCl₃ solution of each of the enones (**67a-c** and **67e**) was subjected to GCMS analysis, which displayed a signal corresponding to a protonated mass peak, as well as a fragmentation peak equivalent to the loss of a hydroxyl group. The infrared spectrum for

each analogue also exhibited the characteristic peaks expected for a free hydroxyl group and that for a *trans* alkene, Table 14. The frequency for a carbon-hydrogen out-of-plane deformation is expected between 970-960 cm^{-1} for a *trans* alkene, whilst for a *cis* alkene a much lower frequency (between 730-675 cm^{-1}) and intensity would be observed.[92] When the double bond is conjugated with a carbonyl group this band is often shifted to a higher frequency, as was observed in most instances.

Table 14. IR frequencies recorded for the *trans* enones (**67a-c** and **67e**).

Functional Group	(**67a**)[a] X = CH$_3$	(**67b**)[a] X = Ph	(**67c**)[a] X = *t*-Bu	(**67e**)[a] X = OCH$_3$
Hydroxyl	3390	3314	3331	3333
Alkene	997	957	1008	1019

[a] IR frequencies recorded in cm^{-1}.

The ^{1}H NMR spectrum for each of the *trans* γ-hydroxy enones (**67a-c** and **67e**) was simple and relatively easy to assign. Two-dimensional NMR experiments helped to confirm the signal assignment, however, in most instances the one-dimensional signal splitting pattern was used. Each enone/enester (**67a-e**) displayed two sets of doublets of triplets due to the two vinylic protons. The large doublet-coupling constant of between 15.4 and 16.0 Hz verified the *trans* geometry about the double bond,[77] whilst the second coupling varied in size as a result of either ^3J coupling for the CH$_2$C<u>H</u>=CH proton, and long-range ^4J coupling for the CH$_2$CH=C<u>H</u> proton.
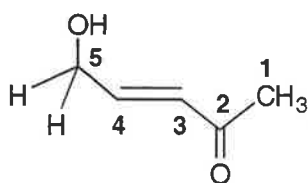
Figure 22. (*E*)-5-hydroxypent-3-en-2-one (**67a**).

For 5-hydroxypent-3-en-2-one (**67a**), Figure 22, a doublet of triplets due to H^3 exhibited a vinylic ^3J coupling constant of 16.0 Hz with H^4 and a long-range ^4J coupling constant of 2.0 Hz with the H^5 protons. This was within the expected range of 0-3.0 Hz for a CH=C–CH– system.[77] A second doublet of triplets for the H^4 proton, showed vinylic ^3J

coupling to H[3] of 16.0 Hz also, with a second ^3J coupling to the H[5] protons of 4.1 Hz. The methylene group protons (H[5]) appeared as a doublet of doublets, with ^3J coupling to H[4] (3.9 Hz) and long range ^4J coupling to H[3] (2.0 Hz).

Each of the four enones synthesised (**67a-c** and **67e**) displayed similar signals for the methylene group protons in the ^{1}H NMR spectrum, either an unresolved multiplet as for 4-hydroxy-1-phenylbut-2-enone (**67b**), or a doublet of doublets as seen for (**67a, 67c** and **67e**). The two-proton integration for these signals and the fact that the two coupling constants for each doublet closely matched the corresponding coupling of the vinylic protons, confirmed the correct assignment of these signals.

With the validity of this new approach to the target *trans* γ-hydroxy enone established, attention was turned to the next step in the research proposal. That is, utilisation of the proposed key intermediate (**67**) for the generation of diastereomerically pure substituted cyclopropanes.

4.3   Synthesis of the disubstituted diastereomerically pure cyclopropanes (69-72).

The ultimate endeavour of this research proposal was to successfully transform the synthesised *trans* γ-hydroxy enones into the corresponding functionalised cyclopropanes. It was originally postulated that treatment of such enones with stabilised ester ylides should result in the generation of cyclopropanes and with the test enones (**67a-c** and **67e**) in hand, it was now possible to put this proposal to trial.

Accordingly, a solution of 5-hydroxypent-3-en-2-one (**67a**) was prepared from glycoaldehyde (**66**) and 1-triphenylphosphoranylidene-2-propanone (**37a**), as detailed in the experimental section of this thesis. The solution was allowed to cool to ambient temperature, at which time 1.5 equivalents of benzyl (triphenylphosphoranylidene)acetate (**37f**) was added directly to the reaction mixture. As previously mentioned, the hydroxy enones (**67a-c** and **67e**) were susceptible to decomposition on attempted purification and were therefore used in their crude state. After heating under reflux for six days the reaction was complete (TLC), Scheme 42. Removal of the solvent *in vacuo* and analysis of

the crude mixture by ^{1}H NMR showed that more than one cyclopropyl derivative had formed. Sequential column chromatography provided pure samples of the major product, *trans* cyclopropane (69a) in a yield of 38 %, and the isomeric all *cis* cyclopropane (69b) in yield of 10% as the minor product, Entry 1 of Table 15. As a reaction yield for the enone intermediate (67a) could not be calculated, all cyclopropane yields are quoted over two steps, determined from the glycoaldehyde dimer (66).

The *trans* (69a):*cis* (69b) ratio of cyclopropane diastereomers was 4:1, a greatly reduced diastereomeric ratio than had been anticipated. Previous studies from 1,2-dioxine precursors (14) had typically afforded a diastereomeric excess of greater than 98%, or a 99:1 diastereomeric ratio.[49] It remains unclear as to why this large difference in diastereoselectivity was obtained.

$$(67a)\ X = CH_3$$
$$(67b)\ X = Ph$$
$$(67c)\ X = t\text{-Bu}$$
$$(67e)\ X = OCH_3$$

$$Ph_3P=CHCO_2R \quad (37e\text{-}f)$$

trans		*cis*
(69a)	X = CH$_3$, R = Bn	(69b)
(70a)	X = CH$_3$, R = OCH$_3$	(70b)
(71a)	X = Ph, R = Bn	(71b)
(72a)	X = t-Bu, R = Bn	(72b)
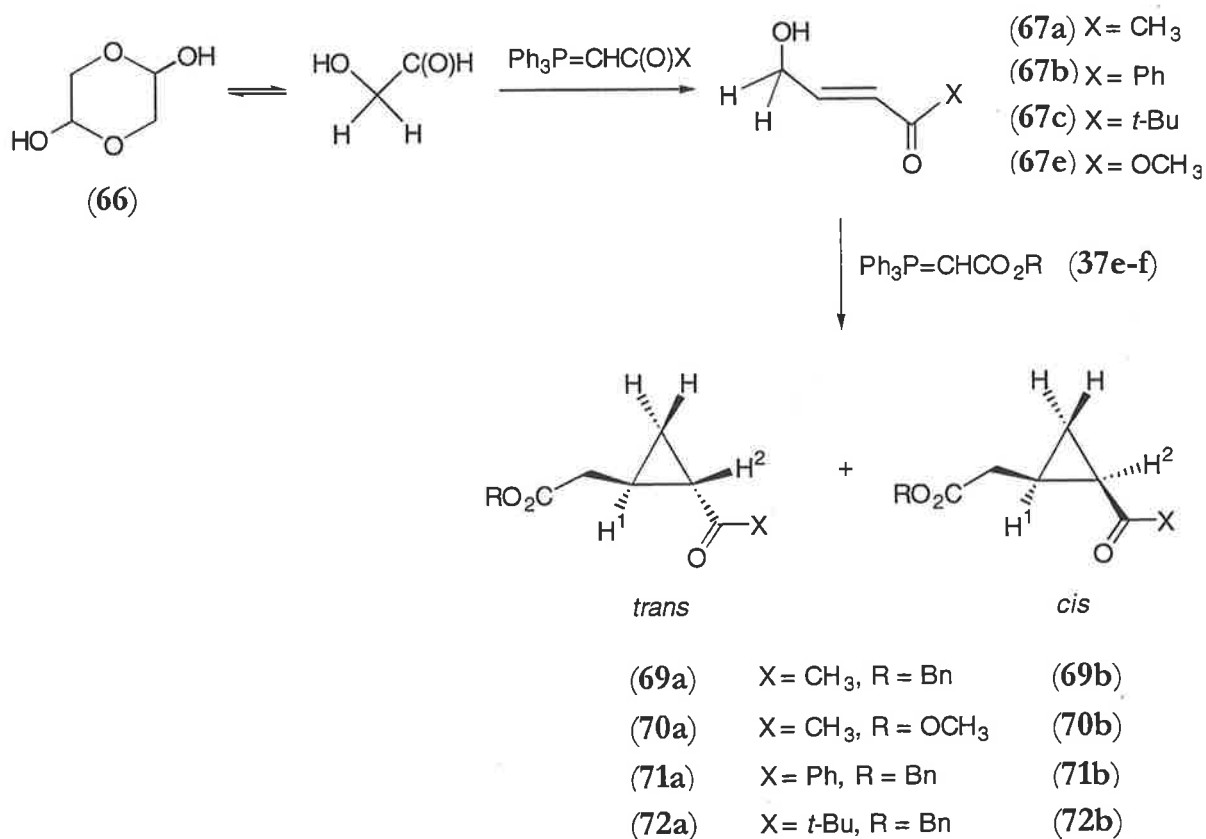
Scheme 42. One-pot synthesis of disubstituted cyclopropanes (69-72).

To further verify the potential of this newly established cyclopropanation methodology, a number of analogous experiments were performed. γ-Hydroxy enones (67b-c) containing varying substitution were employed to synthesise the corresponding disubstituted

cyclopropanes. In each instance, the cyclopropanation reactions were performed on the crude enone precursor in the one reaction vessel and under the standard conditions as set out for the synthesis of cyclopropane (**69**), Scheme 42 and Table 15.

Table 15. Formation of cyclopropanes from the glycoaldehyde dimer (**66**).

	X	Enone	R	Time (days)	Cyclopropane (yield, %)[a]	
					trans	*cis*
1	CH$_3$	(**67a**)	Bn	6	(**69a**) (38)	(**69b**) (10)
2	CH$_3$	(**67a**)	CH$_3$	8	(**70a**) (26)	(**70b**) (6)
3	Ph	(**67b**)	Bn	5[b]	(**71a**) (35)	(**71b**) (0)
4	*t*-Bu	(**67c**)	Bn	6.5[c]	(**72a**) (17)	(**72b**) (4)
5	OCH$_3$	(**67e**)	Bn	10	(**73a**) (0)	(**73b**) (0)

[a] Percentage yields quoted refer to the isolated yields calculated from (**66**). [b] Reaction performed at ambient temperature. [c] Reaction was less than 50% complete, as seen by ^{1}H NMR.

Entries 1-4 of Table 15 show the *trans* enones (**67a-c**) reacted with stabilised ester ylides (**37e-f**) to afford the corresponding cyclopropyl products. The reaction times ranged from 6-10 days and the product yields display only slight variations. Where both the *trans* and *cis* cyclopropanes were afforded, Entries 1-2 and 4, the diastereomeric ratio was approximately 4:1 *trans:cis*.

The optimum yield for cyclopropane (**71a**) was obtained from the phenyl keto enone (**67b**) when the reaction was carried out at ambient temperature, Table 15 Entry 3. The starting enone (**67b**) was generated under reflux conditions, however, if the cyclopropanation step was performed with heating under reflux a large increase in decomposition products was observed. Presumably, this was a result of the instability of enone (**67b**), emphasised by the increased conjugation with the phenyl ring, compared to that with a methyl group in (**67a**). An interesting result of this example was that only the *trans* cyclopropane (**71a**) was afforded, no *cis* isomer (**71b**) was detected in the crude product ^{1}H NMR spectrum. Such high diastereoselectivity is consistent with recent findings.[49]

The corresponding cyclisation reaction with (*E*)-4-hydroxy-1-*tert*-butylbut-2-enone (**67c**) provided a mixture of *trans* (**72a**) and *cis* cyclopropanes (**72b**) in low yield, Entry 4 in Table 15. The reaction was considerably slower than had been observed for other enones (**67a-b**) and was still incomplete after 6.5 days heating under reflux. Irrespective of this, the cyclopropanation was successful and the diversity of the methodology to various substitution patterns had been successfully established.

A further advantage of this methodology was the scale on which the reactions could be performed. While most of the experiments were carried out on approximately 150 mg of glycoaldehyde dimer (**66**), up to 1.5 g of dimer (**66**) was successfully transformed into cyclopropane. In principle, the simplicity of each synthetic step puts no limitation on the scale that the reactions could potentially be performed on.

Unfortunately, no cyclopropyl products (**73a** or **73b**) were obtained from the attempted cyclopropanation of enester (**67e**). As for previous cyclopropanations, the enester (**67e**) was treated with benzyl ester ylide (**37f**) and the reaction progress as monitored by TLC and ^{1}H NMR. After 10 days no cyclopropane products were evident and the reaction mixture consisted primarily of *trans* enester (**67e**). Complex mixtures of unidentified compounds were the only products evident, hence the mixture was discarded. The reactivity of enester analogues will be discussed in further detail in Chapter 5.

With the exception of the signals due to the 'X' and 'R' groups, each of the cyclopropanes (**69-72**) exhibited a very similar ^{1}H NMR spectrum. Two doublets of doublets were observed for the two geminal hydrogens on the methylene group . These two protons are chemically non-equivalent and resonate at different frequencies due to the adjacent chiral centre. H^2 appears as a doublet of doublets of doublets, as does each of the non-equivalent geminal hydrogens H^3 and $H^{3'}$ attached directly to the cyclopropane ring. The H^1 signal is more complex, appearing as an unresolved multiplet, however, it would be expected to be a doublet of doublets of doublets of doublets of doublets.

The assignments for the ^{1}H NMR signals were made through interpretation of the signal splitting patterns and coupling constants, indicative of the neighbouring protons, and, two-dimensional NMR spectroscopy. Table 16 displays a summary of this data for *trans* cyclopropane (**69a**), with the exclusion of the signals due to the benzyl group and the

methyl ketone protons, as they provide no insight into the structural conformation around the cyclopropyl ring.
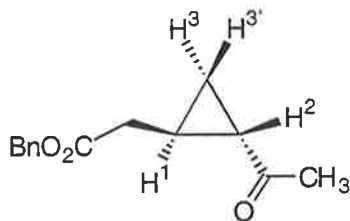
Figure 23. (±)-Benzyl (*trans*)-2-(2-acetylcyclopropyl)acetate (**69a**).

Table 16. One and two-dimensional 600 MHz NMR data for (**69a**), Figure 23.

δH (ppm)	Mult.	J (Hz)	COSY δH (ppm)	HSQC δC (ppm)	HMBC δC (ppm)	Assignment
2.49	dd	6.6 16.2	2.26 1.69	37.8	16.8 20.4 28.3 171.5	CHC$\underline{H}$-HCO$_2$
2.26	dd	7.8 16.2	2.49 1.69	37.8	16.8 20.4 28.3 171.5	CHCH-$\underline{H}$CO$_2$
1.82	ddd	4.2 4.2 8.4	1.69 1.31 0.82	28.3	16.8 20.4 28.3 171.5	H^2
1.69[a]	m	-	2.49 2.26 1.82 1.31 0.82	20.4	28.3 207.2	H^1
1.31	ddd	4.5 4.5 9.0	1.82 1.69 0.82	16.8	20.4 28.3 37.8 207.2	H^3
0.82	ddd	4.5 4.5 9.0	1.82 1.69 1.31	16.8	20.4 28.3 37.8 207.2	H$^{3'}$

[a] Multiplet resonance lies between δ1.71-1.66 ppm, centred around δ1.69 ppm.

The ^{1}H NMR spectrum for each of the corresponding *cis* cyclopropanes (**69b-70b** and **72b**) for each analogue synthesised, shows similar signals to that for the *trans* cyclopropanes. The chemical shift values vary between the geometric isomers, nonetheless, the spectra exhibit the same resonance signals. Depending on the resolution between each signal, for either the *trans* or *cis* analogues, some signals appear as multiplets where overlapping prevents the evaluation of coupling patterns and hence coupling constants.

For all of the *trans* cyclopropanes synthesised, at least one of either the H^1 or H^2 ^{1}H HMR signals was resolved such that the respective vicinal coupling constants could be calculated. However, all of the isomeric *cis* cyclopropanes isolated exhibited only unresolved multiplets in their ^{1}H HMR spectrum and as a result the vicinal coupling constants could not be determined. Generally, coupling between the vicinal protons on a cyclopropane ring occurs in the range of 4 – 9.5 Hz for a *trans* orientation, and 7 – 13 Hz for the *cis* geometry.[77] The average ^3J coupling constant for the *trans* cyclopropanes was 8.4 Hz, lying in the upper end of the range expected. On this basis and that these cyclopropanes were the major product of the cyclopropanations, it was believed that the initial *trans* assignment was correct. This was later confirmed through conversion of a *cis* cyclopropane to a rearranged by-product, discussed in Section 6.2.1.

The methylene protons of the benzyl group would be expected to appear as a singlet in the ^{1}H NMR spectrum, as for (**72a/b**), yet on some instances this signal was an AB quartet (AB$_q$). Each of the cyclopropanes (**69a/b** and **71a**) displayed AB quartets for these methylene protons. Whether the signal appears as a singlet or an AB$_q$ occurs by chance, depending on the difference at which the geminal protons come into resonance.[77]

The yields of the cyclopropanation reactions were quite low, even when accounting for the fact that they are quoted over two steps. It was proposed that this might be due in part to decomposition of the cyclopropane products over the duration of the reaction. ^{1}H NMR analysis of the crude product, for each reaction forming a benzyl ester derivative (**69** and **71-72**), revealed the presence of a singlet signal at approximately 4.7 ppm. This signal corresponds to the methylene group protons of benzyl alcohol, which would be the hydrolysis by-product of the cyclopropyl esters (**69** and **71-72**). Alternatively, hydrolysis of the benzyl ester ylide (**37f**) may have been the source of the alcohol.

Benzyl alcohol was also present in the purified product samples obtained from column chromatography and it was feasible the cyclopropane products may only have been undergoing hydrolysis on the acidic silica gel, employed for chromatography. However, the use of neutral florisil did not prevent this hydrolysis. If formed, the hydrolysed cyclopropyl acids would 'stick' to the column, hence they would not be, and indeed were not recovered following purification by chromatography.

In the hope of determining when the hydrolysis was occurring, both the *trans* (**74a**) and *cis* (**74b**) 2-(2-acetylcyclopropyl)acetic acids were independently synthesised. Basic hydrolysis of the precursor benzyl ester cyclopropanes (**69a** and **69b**) was achieved utilising potassium hydroxide with stirring over two days at ambient temperature, Scheme 43. Standard work-up procedures provided the *trans* cyclopropane (**74a**) in a yield of 66% and *cis* isomer (**74b**) in 68%. The ^{1}H NMR signals for the methyl ketone group protons resonated at 2.27 and 2.32 ppm, for the *trans* (**74a**) and *cis* (**74b**) products respectively.
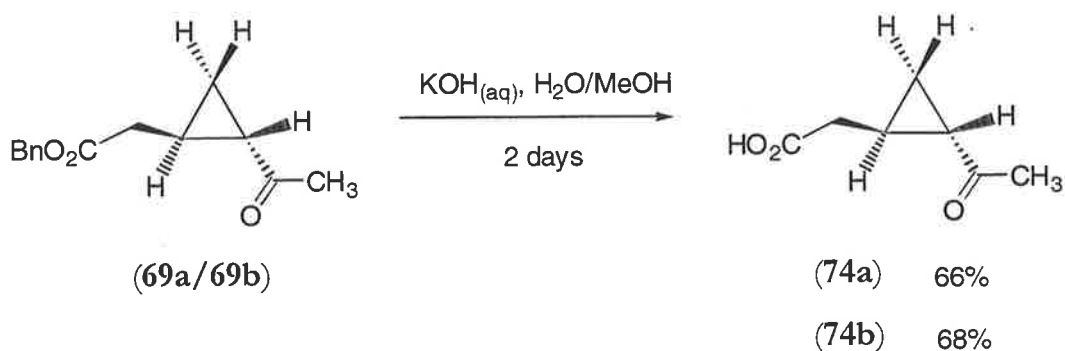
Scheme 43

It was intended that these signals would be used to determine whether or not any acid products were present in the crude product mixture. Disappointingly, no conclusive evidence could be found to either support or discount this proposition, due to the complexity of the corresponding region in the ^{1}H NMR spectrum. Despite this, it was evident that the cyclopropane yields were being significantly reduced due to hydrolysis and subsequent loss of product as the acid derivative. Whether the hydrolysis was occurring throughout the reaction or as a result of the purification techniques does not alter this.

Decomposition of the enone (**67**), prior to Michael addition with the ylide (**37e-f**), may also account for the low cyclopropane yield. Under the lengthy reaction conditions required it is feasible that the enone (**67**) may be decomposing through a mechanism akin to the Kornblum – De La Mare pathway,[80] highlighted in Section 2.3.1 and in Section 4.2 of this Chapter. The resultant 1,4-dicarbonyl species (**68**) contains an aldehyde functional group able to undergo a Wittig reaction with the ylide (**37e-f**) in solution. At this stage it was not possible to determine if any such products were present due to the complexity of the crude product ^{1}H NMR spectrum. However, the existence of the 1,4-dicarbonyl by-product (**68**) was later suggested by the isolation of Wittig olefination products, see Chapter 6.

5   Application of the new synthetic strategy: synthesis of optically pure cyclopropanes.

In Chapter 4 it was established that new proposal to reach the *trans* γ-hydroxy enone target via an α-hydroxy aldehyde was not only possible but highly successful. The test enones (**67a-c**) were synthesised smoothly from the precursor aldehyde dimer (**66**) and were shown to successfully yield cyclopropanes. The next stage was to apply this methodology to the synthesis of the 'elusive' optically pure *trans* γ-hydroxy enones (**17/39**) and subsequently to the corresponding enantiomerically pure trisubstituted cyclopropanes (**16**).

5.1   Synthesis of the *trans* γ-hydroxy enones.

As discussed in Chapter 4, the literature indicates that there are inherent problems associated with the synthesis of α-hydroxy aromatic aldehydes.[63] Therefore, the first intended targets employing this new approach were designated as those derived from the known α-hydroxy lactaldehyde (**65a**).

5.1.1   Synthesis of α-hydroxy lactaldehyde (**65a**) derived *trans* γ-hydroxy enones (**39**).

S-(-)-α-*tert*-Butyldimethylsilyloxy-lactaldehyde (**43a**) had previously been synthesised in excellent yield from *S*-(-)-ethyl lactate (**38a**), Section 2.2.3. All that was required to afford the corresponding α-hydroxy aldehyde (**65a**) was simple cleavage of the silyl group, which should provide a mixture of the monomer and dimer of (**65a**).

The analogous deprotection reaction on silyl ether (**43a**) has been reported in the literature to afford aldehyde (**65a**), through the use of aqueous hydrogen fluoride (HF) as the deprotecting reagent.[65] The only difference between this procedure and the original citation by Newton *et al.*,[93] was that the reaction was reportedly carried out in dry acetonitrile.

Following the literature deprotection procedure, a solution of α-silyloxy-lactaldehyde (**43a**) in dry acetonitrile was treated drop wise with 5 equivalents of aqueous HF, at ambient temperature.[65] The reaction was quenched with the addition of solid sodium hydrogen carbonate (NaHCO₃). and the crude deprotected α-hydroxy propanal (**65a**) was obtained following filtration and removal of the solvent *in vacuo*. Due to the known instability of the aldehyde (**65a**), no further purification was attempted. The crude hydroxy aldehyde (**65a**) was used immediately upon synthesis, following the methodology developed with the test compound, glycoaldehyde dimer (**66**), Section 4.2-4.3. Interestingly, if non-dried acetonitrile was substituted for the anhydrous solvent, the product yield was reduced under otherwise identical conditions. A justification for this phenomenon is unknown at this stage.

The ¹H NMR spectrum of α-hydroxy lactaldehyde (**65a**) was extremely complex, owing to both the monomer and dimer existing in solution. Nevertheless, a signal corresponding to the monomeric aldehyde proton was clearly evident at 9.6 ppm. It is worth mentioning at this point, that reduction of the starting ester (**38a**) directly to the hydroxy aldehyde (**65a**) without protection of the hydroxyl group was attempted, however, no α-hydroxy lactaldehyde (**65a**) was obtained on any occasion.

The weight of the crude product (**65a**) was used to calculate the number of moles of reagent required for the next step in the reaction pathway. This calculation was dependent on the deprotection proceeding in 100%, however, as no purification was possible a more accurate yield could not be determined. Dissolution of crude aldehyde (**65a**) in dry CH₂Cl₂ and treatment with a stabilised ylide (**37a-e**) in 1.05 equivalents, was followed by heating the solution under reflux for five hours, Scheme 44. Each of the olefination reactions was complete after this time period, irrespective of the ylide employed. The aldehyde concentration did not prove to be as crucial to the reaction rate from lactaldehyde (**65a**), unlike the situation with glycoaldehyde dimer (**66**). Presumably, this was due to a higher proportion of the monomer (**65a**) existing in solution.

These reaction conditions proved to be far superior to those employed by Craig, which utilised three equivalents of ylide and required five hours of heating under reflux in benzene.[63] Initially, benzene was trialed as the reaction solvent to enable a direct

comparison with the literature, nonetheless, the optimised conditions developed for the synthesis of the test enones (**67a-c** and **67e**) were substantially more effective.
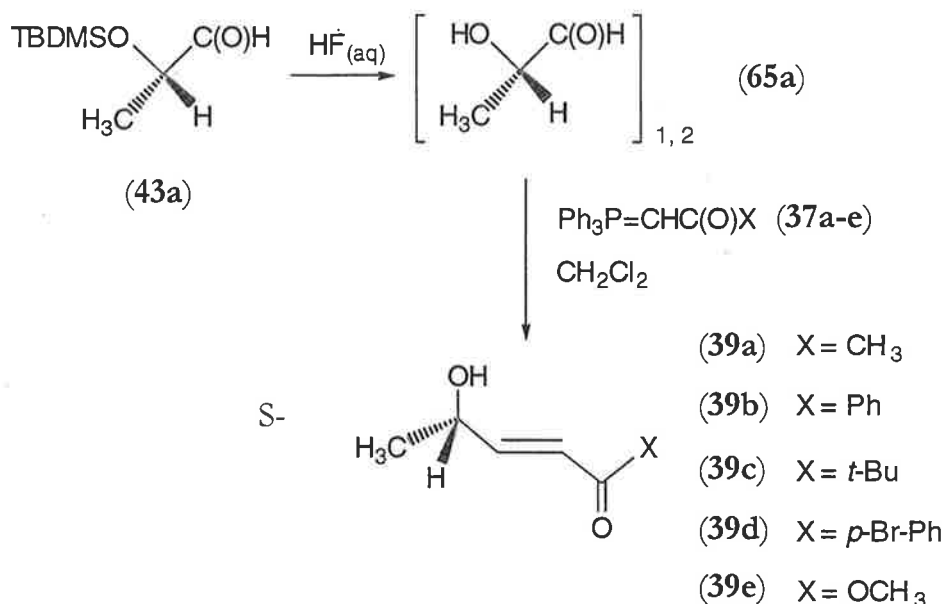
Scheme 44

More importantly, the new reaction pathway had finally generated the targeted *trans* γ-hydroxy enones (**39a-e**). Whilst all previous attempts to synthesise these enones (**39a-e**) from the silyl-protected analogues (**44/45**) had failed, Sections 2.2-2.3, variously substituted optically pure γ-hydroxy enones had now been afforded, Scheme 44.

Triphenylphosphine oxide was removed by precipitation from hexane and gravity filtration. Any further attempt at purification resulted in Kornblum-De La Mare type decomposition of the enone to the corresponding 1,4-diketone (**46a** and **54b-e**) or furan (**55a-d**),[80] seen previously as the major products from deprotection of the TBDMSO-protected derivatives (**45**), Section 2.3.2. The *tert*-butyl (**54c**) and *para*-bromophenyl (**54d**) substituted 1,4-diketones were not isolated or characterised, but identified by comparison with isolated samples of the phenyl substituted derivative (**46a**). Each displayed two characteristic triplet signals in the ^{1}H NMR spectrum due to the two non-equivalent methylene group protons. Similarly, the furan by-products containing *tert*-butyl (**55c**) and *para*-bromophenyl (**55d**) substitution were identified from previously isolated structural analogues.

On some occasions a small amount of the 1,4-diketone (**46/54**) was evident in the crude mixture at the completion of the reaction, this was thought to be a result of the slight excess of the ylide (**37**) acting as a base in solution. Samples of the *trans* γ-hydroxy enones (**39**) for characterisation were partially purified in the above manner, whilst the crude enones were employed for subsequent transformation without purification. Enone samples used for conversion to the next product in the reaction pathway were typically greater than 85% pure by ^{1}H NMR. A small amount of unknown impurities were often present, which were presumed to be either polymerisation products or by-products from the hydroxy aldehyde (**65a**) formation reaction. A solution of the hydroxy enone (**39**) decomposed on standing to the decomposition products (**46/54** and **55**) and was therefore used immediately upon its synthesis.

Each of the γ-hydroxy enones (**39a-e**) synthesised exhibited the anticipated signals in their respective ^{1}H NMR spectrum. Two doublets of doublets were present between 7.2 and 6.0 ppm due to the two olefinic protons. The vinylic coupling constants were consistent with a *trans* orientation about the carbon-carbon double bond, lying between 16.2 and 15.3 Hz. The methine group protons bearing the hydroxyl group resonated at around 4.5 ppm and appeared as either a doublet of doublet of quartets or an unresolved multiplet, due to ^3J and long-range ^4J coupling with both of the alkene protons. The methyl group protons at the hydroxy terminus, resonated at approximately 1.3 ppm with a doublet coupling constant of 6.6 Hz, with one exception. The methyl group protons for 1-*tert*-butyl-4-hydroxypent-2-en-1-one (**39c**) resonated at 1.14 ppm and appeared as a singlet at both 300 and 600 MHz. Figure 24 displays the ^{1}H NMR spectrum for 5-hydroxy-5-methylpent-3-en-2-one (**39a**), illustrating each of the above signals common to all of the enones (**39a-e**) synthesised.

Two-dimensional NMR spectroscopy (including COSY, HMQC and HMBC) confirmed the ^{1}H NMR signal assignments and was also used to determine the corresponding ^{13}C NMR signals. For instance, the ^{13}C NMR aromatic signals for the phenyl keto enone (**39b**) were differentiated where possible, from the residual triphenylphosphine oxide and unreacted ylide in solution. This was achieved using analogous techniques to those described for the assignment of the diastereotopic signals of the hydrochlorin adducts (**56/57**), Section 3.2. As noted in the experimental section of this thesis, this

differentiation was not always possible and any ambiguous signals have been omitted. The COSY, HMQC and HMBC spectrum for enone (**39a**) have been included in the Appendix.
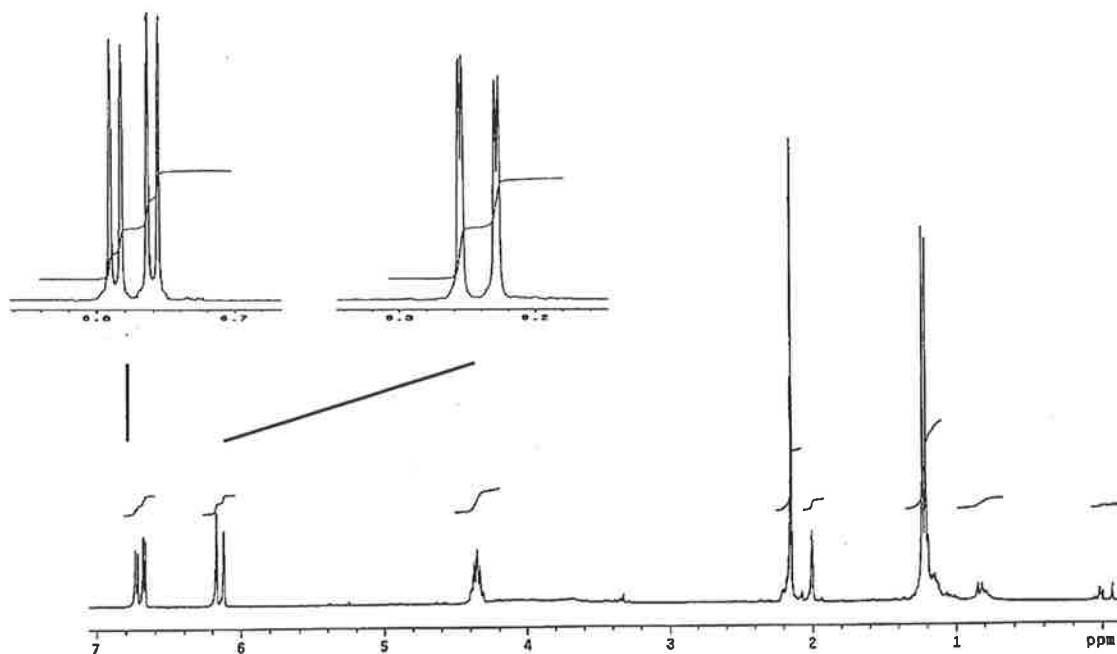
Figure 24. 300 MHz ^{1}H NMR spectrum for *trans* γ-hydroxy enone (**39a**), and 600 MHz expansion of the two olefinic protons.

Optical rotation measurements were conducted for the methyl keto (**39a**) and phenyl keto (**39b**) enones only, on account of these samples being afforded in higher purity compared to (**39c-d**), as determined by ^{1}H NMR. Both enones displayed a positive specific rotation, thus demonstrating that the samples were optically active. These values have not been quoted in the experimental section as they can not be taken as absolute due to the fact that the samples were not 100% pure.

Enantiomeric purity calculations were not carried out for the lactate enones (**39a-e**) due to their instability and the presence of impurities, albeit in a low concentration. Chiral shift NMR experiments did not provide clear separation of the diastereotopic signals due to the presence of other compounds in solution and the complexity of the spectrum. Despite this, the enantiomeric excess was assumed to be high by reasoning that the enantiomeric excess of subsequent cyclopropyl products was excellent, see later Section 5.4.

Finally, the alternate synthetic strategy had provided the target intermediate *trans* γ-hydroxy enones (**39**) smoothly and in good yields. Generation of α-hydroxy lactaldehyde (**65a**) had proven to be relatively easy as suggested by the literature. The next obstacle to overcome, was synthesis of the highly unstable α-hydroxy phenylacetaldehyde (**36**).

5.1.2   Synthesis of α-hydroxy mandelaldehyde (36) derived *trans* γ-hydroxy enones (17).

In order to keep the reaction pathway to a variety γ-hydroxy enones simple and generic, it was hoped that the methodology employed for the synthesis of the lactate derived enones (**39**) could be modified to accommodate for the formation of mandelate derived enones (**17**). The only foreseeable problem was the formation of the intermediate α-hydroxy mandelaldehyde (**36**). If the reported rearrangement of the aromatic hydroxy aldehyde (**36**) to the hydroxy ketone (**34**)[63] could not be prevented, it was doubtful that this new strategy would afford the desired enones (**17**).

The racemic TBDMSO-protected mandelaldehyde (**42**) had previous been synthesised in excellent yields following the standard procedure as for lactaldehyde (**43a**), Section 2.2.2. It was envisaged that deprotection of (**42**) may be achievable, provided that the optimum conditions to stabilise the free hydroxyl derivative (**36**) could be found. The literature states that even under very slightly basic conditions, the rearrangement to ketone (**34**) proceeds.[63] With this in mind, the acidic HF deprotection conditions were trialed to see what effect, if any, they would have on the isolation of the desired hydroxy aldehyde (**36**).

Under the same conditions as employed for the synthesis of α-hydroxy lactaldehyde (**65a**), silyloxy mandelaldehyde (**42**) was dissolved in dry acetonitrile and treated with 5 equivalents of aqueous HF at ambient temperature. The reaction was quenched with the addition of $NaHCO_3$ after 15 minutes stirring and then left to stir until all effervescing had ceased, approximately 25 minutes. The crude reaction mixture was worked-up by an analogous technique as for (**65a**) and analysed by ^{1}H NMR spectroscopy. No deprotection had taken place and the protected aldehyde (**42**) was the only recovered material.

The reaction was repeated with the same reagents and left to stir for 15 hours, whilst checking the reaction progress by ^{1}H NMR every 3 to 4 hours. A small aliquot was removed, CH_2Cl_2 was added and the solution washed with water prior to concentration *in vacuo*. The ^{1}H NMR spectrum for each sample showed progressive formation of a singlet at 9.6 ppm, indicating that the α-hydroxy aldehyde (36) was indeed forming, along with a reducing percentage of the precursor protected species (42). After 15 hours no starting material (42) remained; the crude mixture consisted of what was thought to be the target hydroxy aldehyde (36) and a significant proportion of the rearranged hydroxy ketone (34). The ^{1}H NMR spectrum was complicated due to the mixture of compounds present and presumably, due to the presence of the dimer of aldehyde (36). The ketone by-product (34) was clearly evident as a major constituent by the presence of a broad doublet at 3.50 ppm, known to be a result of the methylene protons for (34).[63]

Whilst the major product was the rearranged hydroxy ketone (34) as expected, the trial had been successful in providing at least some of the deprotected α-hydroxy mandelaldehyde (36). The deprotection was repeated, alternately varying the reaction conditions including the concentration, reaction time, mole equivalents of HF and work-up procedure. It was believed that while formation of aldehyde (36) was occurring, quenching of the excess HF with the mildly basic $NaHCO_3$ was causing the undesirable rearrangement to ketone (34). By reducing the number of mole equivalents of HF employed, the basic work-up could be avoided. Therefore, the reaction was performed with no work-up procedure beyond concentration under reduced pressure, after 3.5 hours stirring at ambient temperature. Any residual HF was left in the crude product, which exhibited a complex ^{1}H NMR spectrum as a result of the monomeric and dimeric mixture of α-hydroxy aldehyde (36).

The existence of the dimeric aldehyde (36) was assumed on the basis of the comparative dimerisation of lactaldehyde (65a), and by analysis of the ^{1}H NMR spectrum. Deprotection of silyloxy aldehyde (42) can result in the formation of three possible products: hydroxy ketone (34), the deprotected monomer (36) and/or the dimerised species (36). By a process of elimination, if no ketone (34) was present then the complexity of the ^{1}H NMR spectrum was most likely due to the presence of a mixture of both the monomer and dimer of α-hydroxy aldehyde (36).

Finally, the ideal conditions were determined which provided the α-hydroxy mandelaldehyde (**36**). No hydroxy ketone (**34**) was observed in the spectrum and to ensure no decomposition occurred, the crude product (**36**) was used immediately with no purification. The successful synthesis of hydroxy aldehyde (**36**), against the indications of the literature, meant there was now potential to meet another of the aims of this research; that is, the development of a general strategy to provide variously substituted *trans* γ-hydroxy enones (**17/39**).

Initially, the same conditions were trialed for the Wittig olefination reaction on deprotected mandelaldehyde (**36**) as were employed for the synthesis of the γ-hydroxy enones (**39**) from hydroxy lactaldehyde (**65a**). These conditions did at last provide the *trans* γ-hydroxy enones (**17**), however, a significant amount of decomposition of the enone (**17**) was occurring.

After heating the solution under reflux for five hours with 1.05 equivalents of ylide (**37**), the corresponding 1,4-diketone (**46**) was formed in a higher percentage than the target enone (**17**). It was discovered that this could be overcome by reducing the number of ylide (**37**) equivalents to slightly less than 1, and by reducing the reaction time to only two hours. After this time, analysis of the crude product by ^1H NMR showed the *trans* γ-hydroxy enone (**17**) formation was complete, Scheme 45.
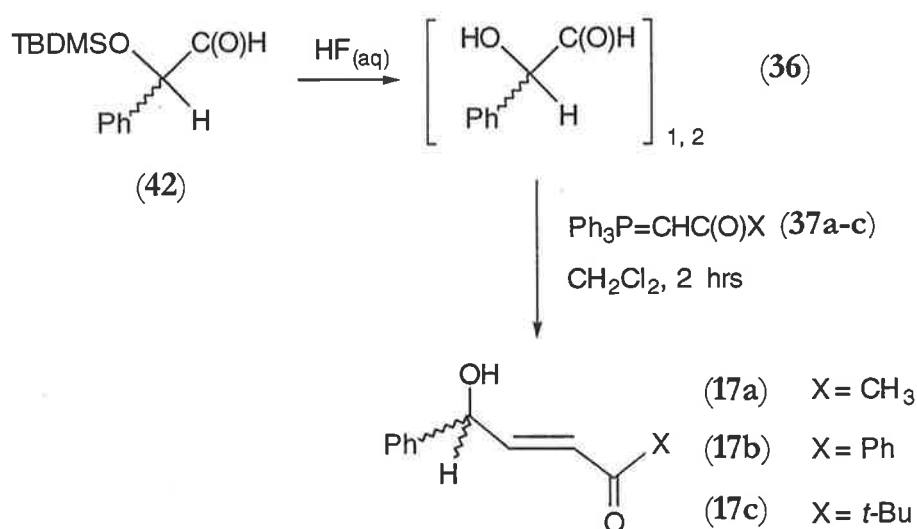
Scheme 45

Even under these optimised conditions, a small amount of the 1,4-diketone (**46a-c**) was still formed on some occasions, indicating the greater instability of the mandelate (**35**) derived enones (**17a-c**), compared to that of the lactate (**38**) derived enones (**39a-e**). This apparent 'hypersensitivity' was further demonstrated when attempts to partially purify the enones (**17a-c**), through precipitation of the by-product triphenylphosphine oxide, resulted in the almost complete decomposition of (**17a-c**) to either 1,4-diketone (**46a-c**) or furan (**51a-c**).

As such, none of the phenyl enones (**17a-c**) where purified and were used for subsequent transformations in their crude state. Accordingly, characterisation was performed on the crude enones (**17a-c**). Each enone (**17a-c**) was subjected to GCMS analysis in a CDCl₃ solution, ready for NMR spectroscopy. While each recorded a fragment ion peak associated with the loss of a hydroxyl group, only methyl keto enone (**17a**) showed a molecular ion peak. The phenyl keto (**17b**) and *tert*-butyl keto (**17c**) enones exhibited a MH⁺ and an M-H⁺ signal respectively.

The ¹H NMR spectrum for enones (**17a-c**) was not adversely effected by the presence of triphenylphosphine oxide, as all of the related proton frequencies resonate in the aromatic region. However, this impurity did complicate the interpretation of the ¹³C NMR spectrum. COSY, HMBC and HMQC spectroscopy were utilised to determine the correct signal assignments for the ¹³C and ¹H NMR signals. Where impurities rendered the designation of signals too difficult, especially the aromatic carbon signals, they have not been included in the experimental section for the relevant enone (**17a-c**).

The ¹H NMR spectrum for each of the mandelate enones (**17a-c**) was very similar to the lactate enones (**39a-e**), with the main exception being the signal for protons of the methine group bearing the hydroxyl group. Due to the replacement of the terminal methyl group with the phenyl grouping, the signal for the methine protons now appeared as only a doublet of doublets, at approximately 5.45 ppm. The down field shift of the signal was due to the intrinsically electron withdrawing nature of the adjacent aromatic ring.

It was postulated in Chapter 2, that the synthesis of the *trans* γ-hydroxy enones (**17a-b**) would help to establish the identity of the unknown deprotection products (**49a-c** and
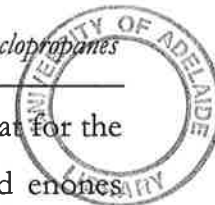
50a-b). Whilst both the ^{1}H and ^{13}C NMR data for (**17a-b**) were very similar to that for the unidentified compounds obtained from deprotection of the TBDMS-protected enones (**45**), none were equivalent. As such, the unknown compounds (**49a-c** and **50a-b**) remain unidentified.

5.2   The optically pure trisubstituted cyclopropanes.

The final synthetic aim of this research was the synthesis of optically pure functionalised cyclopropanes. Now that the methodology for the generation of optically pure *trans* γ-hydroxy enones   (**39**)   had been established it was time to attempt the ultimate goal. The lactaldehyde derived enones (**39a-e**) were selected first for cyclopropanation, as they had been synthesised optically pure, the mandeladehyde derived enones (**17a-c**) had only been generated as racemic mixtures at this stage.

5.2.1   Synthesis of the 3-methylcyclopropane derivatives (16, 76, 78, 80 and 81).

1-Phenyl-4-hydroxybut-2-enone (**39b**) was formed from the reaction of α-hydroxy lactaldehyde (**65a**) and phenyl keto ylide (**37b**) in dry CH_2Cl_2, as described in Section 5.1.1 above. The intermediate enone (**39b**) was not purified but used in the following cyclopropanation step in the crude state. Benzyl ester ylide (**37f**) was added directly to the reaction mixture and heating under reflux was continued for an additional 7.5 days. Aliquots of the reaction mixture were periodically removed and analysed by ^{1}H NMR over this time, which indicated that no observable enone (**39b**) remained in solution after one week.

Trials were performed where the enone (**39b**) was concentrated *in vacuo* and a higher boiling solvent was added, for example benzene or toluene. This resulted in the consumption of the enone (**39b**) at a faster rate; however, the proportion of by-product formation was significantly higher. The optimum conditions for cyclopropane formation were determined to be the simple one-pot technique, from the crude enone (**39b**) to cyclopropane (**16**), with heating under reflux at approximately 40 °C.

Analysis of the crude reaction products by ¹H NMR revealed that the cyclopropanation reaction had been successful. The major product was the *trans* cyclopropane (**16a**), which had formed along with a mixture of products including the all *cis* cyclopropane (**16b**), 1,4-diketone (**46a**) and the rearranged enolene isomer (**16c**), see later for identification and mechanism of formation of (**16c**). No furan (**54a**) was observed in the crude product mixture, which is consistent with the non-acidic nature of these mixtures.

The work-up procedure employed was modified from that used for the isolation of the disubstituted cyclopropyl derivatives (**69-72**). Following removal of the CH₂Cl₂ solvent under reduce pressure, hexane was added to remove the two equivalents of the by-product triphenylphosphine oxide. The crude oil obtained was then subjected to a squat column packed with TLC silica. The reaction products were collected together in one fraction, separate from any residual triphenylphosphine oxide, ylides (**37b**) and (**37f**), and 1,4-diketone (**46a**). The major products exhibited R$_f$ values in the range of 0.40 and 0.33, in the 10:2 hexane:EtOAc eluting solution, allowing for their ready separation from the lower R$_f$ impurities.

Pure *trans*-benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**) was obtained in 29% yield as a white crystalline solid, following recrystallisation from hot heptane. Subsequent column chromatography on the recovered mother liquor provided samples of the pure acyclic enolene (**16c**) and mixtures of (**16c**) and *cis* cyclopropane (**16b**), in a combined yield of 4%. Whilst these percentage yields are considerably low, it must be remembered that they are quoted over two steps. The weight of the crude α-hydroxy aldehyde (**65a**) was used to determine the final cyclopropane yield as neither the aldehyde (**65a**) nor the intermediate enone (**39b**) could be purified. This calculation must also assume that the aldehyde (**65a**) itself formed in 100% purity.

Optically pure *trans* cyclopropane (**16a**) exhibited an interesting ¹H NMR spectrum, which has been reproduced in Figure 25. As was observed for the disubstituted analogues (**69-72**), the two non-equivalent diastereotopic methylene protons appeared as two doublets of doublets. The adjacent chiral center, which forms a part of the cyclopropane, renders these two protons chemically non-equivalent resulting in the observed splitting pattern as each couples with the H² and their geminal partner. Unlike cyclopropanes (**69-72**), the

signal for H^2 is a doublet of doublets. However, the two doublet coupling constants are identical, which results in the signal presenting as a triplet. Both of the signals for H^1 and H^3 are unresolved multiplets, due to extensive ^3J coupling with adjacent protons. H^1 is coupled to four different protons, while H^3 would be expected to appear as a doublet of doublets of quartets. The only other substituent that is coupled to any of the protons attached to the ring is the methyl group, whose protons appear as a doublet. The methylene group protons, forming a part of the benzyl group, appear in the spectrum as a singlet, whilst the two phenyl ring protons signals appear as multiplets in a range between 7.95 and 7.29 ppm.
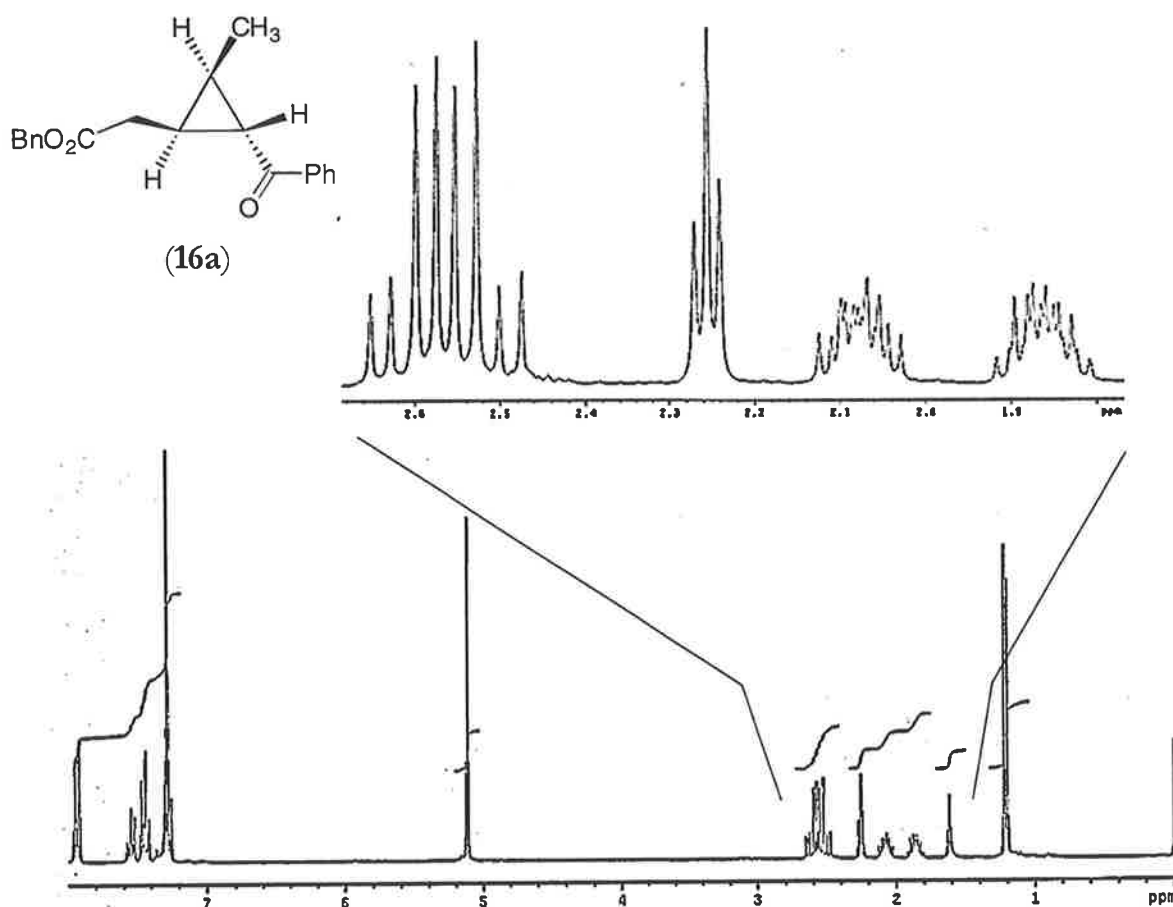
Figure 25. 300 MHz ^{1}H NMR spectrum for the inaugural enantiomerically pure trisubstituted cyclopropane, (-)-*trans*-benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**), see also Table 17.

More convincing was the evidence provided by the fragmentation pattern of the target *trans* cyclopropane (**16a**), obtained from mass spectrometry. Whilst the molecular ion peak had a very low relative intensity of 0.5, the fragmentation peaks correlated with the loss of the benzyl, benzyl ester and phenyl keto groups. Further, microanalytical analysis

confirmed the structural composition to within 0.14% for carbon and 0.02% for hydrogen.

The all *cis* cyclopropane (**16b**) proved to be unstable, slowly undergoing an enolene rearrangement to enolene (**16c**) at ambient temperature. As a result of this instability, complete characterisation of *cis* (**16b**) was not possible. The experimental section of this thesis includes the 600 MHz ^{1}H NMR spectrum data for (**16b**), which was obtained by exclusion of the proton signals corresponding to the isomeric enolene (**16c**). The proton signals for *cis* cyclopropane (**16b**) were similar to those for the *trans* cyclopropane (**16a**), as would be anticipated for geometric isomers. Both the similarities and differences between (**16a**) and (**16b**) are clearly evident from inspection of the information presented in Table 17. Heating a CDCl$_3$ solution of the mixture of (**16b**) and (**16c**) at 55°C over three days resulted in the complete transformation of (**16b**) to (**16c**).

The mechanism for the formation of the enolene isomer (**16c**) is presented in Scheme 46 below and has been noted in the literature.[94] This rearrangement can only occur from the all *cis* cyclopropane (**16b**), whereby the keto and ester groups are on the same face of the ring. In this conformation, the lone pair of electrons on the carbonyl oxygen of the keto group are able to remove a proton from the nearby methylene group. Subsequent rearrangement and ring opening of the cyclopropane affords the open chain isomer (**16c**). This accounts for the observed stability of the *trans* isomer (**16a**), in which the aforementioned substituents are on opposite sides of the cyclopropyl ring and are unable to undergo such a rearrangement.
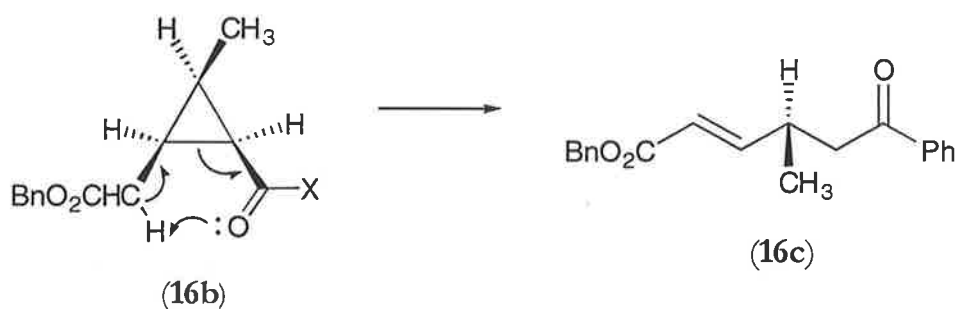
Scheme 46

One difference between the ^{1}H NMR spectrum of the *trans* and *cis* cyclopropanes (**16**) was the signal for the methylene protons of the benzyl group. For each isomer these protons

resonate around 5.1 ppm, yet the appearance of the signal is very different. The *trans* cyclopropane (**16a**) displays a singlet as anticipated for a CH_2 group with no protons on neighbouring carbon atoms. On the other hand, the *cis* cyclopropane (**16b**) exhibits an AB_q for the same protons. The appearance of the methylene protons as either a singlet or an AB_q occurs by chance depending on the difference at which the protons come into resonance.

The most important difference between ^1H NMR spectrum of the (**16a**) and (**16b**) cyclopropanes are the coupling constants observed between the two methine protons (H^1 and H^3), directly attached to the cyclopropyl ring. Only the signal for H^2 can be used to confirm the relative orientation of the cyclopropyl substituents, as it is the only fully resolved signal, see Table 17. The corresponding coupling constants are 4.5 Hz for *trans* (**16a**) and 8.8 Hz for *cis* (**16b**), confirming the geometrical assignment of the isomeric cyclopropyl products.[77]

Table 17. 600 MHz ^1H NMR data for the *trans* (**16a**) and *cis* (**16b**) cyclopropanes, with the exclusion of the aromatic protons.

trans cyclopropane (**16a**)			Assignment	*cis* cyclopropane (**16b**)		
δ (ppm)	Mult.	J (Hz)		δ (ppm)	Mult	J (Hz)
5.12	s	-	C$\underline{H}_2$Ph	5.10 & 5.08	AB_q	12.6
2.62	dd	7.1 16.1	CHC$\underline{H}$-HCO$_2$	2.99	dd	7.8 17.6
2.52	dd	8.1 16.1	CHCH-$\underline{H}$CO$_2$	2.91	dd	6.8 17.6
2.26	dd	4.5 4.5	Ph(O)CC$\underline{H}^2$	2.80	dd	8.8 8.8
2.08	m	-	C$\underline{H}^1$CH$_2$CO$_2$	1.93	m	-
1.87	m	-	C$\underline{H}^3$CH$_3$	1.83	m	-
1.21	d	6.3	CHC$\underline{H}_3$	1.21	d	6.0

Chemical shift values for the multiplet signals are quoted as the center of the range.

Now that this new methodology had been firmly established and proven to provide for the synthesis of benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**), as the major

product, the ability of the technique to accommodate for the formation of variously substituted cyclopropanes needed to be investigated. With this in mind, all of the previously synthesised enones (**39a-e**) derived from *S*-(-)-ethyl lactate (**38a**), were subjected to the identical cyclopropanation conditions as described for the synthesis of (**16**).

A freshly synthesised sample of the enone (**39**) in a CH_2Cl_2 solution was treated with 1.5 equivalents of the methyl (**37e**) or benzyl ester ylide (**37f**) *in situ*, Scheme 47 and Table 18. The reaction mixture was heated under reflux until no enone (**39**) remained, as seen by ^1H NMR. The solvent was removed *in vacuo* and the crude product was firstly treated with hexane to remove the triphenylphosphine oxide, secondly, run through a squat column to remove impurities, and finally, subjected to sequential column chromatography until samples of each of the *trans* cyclopropane (**a**), *cis* cyclopropane (**b**) and enolene (**c**) were obtained as pure as possible.
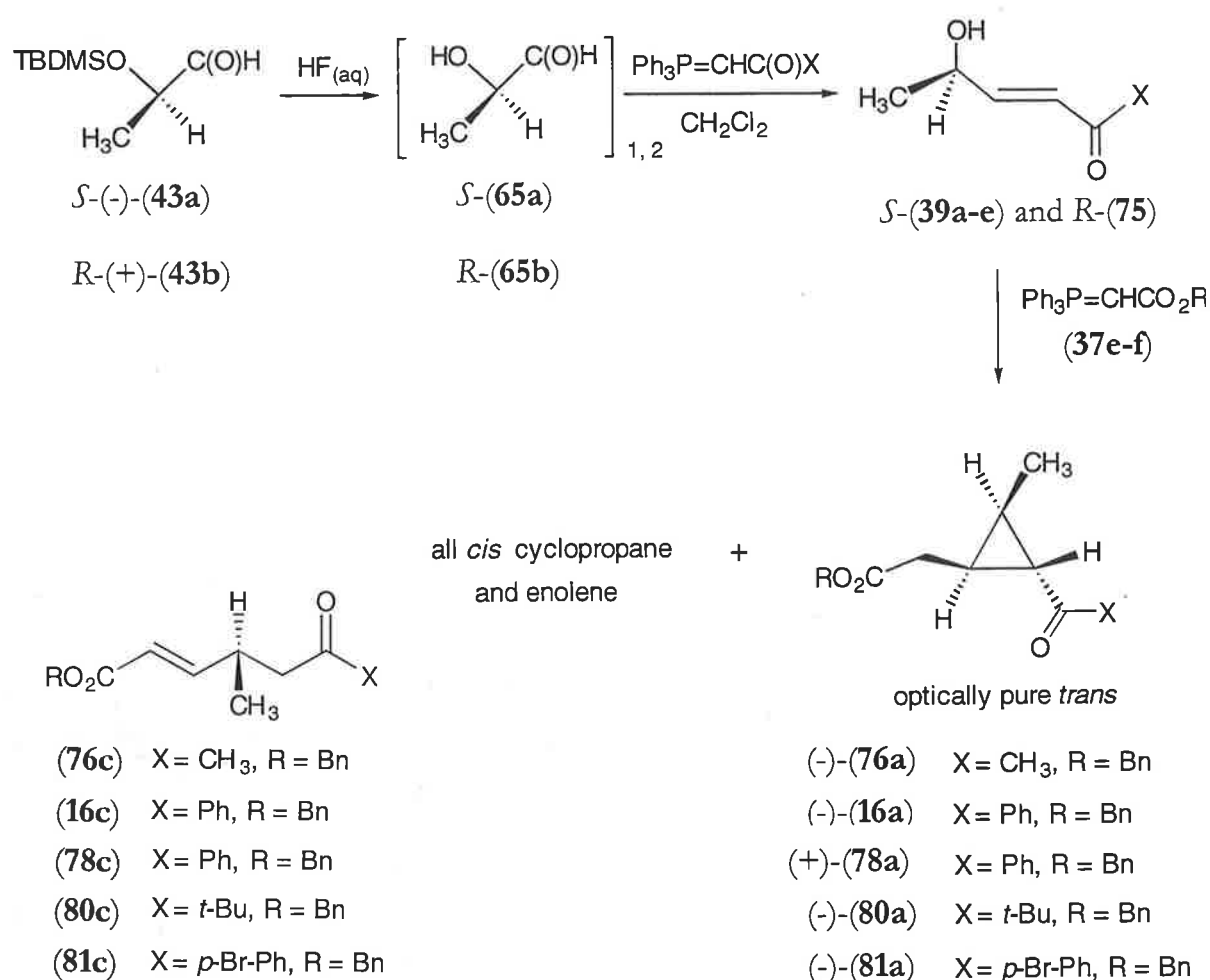
Scheme 47

The (+) enantiomer of *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**78a**) was synthesised to enable the comparison of an enantiomeric pair of cyclopropanes, that is (-)-(**16a**) and (+)-(**78a**). This was achieved following the standard methodology, whereby R-(+) methyl lactate (**38b**) was protected as the TBDMSO-ether (**41b**), and subsequently reduced to provide R-(+)-silyloxy lactaldehyde (**43b**). The reduction was similarly performed using DIBAL-H, however, a lower yield of only 62% was obtained. Deprotection with aqueous HF afforded R-α-hydroxy aldehyde (**65b**), which was converted to the corresponding R-1-phenyl-4-hydroxypent-2-enone (**75**) on treatment with phenyl keto ylide (**37b**), under standard reaction conditions. Cyclopropanation to yield the (+) *trans* cyclopropyl enantiomer (**78a**) was achieved in a comparatively good yield of 34%, Scheme 47 and Entry 4 in Table 18.

Table 18. Formation of enantiomerically pure cyclopropanes from optically pure *S*-(-)-ethyl lactate (**38a**) or R-(+)-methyl lactate (**38b**).

	X	Ent.[b]	Enone	R	Time (hours)	Cyclopropane (yield, %) [a]			
						trans		*cis*/enolene	
1	CH$_3$	-	(**39a**)	Bn	448	(**76a**)	(21)	(**76b/c**)	(9)
2	CH$_3$	-	(**39a**)	CH$_3$	720 [c]	(**77a**)	(0)	(**77b/c**)	(0)
3	Ph	-	(**39b**)	Bn	180	(**16a**)	(29)	(**16b/c**)	(4)
4	Ph	+	(**39b**)	Bn	120	(**78a**)	(34)	(**78b/c**)	(2)
5	Ph	-	(**39b**)	CH$_3$	480 [c]	(**79a**)	(0)	(**79b/c**)	(0)
6	*t*-Bu	-	(**39c**)	Bn	358 [d]	(**80a**)	(13)	(**80b/c**)	(5)
7	*p*-BrPh	-	(**39d**)	Bn	144	(**81a**)	(48)	(**81b/c**)	(3) [e]
8	OCH$_3$	-	(**39e**)	Bn	1440	(**82a**)	(0)	(**82b/c**)	(0)

[a] Percentage yields quoted refer to the isolated yields calculated from aldehyde (**65**). [b] Refers to the enantiomer of lactate (**38**) used. [c] Complex mixture of unidentified products. [d] Reaction did not go to completion. [e] The enolene isomer (**81c**) was observed in the crude ^{1}H NMR, however, was not recovered from chromatography.

On each occasion that an enone (**39a-d**) was treated with the benzyl ester ylide (**37f**), cyclopropyl products (**78/16, 76, 80** and **81**) were obtained. However, on no occasion was any cyclopropane provided from the analogous reaction with methyl ester ylide (**37e**), entries 2 and 5 in Table 18. The reduced reactivity of the methyl ester ylide (**37e**) was not

investigated further at this stage; see following Chapter 6 for successful cyclopropanation results incorporating (**37e**).

Numerous cyclopropanation trials were performed on the methyl enester (**39e**). Reaction conditions including heating under reflux for up to two months in solvents with boiling points ranging between 40 °C and 110 °C, did not afford any of the targeted cyclopropane (**82a**). This result was consistent with the unsuccessful attempts to cyclise the enester (**67e**) to the corresponding disubstituted cyclopropane (**73**), Section 4.3. Presumably, this was a result of the electron donating effect of the ester group, decreasing the nucleophilicity of the alkene β carbon (with respect to the carbonyl), in the proposed *trans* γ-hydroxy enester (**39e**) intermediate, see the proposed mechanism of cyclopropanation in Section 1.3.

Optical rotations were measured for each of the optically pure *trans* cyclopropanes (**16a, 76a, 78a, 80a** and **81a**) synthesised, which displayed varying abilities to bend the plane of polarised light. Unfortunately, the available polarimeter was not sensitive enough to enable reproducible optical rotations to be recorded for the majority of the enolene products (**16c, 76c, 78c, 80c** and **81c**). Typically, only very small samples of the pure compounds (**16c, 76c, 78c, 80c** and **81c**) were isolated (approximately 10 mg) and hence specific rotation measurements were not possible.

Whilst not all of the cyclopropanations had been a success, the prevailing result was cyclisation of the optically pure *trans* γ-hydroxy enones (**39a-d**) to afford the enantiomerically pure trisubstituted cyclopropanes (**16, 76, 78, 80** and **81**), see Section 5.3 for the determination of enantiomeric purity and later Section 7.3 for the determination of absolute stereochemical configuration. The success of these experiments firmly establishes the outstanding potential of this new methodology starting from the simple lactate esters (**38a/b**).

5.2.2   Attempted synthesis of the 3-phenylcyclopropane derivatives (83).

With the cyclopropanation procedure from the lactate derived enones (**39**) confirmed, attention was turned to achieving the same positive results using the mandelate derived enones (**17**). Under the premise that the 'phenyl' enones (**17a-c**) should react in an

analogous manner to (39a-d), each of the enones (17a-c) was subjected to the same reaction conditions as described above (Section 5.2.1), Scheme 48.

The racemic enones (17a-c) were treated *in situ* with the benzyl ester ylide (37f) and heated under reflux until no enone was observed by ^1H NMR analysis of the crude reaction mixture. Unfortunately, no cyclopropyl products were observed on any attempt. Exhaustive experimentation was employed in an attempt to reach the target cyclopropanes; trials included increasing the number of equivalents of ester ylide (37f), increasing the reaction temperature (up to 65 °C), decreasing the reaction temperature (down to ambient temperature), and altering the enone (37) concentration. None of these modifications resulted in any cyclopropane formation. Nevertheless, the problem was overcome with later modifications discussed in the following Chapter 6.
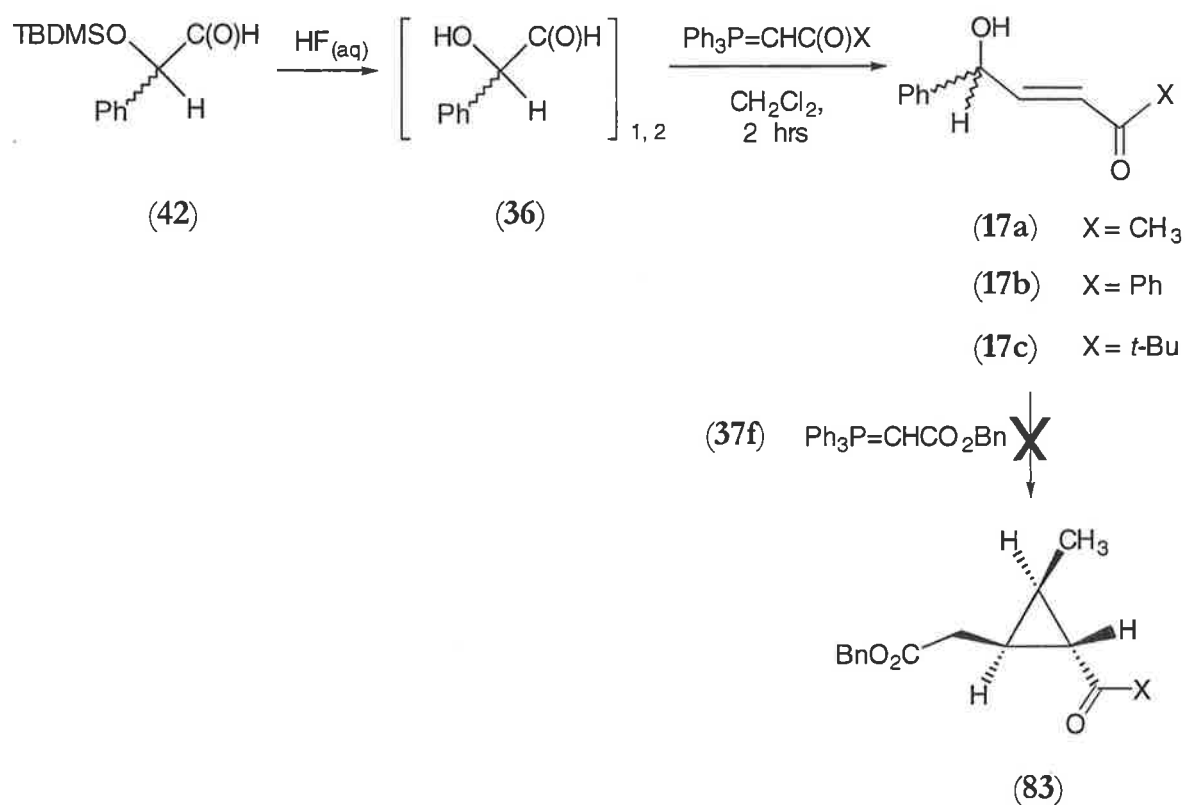
Scheme 48

The reaction products identified from ^1H NMR analysis were the corresponding 1,4-diketone (46) and trace amounts of furan (51), along with a new alkene (84) and a complex mixture of unidentified products. In each case the major product was the 1,4-diketone containing the relevant substitution for 'X', such that where X = CH₃ (46a), X =

Ph (**46b**) and X = *t*-Bu (**46c**). The 1,4-diketones (**46a-c**) were identified either from comparison with the literature,[82,95] or with previously isolated analogues. The new alkene (**84**) was generated in each of the reactions, irrespective of the enone (**17a-c**) employed.

In order to identify this new product (**84**), the solvent was removed from one of the reaction mixtures providing a crude oil, which was subjected to column chromatography on silica gel. ¹H NMR spectroscopy revealed the identity of the olefin to be benzyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (**84**), Figure 26. The enester (**84**) proved to be unstable to prolonged exposure to silica gel and as a result a sample of greater than 85% purity was unobtainable. Despite this, the identity was easily confirmed from comparison of both the ¹H and ¹³C NMR spectrum with the enones (**17a-e**) previously synthesised. The formation of (**84**) indicated that minor amounts of unreacted α-hydroxy aldehyde (**36**) had remained in solution at the time of the introduction of benzyl ester ylide (**37f**). It is believed that the residual aldehyde (**36**) may have been present in the dimeric form and was mistakenly discounted as impurity.
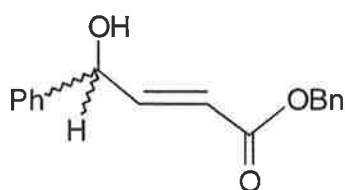
Figure 26. Benzyl (*E*)-4-hydroxy-4-phenylbuten-2-oate (**84**).

5.3   Enantiomeric purity determination of the trisubstituted cyclopropanes.

Section 5.2.1 discussed the formation of the trisubstituted *trans* cyclopropanes (**16a, 76a, 78a, 80a** and **81a**). Consideration of the proposed mechanism would suggest that the cyclopropyl products (**16a, 76a, 78a, 80a** and **81a**) should retain the same level of enantiomeric purity as the starting material. That is to say, the optical purity of the precursor *S*-(-)-ethyl lactate (**38a**) and *R*-(+)-methyl lactate (**38b**), should carry through each of the stereoselective transformations to the final product. An experimental method

to confirm the presumed optical purity of each of the cyclopropanes (**16a, 76a, 78a, 80a** and **81a**) was required.

Optical rotation measurements can be used to calculate the optical purity of a compound, through the use of Equation 1. As the optical rotations had already been measured for each of the cyclopropyl products (**16a, 76a, 78a, 80a** and **81a**), this method would have made the optical purity determination very simple. However, in order to employ this technique the optical rotation of the pure material ($[\alpha]_{max}$) must be known. Since the $[\alpha]_{max}$ values were not known for cyclopropanes (**16a, 76a, 78a, 80a** and **81a**) this method could not be employed.

$$\text{Percentage optical purity} = \frac{[\alpha]_{obs}}{[\alpha]_{max}} \times 100$$

Equation 1

An alternative method involves the use of a chiral molecule, which relies on the formation of a transient diastereomeric species generated when the chiral molecule is mixed with an enantiomeric compound. This method is also dependent on the diastereomeric species formed exhibiting significantly different NMR spectrum.[96] Chiral lanthanide shift reagents have the property of forming coordination compounds with carbonyl compounds (as well as alcohols, amines, etc.) and are capable of shifting the NMR peaks of two enantiomers to varying extents.[97] As such these reagents are commonly employed in chiral shift NMR experiments, europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] is one such reagent and was selected as the chiral shift reagent to be employed.

When using a chiral shift reagent, the NMR experiment is performed in an achiral solvent. Previous studies had shown that the optimum separation and resolution of NMR peaks was obtained when a 4:1 mixture of CCl_4 and d_6-benzene was utilised.[98] CCl_4 aids in the solubility of the compound in question, whilst the presence of d_6-benzene ensures that the NMR spectrometer can be locked to this resonance. In each experiment approximately 2% of tetramethylsilane (TMS) was added to the solvent mixture, whose signal was used as an internal reference.

A racemic sample of benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**), synthesised from the precursor 1,2-dioxine (**14**),[99] was dissolved in the CCl₄:d₆-benzene solution and the ^{1}H NMR spectrum was recorded. Outside of changes in the frequency at which the signals came into resonance, the spectrum was very similar to that obtained in CDCl₃. Europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] was added in small portions, and a ^{1}H NMR spectrum was recorded after every addition. Slowly increasing the concentration of shift reagent enabled each of the peak movements to be closely followed, ensuring that assignment of the corresponding signals would not be confused.

Typically, a ^{1}H NMR signal, which appears as either a singlet or sharp doublet, is sought to use as the peak for determining the ratio of diastereomers present. In the case of cyclopropane (**16a**), two signals were closely followed in the hope that one of them would separate enough to determine the enantiomeric excess of the optically pure substrate. These peaks were a doublet due to the methyl group protons on the cyclopropane ring, and a singlet due to the methylene group protons of the benzyl group. On addition of the chiral shift reagent the ^{1}H NMR spectrum was spread over approximately 12 ppm, and the majority of the peaks appeared as broad multiplets.

The two diastereotopic signals for the methylene protons of the benzyl group were well separated from each other, yet were not separated from other peaks in the spectrum. Fortunately, when the optimum amount of europium *tris*[3-(heptafluoro-propylhydroxymethylene)-(+)-camphorate] had been added to provide base line separation between the doublets of the diastereotopic methyl group protons, both signals were clear of all other signals. Therefore, the methyl group protons were used to determine the enantiomeric purity of the two diastereomers, and hence of the original enantiomeric mixture.

Of course, the ratio of diastereomers was 1:1, which corresponds to an enantiomeric excess of 0%, because a racemic sample of the cyclopropane (**16a**) had been used, Figure 27(a). Now that the chemical shift values were known for both of the diastereotopic peaks of the methyl group protons, at a specific concentration of both cyclopropane and chiral shift regent, the analogous NMR experiment was performed using the optically pure cyclopropanes (-)-(**16a**) and (+)-(**78a**).

Both *trans* (-) benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**), and the opposite enantiomer (+)-(**78a**) were treated under the conditions set out above for the racemic cyclopropane sample. Figure 27 shows the corresponding regions of the ^{1}H NMR spectra recorded for each of these samples, at the indicated field strength. It is obvious from this illustration that the synthesised trisubstituted cyclopropanes (**16a/78a**) were indeed of extremely high enantiomeric purity. From this method of measurement it can be quoted that the enantiomeric excess of each cyclopropane was an excellent ≥ 98%.

Whilst no opposite enantiomeric peak can be seen in the spectrum for either (-)-(**16a**) or (+)-(**78a**), a higher degree of accuracy is not possible. The error margin in determining the enantiomeric excess using this technique is approximately ± 1%. This can be rationalized by considering that, if a small and a large peak are present in a ratio of 1:100 there are inherent problems in determining the percentage of the smaller peak to an accuracy level higher than 1%.[100]

(a)

Racemic

300 MHz

2.96   2.86   2.76   2.66

(b)

(+)-(**78a**)

200 MHz

2.95   2.85   2.75   2.65

Doublet signal due to the protons of the CH_3 group attached to the cyclopropane ring.

(c)

(-)-(**16a**)

200 MHz

2.89   2.79   2.69   2.59
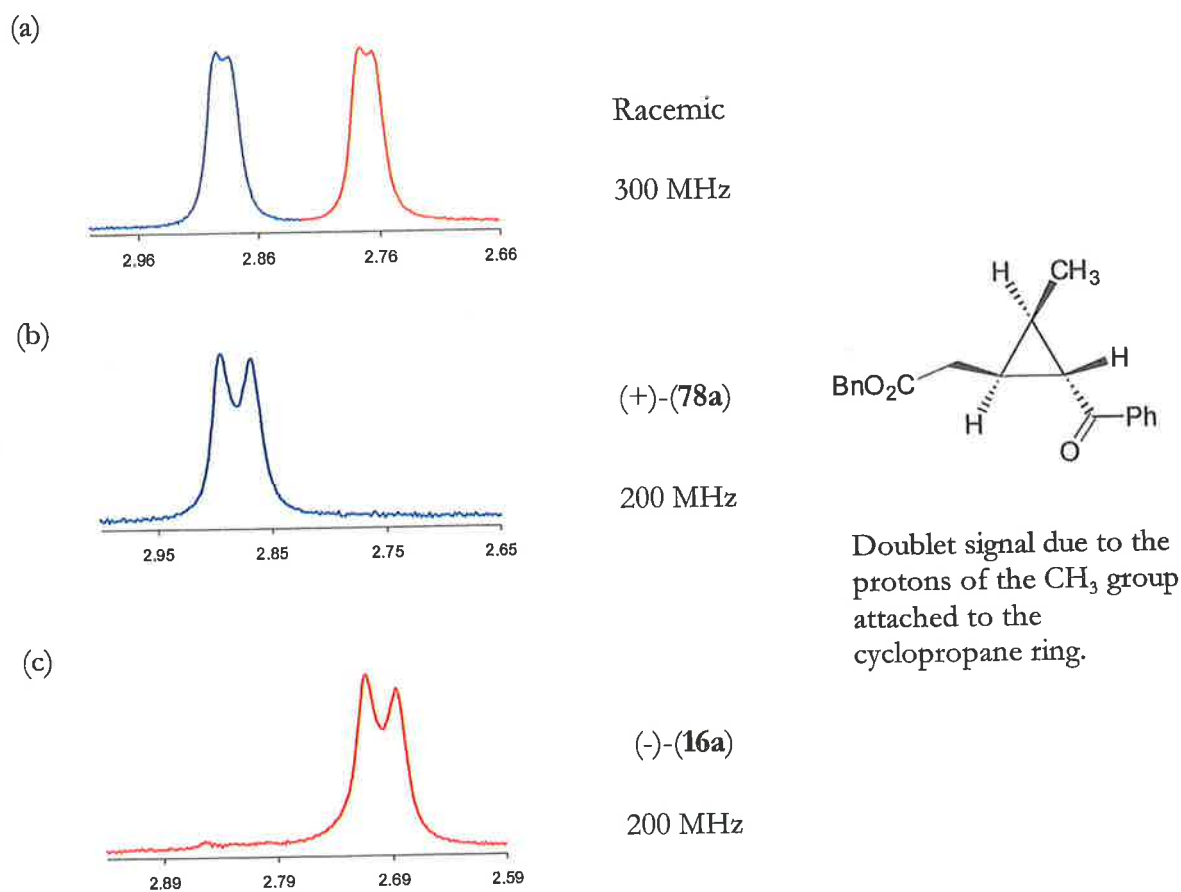
Figure 27. Sections of the ^{1}H NMR spectra from chiral shift experiments with *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate in (a) racemic, (b) (+)-(**78a**) and (c) (-)-(**16a**) forms.

The enantiomeric excess of each of the remaining *trans* cyclopropanes (**76a, 80a** and **81a**) were similarly determined to be ≥ 98%. Whilst these products (**76a, 80a** and **81a**) were not compared to their opposite enantiomer, the signal for the corresponding methyl group protons resonated at comparative frequencies, in the presence of europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

Whilst α-hydroxy aldehyde (**65a**) was known to be unstable to decomposition, it had not been reported if disruption of the enantio-purity occurred over time. A series of 'time-lapse' experiments were conducted in order to determine if epimerisation of the chiral centre in (**65a**) would occur. The procedure affording *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**) was repeated with an increasing time delay between deprotecting the silyloxy aldehyde (**36**), and the dissolution of hydroxy aldehyde (**65a**) and allowing it to react with the phenyl keto ylide (**37b**). Samples of (**65a**) were removed from the same 'batch' of product at 0, 0.5, 1, 2, 4, 8, and 24 hours, and the final product (**16a**) of each trial was purified as per the reported procedure. Chiral shift ^{1}H NMR experiments performed on each 'time-lapse' sample proved the enantiomeric excess to be robust to the prolonged conditions.

The results of the work described in this Chapter 5 were extremely gratifying as they had, in essence, meet all of the original goals set for this research. The *trans* γ-hydroxy enones (**39**) had successfully been synthesised in good yields and in high optical purity. This fact has been confirmed by the subsequent synthesis of the trisubstituted *trans* cyclopropanes (**16a, 76a, 78a, 80a** and **81a**) in both excellent diastero- and enantiomeric excesses. Disappointingly, this success was not carried through to the generation of cyclopropanes (**83**) from the mandelate derived enones (**17**).

Encouraged by the positive results, the next task was fixed on improving the yield of the cyclopropanation step. ^{1}H NMR analysis had shown that the γ-hydroxy enones (**17/39**) were forming smoothly, and as the major product in each case, why then was the average *trans* cyclopropane yield only 29%. Cyclopropane yields from the precursor 1,2-dioxines (**14**) had been shown to yield cyclopropanes in yields typically of greater than 90%,[49] on this basis the yields obtained from the γ-hydroxy enones (**17/39**) are very poor. Chapter 6

discusses the improvement of the overall yield of the cyclopropanation reactions and a justification for the low product yields obtained thus far.

6   Shifting the position of the *trans-cis* equilibrium: a new mechanistic discovery.

At the outset of the current research, it was believed that the *trans* γ-hydroxy enone (**17**) was the resultant product of the 1,2-dioxine (**14**) ring opening and rearrangement, as indicated by initial mechanistic investigations.[49] This early observation was later proven to be misdirected by a parallel study also focussed on the new cyclopropanation methodology.[101] This second study was concerned with the investigation of the mechanism of the reaction, and confirmed that the ylide (**15**) initially acts as a mild base, inducing ring opening of the 1,2-dioxine (**14**), as previously discussed in Section 1.3.[101] However, results from the concomitant research showed that whilst the *trans* enone (**17**) did form in minor amounts throughout the reaction, through isomerisation of the carbon-carbon double bond, it does not directly undergo a Michael addition reaction with the ylide (**15**).[101]

Rather, the study proved that the *cis* γ-hydroxy enone (**85**) was in fact formed on the initial ring opening of the 1,2-dioxine (**14**), and, that the *cis* enone (**85**) was responsible for the subsequent cyclopropanation. It is now known that the *cis* γ-hydroxy enone (**85**) is captured by the ylide (**15**) reacting to afford the cyclic $1,2\lambda^5$-oxaphospholane (**18**), which undergoes intramolecular rearrangement, expulsion of triphenylphosphine oxide and formation of cyclopropanes (**16**),[101] Scheme 49.

Initial consideration of these results would suggest that the objectives of the current research were futile, as the *trans* enone (**17**) will not react with the ylide (**15**). Nevertheless, optically pure cyclopropanes have been successfully synthesised from the *trans* enones (**39/67**), as presented in Chapters 4 and 5. It would therefore, be more accurate to say that cyclopropanation was occurring by slow stereomutation of the *trans* enone (**39/67**) to the reactive *cis* enone (**85**), thus allowing for capture by the ylide (**15**). This proposition was supported by the results of the alternate study in that whilst the *trans* enone (**17**) was observed in the crude reaction mixture from precursor 1,2-dioxines (**14**) (as seen by ^{1}H NMR), no *trans* enone (**17**) remained at the completion of the cyclopropanation reaction. Therefore, isomerisation of *cis* (**85**) to *trans* (**17**), and from *trans* (**17**) to *cis* enone (**85**) must have been taking place.
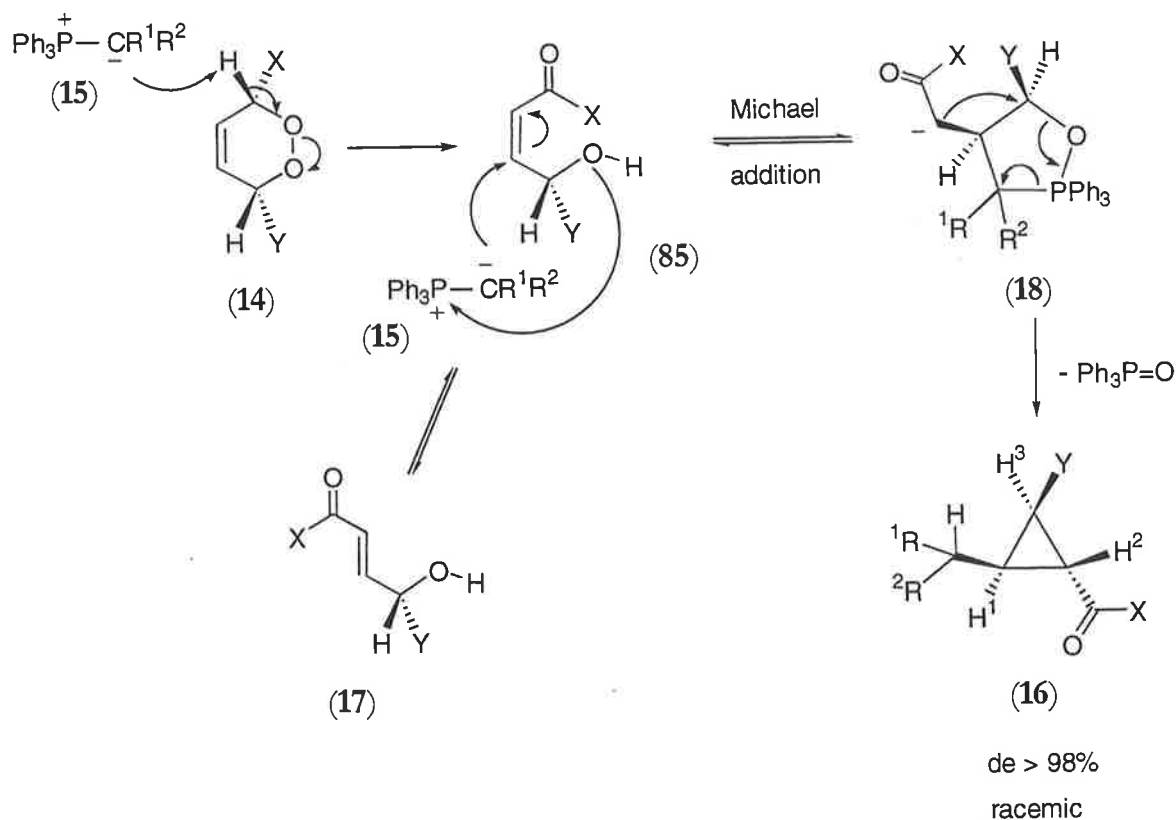
X and Y = combinations of H, aryl and alkyl
R^1 and R^2 = combinations of H, alkyl, keto and ester

Scheme 49

Given that isomerisation from the more thermodynamically stable *trans* enone (**17**) to the *cis* enone (**85**) is an 'up-hill' energy conversion, the low cyclopropane yields that were obtained from the optically pure *trans* enones (**39a-d**) are quite understandable. Additionally, the long reaction times of up to 448 hours, required to complete the cyclopropanation reactions from the *trans* enones (**39/67**), are justifiable. Whilst heating the reaction mixture under reflux eventually provided the high activation energy required to isomerise the carbon-carbon double bond,[102] this method is not an efficient means of promoting alkene isomerisation.

With this new mechanistic information in hand, and considering that enantiomerically pure cyclopropanes had been generated from the optically pure *trans* γ-hydroxy enones (**39a-d**), it was envisaged that dramatic improvements on the previous results should be obtainable. If the position of the *trans-cis* enone equilibrium could be shifted toward the *cis*

enone (**85**), then not only should the cyclopropanation reaction times be significantly reduced, but accordingly, the cyclopropane yields should also be increased.

6.1   Photoisomerisation of the γ-hydroxy enones.

It is well known that isomerisation of geometrical alkene isomers can be induced through the use of photochemistry, i.e. photoisomerisation. The absorption of light by a substrate can result in the formation of an excited species, whose chemistry may be markedly different from that of the ground state (S_0) species. For instance, the double bond in a ground state alkene becomes essentially a single bond in the excited electronic state.[103]

In the case of an alkene, the excited species is generated when an electron is promoted from the highest occupied bonding π orbital to the lowest unoccupied anti-bonding π^* orbital, affording the (π, π^*) excited state. The (π, π^*) transition is said to be spin-allowed, such that no change in electron spin pairing has taken place. This change in electronic configuration removes the constraints holding the molecule in the fixed planar geometry of the S_0 state. Free rotation can now occur about the carbon-carbon 'σ' bond.[103] The lowest excited (π, π^*) states are at an energy minima when the central carbon bond is rotated through 90° from the ground state geometry, that is when the planes of the two substituent groups are mutually perpendicular to one another, Figure 28. [104-107]

(a) Ground state: Planar

(b) Excited state: Orthogonal
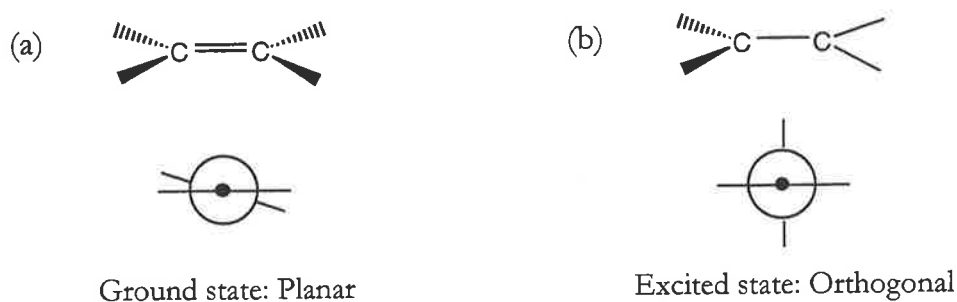
Figure 28. Pictorial representation of the geometrical configuration of (a) the ground state alkene, and (b) the first excited state 'alkene'.[104]

There are in fact two low lying (π, π^*) excited states, one in the singlet (S_1) manifold and one in the triplet (T_1) manifold. The transition from ground state to lowest lying singlet state ($S_0 \rightarrow S_1$) is spin-allowed and is therefore highly probable, however, the ground state to lowest lying triplet state transition ($S_0 \rightarrow T_1$) is spin-forbidden and therefore occurs with very low probability.[108] The $S_0 \rightarrow T_1$ transition involves the promotion of an electron to a state with a different electron spin alignment, as the T_1 state consists of parallel electron spins. In principle, either the S_1 or T_1 (π, π^*) excited states could result in photoisomerisation of the alkene double bond.[104,106] As the inevitable relaxation from either state, back to the ground state will transpire through the (π, π^*) orthogonal configuration, Figure 28. Re-formation of the S_0 planar alkene configuration can occur as either the *trans* or *cis* isomer, irrespective of the original alkene orientation,[103] *vide infra*.

There are a number of factors which render photoisomerisation of an alkene via the S_1 state unattractive. Firstly, formation of the S_1 state of alkenes generally requires the use of short wavelength light (200-210 nm for simple alkenes and slightly longer for substituted or conjugated alkenes), which may be technically problematic due to the absorption of solvents typically employed in homogeneous reactions, and due to the lack of suitable light sources.[109] Secondly, the isomerisation of singlet alkenes occurs in competition with other photoprocesses, for instance structural isomerisation via carbene intermediates [110] and [$\pi^2s + \pi^2s$] cycloaddition.[106]

In the singlet manifold there are three excited states with energies lying in close proximity to each other.[110] The Energy State diagram for a 'non-specific' alkene is presented in Figure 29 and displays not only these three S_n levels but also the two T_n excited state levels. It is because of the relative similarity between the three singlet state energies that various photoprocesses can transpire from the singlet state. As a result, the direct irradiation of alkenes to form the singlet excited state is of little synthetic value for the current proposal. On the other hand, the only major reaction to occur from triplet alkenes is *trans-cis* photoisomerisation.[105,110] This is due to the fact that only one of the excited triplet states is clearly low lying.
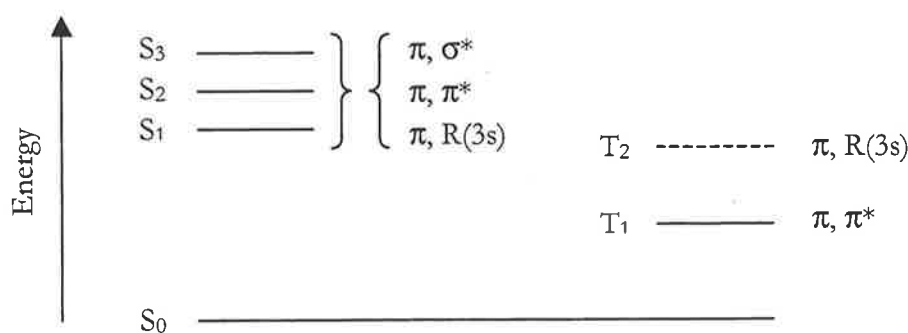
Figure 29. Energy State diagram for a 'non-specific' alkene. Note that the order of the S_n excited state levels may alter with solvent polarity,[104] however, it is generally accepted that (π, π^*) is the low lying triplet state.[110] $(\pi, R(3s))$ is known as the Rydberg excited state[110] and is sometimes referred to as the (n, π^*) excited state, where n is referring to a non-bonding orbital.

Direct irradiation of an alkene will preferentially form the singlet excited state, *vide supra*, yet the triplet state is required for successful photoisomerisation. Although energy exchange from a S_1 to T_1 state would be a favourable reduction in energy, see Figure 29, it would be a transition between excited states of different spin, known as intersystem crossing. Such a transition will only occur when the singlet-triplet energy separation or singlet-triplet splitting is small.[107] Unfortunately, states derived from (π, π^*) configurations typically have a large S_1-T_1 splitting and therefore do not undergo intersystem crossing efficiently,[107,110,111] as is the situation with most simple alkenes. Whilst α,β-unsaturated carbonyl compounds are known to exhibit a smaller S_1-T_1 splitting than simple non-conjugated alkenes, the S_1-T_1 splitting for the enones (**17/39/67**) concerned was not known. Therefore, the literature information reported for simple alkenes has been utilised for the purpose of determining the relevant photoisomerisation requirements.[109]

Fortunately, there are chromophores which posses good intersystem crossing abilities, these compounds are often referred to as 'sensitisers'. Triplet sensitisers are often compounds whose excitation states are derived from the (n, π^*) configuration which have a comparatively small S_1-T_1 splitting energy, resulting in large intersystem crossing rate constants.[108,111] They have the ability to transfer their triplet energy on collision with an 'acceptor' molecule in a conserved energy process, converting the 'acceptor' to its

corresponding triplet excited state. The process can be described as follows; the sensitiser is initially excited to its S_1 state, which undergoes intersystem crossing to its corresponding T_1 electronic excited state. Intermolecular energy transfer from the sensitiser T_1 state to the acceptor (the alkene in this case) provides the corresponding acceptor T_1 state. With the T_1 alkene now formed, photoisomerisation can take place as the excited species contorts into the orthogonal configuration (Figure 28) and subsequently relaxes to either the *cis* or *trans* S_0 planar alkene.[108]

Carbonyl compounds have long been recognised as 'good' triplet sensitisers because their intersystem crossing quantum yields approach unity, implying high intersystem crossing rates.[112,113] Their T_1 state energies are typically higher than that of many acceptors and as a result, carbonyl sensitisers populate the acceptor T_1 state with excellent efficiency in an exothermic energy transfer process.[103] Aromatic substrates such as benzophenone and acetophenone react exclusively from their triplet states, and are therefore, commonly utilised for the photosensitisation of compounds with lower lying triplet states.[109] Specifically, benzophenone exhibits a quantum yield of exactly one for formation of its triplet state.[114]

Triplet photosensitisation provides an indirect yet efficient route to alkene triplets, which does not rely on direct irradiation and intersystem crossing of the S_1 alkene to the T_1 alkene state. It was therefore decided to trial photoisomerisation of the *trans* γ-hydroxy enones (**17/39/67**) with the aid of benzophenone as the triplet sensitiser. Figure 30 depicts the 'Jablonski-type' diagram for the proposed transformation, indicating that excitation of the ground state alkene (**17/39/67**) should be effected by an energy transfer from the T_1 sensitiser. Whilst the exact energy of the T_1 enone (**17/39/67**) was not known, it was assumed that by analogy with similar conjugated alkene species that its energy would be lower than that of the T_1 benzophenone species.[103,115] Following energy transfer from the sensitiser to enone (**39**), the corresponding T_1 state should form. The T_1 enone (**17/39/67**) species should subsequently relax back to the S_0 state, through the energetically low T_1 orthogonal conformation, Figure 28. Thus, a mixture of both the *trans* (**17/39/67**) and *cis* (**85**) enones would be created.

It was proposed to perform the photoisomerisation on the crude reaction mixture, with the ester ylide (**37e-h**) already present in solution. It was most likely that on prolonged irradiation of the *trans* enone (**17/39/67**) a photostationary state would be established, containing a mixture of both geometrical isomers (**17/39/67**) and (**85**). However, as the *cis* γ-hydroxy enone (**85**) is the reactive species in the cyclopropanation manifold, it should be consumed by the ylide (**37e-h**) as formed. Consequently, shifting the position of equilibrium away from the *trans* (**17/39/67**) and towards the *cis* enone (**85**) should be facilitated by both photoisomerisation and removal of *cis* enone (**85**) as it forms.
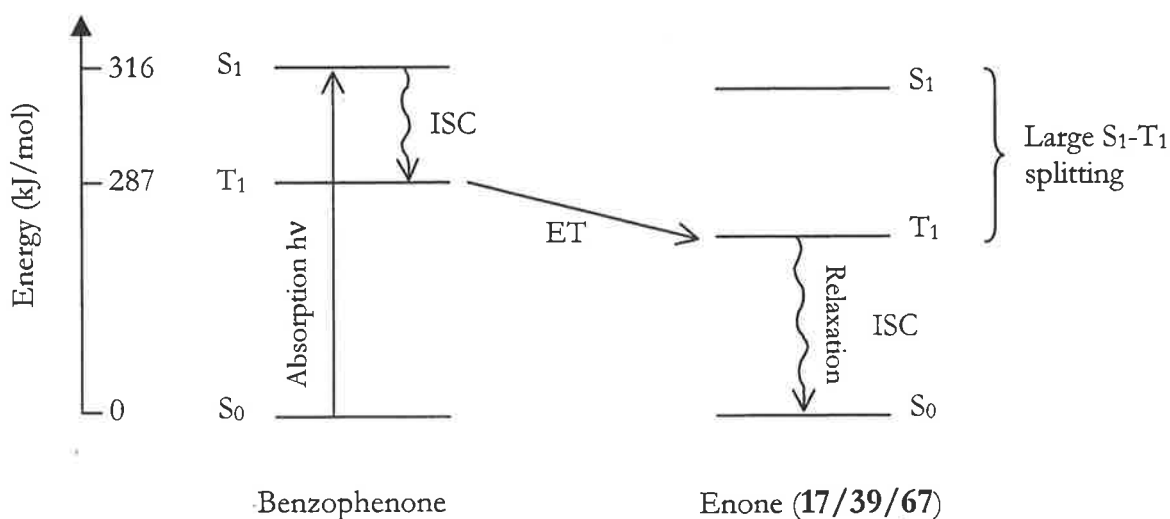
Figure 30. Jablonski diagram for the formation of the T_1 state of the enone (**17/39/67**) employing the triplet sensitiser benzophenone. The vertical scale corresponds to increasing energy, whilst the horizontal scale has no physical significance.[116] Note that the indicated energy of the S_1 and T_1 states for the enones are arbitrary. ISC = intersystem crossing, ET = energy transfer.

6.2   Cyclopropanation results utilsising photoisomerisation.

By virtue of the known instability of both the *trans* (**17/39/67**) and *cis* γ-hydroxy enones (**85**), it was decided that the crude enone solution would be subjected to photochemical isomerisation with no attempt at purification. There was potential for the by-products in solution to absorb radiation, however, it was hoped that they would not interfere with the desired photochemical transformation. In keeping with the simplicity of the optimised

reaction conditions leading to formation of the *trans* enones (**17/39/67**), the photoisomerisation was to be performed in the same reaction vessel, directly following the addition of the ester ylide (**37e-h**).

Development of the ideal conditions for the photoisomerisation reaction were to be determined using the test 'hydrogen' enones (**67a-c**), derived from the commercially available glycoaldehyde dimer (**66**). It was then proposed to employ the same technique for the synthesis of the optically pure trisubstituted derivatives from photoisomerisation of the corresponding enones (**17/39**).

Readily available 300 W sunlamps were to be employed as the light source for the photoisomerisation reactions. The typical emission of a 'Woton' sun lamp is in the range of the visible and IR-A wavelength region of approximately 300 – 1400 nm. As standard laboratory glassware was to be used, light below approximately 350 nm would be absorbed, whilst the solvent should not interfere with the passage of light as CH_2Cl_2 has a cut-off wavelength of 230 nm. Benzophenone requires light of approximately 375 nm to provide enough energy for excitation up to the first singlet (n, π^*) excited state at 316 kJ/mol, Figure 30, which should be adequately supplied by the chosen sunlamp source.

6.2.1   Optimising the synthesis of the disubstituted cyclopropanes.

The 'hydrogen' enones (**67a-c**) were synthesised following the methodology presented in Section 4.2. In Chapter 4, those enones (**67a-c**) were subjected to heating under reflux in the presence of an ester ylide (**37e-f**) to effect cyclopropanation. In the same light, an ester ylide (**37e-g**) was added directly to the reaction flask along with a catalytic amount of benzophenone, and the mixture was irradiated using a 300 W sun lamp, Scheme 50.

It is important to note at this point that photoisomerisation of the *trans* enones (**67a-c**) was attempted in the absence of a triplet sensitiser and that no isomerisation was observed. Additionally, both the mandelate and lactate derived enones (**17/39**) were similarly irradiated without a triplet sensitiser and again no isomerisation occurred.
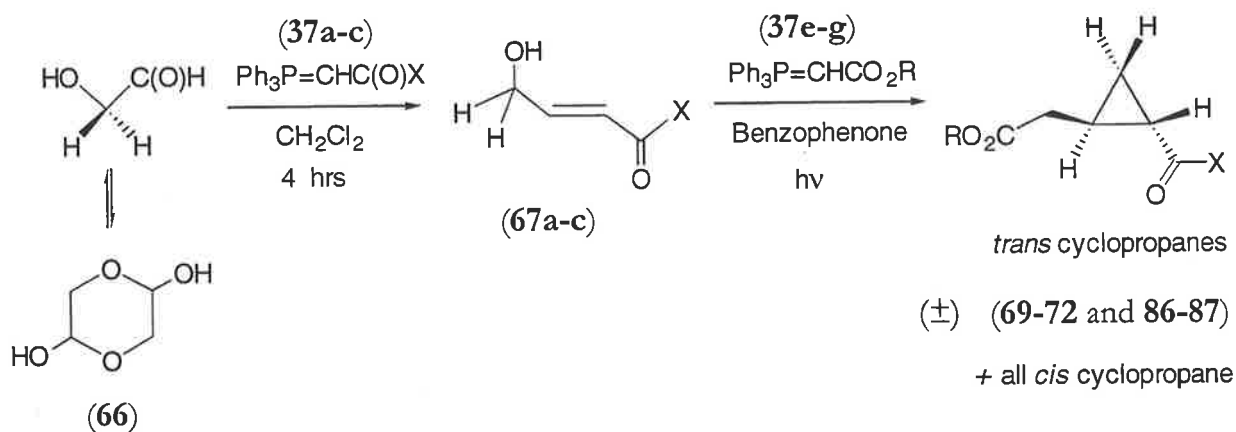
Scheme 50

Initial trials were performed with the reaction vessel submerged in an ice-water bath to prevent heating of the solution. It was hoped that cooling the reaction mixture would reduce the by-product formation previously observed under the thermal cyclopropanation conditions, Section 4.3. However, this set up proved to be inconvenient and was discarded as it was later discovered to have no advantageous effect on the reaction outcome. A result of this was that the reaction mixture was heated to reflux for the duration of the irradiation without the use an external heat source.

In order to maximise the irradiation surface, two 300 W sunlamps were employed for all subsequent photolytic reactions. A direct comparison of reaction times using one or two lamps was not performed, however, it was apparent from the initial trials that the reaction rate was significantly increased when the vessel was surrounded by the light source. The lamps were placed at a distance of 10 cm from the reaction vessel on either side of the flask.

After following the trial reactions by ^{1}H NMR spectroscopy it was clear that the experimental modifications were extremely successful. After only three hours irradiation of 4-hydroxy-1-phenylbut-2-enone (67b), cyclopropyl products were evident in the crude reaction mixture. Varying amounts of benzophenone were added, both in portions over time and in one mass, in order to determine the optimum molar percentage of sensitiser required. From the ratio of the percentage of cyclopropyl products formed over time, it

was concluded that 10 mole percent of benzophenone added at the beginning of the irradiation provided the maximum amount of product in a minimum time period.

With the optimum reaction conditions established, 4-hydroxy-1-phenylbut-2-enone (**67b**) was irradiated employing these parameters as follows. The crude solution of enone (**67b**) in CH$_2$Cl$_2$ was immediately treated with 10 mole percent of benzophenone and *ca.* 1.5 equivalents of the benzyl ester ylide (**37f**). Two sunlamps were used to irradiate the solution, which was heated to reflux throughout the 30-hour irradiation. At this time ^{1}H NMR indicated that a trace amount of the enone (**67b**) remained, however, further irradiation did not effect its consumption. The mixture was concentrated *in vacuo* and the products were isolated, as per the procedure developed in Section 4.3.

The outstanding success of the modified photolytic cyclopropanation was clearly evident from comparison with the previous results obtained from the thermal cyclopropanation procedure, Table 19. Thermal conditions had afforded 35% of the *trans* benzyl 2-(2-benzoylcyclopropyl)acetate (**71a**) in a reaction time of five days, or 120 hours. Photolytic conditions afforded the *trans* cyclopropane (**71a**) in an excellent yield of 68%, a yield increase of 33%. The new reaction time was only 30 hours, reduced to one quarter of that for thermal cyclopropanation.

Only a trace of the corresponding *cis* cyclopropane (**71b**) was observed in the ^{1}H NMR spectrum, which was not recovered during product isolation, akin to the sole formation of the *trans* cyclopropane (**71a**) under the thermal conditions (Section 4.3) and from the precursor 1,2-dioxine (**14**).[49] Approximately 5% of an enolene type product (**71c**) was obtained from the crude reaction mixture, which was identified as benzyl (*E*)-6-oxo-6-phenylhex-2-enoate (**71c**). Whilst the structure of (**71c**) was identical to what would be obtained from an enolene rearrangement of the *cis* cyclopropane (**71b**), it was not believed to have resulted from such a rearrangement. Instead, (**71c**) was thought to have resulted from a Wittig reaction of the by-product keto aldehyde (**68**) and the benzyl ester ylide (**37f**) in solution, Scheme 51. This reasoning was discovered to be only partially correct, *vide infra*.
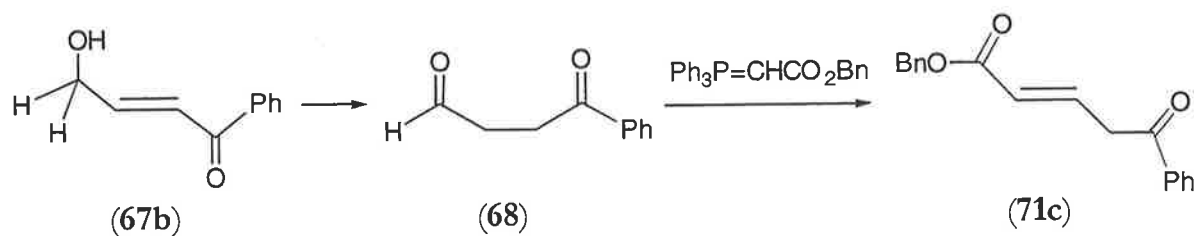
Scheme 51

The keto aldehyde (**68**) was generated by decomposition of the *trans* enone (**67b**) through the Kornblum – De La Mare pathway that was previously credited for the formation of the 1,4-diketone by-products (**46/54**).[80] None of the dicarbonyl by-product (**68**) was obtained subsequent to chromatography, however, the formation of enolene (**71c**) was supportive evidence of its existence. The ^1H NMR spectrum for (**71c**) displayed characteristic signals for a *trans* alkene configuration of two doublets of triplets, at 7.08 and 5.95 ppm, with an olefinic coupling constant of 15.6 Hz. Each of these vinylic protons displayed coupling to the adjacent methylene group protons, through either ^3J or long-range ^4J coupling of 6.6 and 1.5 Hz respectively.

With the new photoisomerisation technique established, all previous cyclopropanations performed under the thermal reaction conditions were repeated. The results of these photolytic experiments are tabulated below alongside the comparative results for the previous thermal cyclopropanations.

The results presented in Table 19 clearly show the vast improvement in both product yields and reaction times achieved from the use of photoisomerisation. The greatest reduction in the required reaction time was observed for the formation of *trans* cyclopropane (**71a**), Entry 3, whilst the average reduction was more than 50%.

In each trial the *trans* cyclopropane yield increased significantly, with the average yield increase being 17%. This average does not include the greater than 100% improvement noted in Entries 4 and 5, both of which where high yielding reactions of 64% for (**86a**) and 56% for (**87a**). On the previous cyclopropanation attempt under thermal conditions, no cyclopropyl products (**86a/87a**) were obtained after approximately 250 hours of heating under reflux. It is interesting to note that neither of these reactions went to

completion, with some enone (**67b**) remaining in solution at the cessation of the reaction. It must also be reiterated that all of the quoted yields are calculated over two-steps starting from the glycoaldehyde dimer (**66**).

Table 19. Formation of the disubstituted cyclopropanes from the glycoaldehyde dimer (**66**), under photolytic and thermal conditions.

Enone (67x)		Ylide	Thermal conditions				Photolytic conditions			
			Cyclopropane (yield, %)[a]			Time (hrs)	Cyclopropane (yield, %)[a]			Time (hrs)
X	(x)	R		*trans* (a)	*cis* (b)			*trans* (a)	*cis* (b)	
1 CH$_3$	a	Bn	(**69**)	(38)	(10)	144	(**69**)	(43)	(4)	96[b]
2 CH$_3$	a	CH$_3$	(**70**)	(26)	(6)	192	(**70**)	(41)	(3)	96[b]
3 Ph	b	Bn	(**71**)	(35)	(0)	120	(**71**)	(68)	(0)[c]	30
4 Ph	b	CH$_3$	(**86**)	(0)	(0)	240	(**86**)	(64)	(0)[c]	30
5 Ph	b	Ad[d]	(**87**)	(0)	(0)	264	(**87**)	(56)	(0)[c]	9[b]
6 *t*-Bu	c	Bn	(**72**)	(17)	(4)	156[b]	(**72**)	(32)	(11)	93[b]

[a] Percentage yields quoted refer to the isolated yields calculated from (**66**). [b] Some enone (**67**) remained at the cessation of the reaction. [c] No *cis* cyclopropane was isolated, however, the corresponding enolene isomer was recovered in between 2-5%. [d] 'Ad' represents the adamantyl group, from adamantyl (triphenylphosphoranylidene)acetate (**37g**).[117]

These two examples, Entries 4 and 5, brilliantly display the tremendous effect of the *trans* to *cis* enone photoisomerisation step seen in each of the experiments presented in Table 19. Where previously heating of the CH$_2$Cl$_2$ solution under reflux had not efficiently reached the activation energy required for isomerisation to occur, photolytic conditions had easily achieved this feat. Once the *cis* γ-hydroxy enone (**85**) had been generated, its Michael addition onto the ylide (**37e-g**) proceeded readily, with high yields of cyclopropane resulting. The addition of the adamantyl ester ylide (**37g**) onto phenyl keto enone (**67b**) and the subsequent rearrangement to cyclopropane (**87a**) was complete after a mere nine hours of irradiation.

Again referring to Entries 4 and 5 of Table 19, no *cis* cyclopropane (**86b** or **87b**) was isolated from the crude product mixture, yet the corresponding enolene isomers (**86c** and **87c**) were recovered from column chromatography. The methyl ester derivative (**86c**) was recovered in a very low yield of 2% and complete characterisation was not achieved, due to the minor sample recovered as a result of decomposition on silica gel. The analogous adamantyl ester derivative (**87c**) was isolated in a slightly higher yield of 4% and was able to be completely characterised. The ^{1}H NMR spectrum for each enolene (**86c/87c**) was consistent with the structural determination established for the former enolene analogue (**71c**).

It was stated earlier, that the formation of the enolene products was thought to be arising solely from decomposition of the enone (**67**) to the corresponding 1,4-dicarbonyl (**68**), i.e. keto aldehyde. Whilst this may well have been the case on some occasions, it was also proven to be forming through an enolene rearrangement of the *cis* cyclopropane, see Section 5.2.1. A trace of *cis* adamantyl 2-(2-benzoylcyclopropyl)acetate (**87b**) was observed in the ^{1}H NMR spectrum of the crude product, but was isolated only as a mixture with the corresponding enolene isomer (**87c**). A CDCl$_3$ solution of the isomeric mixture of (**87b/c**) was heated at 55 °C for six days, at which time no *cis* (**87b**) remained. The sole product of this conversion was the isomeric *trans* adamantyl 6-oxo-6-phenylhex-2-enoate (**87c**), thus substantiating that the enolene rearrangement observed with the trisubstituted cyclopropanes, Section 5.2.1, was also occurring, to some extent from the *cis* disubstituted cyclopropyl derivatives.

A curious observation was the improved diastereoselectivity for the *trans* isomer, obtained in the photolytic cyclopropanation reactions. On all but one occasion where both the *trans* and *cis* cyclopropanes were afforded, the ratio of *trans:cis* cyclopropane improved to 12:1 compared to the 4:1 ratio noted under the thermal conditions, Table 19 Entries 1 and 2. Whereas, Entry 6 shows that the diastereomeric ratio of products actually decreased, with respect to the *trans* isomer (**72a**), down to 3:1 from 4:1 *trans:cis*. Justification for this observation is not known at this stage.

As was postulated in the earlier discussion, shifting the position of equilibrium by photoisomerisation of the *trans* to *cis* enone clearly had a positive effect on the outcome

of the cyclopropanation reactions. Not only does this provide support for the proposed reaction mechanism,[101] it also further establishes the applicability of this procedure for the synthesis of enantiomerically pure functionalised cyclopropanes in high yields.

6.2.2   Optimising the synthesis of the optically pure trisubstituted cyclopropanes.

The results presented in Chapter 5 showed that the synthesis of optically pure cyclopropanes from the *trans* γ-hydroxy enone (39) was a success. Unfortunately, the average yield of the target *trans* cyclopropane was only 29%. Additionally, the reaction times and conditions were unfavourable requiring heating under reflux for between 5 and 18 days. Therefore, it was proposed to re-synthesise the trisubstituted cyclopropanes adopting the photolytic methodology optimised utilising the diastereomerically pure test enones (67), Section 6.2.1.

6.2.2.1   The lactate derived cyclopropanes.

Each of the enantiomerically pure γ-hydroxy enones (39a-d) were synthesised following the methodology developed in Section 5.1.1. The crude enones (39a-d) were immediately treated with 10 mole percent of benzophenone, 1.5 equivalents of an ester ylide (37e-f and h), and the CH_2Cl_2 solution was subjected to irradiation with two 300 W sunlamps. ^{1}H NMR analysis of reaction mixture aliquot's enabled the reaction progress to be followed; each aliquot was subsequently concentrated and returned to the reaction mixture to ensure that product yields were not effected. At the completion of the irradiation the crude product mixtures were concentrated *in vacuo* and purified using the procedures described for their original isolation, Section 5.2.1. The results of these photoisomerisation experiments are presented below in Table 20, along with the parallel results obtained under the thermal reaction conditions.

Entries 3 and 7 provide excellent examples of the positive effect of inducing isomerisation of the enone (39b/d) through the use of photochemistry. The reaction times for these experiments were reduced to one fifth of that required under the thermal cyclopropanation conditions. In addition to the reduced reaction times, the cyclopropane yields increased by 29% and 19%, for (16) and (81) respectively. That is an average yield

increase of 24%. It must be remembered that these product yields are quoted over two-steps, with the assumption that the α-hydroxy lactaldehyde (**65**) was 100% pure.

Importantly, the enantiomeric excess of the *trans* cyclopropanes (**16a/81a**) were confirmed to still be greater than 98%, as seen by chiral shift ^{1}H NMR experiments. The diastereomeric ratio of the *trans:cis* cyclopropanes was slightly reduced on each occasion, however, there was no difficulty in separating the geometric isomers. For simplicity, the yields of the *cis* cyclopropane and enolene isomer have been quoted in Table 20 as a combined percent yield. Isolated samples of the appropriate *cis* cyclopropane from column chromatography were generally contaminated with the enolene isomer and the mixture was subsequently converted into 100% enolene.

Table 20. Formation of enantiomerically pure trisubstituted cyclopropanes from *S*-(-)-α-hydroxy lactaldehyde (**65**), under photolytic and thermal conditions.

Enone (39x)		Ylide	Thermal conditions				Photolytic conditions			
			Cyclopropane (yield, %)[a]			Time (hrs)	Cyclopropane (yield, %)[a]			Time (hrs)
X	(x)	R	*trans* (a)	*cis*/enol. (b/c)			*trans* (a)	*cis*/enol. (b/c)		
1 CH$_3$	a	Bn	(76)	(21)	(9)	448	(76)	(0)	(0)	72[b]
2 CH$_3$	a	CH$_3$	(77)	(0)	(0)	720[b]	(77)	(0)	(0)	96[b]
3 Ph	b	Bn	(16)	(29)	(4)	180	(16)	(50)	(12)	40
4 Ph	b	CH$_3$	(79)	(0)	(0)	480[b]	(79)	(41)	(9)	27
5 Ph	b	Mn[c]	–	–	–	–[d, e]	(88)	(40)	(10)	27
6 *t*-Bu	c	Bn	(80)	(13)	(5)	358[d]	(80)	(0)	(0)	22[b]
7 *p*-BrPh	d	Bn	(81)	(48)	(3)	144	(81)	(65)	(6)	27

[a] Percentage yields quoted refer to the isolated yields calculated from α-hydroxy lactaldehyde (**65**). [b] No cyclopropyl products were observed after the indicated reaction time. [c] 'Mn' represents the menthyl group, from (1*R*,2*S*,5*R*)-menthyl (triphenylphosphoranylidene)acetate (**37h**).[117] [d] Some enone (**39**) remained at the cessation of the reaction. [e] Reaction not performed.

The methyl ester ylide (**37e**) was trialed unsuccessfully under thermal cyclopropanation conditions, Entries 2 and 4 of Table 20. However, it was proposed that the lower

reactivity of (37e), compared to the benzyl ester ylide (37f), might be compensated for under the new photolytic conditions. This was proven to be the case on one occasion, where the reaction of the phenyl keto ylide (39b) and methyl ester ylide (37e) afforded the new *trans* cyclopropane (79a) in a good yield of 41%. This corresponds to a yield increase of greater than 100%, after only 27 hours irradiation. Unfortunately, the same result was not observed with the analogous reaction of the methyl keto enone (39a). Neither 720 hours of heating under reflux, nor 96 hours of irradiation of enone (39a) with methyl ester ylide (37e), provided any cyclopropyl products, Entry 2 of Table 20.

Disappointingly, not all of the thermally successful cyclopropanations provided the anticipated cyclopropanes when employing the photolytic conditions, Table 20 Entries 1 and 6. The *trans* cyclopropanes (76a) and (80a) had been synthesised under reflux in low yields of 21% and 13% respectively. Consequently, it had been expected that yield enhancements, akin to those reported in Section 6.2.1 and in Entries 3 and 7 of Table 20, would result. However, no cyclopropyl products were afforded from the treatment of either the methyl keto enone (39a) or the *t*-Bu derivative (39c) with an ester ylide (37e-f) under irradiation.

Where it is noted in Table 20 that no cyclopropanes were generated on irradiation, the major reaction observed was decomposition of the enone (39) into a complex mixture of unidentifiable products. Approximately 5-10% of the corresponding 1,4-diketone (45/54) was observed, yet typically none of the cyclised furan (55) was noted (with the exception of Entry 7), as seen by ^{1}H NMR spectroscopy.

One final trial employed the phenyl keto enone (39b) and (1*R*,2*S*,3*R*)-menthol (triphenylphosphoranylidene)acetate (37h),[117] Entry 5 of Table 20. This trial was performed in the hope of determining if the large steric bulk of the ester group would have any effect on the outcome of the cyclopropanation. As the reaction provided a high 50% yield of cyclopropyl products (88a-b), after the shortest irradiation time recorded of only 27 hours, it was decided that an increase in steric bulk had no adverse effect on the outcome of the reaction.

With the effect or non-effect of substituent steric bulk in mind, a justification for the failure of the trials represented in Entries 1-2 and 6 of Table 20 was considered. It is

known that the ylide initially adds to the hydroxyl terminus of the enone (**85**), Scheme 49. Since the 'Y' substituent remained unchanged for all of the reactions summarised in Table 20, the size of the methyl grouping can be discounted as causing the selective failure of some cyclopropanation reactions. Similarly, the 'X' substituent does not seem to be the cause, as when 'X' was equivalent to the larger phenyl group, i.e. enone (**39b**), all of the photolytic reactions trialed were a success. The only other substituent that needs be considered is that of the ester ylide (**37e-f, h**). Again, analysing the results accomplished from enone (**39b**), it is clear to see that going from the sterically small methyl group (**37e**) through to the comparatively bulky menthyl group (**37h**), no adverse effect was observed. Based on these observations it can be stated, that within the bounds of the substituents utilised, no steric effect was detected.

Another possible explanation for the unsuccessful photolytic reactions on the methyl keto enone (**39a**) and the *t*-Bu enone (**39c**), is perhaps associated with the energy of the excited state triplet enones (**39a/c**). As discussed earlier, for the purposes of this research it was assumed that the energy of the triplet states of each enone (**39a-d**) would be lower than that of the corresponding triplet sensitiser, Section 6.1. This assumption was made on the basis that the energy of most simple alkene and/or conjugated alkenes triplets are lower lying than the benzophenone triplet, as reported in the literature.[103,115] However, if this were not the case, then excitation of the enone (**39a/c**) to the corresponding triplet state would not be occurring. Subsequently, if the enone (**39a/c**) is not in the triplet state then photoisomerisation can not transpire as the orthogonal configuration will not be assumed, Figure 28.

There is potential to determine whether or not this was the situation, by recording an ultraviolet-visible (UV-Vis) spectrum of the enone (**39**). UV-Vis spectra are not reported in this thesis for the enones (**39a-d**), although recording of their spectrum was attempted. The impurities in solution, resulting from the one-pot procedure employed, complicated the spectrum such that the maximum absorption could not be accurately determined. Despite this, it is unlikely that both the singlet and triplet excitation absorptions would have been visible. Firstly, the intersystem crossing ability of simple alkenes is known to be extremely poor and slightly better for α,β-unsaturated carbonyl compounds, as noted in the earlier discussion on photoisomerisations, Section 6.1. Secondly, if either of the

enones (**39a/c**) were able to transform from their singlet to the triplet state, without sensitisation, then photoisomerisation and hence cyclopropane formation would have been observed. It is unlikely that quenching of the T_1 enone by the sensitiser would have prevented photoisomerisation only for enones (**39a/c**), and not for all other successful photoisomerisations.

Without knowing the values of the triplet state energies for the enones (**39a/c**), failure of the chosen sensitiser to populate their triplet state cannot be discounted. As an alternative to measuring those triplet energies, it may be possible to experiment with triplet sensitisers, which exhibit different triplet energies to benzophenone. See Section 6.3 for a discussion on alternative triplet sensitisers.

Whilst the results obtained from photoisomerisation of the lactate (**38**) derived enones (**39a-d**) had not been as universally successful as the analogous experiments for the 'hydrogen' enones (**67a-c**), the new photolytic conditions did improve both the reaction times and product yields for some cyclopropanes. All of the *trans* cyclopropanes synthesised employing this new modification were obtained in excellent yield of up to 65% in times greatly reduced from the thermal reaction conditions.

6.2.2.2   The mandelate derived cyclopropanes.

All previous attempts under thermal conditions, to generate cyclopropanes from the mandelate (**35**) derived *trans* γ-hydroxy enones (**17a-c**) had been unsuccessful. However, when taking into consideration the new mechanistic information and the recent success of the photoisomerisation technique, it was believed that cyclopropanation from the γ-hydroxy enones (**17a-c**) should be possible. It is now assumed that the provision of energy through heating under reflux was not sufficient to reach the activation energy required to effect *trans* to *cis* isomerisation of these enones (**17a-c**). Sensitised photoisomerisation may allow for the formation of cyclopropanes by successfully providing the *cis* enone (**85**).

Section 5.1.2 of the previous Chapter discussed the development of the synthetic procedure allowing for the synthesis of the *trans* γ-hydroxy enone derivatives (**17a-c**), Scheme 45. This methodology was repeated starting from the commercially available and

optically pure *S*-(+)-ethyl mandelate (**35a**). Protection of (**35a**) as the TBDMSO-ether (**40a**) was followed by reduction utilising DIBAL-H in toluene, providing the corresponding α-silyloxy mandelaldehyde (**42a**), in a yield of 80%. The aldehyde (**42a**) was subsequently deprotected employing aqueous HF to afford *S*-(+)-α-hydroxy phenylacetaldehyde (**36a**), which was used without further purification to yield the enantiomerically pure R-(*E*)-γ-hydroxy enones (**17a-c**) by reaction with the corresponding keto ylides (**37a-c**). The enantiomerically pure enones (**17a-c**) were synthesised under identical conditions as for the racemates (Section 5.1.2) and, similarly, could not be characterised in their pure form. Therefore, the procedures for the optically pure enones (**17a-c**) have not been repeated in the experimental section of this thesis.

Immediately upon their synthesis, each optically pure enone (**17a-c**) was treated *in situ* with the triplet sensitiser benzophenone, benzyl ester ylide (**37f**), and subjected to irradiation from two 300 W sunlamps. The reactions were analysed at regular intervals by ^{1}H NMR spectroscopy, as per the trials performed in Section 6.2.2.1, and the results obtained are presented in Table 21. Note that as no cyclopropyl products were provided under thermal reaction conditions, Table 21 does not include a comparison of the 'old' and 'new' methodology.

Table 21. Formation of enantiomerically pure trisubstituted cyclopropanes from *S*-(+)-α-hydroxy mandelaldehyde (**36a**), under photolytic reaction conditions.

	X	Enone	*trans* Cyclopropane (yield, %)[a]	Time (hours)
1	CH$_3$	(**17a**)	(0)	30
2	Ph	(**17b**)	(**83a**) (10)	17.5
3	*t*-Bu	(**17c**)	(0)	30

[a] Percentage yields quoted refer to the isolated yields calculated from α-hydroxy mandelaldehyde (**36a**).

At last, an optically pure trisubstituted cyclopropane (**83a**) was synthesised from the enantiomerically pure mandelate derived enone (**17b**), albeit in a low yield of 10%. *trans* Benzyl 2-(2-benzoyl-3-phenylcyclopropyl)acetate (**83a**) was recovered as a white

crystalline solid following removal of the bulk impurities through a squat chromatography column and recrystallisation of the subsequent oil from hot heptane. The enantiomeric excess of (83a) was determined to be an excellent ≥ 98% by chiral shift ^{1}H NMR experimentation, as described in Section 5.3.

As would be expected, the ^{1}H NMR spectrum of the *trans* cyclopropane (83a) was similar to that of the previously synthesised cyclopropanes derived from the 'lactate' enones (39a-d). The characteristic splitting pattern of; two doublets of doublets (dd) due to the diastereotopic methylene group protons attached directly to the ring, and three separate signals for each of the methine protons on the cyclopropane ring (dd, dddd, and dd signals appearing at increasing field strength) were all present. No *cis* cyclopropane (83b) and accordingly, no enolene isomer (83c) was observed in the crude product ^{1}H NMR spectrum.

Unfortunately, this was the only enone (17b) to provide any cyclopropyl products under the photolyic conditions. On each occasion, Entries 1-3 of Table 21, the major product was the corresponding 1,4-diketone (46a-c), arising from the Kornblum-De La Mare rearrangement of the highly susceptible enones (17a-c).[80] A small amount of the furan derivative (51a-c) was also observed in the crude ^{1}H NMR spectrum of each reaction, along with a significant proportion of a complex mixture of unidentified decomposition products.

The facile decomposition of the *trans* enones (17a-c) had previously been observed (Section 5.1.2), however, under the conditions employed for the photoisomerisation reaction this decomposition seemed to dramatically increase. It was assumed this was a result of the generated *cis* γ-hydroxy enone (85) existing in equilibrium with the isomeric cyclic hemiacetal (89). The basic ylides (37a-c and 37f) in solution were further promoting the already rapid rearrangement to 1,4-diketone (46), which was clearly occurring at a much faster rate than the ylide (37f) could undergo Michael addition with the *cis* enone (85). The scheme below indicates the complex equilibrium system existing between all of the reactive species, Scheme 52.

Where X= CH₃, Ph, *t*-Bu.
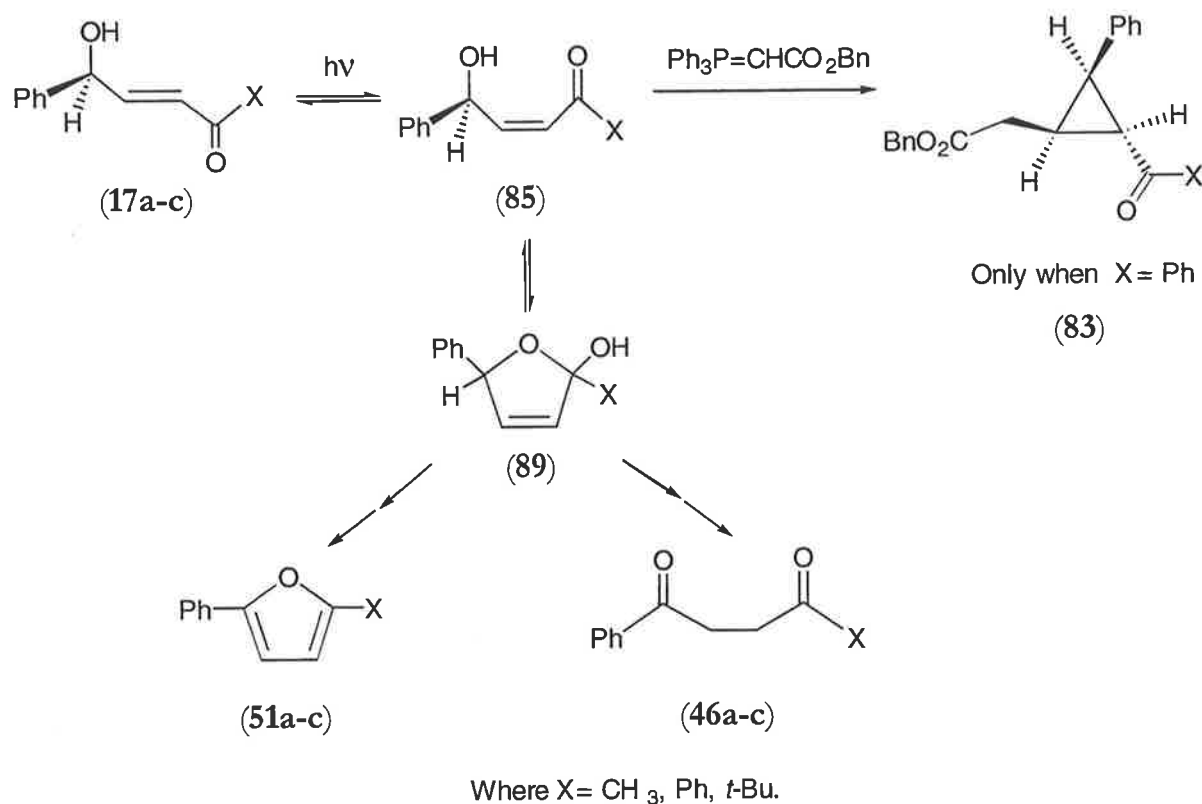
Scheme 52

Attempting to trap the reactive *cis* γ-hydroxy enone (85) by increasing the concentration of the ester ylide (37f) was futile, as it merely aided decomposition, presumably due to the basic character of stabilised ylide. On the other hand, decreasing the ylide (37f) concentration in order to reduce the basicity of the solution also assisted in decomposition to 1,4-diketone (46), by virtue of allowing enough time for the enone (85) to rearrange on its own accord. A third modification involved the trialing of alternative triplet sensitiser, which is discussed in the following section.

Employing the photoisomerisation technique had been successful in yielding an enantiomerically pure trisubstituted cyclopropane (83a), containing phenyl substitution directly attached to the cyclopropyl ring. Whilst only one enone (17b) had been induced to cyclise using this technique, it was a marked improvement over the complete inadequacy of the initial thermal reaction conditions with the 'mandelate' enones (17a-c).

6.3   Investigating the effect of the triplet sensitiser.

Benzophenone was selected as the triplet sensitiser for photoisomerisation of the *trans* γ-hydroxy enones (**17/39/67**), from assimilation with sensitised isomerisations of similar substituted alkenes, Section 6.1. As presented above in Section 6.2, on most occasions the benzophenone triplet was able to efficiently populate the triplet state of the enone in question and effect the desired photoisomerisation. However, there are other triplet sensitisers that are worthy of investigation, which have the potential to effect the same result.

Two alternative carbonyl triplet sensitisers were chosen for investigation, based on their triplet energies, Table 22. Only those photosensitisers with triplet energies greater than that of benzophenone were chosen. It was hoped that if any of these did prove to be comparative sensitisers, then perhaps they might be able to populate the triplet state of the enones not excited by the energy transfer from triplet benzophenone.

Additionally, it was thought that non-carbonyl based sensitisers should be tested to ensure that a thorough investigation was conducted. 9,10-Dicyanoanthracene (DCA) was chosen as one such triplet sensitiser due to its frequent and successful use in literature,[118-120] along with the analogous tetracyanoethylene (TCNE).[121] In order to provide a diverse range of mechanisms of action, diphenyl disulphide was also selected, which is thought to react by a radical mechanism.[122-124]

Table 22. Triplet energies (E_T) of the selected carbonyl triplet sensitisers.

	Sensitiser	E_T (kcal/mol)
1	Benzophenone	67.0 [115]
2	Acetophenone	74.0 [125]
3	Acetone	80.0 [126]

The most successful cyclopropanation reaction performed thus far was the formation of *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**), synthesised in a 50% yield after 40 hours of irradiation with triplet sensitiser benzophenone. As a result, it was

decided to perform the sensitisation experiments employing the precursor *trans* γ-hydroxy enone (**39b**) and benzyl ester ylide (**37f**) to generate (**16a**). At the completion of the trials a direct comparison with the results obtained utilising benzophenone, of both the product yields and reaction times would be carried out.

The *trans* phenyl keto enone (**39b**) was synthesised as previously described, Section 5.1.1, and 1.5 equivalents of benzyl ester ylide (**37f**) were added. The selected sensitiser was added to the reaction vessel and the mixture was irradiated with stirring. The reaction progress was followed by ^{1}H NMR analysis and at the termination of the reaction the crude product was partially purified by squat column chromatography, to remove the triphenylphosphine oxide and ylide impurities. Product yields were then determined from the ^{1}H NMR spectrum of the isolated product mixture, as a percentage of the combined product yield. Table 23 displays the reagents, reaction conditions and results obtained for these experiments.

Table 23. Formation of *trans* cyclopropane (**16a**) under photolytic conditions, utilising various photosensitisers.

	Sensitiser	Equiv.[a]	Time (hrs)	Cyclopropane (yield, %)[b]		Diketone (yield, %)[b]	Enone (yield, %)[b]
				trans (**16a**)	*cis*/enolene (**16b/c**)	(**46a**)	(**39b**)
1	Benzophenone	0.1	40	50	12	5	0
2	Acetophenone	0.1	17.5	41	7	33	5
3	Acetone	0.2	20	24	5	9	5
4	Acetone	neat[c]	20	41	10	5	5
5	DCA	0.05	25	54	8	8	trace
6	TCNE	0.05	20	31	9	9	5
7	Ph_2S_2	0.2	15	0	0	*ca.* 20	0
8	Ph_2S_2	5.0	5	0	0	*ca.* 30	0

[a] Number of mole equivalents of sensitiser used. [b] Percentage yields quoted refer to yields calculated from the ^{1}H NMR spectrum of the purified product mixture. [c] Acetone was used as the reaction solvent.

Entries 1-4 of Table 23 show that the highest yielding cyclopropanation reaction, employing a carbonyl triplet sensitiser, was that performed with the standard benzophenone. However, in only a slightly reduced *trans* cyclopropane (16a) yield of 41%, acetophenone photosensitisation provided (16a) in half the reaction time, Entry 2. This reduced cyclopropane yield was evidently due to the increase in by-product formation, specifically 1,4-diketone (46a), which was formed in 33%. A much lower product yield was obtained when a catalytic amount of acetone was used rather than acetone serving as both photosenstitiser and solvent, Entries 3-4. All other sensitisers were only present in catalytic amounts, nevertheless, this anomaly is supported by the literature.[126]

DCA photosensitisation provided the highest *trans* cyclopropane (16a) yield out of all of the sensitisers trialed, Entry 5 in Table 23. The product yields were in comparable ratios to those afforded utilising benzophenone, yet the irradiation time required was only 25 hours. Clearly the efficiency of the triplet state DCA species to populate the enone (39b) triplet state was much greater than that of the benzophenone triplet. Whilst this did result in an excellent improvement in the reaction time, the *trans* cyclopropane (16a) yield was only increased by 4%, which lies within the margin of error associated with the yield calculation. TCNE photosensitisation also greatly reduced the required reaction time, however, the yield of (16a) was likewise reduced, Entry 6.

The final sensitiser trialed was diphenyl disulphide, which was separately employed in 0.2 and 5.0 equivalents,[122,123] Table 23 Entries 7-8. On neither occasion were any cyclopropyl products produced. 1,4-Diketone (46a) was the major product generated under the catalytic diphenyl disulphide conditions,[123] along with a minor amount of an unknown product (90). Conversely, when an excess of diphenyl disulphide[122] was employed the ratio of products, (46a) and (90) was reversed.

The mechanism of alkene isomerisation when employing diphenyl disulphide involves the addition and elimination of thiyl radical intermediates, as illustrated in the literature example reported by Harrowven and co-workers in 1999, Scheme 53.[122] Unfortunately, when this protocol was applied to the isomerisation of enone (39b), the only products obtained were the 1,4-diketone (46a) and a new compound identified to be the thiyl addition product (90), Scheme 54.

Scheme 53 [122]

(39b)   (46a)   (90)
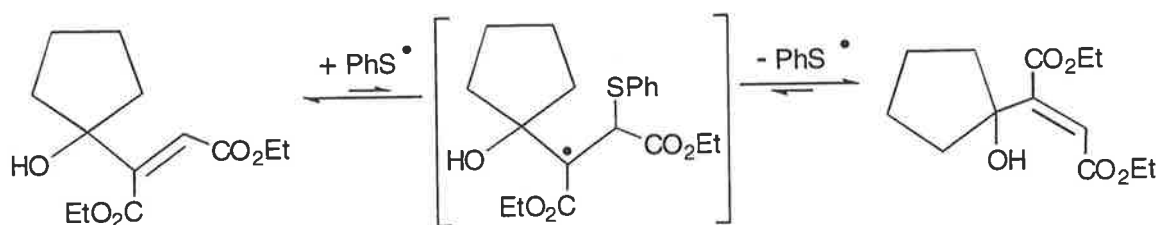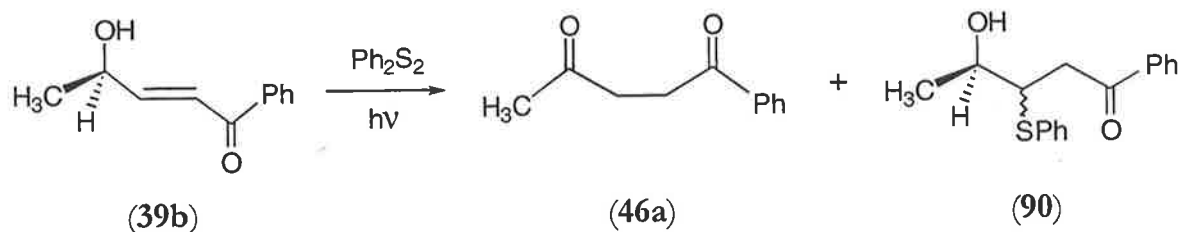
Scheme 54

The ^{1}H NMR spectrum for the thiyl radical addition product (90) can be described as follows. A complex system of overlapping multiplets resonated between 7.95 and 6.95 ppm due to the aromatic protons. A doublet of quartets and a doublet of triplets, each equivalent to one proton, were present at 4.01 and 3.87 ppm respectively. The signal at 4.01 ppm corresponds to the methine group bearing the hydroxyl group, split by the adjacent methyl and methine group protons. The signal for the methine group proton attached to the thiyl group appeared as the doublet of triplets at 3.87 ppm, coupling to both the neighbouring HOC<u>H</u> and methylene group protons. Continuing up field, the two geminal protons of the methylene group resonated separately as two doublets of doublets at 3.10 and 3.35 ppm. Two signals were recorded, as the protons are rendered non-equivalent as a result of the neighbouring chiral centre. The hydroxyl proton appeared as a broad singlet at 1.61 ppm and a doublet at 1.31 ppm was a result of the methyl group protons.

All of the spectral data recorded for (90) was consistent with the assigned structure. An interesting point to note is that only one diastereisomer was formed. Unlike the situation when HCl was deliberately added across the double bond of the enones (17/39), in which case two diastereomers formed in almost a 1:1 ratio, Chapter 3. This selectivity was presumably due to the structural differences of the intermediate species. Addition of the

thiyl radical initially generates a radical intermediate, which subsequently abstracts a proton. The analogous intermediate following the addition of hydrogen to the double bond results in the formation of a planar carbocation, whereby the chloride ion 'attack' is possible from either face with no discrimination.

The first step of the isomerisation mechanism was obviously successful in that the thiyl radical did add to the carbon-carbon double bond, however, elimination and subsequent isomerisation did not occur. This was presumably a result of the intermediate radical species abstracting a proton to afford (**90**). The reaction was repeated in an aprotic solvent in the hope of preventing this apparent H$^+$ abstraction, which may have been supplied by the solvent. Unfortunately, this modification had no effect and the same products were generated on each occasion.

In summary, the results of the investigation into alternate photoisomerisation sensitisers were mixed. Benzophenone was proven to be a good choice for photoisomerisation of the *trans* γ-hydroxy enones (**39b**), such that a high yield of *trans* cyclopropane (**16a**) was afforded in a reasonable reaction time. The other carbonyl triplet sensitisers tested did not display an improved all-round efficiency, i.e. whilst reaction times were reduced the yields were also down. The cyano sensitisers exhibited good results, especially DCA, which afforded the target cyclopropane (**16a**) in a comparative yield in approximately half the reaction time. Diphenyl disulphide was clearly of no value for the required isomerisation.

Considering the good results obtained with the DCA sensitiser, it was proposed that DCA might be more effective for photoisomerisation of the enones that had not been isomerised utilising benzophenone. As such the methyl keto enone (**39a**) was irradiated in the presence of 5% DCA and benzyl ester ylide (**37f**). The reaction was follow by ^{1}H NMR spectroscopy and was stopped after 40 hours of irradiation. At which time no cyclopropyl products had been formed and the majority of the enone (**39a**) had decomposed.

Not yet willing to concede defeat, the trial was repeated again, this time using the 'mandelate' derived methyl keto enone (**17a**). Unfortunately, the almost equivalent result was evident after 20 hours of irradiation. Only a trace of *trans* cyclopropane (**83a**) was

produce, with 1,4-diketone (**46a**) being the major product as a result of decomposition of the enone (**17a**).

Apparently, the initial choice of benzophenone as the triplet sensitiser was extremely fortunate. It successfully improved the yields and reduced the reaction times of the majority of the cyclopropanations trialed and has been proven to be more successful than many other sensitisers. The cyclopropanes obtained utilising the photoisomerisation technique were generated in good two-step yields of up to 65%, and in excellent enantiomeric purity of ≥ 98%.

7   Application of the new methodology: a practical example.

In order to demonstrate the potential of this new methodology for the provision of enantiomerically pure cyclopropanes, a practical example was proposed. As discussed earlier in Chapter 2, the chiral pool of natural products incorporates an almost infinite array of chiral building blocks from which γ-hydroxy enone precursors can be drawn. One such unit is the sugar D-glucono-1,5-lactone (**91**), which has been employed by numerous synthetic chemists over recent decades for a variety of synthetic projects,[127-130] as a cheaper alternative to the more traditional substrate D-mannitol.[131]

D-Glucono-1,5-lactone (**91**) is inexpensive and readily available in its optically pure form. As such, this building block was selected as the starting point for the synthesis of the enantiomerically pure cyclopropane (**92**), which will contain a total of six chiral centres. The new cyclopropane (**92**) will have boundless potential for possible functional group manipulation including synthetic transformations leading to elongation of the side chain, selective deprotection and/or cleavage of the isopropylidene groups, and subsequent cyclisation or derivatisation of the hydroxyl groups (e.g. OH → NH$_2$).

An additional motive for utilising gluconolactone (**91**) was the three pre-existing chiral centres of known absolute stereochemical configuration. It was envisaged that once formed, the 'sugar arm' of cyclopropane (**92**) would allow for the absolute configuration of the three chiral centres forming a part of the cyclopropyl ring to be unequivocally determined. Clearly, this relied on the product (**92**) being a crystalline solid suitable for crystallographic analysis.

7.1   Formation of the sugar-derived *trans* γ-hydroxy enone (**96**).

The original proposal to reach the target *trans* γ-hydroxy enone (**17/39**) had involved the synthesis and subsequent deprotection of the corresponding γ-silyloxy enone (**44/45**), Chapter 2. Much to the dismay of the researchers, all attempts to execute this strategy

proved futile. The intended pathway was abandoned and replaced by a more successful strategy, Chapter 4. However, it was postulated that the 'sugar arm' of the corresponding silyloxy enone (**93**) might allow for deprotection of the silyl group without spontaneous decomposition to 1,4-diketone (**94**) or furan (**95**). Thus, it was hoped that with the added stability gained from the large 'sugar arm,' the γ-hydroxy enone (**96**) would be stable and able to withstand the necessary deprotection environment. Scheme 55 depicts the synthetic strategy proposed, providing for the formation of the D-glucono-1,5-lactone (**91**) derived *trans* γ-hydroxy enone (**96**).
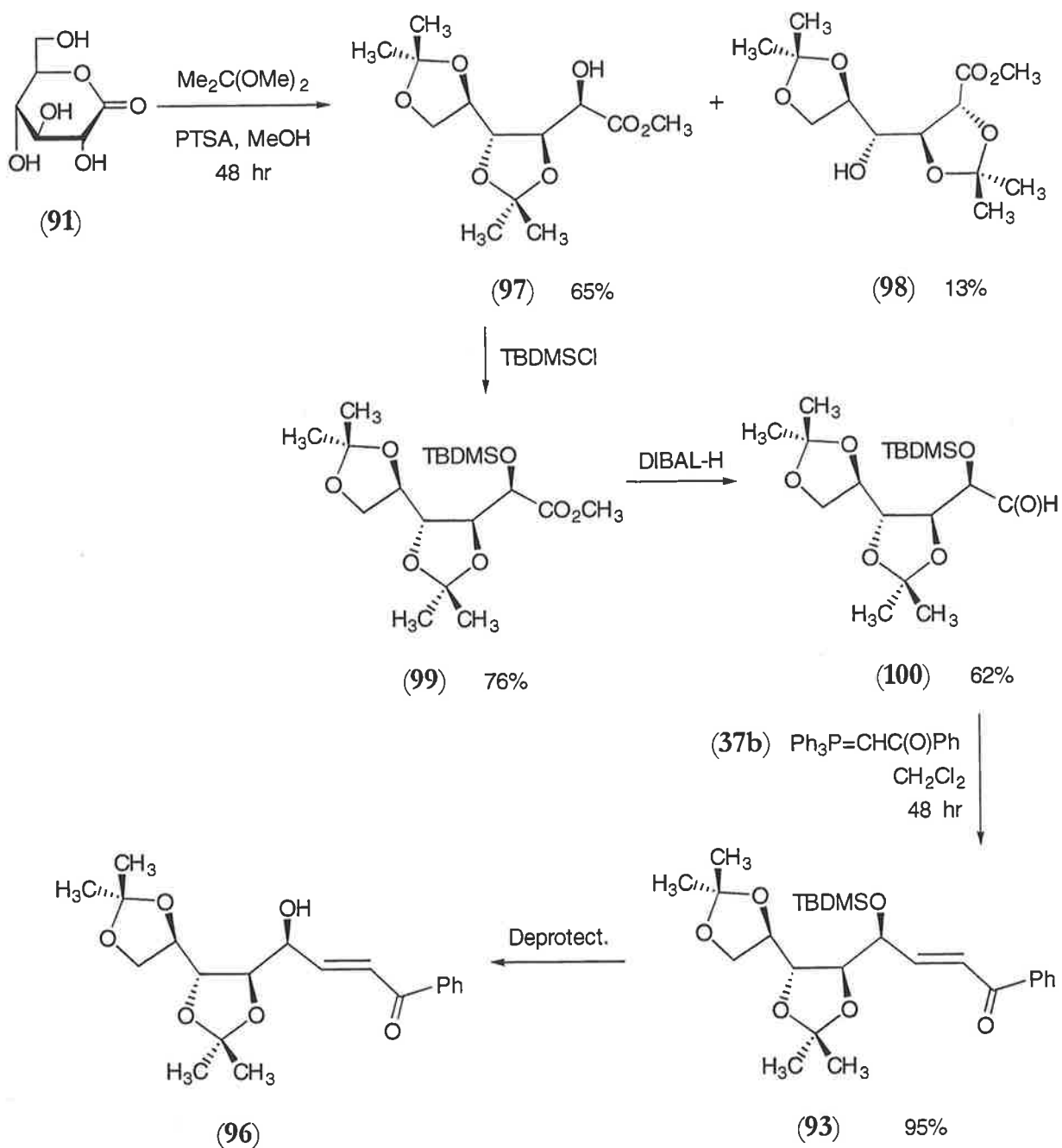
Scheme 55

The first step in the pathway involved conversion of the precursor D-glucono-1,5-lactone (91) into methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (97), which was achieved according to the method of Regeling *et al.*[132] Selective protection of the 3,4 and 5,6-diol functionalities of (91) with a catalytic amount of *para*-toluene sulfonic acid, 2,2-dimethoxypropane and methanol was followed by work-up and distillation to provide 81% of slightly impure (97). Regeling reported that the product was sufficiently pure for subsequent routine reactions, however, the impurity proved to complicate the ensuing silyl protection step. Eleven years later, de Souza and co-workers reported the identity of this impurity to be the isomeric 2,3:4,5-protected species (98).[133] Column chromatography of the isomeric mixture enabled their separation and provided 65% of the 3,4:5,6-protected product (97), and 13% of the 2,3:4,5-protected by-product (98). Note that all D-glucono-1,5-lactone (91) derived products have been named in accordance with the literature nomenclature.[133,134]

The free hydroxyl group of (97) was protected as the TBDMS-ether (99) in a yield of 76% following purification by reduced pressure distillation of the extremely viscous oil, as described for the preparation of (40/41). The corresponding α-silyloxy aldehyde (100) was produced as a clear colourless oil from the DIBAL-H reduction of the ester (99) over 1.5 hours. The ^{1}H NMR spectrum of aldehyde (100) displayed characteristic signals for the two isopropylidene protecting groups and alkyl chain of the 'sugar arm', including a broad multiplet for the combined methylene protons and four singlets for each of the methyl group protons. The aldehyde proton resonated as a doublet down field at 9.62 ppm. Stored in its concentrated state, aldehyde (100) was stable for up to one week at ambient temperature.

Formation of the Wittig product *trans* 1-phenyl-2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-4-silyloxy-D-*gluco*-oct-2-enone (93) was achieved over a period of two days heating under reflux in the presence of 1.05 equivalents of phenyl keto ylide (37b), in an excellent yield of 95%. The γ-silyloxy enone (93) was greater than 95% pure following precipitation and removal of triphenylphosphine oxide with hexane, as estimated by ^{1}H NMR. No vinylic coupling constant was apparent in the ^{1}H NMR spectrum for (93) and the olefinic protons appeared as one doublet, equivalent to two protons, rather than the two anticipated doublet of doublets. This was presumably due to the chance occurrence of the

non-equivalent protons resonating at exactly the same frequency. The small coupling constant of 1.8 Hz for the doublet was reciprocated in the coupling constants calculated for the neighbouring methine group proton bearing the TBDMSO-group, of 1.6, 1.6 and 3.2 Hz.

Cleavage of the silyl group was then attempted avoiding the use of the strongly acidic deprotection conditions of TFA and HF, due to the known instability of the cyclic isopropylidene groups.[70] Under analogous procedures to those described in Chapter 2, TBAF and BF_3-Et_2O were employed with no success and the regenerated alcohol functionality was not afforded. Literature procedures reporting the removal of a silyl group in the presence of isopropylidene protecting groups were subsequently trialed, including the use of ceric ammonium nitrate in methanol[135] and peroxymonosulphate on alumina with microwave irradiation.[136] Additionally, alternative silyl group cleavage procedures including the use of the trityl cation $Ph_3C^+BF_4^-$ [70] and potassium superoxide with crown ether[137] were attempted. Unfortunately, the recurring result of each of these trials was either recovery of the starting enone (**93**) or isolation of an unidentified mixture of decomposition products. Due to the ineffectiveness of these trials, the procedures have not been included in the experimental section of this thesis.

Whilst an exhaustive investigation of potential deprotecting reagents and conditions was not carried out, it was decided not to continue with this line of approach. Unlike the earlier attempts to effect deprotection of the γ-silyloxy enones (**44/45**), which generally afforded the respective 1,4-diketones (**46/54**) and furans (**51/55**), the main problem in this system appeared to be the extraordinary stability of the TBDMS-group in (**93**) to cleavage. One last attempt to remove the silyl group from the silyloxy enone (**93**) was successful, however, as expected the use of HF (in both water and pyridine[138,139]) not only removed the TBDMS-group but also cleaved the isopropylidene protecting groups.

At this point, attention once again returned to deprotection of the α-silyloxy aldehyde (**100**) to afford 3,4:5,6-di-*O*-isopropylidene-D-glucose (**101**), Scheme 56, which had previously been the only successful route for the generation of the *trans* γ-hydroxy enones (**17/39**), Sections 5.1.1-5.1.2. Unexpectedly, the results of analogous deprotection reactions to those described above were also negative. The major component of the crude

reaction mixtures was once more unreacted starting material (**100**). On some occasions, ^{1}H NMR spectroscopy revealed a trace of a new aldehyde-type signal, however, the reactions proved to be non-reproducible and the yield of the compound responsible for this new peak was unable to be increased to a significant level.

(100)   **(101)**
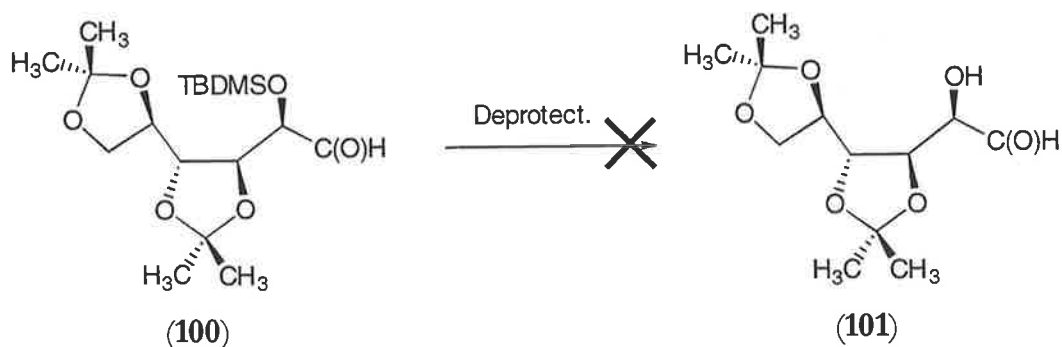
Scheme 56

Despite the disheartening results reported above, a literature procedure was discovered for the formation of the α-hydroxy aldehyde (**101**). D-Glucono-1,5-lactone (**91**) was again the starting material, yet the intermediate species and hence the synthetic approach were dissimilar. The methodology allowing for the generation of the aldehyde (**101**) is presented in Scheme 57, as described by Jarosz *et al*.[134]

(91)   **(102)**   **(103)**

(101)
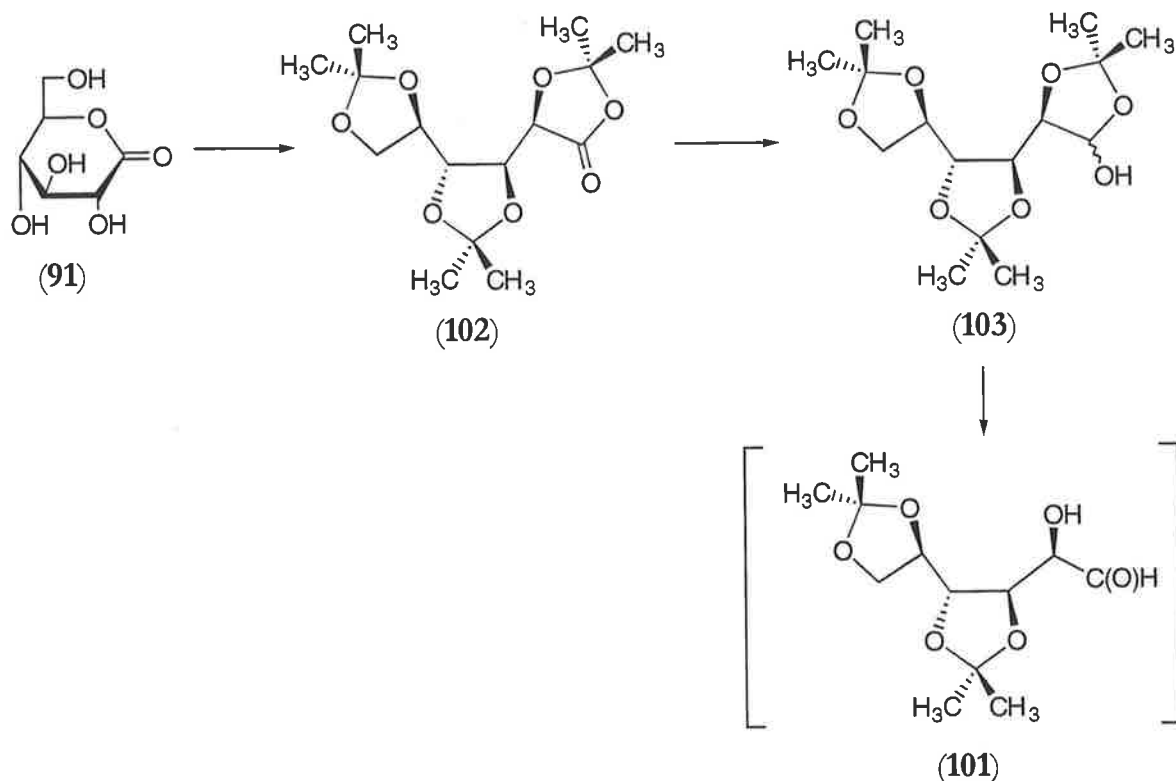
Scheme 57

The α-hydroxy aldehyde (**101**) is a valuable synthetic building block and has been employed by Jarosz for use in a number of syntheses, including employing the aldehyde (**101**) for coupling with an ester ylide to afford the corresponding alkene product.[134,140,141] Therefore, we were confident that following this procedure for the synthesis of the α-hydroxy aldehyde (**101**), and the ensuing Wittig reaction to afford the enone (**96**), would occur smoothly.

Triacetonilide (**102**) was synthesised from the treatment of (**91**) with acetone and zinc chloride with stirring overnight. The reported work-up procedure was modified to include neutralisation of the crude product mixture with aqueous sodium hydroxide and sodium hydrogen carbonate, as the suggested washings with brine did not achieve neutrality. Batch-wise recrystallisation from methanol afforded crystalline triacetonilide (**102**) in a slightly lower yield of 64%, than the reported 76% yield.[134]

A mixture of the cyclic hemiacetal (**103**) and the open chain α-hydroxy aldehyde (**101**) was formed from the DIBAL-H reduction of (**102**), as per the literature procedure.[134] The major product of the latter reduction was hemiacetal (**103**), however, following purification by chromatography on silica gel, partial hydrolysis of (**103**) to α-hydroxy aldehyde (**101**) was observed.[142] Complete conversion to α-hydroxy aldehyde (**101**) was achieved by treatment of the triacetonilide hemiacetal (**103**) with a methanol/triethylamine/water mixture overnight at ambient temperature. Despite some of the aldehyde (**101**) being chromatographically isolated from (**103**), the crude product (**101**) was prone to decomposition on silica gel. Therefore, α-hydroxy aldehyde (**101**) was utilised for the Wittig olefination reaction without purification and was not characterized. The aldehyde proton signal was, however, clearly evident at 9.77 ppm in the ^{1}H NMR spectrum.

The crude α-hydroxy aldehyde (**101**) was taken up in dry CH_2Cl_2 and 1-phenyl 2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (**37b**) was added in 1.1 equivalents. The solution was heated under reflux in an atmosphere of nitrogen for four hours, at which time ^{1}H NMR spectroscopy indicated that no starting aldehyde (**101**) remained. No signals corresponding to either 1,4-diketone (**94**) or furan (**95**) were present in the crude ^{1}H NMR spectrum, however, the spectrum was complicated due to the presence of an

unknown mixture of decomposition products. 1-Phenyl-2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enone (**96**) was shown to be stable to column chromatography and was isolated as a pure white solid in a yield of 49%.

The moderate yield of the sugar-derived *trans* γ-hydroxy enone (**96**) was ascribed to decomposition of the α-hydroxy aldehyde (**101**) prior to its reaction with the ylide (**37b**). This theory was supported by the aforementioned decomposition products observed in the ¹H NMR spectrum. More importantly, the enone (**96**) had been synthesised and was the first enone derivative produced to be stable to isolation and purification. This allowed for the complete characterisation of (**96**) in its pure form including an optical rotation measurement and microanalysis, which confirmed the chemical composition within the accepted boundaries.

The ¹H NMR spectrum recorded for (**96**) displayed the now anticipated signals of two doublets of doublets due to the olefinic protons, with the ³*J* coupling constant of 15.6 Hz confirming the *trans* orientation. The hydroxyl proton resonated as a doublet at 3.12 ppm, split by the adjacent methine proton. A 600 MHz ¹H NMR spectrum was recorded that resulted in the proton signals of 'sugar arm' being well resolved, enabling their complete elucidation, see Figure 1.
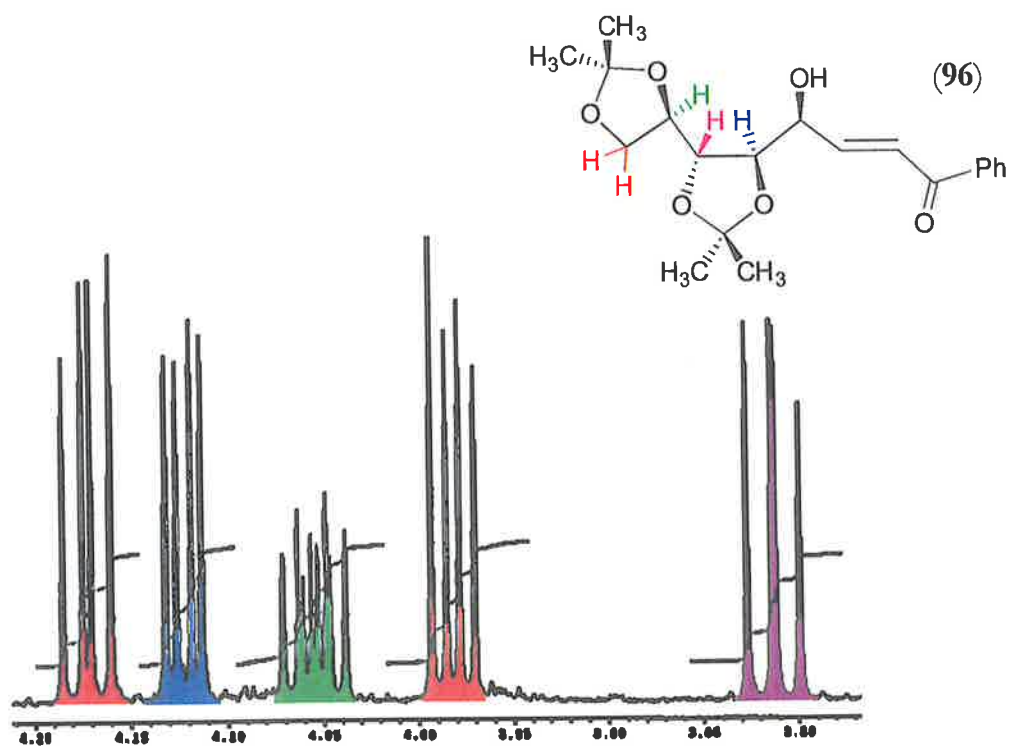
Figure 31. 600 MHz ¹H NMR expansion for 'sugar arm' of *trans* γ-hydroxy enone (**96**).

Whilst the intended synthetic pathway to reach the optically pure *trans* γ-hydroxy enone (96) had not been successful, Scheme 55, the target (96) was synthesised in moderate yield and excellent purity using an alternate strategy.[134] This was the first occasion on which the *trans* enone was a stable solid that was able to be fully characterised and did not require immediate transformation into the corresponding enantiomerically pure 'sugar arm' cyclopropane (92).

7.2 Formation of the sugar-derived optically pure cyclopropane (92).

Cyclopropanation of *trans* γ-hydroxy enone (96) was first attempted employing the sensitised photoisomerisation technique, optimised in Chapter 6. As such, a CH_2Cl_2 solution of (96) was irradiated with two 300 W sunlamps in the presence of the benzyl ester ylide (37e) and 10 mole percent of benzophenone, Scheme 58. The target 1,2:3,4-di-*O*-isopropylidene version of benzyl 2-[2-benzoyl-3-(1,2,3,4-tetrahydroxybutyl)cyclopropyl] acetate (92), correctly named benzyl 2-{2-benzoyl-3-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropyl}acetate, was evident in the crude ^{1}H NMR spectrum after 15 hours of irradiation and isolated as a pure white crystalline solid in a low yield of 7.5%, following chromatography. The major product of the reaction was the 1,4-diketone (94), which was recovered in a yield of 18%, whilst the large portion of decomposition products observed in the crude ^{1}H NMR spectrum where neither recovered nor identified.
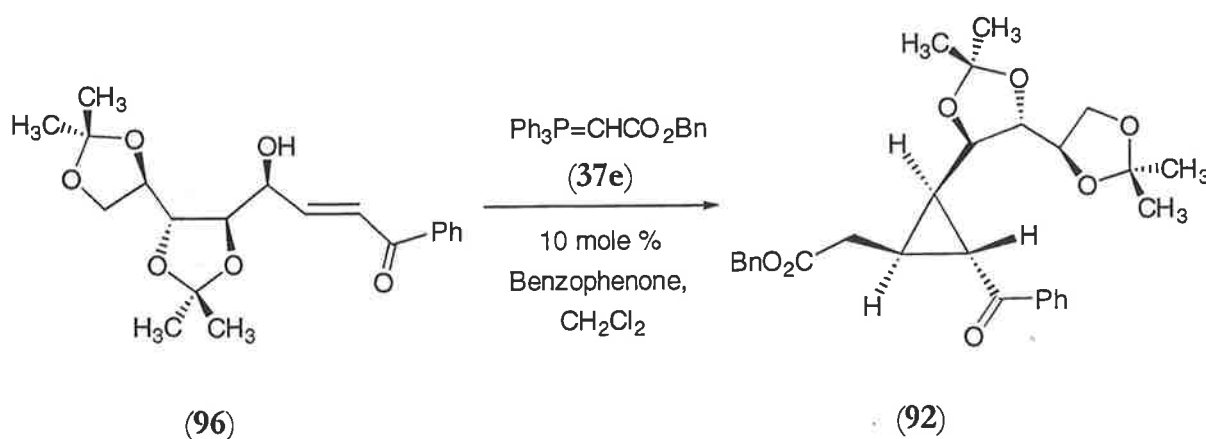
Scheme 58

The ¹H NMR spectrum for cyclopropane (**92**) was highly complex due to the large number of non-equivalent protons, amplified by the six chiral centres existent within the molecule. The details of this spectrum will not be discussed here but are included in the experimental section of this thesis. More conclusive evidence for the existence and structural configuration of (**92**) is presented in Figure 32. Crystallisation of the cyclopropane (**92**) from a 10:1 mixture of EtOAc and toluene by slow diffusion with hexane, provided clear crystals suitable for X-ray analysis, Figure 32 depicts the crystal structure obtained.[143]
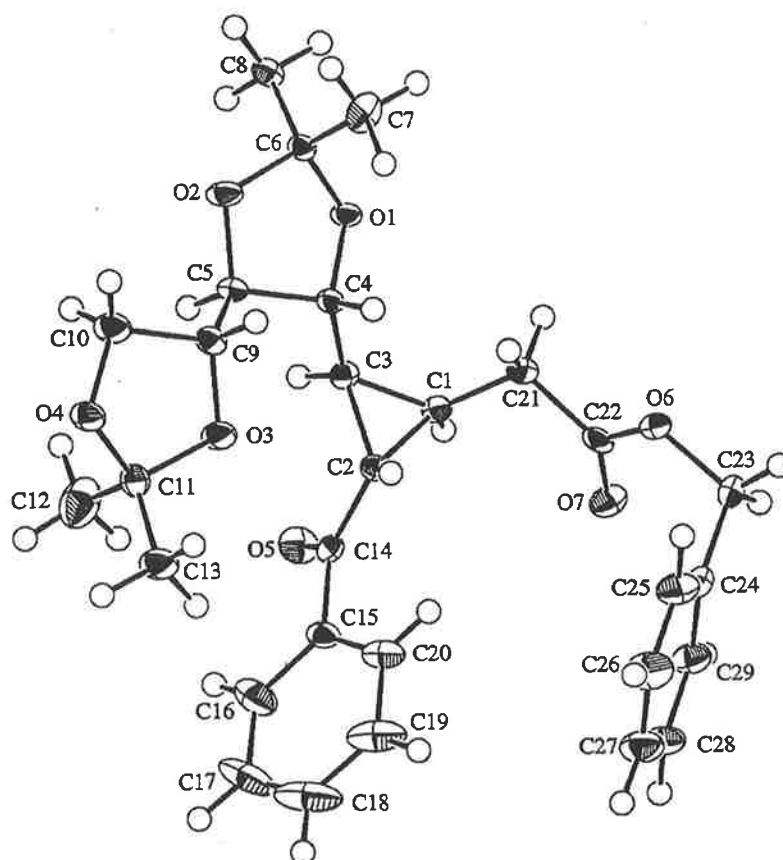
Figure 32. Molecular structure of cyclopropane (**92**), derived from the *trans* γ-hydroxy enone (**96**), with crystallographic numbering scheme indicated.[143]

The low yield of cyclopropane (**92**) prompted trials to improve the yield of (**92**) and reduce the formation of the 1,4-diketone (**94**). The photolytic cyclopropanation was repeated replacing benzophenone with the DCA photosensitiser, whilst keeping all other reaction conditions the same. The same 15 hour irradiation time was required for all of

the precursor enone (**96**) to be consumed and the crude ^{1}H NMR indicated that the 1,4-diketone (**94**) was now present in a lower ratio than the target (**92**). To the delight of the researchers, the cyclopropane (**92**) yield more than doubled, although it was still quite low at 18%.

It should be noted that formation of cyclopropane (**92**) was also trialed under the initial thermal reaction conditions, as in Sections 4.3 and 5.2. After 78 hours of heating under reflux some enone (**96**) still remained, however, no cyclopropyl products (**92**) were evident, as seen by ^{1}H NMR.

7.3   Determination of the absolute configuration about the cyclopropyl ring.

Whilst the stereochemical orientation of the substituents about the cyclopropyl ring, with respect to each other, had previously been established,[49] the absolute configuration was not conclusively known. With the synthesis of the sugar-derived cyclopropane (**92**) complete, it should now be possible to determine the absolute stereochemical configuration by comparison with the pre-existent chiral centres in the 'sugar arm'.

From consideration of the cyclopropanation mechanism, Scheme 49, it would be expected that inversion of the original chiral centre, from the starting α-hydroxy ester (**35/38/97**), would occur, C^3 in Figure 32. Collapse of the intermediate oxaphospholane (**18**) resulting in the formation of cyclopropane (**16**), is initiated by intramolecular nucleophilic 'attack', proceeding by a S_N2 mechanism. It is well known that a S_N2 process proceeds with inversion of configuration when substitution occurs at a chiral carbon and this effect is commonly called the *Walden inversion*. This was in fact the case, which adds further support to the mechanism of cyclopropanation investigated and reported by Avery *et al.*[101]

The three chiral centres of the 'sugar arm' in cyclopropane (**92**) have an R,R,R configuration, C^4, C^5 and C^9 in Figure 32. Extrapolating from this, the absolute configuration of the C^1, C^2 and C^3 chiral centres were determined to be R,S,S respectively. Therefore, the absolute configuration accounting for each of the chiral centres present in

(92) is R,S,S,R,R,R, in increasing crystallographic number, see Figure 33. The configuration at C^3 is now S, which is consistent with inversion of the R-chiral centre bearing the hydroxyl group in the precursor 3,5:5,6-di-O-isopropylidene-D-glucose (101). The same chiral centre in the *trans* γ-hydroxy enone (96) exhibits S configuration, however, it is important to realise that this is only due to a change in the priority order of the substituents about the chiral centre and not a result of inversion of configuration.
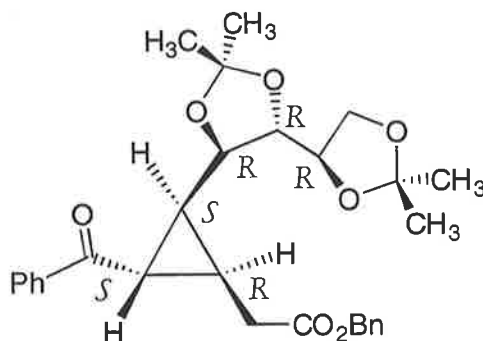
Figure 33. Absolute stereochemical configuration of the sugar-derived cyclopropane (92), drawn as depicted in the crystal structure, Figure 32.

From this, it is possible to determine the absolute configuration for each of the optically pure trisubstituted cyclopropanes synthesised in the earlier Chapters 5 and 6. For example, *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (78a) can now be assigned with R,R,S absolute configuration, Figure 34. Knowing that the configuration about C^3 must be inverted from that of the precursor R-(+)-methyl lactate (38b), therefore S since the group priority order does not change, the remaining two chiral centres were assigned.
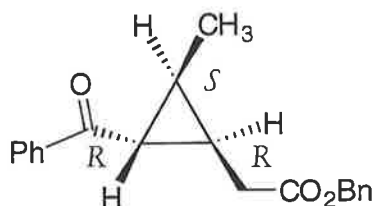
Figure 34. Absolute stereochemical configuration of *trans* benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (78a).

As such, each cyclopropane (16, 76, 78-81 and 83) has been included in the experimental section of this thesis with the correct absolute stereochemical configuration quoted.

7.4   Summary of results.

A new approach to diastereomerically and enantiomerically pure functionalised cyclopropanes employing optically pure *trans* γ-hydroxy enones has been outlined. Modification of the initially proposed synthetic strategy resulted in the successful generation of a variety of optically pure *trans* γ-hydroxy enones/enesters. Treatment of these enones with stabilised phosphorus ylides provided the enantiomerically pure *trans* cyclopropanes in low to medium yields, which were greatly enhanced through the inclusion of a sensitised photoisomerisation step. The absolute stereochemical configuration of the cyclopropyl products was conclusively determined as outline in this Chapter from a practical cyclopropanation example, which highlights the enormous potential of this new methodology.

8   Experimental.

8.1   General notes.

Melting points were recorded using a Kofler hot stage micro-melting point apparatus and are quoted as uncorrected values.

Optical rotations were determined using a Steeg and Reuter SR 100 Digital Polarimeter. Concentration (*c*) is quoted in g/100 mL in chloroform and specific rotations ([α]$_D$) are reported at the specified temperature. Due to the sensitivity limitation of the polarimeter, specific rotations have not been reported for compounds where less than 10 mg of pure sample was available.

Infrared spectra were recorded on a Jasco A-102 spectrometer or on an ATI Mattson Genisis series FTIR spectrometer. Spectra were recorded as indicated, either Nujol mulls or liquid films between sodium chloride plates, or, in solution cells as dilute deuterated chloroform ($CDCl_3$) solutions. Peak intensities are indicated in parentheses as: strong (s), medium (m) and weak (w).

^{1}H NMR spectra were measured at 200, 300 or 600 MHz (50, 75, and 150 MHz respectively for ^{13}C NMR) on Varian NMR spectrometers using a dual 5 mm ^{13}C/^{1}H probe. All spectra were recorded as $CDCl_3$ solutions with tetramethylsilane added as the internal standard. ^{1}H NMR multiplicities are given the abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (b), and are quoted in parts per million. All regiochemical NMR assignments were determined by 2-dimensional NMR experiments or by comparison with previously published chemical shift values for analogous compounds (as cited).

^{13}C NMR resonances are quoted to 1 decimal place with the exception of signals falling within 0.05 ppm of each other, whereby 2 decimal places are reported. Where indicated, only the significant ^{13}C signals are quoted, indistinct aromatic peaks are not quoted due to ambiguity with impurities. Chiral shift NMR experiments were performed in a 4:1 mix of deuterated benzene and carbon tetrachloride employing europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] shift reagent.

Microanalyses were carried out by the University of Otaga, New Zealand.

Mass spectra were typically measured on a Vacuum Generators ZAB 2HF mass spectrometer operating at 70 eV, by electron impact (EI) techniques. Where indicated mass spectra were determined by fast atom bombardment (FAB) techniques, liquid secondary ionisation mass spectrometry (LSIMS) or GC-MS on a Finnigan MAT GC-MS spectrometer. Relative intensities are quoted in parentheses. Accurate mass spectra were recorded by the Organic Mass Spectrometry Facility at the University of Tasmania, Australia. The Finnigan GC-MS is fitted with an electrospray ionisation source.

Thin layer chromatography (TLC) was performed on Merck Silica gel 60 F_{254} aluminium backed plates and visualised using 253 nm ultra violet light and/or by staining with ammonium molybdate dip [ammonium molybdate (20 g) dissolved in concentrated sulfuric acid (11.2 mL) and water (188 mL)]. Squat chromatography was run on Merck Silica gel 60 PF_{254} containing gypsum for preparative layer chromatography. Flash chromatography was carried out with Merck Silica gel 60 (230-400 mesh ASTM).

All photolysis reactions were performed in standard laboratory pyrex glassware with 2 x 300 W Ultra-Vitalux Woton sunlamps. The sunlamps were set 10 cm away from the reaction vessel and each solution contained approximately 10 mole % of the triplet sensitiser, benzophenone. While no additional heat source was supplied, these CH_2Cl_2 solutions were prone to reflux throughout irradiation.

Solvents were distilled and purified as per standard laboratory procedures.[144] Anhydrous solvents were either freshly distilled[144] or stored over molecular sieves under an atmosphere of nitrogen.

Movement away from IUPAC nomenclature for some functionalisation has been utilised in order to aid in clarity of structure reference. For instance, phenyl methyl has been referred to as benzyl. For further examples see abbreviations at the beginning of this thesis.

8.2 Experimental procedures.

1-Phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (37b)

A solution of triphenylphosphine (10.89 g, 41.95 mmol) in ether (300 mL) was prepared. To this stirred solution was added 2-bromoacetophenone (8.35 g, 41.52 mmol) in portions (3 x *ca.* 2.7 g). The resulting emulsion was heated under reflux. After cooling, additional ether (200 mL) was added to the mixture in order to ensure complete precipitation of the intermediate phosphonium salt (37b'), which was collected by vacuum filtration, 17.04 g (89%). Analysis of the precipitate deemed the phosphonium salt to be of excellent purity. **¹H NMR** δ (300 MHz); 8.37-8.36(m, aromatic), 7.98-7.48(m, aromatic), 6.39(d, 2, $^2J_{HP}$ =12.3 Hz, PC$\underline{H}_2$C=O) Formation of the stabilised ylide was achieved by stirring the crude salt in a 10% aqueous Na₂CO₃ solution (1350 mL) for 2 days. The fine precipitate was collected by vacuum filtration to provide 27.84 g of white powdery ylide (37b) in an 88% overall yield. **Mp** 176-179°C (lit. **Mp** 176-178°C);[76] **IR** (Nujol mull); 3049(s), 1720(w), 1587(w), 1525(m), 748(m) cm⁻¹; **¹H NMR** δ (300 MHz); 7.99-7.34(m, 20, aromatic), 4.44(bd, 1, $^2J_{HP}$ =24.6 Hz, P=C$\underline{H}$C=O); **¹³C NMR** δ (75 MHz); 184. 85(d, $^2J_{CP}$ =3.2 Hz), 141.21(d, $^1J_{CP}$ =14.6 Hz), 133.14, 133.00, 132.06, 131.97, 131.93, 131.86, 131.82, 129.25, 128.86, 128.70, 128.49, 128.33, 127.64, 126.84, 126.83, 126.42, 50.64(d, $^1J_{CP}$ =111.5 Hz). Carbon-phosphorus couplings (J_{CP}) are quoted as a doublet where the assignment was indisputable; all other signals have been listed as singlets.

1-*tert*-Butyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (37c)

1-Chloropinacolone (2.00 g, 14.9 mmol) was added to a solution of triphenyl phosphine (3.85 g, 14.7 mmol) in toluene (20 mL) with stirring. The reaction mixture was heated under reflux for 15 hours after which time the suspension was cooled on an ice bath and subsequent vacuum filtration provided 4.95 g of the targeted intermediate salt (37c') in a yield of 85%. **Mp** 186-189°C; **IR** (Nujol mull); 1698(s), 1616(w), 1588(w), 1438(s), 1117(m), 748(m) cm⁻¹; **¹H NMR** δ (300 MHz); 7.94-7.64(m, 15, aromatic), 6.04(d, 2, $^2J_{HP}$=11.7 Hz, PC$\underline{H}_2$), 1.23(s, 9, C(C$\underline{H}_3$)₃); **¹³C NMR** δ (75 MHz); 208.4(d, $^2J_{CP}$ =6.8 Hz), 134.3(d, $^4J_{CP}$ =2.9 Hz), 133.5(d, $^3J_{CP}$ =10.6 Hz), 129.7(d, $^2J_{CP}$ =12.8 Hz), 118.7(d, $^1J_{CP}$

=88.5 Hz), 45.3(d, $^3J_{CP}$ =4.3 Hz), 36.5(d, $^1J_{CP}$ =59.5 Hz), 25.8; **mass spectrum** (FAB, CHCl$_3$) **m/z** 362(100), 304(4), 276(8). Without supplementary purification, (**37c'**) (4.95 g, 12.50 mmol) was dissolved in a 10% aqueous solution of NaOH (30 mL) and stirred for 15 minutes. Product (**37c**) was observed immediately as a suspended powder which upon collection by vacuum filtration and drying under an IR lamp, yielded 4.36 g of white powdery solid (82%). The titled ylide (**37c**) was employed without further purification. **Mp** 184.5-186°C; **IR** (Nujol mull); 1530(s), 1434(s), 1108(m), 752(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.63-7.43(m, 15, aromatic), 3.79(d, 1, $^2J_{HP}$ =26.4 Hz, P=C$\underline{H}$), 1.20(s, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** δ (75 MHz); 200.3, 132.9(d, $^3J_{CP}$ =9.9 Hz), 131.6(d, $^4J_{CP}$ =2.9 Hz), 128.6(d, $^2J_{CP}$ =11.9 Hz), 127.8(d, $^1J_{CP}$ =90.2) Hz, 47.3(d, $^1J_{CP}$ =109.3 Hz), 40.5(d, $^3J_{CP}$ =11.7 Hz), 28.7; **mass spectrum** (FAB, CHCl$_3$) **m/z** 362(MH$_2^+$, 100), 304(70), 276(6); Anal. Calc. for C$_{24}$H$_{25}$OP: C: 79.93% H: 6.99%; Found: C: 79.89% H: 6.90%.

1-(4-Bromophenyl)-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (37d)

4-Bromo-phenacylbromide (23.35 g, 84.0 mmol) and triphenylphosphine (21.80 g, 83.2 mmol) in ether (600 mL) were heated under reflux overnight under an atmosphere of nitrogen, as set out for (**37b**). Additional ether (150 mL) was then added after cooling and the fine white precipitate (**37d'**, 88%, 39.92 g) was collected and dried by vacuum filtration. **Mp** 215-219°C; **IR** (Nujol mull); 1663(s), 1584(m), 1432(s), 1111(m), 989(s) cm^{-1}; **^{1}H NMR** δ (300 MHz); 8.30-8.27(m, 2, aromatic), 7.97-7.62(m, 17, aromatic), 6.38(bd, 2, $^2J_{HP}$ =12.3 Hz, PC$\underline{H}_2$); **^{13}C NMR** δ (75 MHz); 191.24(d, $^2J_{CP}$ =6.0 Hz), 134.71, 134.67, 134.02, 133.87, 133.79, 132.67, 132.63, 132.30, 132.16, 131.46, 130.32, 130.16, 129.99, 128.82, 128.65, 118.68(d, $^1J_{CP}$ =89.1 Hz), 38.53(d, $^1J_{CP}$ =61.2 Hz). Carbon-phosphorus couplings ($^xJ_{CP}$) are quoted as a doublet where the assignment was indisputable; all other signals have been listed as singlets. **mass spectrum** (FAB, CHCl$_3$) **m/z** 464(^{81}Br, 49), 462(Br^{79}, 49), 153(100), 136(77). The phosphonium salt (**37d'**) was transformed into ylide (**37d**) after stirring in 10% aqueous Na$_2$CO$_3$ solution (1500 mL). Analogous work-up to that of (**37b**) afforded the *p*-bromophenyl keto ylide (**37d**) (32.78 g) as an off white solid in an 86% yield. **Mp** 197-199°C; **IR** (Nujol mull); 1715(w), 1578(w), 1519(m), 1435(s), 1103(w) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.84-7.45(m, 19, aromatic), 4.39(d, 1, $^2J_{HP}$ =24.0 Hz, PC$\underline{H}$); **^{13}C NMR** δ (75 MHz); 183.52, 140.18(d, $^1J_{CP}$ =14.8 Hz), 133.18, 133.04,

132.15, 132.11, 132.00, 131.90, 131.866, 130.76, 128.98, 128.81, 128.64, 128.54, 128.38, 127.42. 126.21, 123.63, 51.06(d, $^1J_{CP}$ =111.2 Hz). Carbon-phosphorus couplings ($^xJ_{CP}$) are only quoted as a doublet where the assignment was indisputable; all other signals have been listed as singlets. **mass spectrum** (FAB, CHCl$_3$) **m/z** 463(M$^+$, ^{81}Br, 49), 461(M$^+$, Br^{79}, 49), 276(32), 136(77); Anal. Calc. for C$_{26}$H$_{20}$OPBr: C: 67.99% H: 4.39%; Found: C: 68.05% H: 4.38%.

(±) Ethyl-2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-phenylacetate (40)

To a stirred solution of ethyl mandelate (**35**) (19.04 g, 0.106 mol) in dry dimethyl formamide (120 mL) was added imidazole (10.64 g, 0.156 mol) and *tert*-butyldimethylsilyl chloride (19.44 g, 0.129 mol) under a nitrogen atmosphere. The mixture was allowed to stir at room temperature for 1.5 hours at which time the reaction was deemed complete by tlc analysis (10:1 hexane:EtOAc). Hexane (150 mL) and water (70 mL) were added to the mixture followed by separation of the two phases. The organic phase was washed with water (3 x 100 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The protected product (**40**) was obtained as a clear colourless oil (30.53 g, 98%) and used without further purification. **R$_f$** (10:1 hexane:EtOAc)= 0.68; **IR** (liquid film); 2931(s), 1756(s), 1727(m), 1472(w), 1255(s), 1130(s) cm $^{-1}$; **^{1}H NMR** δ (300 MHz); 7.48-7.27(m, 5, aromatic), 5.22(s, 1, C$\underline{H}$CO$_2$CH$_2$CH$_3$), 4.14(q, 2, J =7.2 Hz, CHCO$_2$C$\underline{H}_2$CH$_3$), 1.21(t, 3, J =7.2 Hz, CO$_2$CH$_2$C$\underline{H}_3$), 0.92(s, 9, C(C$\underline{H}_3$)$_3$), 0.11(s, 3, SiC$\underline{H}_3$), 0.04(s, 3, SiC$\underline{H}_3$); **^{13}C NMR** δ (75 MHz); 172.3, 139.4, 128.3, 128.1, 126.4, 74.5, 61.0, 25.5, 18.2, 13.9, -5.2, -5.3; **m/z** 294(M$^+$, 12), 279(29), 238(76), 237(100), 223(68), 222(79), 163(61). The spectral data corresponded to that of the literature reported for the S-enantiomer (**40a**).[145]

(±)-2-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-2-phenylacetaldehyde (42)

To a solution of the protected ethyl mandelate (**40**) (7.00 g, 23.77 mmol) in dry toluene (60 mL) at −78°C under an inert atmosphere, was added DIBAL-H (15.47 mL, 23.77 mmol, 1.5 M in toluene). Stirring was continued for 3.5 hours after which time the reaction was quenched with the cautious addition of water (40 mL). Ether (100 mL) was added and the resulting emulsion was filtered through kenite prior to extraction with

ether (3x 100 mL). The combined organic extracts were desiccated over MgSO$_4$, filtered and concentrated under reduced pressure yielding 5.47 g (92%) of (**42**). This material was used without further purification within one week in order to prevent decomposition to the corresponding acid. **IR** (liquid film); 2926(m), 1705(s), 1452(w), 1256(m), 838(w) cm^{-1}; **^{1}H NMR** δ (300 MHz) 9.51(d, 1, *J* =2.2 Hz, CHC<u>H</u>=O), 7.49-7.21(m, 5, aromatic), 5.00(d, 1, *J* =2.2 Hz, C<u>H</u>CH=O), 0.95(s, 9, C(C<u>H</u>$_3$)$_3$), 0.12(s, 3, SiC<u>H</u>$_3$), 0.04(s, 3, SiC<u>H</u>$_3$); **^{13}C NMR** δ (75 MHz); 199.5, 136.4, 128.7, 128.4, 126.4, 80.0, 25.7, 18.3, -4.9; **m/z** 222(20), 221(96), 193(78), 179(78), 135(36), 105(98). The spectral data corresponded to that of the literature reported for the S-enantiomer (**42a**).[145]

(±) Methyl (*E*)-4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-4-phenylbut-2-enoate (44e)

<u>Method 44A</u> (one pot)[31]:

To a solution of protected ethyl mandelate (**40**) (5.66 g, 19 mmol) in dry toluene (110 mL) at -78°C under a nitrogen atmosphere was added DIBAL-H (12.67 mL, 19 mmol, 1.5 M in toluene) dropwise over 15 minutes. After 2 hours of additional stirring a prepared solution of the methyl (triphenylphosphoranylidene)acetate (**37e**) (8.40 g, 25 mmol) in dry methanol (150 mL) was added to the reaction mixture (TLC analysis indicated consumption of starting material, 10:1 hexane:EtOAc using Brady's reagent as the developing solution). The cooling bath was removed after an additional 10 minutes and the reaction was allowed to attain ambient temperature. After 2.5 hours TLC analysis showed no intermediate aldehyde (**42**) remained and the reaction was quenched by the cautious addition of water (50 mL). Ether (100 mL) was added and the resulting white emulsion was filtered under vacuum through a pad of kenite. The methanol was removed under reduced pressure from the filtrate prior to extraction of the organic phase with ether (3 x 100 mL). The combined organic extracts were washed with water (2 x 50 mL), dried over MgSO$_4$, filtered and the solvent removed *in vacuo*. Triphenylphosphine oxide was removed from the product by precipitation with hexane (200 mL) prior to purification by column chromatography (10:1 hexane:EtOAc). A mixture of *cis/trans* isomers of (**44e**) were obtained (ratio of 3:5 by ^{1}H NMR) in a yield of 4.63 g, 79%.

Data for *trans* (**44e**); **R$_f$** (10:1 hexane:EtOAc)= 0.49; **IR** (liquid film); 2954(s), 1727(m), 1278(m), 1124(w), 840(m) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.48-7.23(m, 5, aromatic),

6.98(dd, 1, J =4.8, 15.6 Hz, CHC$\underline{H}$=CH), 6.12(d, 1, J =15.6 Hz, CHCH=C$\underline{H}$), 5.31(d, 1, J =3 Hz, C$\underline{H}$CH=CH), 3.70(s, 3, OC$\underline{H}_3$), 0.92(s, 9, C(C$\underline{H}_3)_3$), 0.06(s, 3, SiC$\underline{H}_3$), -0.06(s, 3, SiC$\underline{H}_3$); ^{13}**C NMR** δ (150 MHz); 167.0, 150.6, 141.6, 128.5, 127.7, 126.2, 118.3, 74.1, 51.5, 25.7, 18.2, -4.9, -5.0; **m/z** 306(M$^+$, 3), 291(4), 275(10), 249(100), 115(60), 89(36); Anal. Calc. for $C_{17}H_{26}O_3Si$; C: 66.62% H: 8.55%; Found C: 66.87% H: 8.85%.

Data for *cis* (**44e'**); **R$_f$** (10:1 hexane:EtOAc)= 0.67; **IR** (liquid film); 2954(m), 2360(w), 1724(s), 1400(m), 1200(s), 1068(m), 837(m); ^{1}**H NMR** δ (600 MHz); 7.48-7.22(m, 5, aromatic), 6.57(bd, 1, J =9.0 Hz, C$\underline{H}$CH=CH), 6.22(dd, 1, J =9, 11.4 Hz, CHC$\underline{H}$=CH), 5.72(d, 1, J =11.4 Hz, CHCH=C$\underline{H}$), 3.76(s, 3, OC$\underline{H}_3$), 0.91(s, 9, C(C$\underline{H}_3)_3$), 0.07(s, 3, SiC$\underline{H}_3$), 0.03(s, 3, SiC$\underline{H}_3$); ^{13}**C NMR** δ (150 MHz); 166.5, 151.7, 142.8, 128.2, 127.3, 125.9, 116.5, 69.3, 51.3, 25.8, 18.2, -4.7, -4.9; **m/z** 306(M$^+$, 2), 291(8), 275(11), 249(100), 115(98), 89(78), 163(61); Anal. Calc. for $C_{17}H_{26}O_3Si$; C: 66.62% H: 8.55%; Found C: 66.54% H: 8.50%.

Method 44B (two pot):

A solution of O-protected mandelaldehyde (**42**) (2.50 g, 9.97mmol) and methyl (triphenylphosphoranylidene)acetate (**37e**) (3.50 g, 10.47 mmol) was prepared under a nitrogen atmosphere in dry CH_2Cl_2 (15 mL) at ambient temperature. After cessation of the reaction (2 hours, TLC) the mixture was washed with water (3 x 10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product. Precipitation of the triphenylphosphine oxide byproduct was achieved by the addition of hexane (100 mL) and removed by filtration. Subsequent column chromatography provided 2.36 g of pure (**44e**) in 65% yield and ratio of *cis/trans* isomers equal to 5:95 (determined by ^{1}H NMR analysis).

(±)-(*E*)-5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-5-phenylpent-3-en-2-one (44a)

Protected mandelaldehyde (**42**) (780 mg, 3.10 mmol) and 1-triphenylphosphoranylidene-2-propanone (**37a**) (1.02 g, 3.27 mmol) were stirred for 2 hours in dry CH_2Cl_2 (5 mL) under identical reaction conditions of method 44B. Analogous work-up provided the pure titled alkene (**44a**) (847 mg, 94%) requiring no further purification. **R$_f$** (10:1 hexane:EtOAc)= 0.53; **IR** (liquid film); 2955(s), 1678(s), 1361(w), 1266(s), 1124(m), 843(s) cm^{-1}; ^{1}**H NMR** δ (300 MHz); 7.38-7.26(m, 5, aromatic), 6.77(dd, 1, J =5.0, 15.8

Hz, CHCH=CH), 6.33(dd, 1, J =1.8, 15.6 Hz, CHCH=CH), 5.33(dd, 1, J =1.5, 4.8 Hz, CHCH=CH), 2.24(s, 3, C(O)CH$_3$), 0.91(s, 9, C(CH$_3$)$_3$), 0.07(s, 3, SiCH$_3$), -0.05(s, 3, SiCH$_3$); **^{13}C NMR** δ (75 MHz); 198.9, 149.2, 141.8, 128.6, 128.1, 127.9, 126.3, 74.3, 27.0, 25.7, 18.2, -4.96, -4.99; **m/z** 290(M$^+$, 0.5), 275(4), 233(100), 115(20), 105(25), 75(71); Anal. Calc. for C$_{17}$H$_{26}$O$_2$Si: C: 70.29% H: 9.02%; Found: C: 70.56% H: 9.00%.

(±)-(*E*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-1,4-diphenylbut-2-en-1-one (44b)

Racemic mandelaldehyde derivative (42) (584 mg, 2.33 mmol), phenyl ketone ylide (37b) (947 mg, 2.56 mmol) and dry CH$_2$Cl$_2$ (4 mL) were combined in an analogous manner to method 44B. Equivalent work-up was performed after stirring overnight at room temperature, and pure product (44b) (628 mg) was provided in an 80% yield. **R$_f$** (10:1 hexane:EtOAc)= 0.53; **IR** (liquid film); 2954(s), 1736(w), 1626(m), 1471(m), 1255(m), 1122(m), 698(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.94-7.91(m, 2, aromatic), 7.56-7.27(m, 8, aromatic), 7.22(dd, 1, J =1.7, 15.5 Hz, CHCH=CH), 7.07(dd, 1, J =4.2, 15.0 Hz, CHCH=CH), 5.43(dd, 1, J =1.7, 4.1 Hz, CHCH=CH), 0.95(s, 9, Si(CH$_3$)$_3$), 0.11(s, 3, SiCH$_3$). –0.01(s, 3, SiCH$_3$); **^{13}C NMR** δ(75 MHz); 190.1, 150.4, 133.2, 128.5, 127.7, 126.3, 122.7, 74.6, 25.8, 18.2, -4.9; **m/z** 337(M$^+$, 4), 295(100), 221(29), 105(47), 77(33). Anal. Calc. for C$_{22}$H$_{28}$O$_2$Si: C: 74.95% H: 8.01%; Found: C: 74.86% H: 7.94%.

S-(-)-Ethyl 2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-propanoate (41a)

S-(-)-ethyl lactate (38a) (12.00 g, 0.102 mol), imidazole (10.38 g, 0.152 mol) and *tert*-butyldimethylsilyl chloride (18.37 g, 0.122 mol) were dissolved in dry dimethyl formamide (50 mL) following the standard reaction procedure and work-up as for (40). The title compound was provided in a 98% yield (22.38 g) as a clear colourless liquid requiring no further purification. [α]$_D^{21}$ = -26.4° (*c* 2.36, CHCl$_3$); Lit. [α]$_D^{20}$ = -28.7° (*c* 2.36, CHCl$_3$);[78] **^{1}H NMR** δ (300 MHz); 4.31(q, 1, J =6.6 Hz, CH$_3$CHCO$_2$), 4.18(dq, 2, J =3.5, 10.7 Hz, CO$_2$CH$_2$CH$_3$), 1.40(d, 3, J =6.9 Hz, CH$_3$CHCO$_2$), 1.28(t, 3, J =7.1 Hz, CH$_2$CH$_3$), 0.92(s, 9, C(CH$_3$)$_3$), 0.10(s, 3, SiCH$_3$), 0.07(s, 3, SiCH$_3$); **^{13}C NMR** δ (75 MHz); 174.3, 68.4, 60.7, 25.6, 21.2, 18.2, 14.1, -5.1, -5.4. The spectral data corresponded to that of the literature.[78]

S-(-)-2-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-propanal (43a)

Under dry and inert reaction conditions, a solution of protected *S*-(-)-ethyl lactate (41a) (5.50 g, 23.67 mmol) was prepared in dry ether (65 mL). Prior to the dropwise addition of DIBAL-H (35.50 mL, 35.50 mmol, 1 M in hexanes), the solution was cooled with stirring to –78°C, and subsequently left to stir for 10 mins. Methanol (1.5 mL) and then water (*ca.* 4 mL) were cautiously added to the mixture and the cold bath removed to allow the mixture to attain ambient temperature. Stirring of the mixture continued for an additional 1 hour after which the emulsion was filtered under vacuum through a pad of kenite using ether (3 x 40 mL) to wash residual product through the filter. Desiccation (MgSO₄) of the combined filtrates, concentration and distillation by reduced pressure short path distillation (95°C, 15 mmHg; lit. bp 90°C, 20 mmHg[78]) yielded 3.60 g (81%) of the pure titled aldehyde (43a). $[\alpha]_D^{20}$ = -11.5° (*c* 1.50, CHCl₃); Lit. $[\alpha]_D^{19}$ = -12.0° (*c* 1.50, CHCl₃);[146] **¹H NMR** δ (300 MHz); 9.62(d, 1, *J* =1.2 Hz,C**H**=O), 4.10(dq, 1, *J* =1.3, 6.8 Hz, CH₃C**H**), 1.28(d, 3, *J* =6.9 Hz, C**H₃**CH), 0.93(s, 9, C(C**H₃**)₃), 0.11(s, 3, SiC**H₃**), 0.09(s, 3, SiC**H₃**); **¹³C NMR** δ (75 MHz); 204.0, 73.8, 25.7, 18.4, -4.8, -4.9. The spectral data corresponds with the literature.[78]

(+)-(*E*)-5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-hex-3-en-2-one (45a)

Protected enone (45a) was prepared similarly to enone (44e) following the procedure set out in method 44B with the reagents; *S*-(-)-lactaldehyde (43a) (290 mg, 1.54 mmol), 1-triphenylphosphoranylidene-2-propanone (37a) (540 mg, 1.69 mmol) and dry CH₂Cl₂ (4 mL) as the solvent. After 24 hours stirring at room temperature, column chromatography yielded 272 mg (77%) of the titled compound (45a). **R**ₑ (10:2 hexane:EtOAc)= 0.55; **IR** (liquid film); 1709(m), 1682(s), 1485(w), 1255(m), 1095(m) cm⁻¹; $[\alpha]_D^{22}$ = +88.9 (*c* 0.75, CHCl₃); **¹H NMR** δ (600 MHz); 6.75(dd, 1, *J* =4.5, 15.9 Hz, CHC**H**=CH), 6.23(dd, 1, *J* =1.8, 15.6 Hz, CHCH=C**H**), 4.48(m, 1, C**H**CH=CH), 2.27(s, 3, OCC**H₃**), 1.28(d, 3, *J* =6.6 Hz, C**H₃**CH), 0.91(s, 9, C(C**H₃**)₃), 0.08(s, 3, SiC**H₃**), 0.07(s, 3, SiC**H₃**); **¹³C NMR** δ (150 MHz); 198.9, 150.9, 128.1, 67.8, 27.3, 25.8, 23.6, 18.2, -4.8; **m/z** 228(M⁺, 2), 227(4), 159(33), 131(45), 69(100), 57(56); Acc. Mass Calc. for (M -H⁺) C₁₂H₂₃O₂Si 227.1467; Found 227.1474.

(+)-(*E*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-1-phenylpent-2-en-1-one (45b)

Procedure 44B was modified to allow for the synthesis of the titled enone (45b) employing *S*-(-)-lactaldehyde (43a) (400 mg, 2.12 mmol), 1-phenyl-2-(1, 1, 1-triphenyl-1-phosphanylide)-1-ethanone (37b) (595 mg, 2.34 mmol) and dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux over night prior to standard work-up and purification by column chromatography to afford 439 mg (71%) of the clear colourless oil (45b). R_f (10:1 hexane:EtOAc)= 0.42; **IR** (liquid film); 1674(s), 1628(s), 1471(w), 1281(m), 1151(m) cm^{-1}; $[\alpha]_D^{26}$ = +5.9 (*c* 0.3, CHCl$_3$); **^{1}H NMR** δ (600 MHz); 7.95-7.46(m, 5, aromatic), 7.12(dd, 1, *J* =1.2, 15.0 Hz, CHCH=CH), 7.04(dd, 1, *J* =3.6, 15.0 Hz, CHCH=CH), 4.58(m, 1, CHCH=CH). 1.32(d, 3, *J* =6.0 Hz, CH$_3$CH), 0.96(s, 9, C(CH$_3$)$_3$), 0.11(s, 6, Si(CH$_3$)$_2$); **^{13}C NMR** δ (150 MHz); 190.8, 152.0, 138.0, 132.7, 128.5, 122.8, 68.2, 25.8, 23.5, 18.2, -4.8; **m/z** 291(MH$^+$, 71), 275(33), 233(100), 159(27), 75(44); Acc. Mass Calc. for (MH$^+$) C$_{17}$H$_{27}$O$_2$Si 291.1780; Found 291.1770.

(±) Methyl (*E*)-4-hydroxy-4-phenylbut-2-enoate (17e)

Method A:

To a stirred solution of protected hydroxy enester (44e) (600 mg, 1.95 mmol) in dry CH_2Cl_2 (10 mL) was added BF$_3$-Et$_2$O (1.95 mmol, 0.24 mL), drop wise over 5 minutes at -10°C. The reaction mixture changed from colourless to brown simultaneously on addition of the BF$_3$ reagent. After 10 minutes the reaction was quenched by pouring onto ice water. The organics were washed further with water (3 x 5 mL), dried over MgSO$_4$, filtered and the solvent removed *in vacuo* to afford the crude product as a yellow oil. Purification was achieved by column chromatography resulting in isolation of the deprotected structural isomers (49a/b), in a ratio of approximately 1:1 by ^{1}H NMR, in a combined yield of 122 mg, 32%. Chromatography also provided 56 mg, 15% yield of 1,4-diketone (46e).

Data for (49a); R_f (10:3 hexane:EtOAc)= 0.49; **^{1}H NMR** δ (300 MHz); 7.38-7.25(m, 5, aromatic), 6.98(dd, 1, *J* =5.6, 15.8 Hz, CH=CHCO$_2$CH$_3$), 6.13(dd, 1, *J* =1.5, 15.6 Hz, CH=CHCO$_2$CH$_3$), 5.07(dd, 1, *J* =1.4, 5.6 Hz, CHCH=CH), 3.74(s, 3, CO$_2$CH$_3$); **^{13}C NMR** δ (75 MHz); 166.7, 147.1, 138.6, 128.8, 128.5, 127.2, 121.1, 77.9, 51.6.

Data for (49b); R$_f$ (10:3 hexane:EtOAc)= 0.44; **¹H NMR** δ (300 MHz); 7.38-7.24(m, 5, aromatic), 6.92(dd, 1, *J* =4.7, 15.7 Hz, C$\underline{H}$=CHCO$_2$CH$_3$), 6.15(dd, 1, *J* =2.1, 15.6 Hz, CH=C$\underline{H}$CO$_2$CH$_3$), 4.87(dd, 1, *J* =1.8, 4.5 Hz, C$\underline{H}$CH=CHCO$_2$CH$_3$), 3.72(s, 3, CO$_2$CH$_3$); **¹³C NMR** δ (75 MHz); 166.8, 147.5, 138.2, 129.0, 128.6, 127.4, 120.0, 77.4, 51.6.

Data for combined (49a/b); **IR** (liquid film); 2951(w), 1728(s), 1655(w), 1436(w), 1274(m), 1170(m) cm^{-1} **mass spectrum** (FAB, CDCl$_3$) **m/z** 192(M$^+$, 1), 175(11), 133(13), 67(75), 55(97), 53(100). GC-MS analysis suggests the formation of dimeric/polymeric products with very low M$^+$ of 192. Accurate mass (LSIMS) spectrometry did not support the M$^+$ peak at 192, it did however confirm the loss of the TBDMS-group as a 155 fragment ion and the 175 structural backbone of PhCHCH=CHC(O)OCH$_3$. The identity of these two seeming structural isomers (49a/b) has not been conclusively determined.

Data for (46e); R$_f$ (10:2 hexane:EtOAc)= 0.26; **¹H NMR** δ (300 MHz);8.01-7.98(m, 2, aromatic), 7.58-7.45(m, 3, aromatic), 3.72(s, 3, OC$\underline{H}$$_3$), 3.34(t, 2, *J* =6.8 Hz, C$\underline{H}$$_2CO_2CH_3$), 2.78(t, 2, *J* =6.8 Hz, O=CC$\underline{H}$$_2CH_2$).[147]

Method B:

Deprotection of enester (44e) (30 mg, 0.10 mmol) was attempted using a mixture of TFA: water (0.044 mL, 0.49 mmol, 9:1) in CH$_2$Cl$_2$ (2 mL). The reactants were stirred for 11 days at ambient temperature prior to concentration under reduced pressure and separation of the crude mixture by column chromatography (10:2 hexane:EtOAc). A mixture of alkene derivatives (none containing a TBDMS-protecting group) were collected in considerably small yields. Approximately 12% of the recovered material contained a 1:1 mixture of (49a/b). A new product isolated was yet another unidentified product (49c), collected in a yield of *ca.* 8%, 4 mg. The titled enester (17e) was isolated as the major product in a yield of 35%, 8 mg.

Data for enester (17e); R$_f$ (10:2 hexane:EtOAc)= 0.16; **¹H NMR** δ (300 MHz); 7.39-7.29(m, 5, aromatic), 7.06(dd, 1, *J* =4.7, 15.8 Hz, CHC$\underline{H}$=CH), 6.18(dd, 1, *J* =2.0, 15.5 Hz, CHCH=C$\underline{H}$), 5.37(dd, 1, *J* =1.7, 4.9 Hz, C$\underline{H}$CH=CH), 3.73(s, 3, OC$\underline{H}$$_3$), 2.02(bs, 1, O$\underline{H}$); **¹³C NMR** δ (150 MHz); 166.8, 148.7, 140.8, 128.8, 128.4, 126.5, 119.8, 73.5, 51.6; **m/z** 192(M$^+$, 2), 175(4), 105(12), 69(41), 55(100). The spectral data was consistent with the literature.[54]

Data for (**49c**); **R_f** (10:2 hexane:EtOAc)= 0.14; **¹H NMR** δ (600 MHz); 7.43-7.26 (m, 5, aromatic), 7.03(dd, 1, *J* =5.4, 15.6 Hz, CHC**H**=CH), 6.49(dd, 1, *J* =1.8, 5.4 Hz, CHCH=C**H**), 6.11(dd, 1, *J* =1.5, 15.9 Hz, C**H**CH=CH), 3.76(s, 3, OC**H**₃); **¹³C NMR** δ (150 MHz); 165.8, 141.9, 134.8, 129.8, 129.2, 127.4, 122.9, 78.1, 52.0. No further characterisation was achieved due to the small amounts of pure compound (**49c**) obtained.

Method C:

Protected enester (**44e**) (416 mg, 1.35 mmol) in THF (3 mL) was treated with TBAF (1.35 mL, 1.35 mmol, 1 M in THF) at 0-5°C. A spontaneous colour change to a brown solution was noted, deepening throughout a one hour reaction time. The solvent was removed *in vacuo* and the resultant oil was subjected to column chromatography. The sole product isolated was the isomeric 1,4-dicarbonyl derivative (**46e**) of enone (**17e**), in a quantitative yield.

(*E*)-5-Hydroxy-5-phenylpent-3-en-2-one (17a)

Method A:

Boron triflouride etherate (0.285 mL, 2.32 mmol) was added drop wise to a solution of the TBDMS-protected 5-phenylpent-3-en-2-one (**44a**) (675 mg, 2.32 mmol) in dry CH₂Cl₂ (10 mL) at ambient temperature, following the standard procedure set out in method 0A. The organic phase was subsequently washed with water (2 x 10 mL), dried over Na₂SO₄, filtered and concentrated. Column chromatography provided product isomers (**50a/b**) in a 1:1 ratio in greater than 95% purity with a 31% yield, 125 mg.

Data for (**50a**); **R_f** (10:3 hexane:EtOAc)= 0.21; **IR** (liquid cell, CDCl₃); 1793(w), 1225(m), 908(s), 735(s) cm⁻¹; **¹H NMR** δ (600 MHz); 7.39-7.27(m, 5, aromatic), 6.78(dd, 1, *J* =5.7, 16.1 Hz, CHC**H**=CH), 6.33(dd, 1, *J* =1.4, 16.1 Hz, CHCH=C**H**), 5.02(dd, 1, *J* =1.2, 5.7 Hz, C**H**CH=CH), 2.28(s, 3, C(O)C**H**₃);); **¹³C NMR** δ (150 MHz); 198.3, 145.4, 138.5, 130.4, 128.9, 128.5, 127.1, 78.3, 27.2.

Data for (**50b**); **R_f** (10:3 hexane:EtOAc)= 0.25; **IR** (liquid cell, CDCl₃); 1714(w), 1643(w), 1217(m), 908(s), 733(s) cm⁻¹; **¹H NMR** δ (600 MHz); 7.41-7.26(m, 5, aromatic), 6.73(dd, 1, *J* =4.8, 16.2 Hz, CHC**H**=CH), 6.31(dd, 1, *J* =1.5, 15.9 Hz, CHCH=C**H**), 4.90(dd, 1, *J*

=1.8, 4.8 Hz, CHCH=CH), 2.23(s, 3, C(O)CH$_3$); ^{13}C NMR δ (150 MHz);198.6, 146.0, 138.2, 129.3, 129.0, 128.8, 127.4, 77.8, 27.2; **m/z** both GC-MS and AM show no M$^+$ peak.

Method B:

In an analogous manner to method B for (**17e**), protected enone (**44a**) (50 mg, 0.17 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with a mixture of TFA: water (0.014 mL, 0.17 mmol, 9:1). Complete consumption of the starting material (**44a**) was confirmed by TLC subsequent to stirring at room temperature for 72 hours. Column chromatography provided the major product 1-phenyl-1,4-pentanedione (**46a**) as a white solid, in a recovered yield of 80%.

Data for (**46a**); **R$_f$** (10:2 hexane:EtOAc)= 0.19; ^{1}**H NMR** δ (300 MHz); 8.00-7.97(m, 2, aromatic), 7.58-7.45(m, 3, aromatic), 3.29(t, 2, J =6.3 Hz, PhC(O)CH$_2$), 2.90(t, 2, J =6.3 Hz, CH$_2$C(O)CH$_3$), 2.27(s, 3, C(O)CH$_3$); ^{13}**C NMR** δ (75 MHz); 207.1, 198.4, 136.6, 133.1, 128.5, 128.0, 37.0, 32.4, 30.0; **mass spectrum** (FAB, CDCl$_3$) **m/z** 177(MH$^+$, 72), 163(30), 136(52), 105(100), 73(53), 55(95). The spectral data for (**46a**) was consistent with the literature.[95]

Method D:

α-Hydroxy mandelaldhyde (**36**) (0.60 mmol) was prepared in solution from the treatment of O-protected mandelaldehyde (**42**) (150 mg, 0.60 mmol) with HF (2 drops, *ca.* 3.0 mmol, 48%) in dry acetonitrile (1.25 mL). Stirring of the mixture was continued for 3.5 hours after which time the solvent was removed *in vacuo* and the crude oil was taken up in dry CH$_2$Cl$_2$ (1.25 mL). Slightly less than one equivalent of 1-triphenylphosphoranylidene-2-propanone (**37a**) (180 mg, 0.57 mmol) was added to the solution. The mixture was heated to reflux for 2 hours in a nitrogen atmosphere at which time ^{1}H NMR indicated no aldehyde (**42**) remained. No attempt to further purify the *trans* γ-hydroxy enone (**17a**) was made due to the extreme sensitivity of this compound. Characterisation was therefore carried out on the crude enone (**17a**) mixture. **IR** (liquid film); 3298(s), 1716(m), 1628(w), 1591(w), 1402(s), 1118(s) cm^{-1}; ^{1}**H NMR** δ (600 MHz); 7.69-7.37(m, 5, aromatic), 6.86(dd, 1, J =5.0, 15.9 Hz, CHCH=CH), 6.37(dd, 1, J =1.8, 16.2, CHCH=CH), 5.38(dd, 1, J =1.5, 5.1 Hz, CHCH=CH), 2.25(s, 3, (O)CCH$_3$); ^{13}**C NMR** δ (150 MHz); 198.4, 147.6, 141.2, 130.4, 126.6, 73.6, 27.3. Incomplete ^{13}C NMR data is quoted for enone (**17a**)

due to inconclusive assignment of the aromatic signals. **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 176(M$^+$, 1), 175(3), 159(78), 105(100), 77(70), 43(14).

(*E*)-4-Hydroxy-1,4-diphenylbut-2-en-1-one (17b)

Two major by-products, 1,4-diketone (**46b**) and furan (**51b**), were obtained and isolated from the trialed deprotection reactions of the corresponding protected di-phenyl enone (**44b**), as described in methods A-C for (**17e**). The yield of each of these compounds differed greatly depending on the reaction conditions employed. Under predominately basic conditions 1,4-diphenyl-1, 4-butanedione (**46b**) was the major product. Conversely, under acidic conditions the isomeric 2,5-diphenylfuran (**51b**) dominated the product mixture.

Date for (**46b**); **R$_f$** (10:1 hexane:EtOAc)= 0.20; **Mp** 141-142°C (lit. **Mp** 142-143°C);[82] **^{1}H NMR** δ (200 MHz); 8.07-7.45(m, 10, aromatic), 3.48(s, 4, O=CC$\underline{H}_2$C$\underline{H}_2$C=O).[148]

Data for (**51b**); **R$_f$** (10:2 hexane:EtOAc)= 0.73; **Mp** 87-88°C (lit. **Mp** 88-89°C);[82] **^{1}H NMR** δ (300 MHz); 7.77-7.25(m, 10, aromatic), 6.75(s, 2, C$\underline{H}$=C$\underline{H}$); **m/z** 220(M$^+$, 100), 115(28), 105(19), 89(6), 77(24). Spectral data for both (**46b**) and (**51b**) corresponds with the literature.[82,149]

<u>Method D:</u>

The procedure was analogous to that reported for (**17a**) (Method D) with the same reagent amounts employed with the exception that 1-phenyl-2-(1, 1, 1-triphenyl-1-phosphanylide)-1-ethanone (**37b**) (217 mg, 0.57 mmol) was the ylide utilised. Similarly enone (**17b**) was extremely sensitive to purification and as such was analysed in the crude state. **IR** (liquid film); 3278(m), 1670(s), 1621(m), 1567(w), 1485(w), 1120(s) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.75-7.72(m, 2, aromatic), 7.66-7.34(m, 3, aromatic), 7.26(dd, 1, *J* =7.2, 15.0 Hz, CHC$\underline{H}$=CH), 7.12(dd, 1, *J* =4.2, 15.0 Hz, CHCH=C$\underline{H}$), 5.46(dd, 1, *J* =1.5, 4.5 Hz, C$\underline{H}$CH=CH), 2.22(bs, 1, O$\underline{H}$); **^{13}C NMR** δ (150 MHz); 127.4, 123.7, 73.9. Incomplete ^{13}C NMR data is quoted for enone (**17b**) due to inconclusive assignment of aromatic and alkene signals. **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 239(MH$^+$, 7), 221(14), 161(5), 105(54), 77(100), 51(61).

(2-Methoxy-2-oxoethyl)(triphenyl)phosphonium bromide (53)

A solution of bromomethyl acetate (2.38 g, 15.1 mmol) and triphenylphosphine (3.78 g, 14.4 mmol) in ether (100 mL), was stirred at ambient temperature overnight. The solution was cooled to 0°C and further ether (20 mL) was added to the suspension. The fine white precipitate was collected by vacuum filtration to provide 4.43 g (77%) of the ylide salt (53). IR (Nujol mull); 1722(s), 1587(w), 1439(s), 1111(m) cm^{-1}; ^{1}H NMR δ (300 MHz); 7.95-7.60(m, 15, aromatic), 5.68(d, 2, J_{HP} =13.5 Hz, PC$\underline{H}_2$), 3.63(s, 3, OC$\underline{H}_3$). Complete characterisation of (53) was not warranted as the ylide salt was of no synthetic value.

S-(*E*)-5-Hydroxyhex-3-en-2-one (39a)

Method A:

After 2 hours at ambient temperature, a solution of silyloxy enone (45a) (50 mg, 0.22 mmol) and BF$_3$-Et$_2$O (0.22 mmol, 0.03 mL) in CH$_2$Cl$_2$ (4 mL) was quenched with pouring onto ice water. Work-up as described for (17e) Method A, provided a crude oil consisting of approximately 10% 2,5-hexanedione (54a) and 80% unreacted enone (45a), as seen by ^{1}H NMR. The by-product 1,4-diketone (54a) was not isolated, but identified by comparison with the literautre.[150] ^{1}H NMR δ (300 MHz); 2.72(s, 4, CH$_3$(C$\underline{H}_2$)$_2$), 2.19(s, 6, (C$\underline{H}_3$C=O)$_2$). The spectral data corresponded to that of the literature.[150]

Method B:

TFA:H$_2$O (0.001 mL, 0.11 mmol, 9:1) was allowed to react with a solution of enone (45a) (50 mg, 0.22 mmol) in CH$_2$Cl$_2$ (5 mL) at ambient temperature under the conditions set out for (17e) in Method B. The reaction mixture was concentrated after 2 hours stirring and analysed by ^{1}H NMR. The crude ^{1}H NMR spectrum showed that *ca.* 30% of the starting enone (45a) remained, whilst the reaction products were, a trace of 1,4-diketone (54a), *ca.* 50% of 2,5-dimethylfuran (55a) and a mixture of unidentified decomposition products. Furan (55a) was identified by comparison with the literate,[151] no sample was isolated for characterisation as it was deemed unnecessary. ^{1}H NMR δ (300 MHz); 5.82(s, 2, (=C$\underline{H}$)$_2$), 2.23(s, 6, C$\underline{H}_3$COCC$\underline{H}_3$). Spectral data was consistent with that quoted in the literature.[151]

Method C:

Following the standard conditions described in Method C for (**17e**), protected enone (**45a**) (50 mg, 0.22 mmol) in CH₂Cl₂ (4 mL) was treated with TBAF (0.22 mL, 0.22 mmol, 1 M in THF) with stirring at 0°C. The reaction mixture was concentrated after 10 minutes, at which time the ¹H NMR spectrum revealed that 1,4-diketone (**54a**) was the sole product, in approximately 20%, and 70% of the silyloxy enone (**45a**) remained. Unidentified decomposition products were also observed in the crude spectrum in *ca.* 10%.

Method D:

Aqueous hydrogen fluoride (*ca.* 50 drops, *ca.* 40 mmol, 48%) was added to a mixture of *S*-(-)-O-protected lactaldehyde (**43a**) (1.50 g, 8.03 mmol) in dry acetonitrile (40 mL) following the procedure as described for the synthesis of (**65a**). The solution was quenched by the addition of solid NaHCO₃ (*ca.* 1.50 mg) prior to work-up. The crude intermediate hydroxy aldehyde (**65a**) (0.38 g, 65%) was immediately taken up in CH₂Cl₂ (15 mL) and treated with 1-triphenylphosphoranylidene-2-propanone (**37a**) (1.69 g, 5.31 mmol) with no further purification. The reaction mixture was heated under reflux for 5 hours followed by concentration *in vacuo* to afford the crude γ-hydroxy enone (**39a**), which was partially purified by precipitation and removal of triphenylphosphine oxide with hexane, as a clear colourless oil. **IR** (liquid film); 3421(s), 1674(m), 1633(w), 1196(s), 1120(s) cm⁻¹; **¹H NMR** δ (600 MHz); 6.77(dd, 1, *J* =4.8, 16.2 Hz, CHC$\underline{H}$=CH), 6.24(dd, 1, *J* =1.5, 15.9 Hz, CHCH=C$\underline{H}$), 4.48(ddq, 1, *J* =1.3, 5.1, 6.6 Hz, C$\underline{H}$CH=CH), 2.62(bs, 1, O$\underline{H}$), 2.26(s, 3, (O)CC$\underline{H}$₃), 1.33(d, 3, *J* =6.6 Hz, C$\underline{H}$₃CH); **¹³C NMR** δ (150 MHz); 202.7, 150.0, 128.4, 67.0, 27.3, 22.7; **mass spectrum** (GC-MS, CDCl₃) **m/z** 115(MH⁺, 16), 97(10), 71(20), 39(45), 43(100).

S-(*E*)-1-Phenyl-4-hydroxypent-2-enone (39b)

Method A:

TBDMS-O-protected enone (**45b**) (30 mg, 0.10 mmol) was dissolved in CH₂Cl₂ (3 mL) and treated with BF₃-Et₂O (0.01 mL, 0.10 mmol) as for (**17e**), Method A. Quenching with

pouring onto ice water after 30 minutes and purification afforded a mixture of 1-phenyl-1,4-pentanedione (**46a**)[95] and 2-methyl-5-phenylfuran (**55b**) in a ratio of 99:1.

Repeating the reaction as above with the exception of cooling to 0°C did not provide any targeted enone (**39b**) rather affording (**55b**) as the sole product.

Data for (**55b**); **¹H NMR** δ (600 MHz, CDCl₃); 7.66-7.18(m, 5, aromatic), 6.52(d, 1, J =3.0 Hz, C<u>H</u>=CH), 6.03(bd, 1, J =3.0 Hz, CH=C<u>H</u>), 2.35(s, 3, =CC<u>H</u>₃). The spectral data for 2-methyl-5-phenylfuran (**55b**)were consistent with the literature.[152,153]

Method B:

As for (**17e**), Method B, enone (**45b**) (23 mg, 0.08 mmol), CH₂Cl₂ (2 mL) and TFA:H₂O (0.004 mL, 0.04 mmol, 9:1) were allowed to react for 15 hours. Analysis of the crude reaction mixture revealed the reaction was approximately one quarter complete with furan (**55b**) as the sole product.

Method C:

Following the methodology of (**17e**)-C, TBAF (0.10 mL, 0.10 mmol, 1 M in THF) was added to a mixture of (**45b**) (30 mg, 0.10 mmol) in THF (2 mL). After 20 minutes analysis by ¹H NMR showed that the reaction was only 50% complete and that no deprotected enone (**39b**) was present. The major component was an unidentified decomposition product along with minor amounts of (**46a**) and (**55b**).

Method D:

Following the standard procedure set out in Method D for (**39a**), protected (-)-lactaldehyde (**43a**) (0.90 g, 4.77 mmol) in dry acetonitrile (23 mL) was treated with aqueous HF (*ca.* 30 drops, *ca.* 24 mmol, 48%). After an additional 15 minutes reaction time, quenching with solid NaHCO₃ (*ca.* 0.90 g) and similar work-up provided 0.31 g (4.19 mmol, 86%) of crude α-hydroxy aldehyde (**65a**). This material was immediately dissolved in dry CH₂Cl₂ (11 mL), followed by introduction of phenyl keto ylide (**37b**) (1.39 g, 4.36 mmol). This mixture was heated under reflux for 5hrs. After partial purification by precipitation and filtration of the triphenylphosphine oxide with hexane, (**39b**) was obtained as a clear colourless oil. Analysis by ¹H NMR indicated compound (**39b**) was greater than 85% pure, and as further attempts at purification resulted in decomposition to 1,4-diketone (**46a**), it was used immediately for further synthetic

manipulation. **IR** (liquid film); 3361(s), 1668(s), 1621(s), 1509(m), 1402(s), 1120(s), 1012(w) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.96-7.35(m, 5, aromatic), 7.16(dd, 1, J =0.9, 15.3 Hz, CHCH=C<u>H</u>), 7.04(dd, 1, J =3.6, 15.6 Hz, CHC<u>H</u>=CH), 4.54(m, 1, C<u>H</u>CH=CH), 2.96(bs, 1, O<u>H</u>), 1.34(d, 3, J =6.6 Hz, C<u>H</u>$_3$CH); **^{13}C NMR** δ (150 MHz); 190.6, 152.4, 122.5, 66.5, 22.5. Incomplete ^{13}C NMR data is quoted for enone (**39b**) due to inconclusive assignment of aromatic and alkene signals. **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 177(M$^+$, 5), 133(25), 105(44), 77(100), 51(98).

4-Chloro-5-{[1-(*tert*-butyl)-1, 1-dimethylsilyl]oxy}-5-phenylpentan-2-one (56a)

Protected enone (**44a**) (400 mg, 1.38 mmol) was dissolved in CH$_2$Cl$_2$ (40 mL) and treated with conc. HCl (0.80 mL) with rapid stirring for 2 hours. Removal of the solvent under reduced pressure, followed by washing with water (2 x 5mL), brine (5 mL) and desiccation over Na$_2$SO$_4$ provided a mixture of the two diastereomeric adducts (**56a**) and (**56a***) in a 1:1 ratio. The crude oils were obtained in > 95% purity by ^{1}H NMR analysis in a yield of 434 mg (96%), and were analysed as the isomeric mixture. **IR** (liquid film); 3027(w), 1723(s), 1492(w), 1362(m), 1255(s), 838(s) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.35-7.27(m, 5, aromatic), 4.90(d, 1, J =4.2 Hz, C<u>H</u>CHCl), 4.81(d, 1, J =4.2 Hz, C<u>H</u>*CHCl), 4.41(m, 1, CHC<u>H</u>Cl), 2.92 (dd, 1, J =9.9, 17.1 Hz, ClCHCH-<u>H</u>), 2.76(dd, 1, J =10.8, 17.4 Hz, ClCHCH-<u>H</u>*), 2.75(dd, 1, J =9.9, 17.1 Hz, ClCHC<u>H</u>-H), 2.62(dd, 1, J =9.3, 17.1 Hz, ClCHC<u>H</u>*-H), 2.12(s, 3, OCC<u>H</u>$_3$), 2.10(s, 3, OCC<u>H</u>*$_3$), 0.91 & 0.87(2 x s, 9, C(C<u>H</u>$_3$)$_3$), 0.09, 0.05, -0.14 & -0.15 (4 x s, 3, Si(C<u>H</u>$_3$)$_2$); **^{13}C NMR** δ (150 MHz); 205.3, 205.0*, 140.8, 140.1*, 128.3, 128.1, 127.3, 126.6, 126.2, 78.0, 77.0*, 61.1, 60.7*, 46.9, 45.3*, 30.8, 30.7, 25.8, 25.7, 18.3, 18.2, -4.7, -4.8, -5.0, -5.1; **m/z** 329(MH$^+$, ^{37}Cl, 3), 327(MH$^+$, ^{35}Cl, 8), 291(37), 233(53), 159(100); Acc. Mass Calc. for (MH$^+$) C$_{17}$H$_{28}$O$_2$Si^{35}Cl 327.1547; Found 327.1542.

The title compound (**56a**) decomposes over time to isomeric furan (**54a**). 100% conversion after approximately 1 month standing.

3-Chloro-4-{[1-(*tert*-butyl)-1, 1-dimethylsilyl]oxy}-1,4-diphenylbutan-1-one (56b)

Similarly to (56a), HCl adduct (56b) was obtained as a 1:1 diastereomeric mixture from the treatment of enone (44b) (400 mg, 1.19 mmol) in CH_2Cl_2 (5 mL) with conc. HCl (1.0 mL) over 24 hours at ambient temperature. The combined yield of isomeric products (56b/56b*) was 82 % (364 mg), deemed > 95% by ^{1}H NMR. **IR** (liquid film); 1737(m), 1688(s), 1596(w), 1256(s), 1121(m), 835(s), 776(s) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.87-7.32(m, 10, aromatic), 5.04(d, 1, J =4.2 Hz, CHCHCl), 4.98(d, 1, J =4.5 Hz, CHCHCl), 4.67(m, 1, CHCHCl), 3.58(dd, 1, J =9.2, 17.1 Hz, ClCHCH-H*), 3.36 (dd, 1, J =4.4, 17.3 Hz, ClCHCH-H), 3.26(dd, 1, J =8.4, 17.1 Hz, ClCHCH*-H), 3.23(dd, 1, J =2.9, 17.1 Hz, ClCHCH-H), 0.95 & 0.89(2 x s, 9, C(CH$_3$)$_3$), 0.15, 0.03, -0.09 & -0.13 (4 x s, 3, SiCH$_3$); **^{13}C NMR** δ (75 MHz); 196.9, 196.6, 140.9, 140.4, 133.3, 133.2, 128.6, 128.0, 127.3, 126.7, 78.2, 76.9, 61.5, 61.2, 42.4, 40.7, 25.9, 25.7, 18.3, 18.2, -4.6, -4.7, -4.9, -5.1; **m/z** 333(M$^+$-*t*-Bu, ^{37}Cl, 7), 331(M$^+$-*t*-Bu, ^{35}Cl, 17), 259(^{37}Cl,3), 257(^{35}Cl,8), 221(95), 105(100), 77(23).

On standing the neat compound (56b) decomposes over approximately 2 months, to the furan by-product (51b).

Attempted synthesis of Methyl 3-chloro-4-{[1-(*tert*-butyl)-1, 1-dimethylsilyl]oxy}-4-phenylbutan-1-oate (56e)

HCl (1.0 mL) was added to a rapidly stirred solution of protected enone (44e) (400 mg, 1.3 mmol) in CH_2Cl_2 (40 mL) at room temperature. Work-up of the reaction mixture after 24 hours was performed as for (56a). Analysis of the crude mixture by ^{1}H NMR indicated complete conversion of starting material to a mixture of isomeric products including the γ-hydroxy enester (17e), a chlorinated adduct (60) and dicarbonyl (46e) as the major components. Column chromatography using an eluting solution of 10:2 hexane:EtOAc, provided 12% (30 mg) of (17e), 18% (50mg) of (60) and 8% (20 mg) of (46e).

(±) Methyl (*E*)-4-chloro-4-phenylbut-1-enoate (60)

R$_f$ (10:2 hexane:EtOAc)= 0.53; **^{1}H NMR** δ (600 MHz); 7.42-7.34(m, 5, aromatic), 7.15(dd, 1, J =6.8, 15.4 Hz, CHCH=CH), 6.08(dd, 1, J =1.5, 15.4 Hz, CHCH=CH), 5.54(dd, 1, J =1.5, 6.8 Hz, CHCH=CH), 3.75(s, 3, OCH$_3$); **^{13}C NMR** δ (150 MHz); 166.1,

145.4, 138.4, 128.9, 127.5, 122.3, 60.7, 51.8; **mass spectrum** (GC-MS, CDCl₃) **m/z** 213(MH⁺, ³⁷Cl, 7), 211(MH⁺, ³⁵Cl, 12), 175(100), 143(35), 115(21), 89(27).

Methyl (*E*) 4-chloro-4-phenylbut-3-enoate (61)

The hydrochlorin (**60**) (30 mg, 0.14 mmol) was heated under reflux for 15 days in a solution of CH₂Cl₂ (1 mL) and methyl (triphenylphosoranylidene)acetate (**37e**) (70 mg, 0.21 mmol). The reaction was followed by TLC until no starting material (**60**) was observed in the mixture, at which time the solution was concentrated *in vacuo* to provide a clear colourless oil. Column chromatography resulted in the isolation of only one identifiable product, the titled compound (**61**) in a yield of 23%, 7 mg. The remaining compounds recovered from chromatography were not identified and were assumed to be a result of decomposition. **R**$_f$ (10:1 hexane:EtOAc)= 0.41; **¹H NMR** δ (300 MHz, CDCl₃); 7.62-7.59(m, 2, aromatic), 7.37-6.34(m, 3, aromatic), 6.38(t, 1, *J* =6.6 Hz, C**H**CH₂), 3.75(s, 3, OC**H**₃), 3.48(d, 2, *J* =6.6 Hz, CHC**H**₂); **¹³C NMR** δ (75 MHz, CDCl₃); 171.2, 137.6, 135.5, 128.8, 128.3, 126.5, 119.2, 52.0, 34.9. Spectral data was consistent with that reported in the literature.[91]

4-Chloro-5-{[1-(*tert*-butyl)-1, 1-dimethylsilyl]oxy}-5-methylpentan-2-one (57a)

Treatment of a solution of compound (**45a**) (300 mg, 1.31 mmol) in CH₂Cl₂ (30 mL) with conc. HCl (0.74 mL) for 1.25 hours under the standard conditions set out for (**56a**), afforded a crude oil of a diastereomeric mix of the titled adduct (**57a**) (318 mg) in 92% yield. Analysis (¹H NMR) of the mixture showed diastereomer formation of **57a:57a*** to be in a 1.5:1 ratio, requiring no further purification. **IR** (liquid film); 1724(s), 1468(w), 1257(m), 1092(m), 837(m), 776(m) cm⁻¹; **¹H NMR** δ (300 MHz); 4.27(ddd, 1, *J* =3.9, 3.9, 9.0 Hz, ClC**H***CH₂), 4.17(ddd, 1, *J* =3.9, 5.1, 9.0 Hz, ClC**H**'CH₂), 4.03(dq, 1, *J* =3.7, 6.4 Hz, C**H***CHCl), 3.94(dq, 1, *J* =5.2, 6.2, 11.1 Hz, C**H**'CHCl), 2.94(dd, 1, *J* =7.4, 16.9 Hz, ClCHCH-**H**), 2.94(dd, 1, *J* =16.8, 16.8 Hz, ClCHCH-**H**), 2.83(dd, 1, *J* =9.3, 19.2 Hz, ClCHC**H**-H), 2.83(dd, 1, *J* =9.0, 15.0 Hz, ClCHC**H***-H), 2.22(s, 3, OCC**H**'₃), 2.21(s, 3, OCC**H***₃), 1.22(d, 3, *J* =6.0 Hz, C**H**'₃CH), 1.21(d, 3, *J* =6.3 Hz, C**H***₃CH), 0.90(s, 9, C(C**H**'₃)₃), 0.88(s, 9, C(C**H***₃)₃), 0.10(s, 3, SiC**H**'₃), 0.08(s, 3, SiC**H**'₃), 0.07(s, 3, SiC**H***₃), 0.06(s, 3, SiC**H***₃); **¹³C NMR** δ (75 MHz); 205.3', 205.2*, 71.7', 70.0*, 61.2', 59.6*, 46.9',

45.9*, 30.7', 30.6*, 25.8', 25.7*, 18.6', 18.0*, -4.4', -4.6*, -4.8', -4.9*; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 267(M$^+$, ^{37}Cl, 2), 265(M$^+$, ^{35}Cl, 6), 228(2), 113(10), 75(75), 43(100).

Concentrated product (**57a**) decomposed over night to a black solid, consisting primarily of isomeric 1,4-dicarbonyl (**54a**).

3-Chloro-4-{[1-(*tert*-butyl)-1, 1-dimethylsilyl]oxy}-1-phenylpentan-1-one (57b)

The two diastereomers (**57b/57b***) were the sole products obtained from the reaction of enone (**45b**) (120 mg, 0.41 mmol) and conc. HCl (0.24 mL) in CH$_2$Cl$_2$ (12 mL) for 1.5 hours following an analogous reaction procedure and work-up to that described for the synthesis of compound (**56a**). The combined yield of colourless oil was 121 mg (90%) and proved to be a ratio of the isomers **57b:57b*** equivalent to 1:1.2 (^{1}H NMR). **IR** (liquid film); 1691(s), 1597(w), 1257(m), 1090(m), 837(s), 777(m); **^{1}H NMR** δ (600 MHz); 7.97-7.93(m, 2, aromatic), 7.59-7.56(m, 1, aromatic), 7.49-7.46(m, 2, aromatic), 4.50(ddd, 1, *J* =3.5, 4.7, 8.0 Hz, ClCH*CH$_2$), 4.41(ddd, 1, *J* =4.1, 5.0, 8.9 Hz, ClCHCH$_2$), 4.13(dq, 1, *J* =3.6, 6.2 Hz, CH*CHCl), 4.06(dq, 1, *J* =5.1, 6.2 Hz, CHCHCl), 3.49-3.39(m, 2, ClCHCH$_2$), 1.29(d, 3, *J*=6.0 Hz, OCCH*$_3$), 1.27(d, 3, *J*=6.0 Hz, OCCH$_3$), 0.92(s, 9, C(CH$_3$)$_3$), 0.88(s, 9, C(CH*$_3$)$_3$), 0.13, 0.11, 0.08 and 0.3(4 x s, 3, SiCH$_3$); **^{13}C NMR** δ (150 MHz); 197.0/196.9*, 136.9, 136.8, 133.3, 132.7, 128.7, 128.6, 128.5, 126.7, 104.6, 105.8, 71.8, 70.0*, 61.5, 60.1*, 42.1, 41.3*, 25.8, 25.7*, 21.0, 19.0*, 18.0, 13.7*, -4.4, -4.5, -4.8, -4.9; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 327(M$^+$, ^{35}Cl, 4), 291(2), 179(^{37}Cl, 5), 177(^{35}Cl, 18), 105(88), 77(100).

A concentrated sample of hydrochlorin (**57b**) decomposed over 1 month to furan (**55b**).

(*E*)-5-Hydroxypent-3-en-2-one (67a)

In a dry reaction vessel under a nitrogen atmosphere glycoaldehyde dimer (**66**) (0.25 g, 2.10 mmol) was added in two portions to warm (*ca.* 35°C), dry CH$_2$Cl$_2$ (16 mL). 1-Triphenylphosphoranylidene-2-propanone (**37a**) (1.69 g, 4.41 mmol) was then introduced with stirring and the mixture was heated under reflux. Analysis of a reaction mixture aliquot by *in vacuo* concentration and ^{1}H NMR showed complete enone (**67a**) formation after 4 hours. 5-Hydroxypent-3-en-2-one (**67a**) was immediately treated with further

reagents without additional purification, to affect conversion to the desired cyclopropane derivatives. Provision of a semi-purified sample for characterisation was obtained by concentration under reduced pressure, followed by precipitation and filtration of by-product triphenylphosphine oxide from hexane (*ca.* 20 mL). Further attempts at purification resulted in facile decomposition of (**67a**) to the isomeric dicarbonyl analogue (**68**). Similarly, (**67a**) gradually decomposed on standing in solution at room temperature to (**68**). The decomposition product (**68**) was not isolated but identified by comparison with similar 1,4-diketone analogues (**46/54**) Consequently structural characterisation of (**67a**) was performed on the crude mixture. **IR** (liquid film); 3390(m), 1673(m), 1631(w), 1181(s), 1120(s), 997(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 6.84(dt, 1, J =4.1, 16.0 Hz, CH$_2$C$\underline{H}$=CH), 6.33(dt, 1, J =2.0, 16.0 Hz, CH$_2$CH=C$\underline{H}$), 4.31(dd, 2, J =2.0, 3.9 Hz, C$\underline{H}_2$CH=CH), 3.82(bs, 1, O$\underline{H}$), 2.23(s, 3, (O)CC$\underline{H}_3$); **^{13}C NMR** δ (150 MHz); 198.3, 146.6, 128.8, 61.5, 27.3; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 101(MH$^+$, 13), 83(8), 71(20), 43(100), 39(37).

(*E*)-4-Hydroxy-1-phenylbut-2-en-1-one (67b)

Under similar conditions as for (**67a**), glycoaldehyde dimer (**66**) (0.50 g, 4.20 mmol), phenyl keto ylide (**37b**) (3.80 g, 10.0 mmol) and dry CH$_2$Cl$_2$ (32 mL) were heated under reflux for 4 hours. ^{1}H NMR analysis of the crude reaction mixture confirmed cessation of reaction and provided evidence for the formation of (**67b**) as the major product. Due to the sensitivity of (**67b**), characterisation was performed on the crude product after partial purification by removal of triphenylphosphine oxide with hexane (*ca.* 30 mL). **IR** (liquid film); 3314(m), 1672(s), 1625(s), 1183(s), 1120(s), 957(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.89-7.87(m, 2, aromatic), 7.66-7.31(m, 3, aromatic), 7.21(dt, 1, J =2.2, 15.5 Hz, CH$_2$CH=C$\underline{H}$), 7.08(dt, 1, J =3.6, 15.4 Hz, CH$_2$C$\underline{H}$=CH), 4.37(m, 2, C$\underline{H}_2$CH=CH), 4.05(t, 1, J =5.5 Hz, $\underline{H}$OCH$_2$), 3.74(bs, 1, O$\underline{H}$); **^{13}C NMR** δ (150 MHz); 190.5, 148.1, 132.6, 123.4, 61.9, 22.5. Incomplete ^{13}C NMR data is quoted for enone (**67b**) due to inconclusive assignment of aromatic signals. **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 163(MH$^+$, 12), 146(5), 105(38), 77(88), 51(100), 39(29).

(*E*)-4-Hydroxy-1-*tert*-butylbut-2-en-1-one (67c)

Following the procedure reported for (**67a**), glycoaldehyde dimer (**66**) (0.30 g, 2.52 mmol), *tert*-butyl keto ylide (**37c**) (1.91 g, 5.29 mmol) and dry CH_2Cl_2 (19 mL) were combined and heated under reflux with stirring for 4 hours. Concentration, dissolution in hexane (*ca.* 20 mL) and subsequent filtration to remove precipitated triphenylphosphine oxide achieved moderate purification of 1-*tert*-butyl-4-hydroxy-2-butenone (**67c**) suitable for structural analysis. **IR** (liquid film); 3331(m), 1688(s), 1628(s), 1365(w), 1181(m), 1120(s), 1008(w) cm^{-1}; **¹H NMR** δ (600 MHz); 7.98(dt, 1, *J* =3.8, 15.4 Hz, CH₂CH̲=CH), 6.80(dt, 1, *J* =2.3, 15.4 Hz, CH₂CH=CH̲), 4.31(dd, 2, *J* =2.1, 3.3 Hz, CH̲₂CH=CH), 2.55(bs, 1, OH), 1.16(s, 3, C(CH̲₃)₃); **¹³C NMR** δ (150 MHz); 204.1, 145.4, 122.2, 62.1, 43.1, 26.1; **mass spectrum** (GC-MS, CDCl₃) **m/z** 143(MH⁺, 13), 125(6), 85(8), 57(34), 41(55), 39(100).

Methyl (*E*)-4-hydroxybut-2-en-1-oate (67e)

A solution containing glycoaldehyde dimer (**66**) (50 mg, 0.42 mmol), methyl (triphenylphosphoranylidene)acetate (**37e**) (296 mg, 0.88 mmol) and dry CH_2Cl_2 (3.5 mL) was heated under reflux for 4 hours following the standard procedure for (**67a**). Removal of the solvent under reduced pressure and precipitation/filtration of triphenylphosphine oxide with hexane (*ca.* 10 mL) accomplished partial purification of enester (**67e**). Methyl-4-hydroxy-2-butenoate (**67e**) was not subjected to further purification and was analysed in the crude state. **IR** (liquid film); 3333(m), 1722(s), 1661(w), 1277(m), 1173(m), 1120(s), 1019(w) cm^{-1}; **¹H NMR** δ (600 MHz); 7.04(dt, 1, *J* =3.9, 15.6 Hz, CH₂CH̲=CH), 6.11(dt, 1, *J* =2.1, 15.6 Hz, CH₂CH=CH̲), 4.34(dd, 2, *J* =2.0, 3.9 Hz, CH̲₂CH=CH), 3.74(s, 3, OCH̲₃), 2.38(bs, 1, OH̲); **¹³C NMR** δ (150 MHz); 166.9, 147.4, 119.6, 61.7, 51.5; **mass spectrum** (GC-MS, CDCl₃) **m/z** 117(MH⁺, 44), 99(31), 85(88), 57(58), 55(92), 31(75).

trans (±) Benzyl 2-(2-acetylcyclopropyl)acetate (69a)

Method A:

Glycoaldehyde dimer (**66**) (0.18 g, 1.49 mmol), 1-triphenylphosphoranylidene-2-propanone (**37a**) (1.00 g, 3.12 mmol) and CHCl₃ (4 mL) were combined as for (**71a**),

Method A. Formation of enone (**67a**) was confirmed after heating under reflux for 24 hours by ^{1}H NMR analysis. Benzyl (triphenylphosphoranylidene)acetate (**37f**) (1.71 g, 4.17 mmol) was added and the mixture was again heated under reflux for 144 hours. Sequential chromatography afforded the titled *trans* cyclopropane (**69a**) and isomeric *cis* cyclopropane (**69b**) in a ratio of 4:1 respectively. Yields of each isomer were (**69a**) 264 mg (38%) and (**69b**) 66 mg (10%). The presence of benzyl alcohol in samples collected from chromatography suggested some hydrolysis was occurring on the silica. $\mathbf{R_f}$ (10:3 hexane:EtOAc)= 0.23; **IR** (liquid film); 3030(w), 1738(s), 1697(s), 1492(w), 1454(m), 1167(s), 739(m) cm^{-1}; ^{1}**H NMR** δ (600 MHz); 7.38-7.30(m, 5, aromatic), 5.11 and 5.08(AB$_q$, 2, *J* =12.4 Hz, CH$_2$Ph), 2.49(dd, 1, *J* =6.6, 16.2 Hz, CHCH-HCO$_2$), 2.26(dd, 1, *J* =7.8, 16.2 Hz, CHCH-HCO$_2$), 2.18(s, 3, O=CCH$_3$), 1.82(ddd, 1, *J* =4.2, 4.2, 8.4 Hz, CHC(O)CH$_3$), 1.71-1.66(m, 1, CHCH$_2$CO$_2$), 1.31(ddd, 1, *J* =4.5, 4.5, 9.0 Hz, CHCH-HCH), 0.82(ddd, 1, *J* =4.5, 4.5, 9.0 Hz, CHCH-HCH); ^{13}**C NMR** δ (150 MHz); 207.2, 171.5, 140.9, 128.6, 128.5, 128.3, 66.4, 37.8, 30.3, 28.3, 20.4, 16.8; **m/z** 232(M$^+$, 1), 141(4), 125(8), 91(100), 77(9), 42(35); Acc. Mass Calc. for (MH$^+$) C$_{14}$H$_{17}$O$_3$ 233.1178; Found 233.1175.

Method B:

Following the procedure reported for (**71a**) in Method B, glycoaldehyde dimer (**66**) (0.25 g, 2.10 mmol), 1-triphenylphosphoranylidene-2-propanone (**37a**) (1.69 g, 4.41 mmol), CH$_2$Cl$_2$ (16 mL), benzyl (triphenylphosphoranylidene)acetate (**37f**) (2.24 g, 5.46 mmol) and benzophenone (0.08 g, 0.41 mmol) were combined. The mixture was irradiated for 96 hours, at which time some enone (**67a**) remained. Concentration and chromatography of the crude product provided a combined yield of (**69a**) and (**69b**) of 47%, 0.46 g. The ratio of *trans:cis* cyclopropanes was determined by ^{1}H NMR of the pure mixture to be 12:1.

cis (±) Benzyl 2-(2-acetylcyclopropyl)acetate (69b)

$\mathbf{R_f}$ (10:3 hexane:EtOAc)= 0.36; **IR** (liquid film); 3034(w), 1737(s), 1693(s), 1641(w), 1498(w), 1170(s), 750(m) cm^{-1}; ^{1}**H NMR** δ (600 MHz); 7.37-7.30(m, 5, aromatic), 5.14 and 5.12(AB$_q$, 2, *J* = 12.5 Hz, CH$_2$Ph), 2.71(dd, 1, *J* =5.7, 17.1 Hz, CHCH-HCO$_2$), 2.52(dd, 1, *J* =9.0, 17.4 Hz, CHCH-HCO$_2$), 2.24(s, 3, CH$_3$C=O), 2.20-2.16(m, 1, CH$_3$(O)CCH), 1.67-1.60(m, 1, CHCH$_2$CO$_2$), 1.11-1.05(m, 2, CHCH$_2$CH); ^{13}**C NMR** δ

(150 MHz); 207.2, 172.6, 135.9, 128.5, 128.2, 128.1, 66.2, 31.9, 31.3, 25.3, 19.8, 14.1; **m/z** 233(MH⁺, 1), 126(6), 107(7), 91(100), 42(41); Acc. Mass Calc. for (MH⁺) $C_{14}H_{17}O_3$ 233.1178; Found 233.1181.

trans (±) Methyl 2-(2-acetylcyclopropyl)acetate (70a)

Method A:

A mixture of glycoaldehyde dimer (**66**) (1.00 g, 8.35 mmol) and 1-triphenylphosphoranylidene-2-propanone (**37a**) (5.61 g, 17.5 mmol) in $CHCl_3$ (22.5 mL) was heated under reflux for four days affording enone (**67a**). Addition of methyl (triphenylphosphoranylidene)acetate (**37e**) (8.38 g, 25.05 mmol) was followed by heating at 60°C for 192 hours. Work-up as for (**71a**) yielded *trans* (**70a**) and *cis* (**70b**) cyclopropanes in a ratio of 4:1. Despite incomplete enone (**67a**) consumption, 26% (0.67 g) of (**70a**) and 6% (0.17 g) of (**70b**) were recovered. Flash chromatography was utilised due to the apparent instability of the product to exposure to silica. R_f (10:3 hexane:EtOAc)= 0.19; **IR** (liquid film); 1740(s), 1696(s), 1435(m), 1357(w), 1174(s), cm⁻¹; **¹H NMR** δ (600 MHz); 3.68(s, 3, C**H**₃O), 2.42(dd, 1, J =6.9, 15.9 Hz, CHC**H**-HCO₂), 2.25(dd, 1, J =7.8, 16.2 Hz, CHCH-**H**CO₂), 2.25(s, 3, C**H**₃C=O), 1.84(ddd, 1, J =4.4, 4.4, 8.7 Hz, CH₃(O)CC**H**), 1.70-1.64(m, 1, C**H**CH₂CO₂), 1.32(ddd, 1, J =4.7, 4.7, 9.0 Hz, CHC**H**-HCH), 0.83(ddd, 1, J =4.0, 4.2, 6.3 Hz, CHC**H**-**H**CH); **¹³C NMR** δ (150 MHz); 207.6, 172.5, 52.0, 37.8, 30.6, 28.6, 20.6, 17.0; **m/z** 156(M⁺, 2), 141(2), 97(16), 83(49), 59(19), 42(100); Acc. Mass Calc. for (M⁺) $C_8H_{12}O_3$ 156.0786; Found 156.0779.

Method B:

Employing Method B as for (**71a**), glycoaldehyde dimer (**66**) (0.25 g, 2.10 mmol) and 1-triphenylphosphoranylidene-2-propanone (**37a**) (1.69 g, 4.41 mmol), CH_2Cl_2 (16 mL), methyl (triphenylphosphoranylidene)acetate (**37e**) (2.81 g, 8.40 mmol) and benzophenone (0.08 g, 0.44 mmol) were allowed to react under irradiation for 96 hours. ¹H NMR showed some enone (**67a**) remained unconsumed, yet chromatography yielded 44% (0.29 g) of a pure mixture of *trans* (**70a**) and *cis* (**70b**). The *trans:cis* ratio of 12:1 was determined by ¹H NMR analysis of the stereomeric mixture.

cis (±) Methyl 2-(2-acetylcyclopropyl)acetate (70b)

R_f (10:3 hexane:EtOAc)= 0.29; **IR** (liquid film); 1739(s), 1694(s), 1439(m), 1388(m), 1195(m), 1172(s) cm^{-1}; **¹H NMR** δ (600 MHz); 3.64(s, 3, C$\underline{H}_3$CO), 2.66(dd, 1, J =5.4, 16.8 Hz, CHC$\underline{H}$-HCO$_2$), 2.46(dd, 1, J =9.0, 17.4 Hz, CHCH-$\underline{H}$CO$_2$), 2.31(s, 3, C$\underline{H}_3$C=O), 2.21-2.17(m, 1, CH$_3$(O)CC$\underline{H}$), 1.64-1.60(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.10-1.05(m, 2, CHC$\underline{H}_2$CH); **¹³C NMR** δ (150 MHz); 207.2, 173.3, 51.5, 32.0, 31.0, 25.3, 19.8, 14.1; **m/z** 156(M$^+$, 3), 141(2), 97(9), 83(29), 59(13), 42(100).

cis Cyclopropane (**70b**) decomposed over a few days at ambient temperature to an unrecovered compound.

trans (±) Benzyl 2-(2-benzoylcyclopropyl)acetate (71a)

Method A:

Under dry reaction conditions glycoaldehyde dimer (**66**) (0.205 g, 1.72 mmol) was added to warm CHCl$_3$ (10 mL, ethanol free) with stirring. Phenyl keto ylide (**37b**) (1.38 g, 3.61 mmol) was added and the solution was heated under reflux for 5 days. The *trans* γ-hydroxy enone (**67b**) solution was allowed to cool prior to the addition of benzyl (triphenylphosphoranylidene)acetate (**37f**) (2.10 g, 5.13 mmol). ¹H NMR analysis showed no enone (**67b**) remained after heating the mixture under reflux for an additional 120 hours. Removal of the solvent *in vacuo* was followed by partial purification on a squat chromatography column (10:3 hexane:EtOAc) (decomposition of (**71a**) was observed on prolonged exposure to silica) and subsequent recrystallisation provided fine white crystals of the titled cyclopropane (**71a**) in a 35% yield (0.345 g). **Mp** 42-44 °C (heptane); R_f (10:3 hexane:EtOAc)= 0.38; **IR** (Nujol mull); 3056(w), 1722(s), 1664(s), 1594(w), 1402(s), 1176(w) cm^{-1}; **¹H NMR** δ (300 MHz); 7.98-7.95(m, 2, aromatic), 7.57-7.54(m, 1, aromatic), 7.47-7.44(m, 2, aromatic), 7.31-7.28(m, 5, aromatic), 5.13 and 5.11(AB$_q$, J =12.6 Hz, PhC$\underline{H}_2$), 2.62(dd, 1, J =6.5, 15.8 Hz, CHC$\underline{H}$-HCO$_2$), 2.59(ddd, 1, J =4.1, 4.1, 8.3 Hz, CH$_3$(O)CC$\underline{H}$), 2.38(dd, 1, J =8.0, 15.8 Hz, CHCH-$\underline{H}$CO$_2$), 1.95-1.88(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.55(ddd, 1, J=4.4, 4.4, 8.9 Hz, CHC$\underline{H}$-HCH), 1.03-0.97(m, 1, CHCH-$\underline{H}$CH); **¹³C NMR** δ (75 MHz); 199.04, 171.54, 137.82, 135.74, 132.74, 128.53, 128.48, 128.23, 128.12,

128.04, 66.44, 38.10, 24.34, 21.39, 17.64; **m/z** 294(M^+, 1), 165(38), 105(97), 91(100), 77(17); **Anal. Calc.** for $C_{19}H_{18}O_3$: C: 77.53% H: 6.16%; Found: C: 77.73% H: 6.14%.

Method B:

Hydroxy enone (**67b**) was synthesised by analogous methodology to Method A, with the exception that dry CH_2Cl_2 (32 mL) was the solvent of choice for the dissolution of glycoaldehyde dimer (**66**) (0.50 g, 4.20 mmol) and ylide (**37b**) (3.80 g, 10.00 mmol). Additionally, the increased dilution resulted in only 4 hours of heating under reflux being required for complete formation of (**67b**). Benzyl (triphenylphosphoranylidene)acetate (**37f**) (5.33 g, 13.0 mmol) and benzophenone (0.13 g, 0.71 mmol) were added directly to the reaction flask and irradiation with 2 x 300 W sun lamps was initiated. The reaction did not go to completion with a minor amount of enone (**67b**) remaining in solution after 30 hours. Isolation of the reaction products was performed as for Method A, providing 68% (1.66 g) of *trans* cyclopropane (**71a**) and after further chromatography 5% (0.12 g) of the pale yellow oil (**71c**). A trace of the *cis* cyclopropane of (**71b**) was observed in the crude mixture ^{1}H NMR spectrum, however, characterisation was not carried out due to insufficient material being isolated.

Benzyl (*E*)-6-oxo-6-phenylhex-2-enoate (71c)

R$_f$ (10:0.1 CH_2Cl_2:EtOAc)= 0.35; **IR** (Nujol mull); 1711(s), 1684(s), 1645(m), 1265(m), 1084(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.98-7.53(m, 2, aromatic), 7.58-7.53(m, 1, aromatic), 7.48-7.44(m, 2, aromatic), 7.43-7.19(m, 5, aromatic), 7.08(dt, 1, *J* =6.6, 15.6 Hz, CH=C<u>H</u>CH₂), 5.95(dt, 1, *J* =1.5, 15.6 Hz, C<u>H</u>=CHCH₂), 5.17(s, 2, PhC<u>H</u>₂), 3.14(t, 2, *J* =7.5 Hz, C<u>H</u>₂C=O), 2.68-2.64(m, 2, CH₂C<u>H</u>₂CH); **^{13}C NMR** δ (150 MHz); 198.08, 166.18, 148.08, 136.59, 136.04, 133.24, 128.66, 128.52, 128.21, 128.17, 128.02, 121.81, 66.11, 36.57, 26.34; **m/z** 295(MH^+, 24), 187(100), 160(49), 105(36), 91(25), 77(5); **Anal. Calc.** for $C_{13}H_{14}O_3$: C: 77.53% H: 6.16%; Found: C: 77.75% H: 6.06%.

trans (±) Benzyl 2-[2-(2,2-dimethylpropanoyl)cyclopropyl]acetate (72a)

Method A:

Under similar conditions to those described for (71a), glycoaldehyde dimer (66) (0.10 g, 0.84 mmol), *t*-butyl keto ylide (37c) (0.64 g, 0.76 mmol) and dry CH_2Cl_2 (6.5 mL) were heated under reflux for 4 hours, and subsequently treated with benzyl (triphenylphosphoranylidene)acetate (37f) (1.03 g, 2.52 mmol) under reflux for 157 hours. At this time approximately 50% of enone (67c) still remained. Standard chromatographic purification was employed to provide two major products, *trans* cyclopropane (72a) in 17% (76 mg) and *cis* cyclopropane (72b) in 4% (18 mg). R_f (10:0.5 hexane:EtOAc)= 0.28; IR (liquid film); 3038(w), 1738(s), 1687(s), 1498(w), 1168(s), 750(w) cm^{-1}; ^{1}H NMR δ (300 MHz); 7.36-7.26(m, 5, aromatic), 5.12(s, 2, CH$_2$Ph), 2.54(dd, 1, J =6.3, 15.6 Hz, CHCH-HCO$_2$), 2.24(dd, 1, J =7.8, 15.6 Hz, CHCH-HCO$_2$), 2.04(ddd, 1, J =4.2, 4.2, 8.4 Hz, (CH$_3$)$_3$C(O)CH), 1.69-1.59(m, 1, CHCH$_2$CO$_2$), 1.27(ddd, 1, J =4.2, 4.2, 8.7 Hz, CHCH-HCH), 1.15(s, 9, C(CH$_3$)$_3$), 0.81-0.76(m, 1, CHCH-HCH); ^{13}C NMR δ (75 MHz); 213.8, 171.6, 135.8, 128.6, 128.3, 128.2, 66.4, 44.0, 38.0, 26.2, 22.9, 20.6, 17.0; m/z 274(M$^+$, 1), 273(2), 217(15), 91(100), 57(52); Anal. Calc. for C$_{17}$H$_{22}$O$_3$: C: 74.42% H: 8.08%; Found: C: 74.66% H: 8.20%; Acc. Mass Calc. for (M$^+$) C$_{17}$H$_{22}$O$_3$ 274.1569; Found 274.1563.

Method B:

An analogous procedure to (71a) in Method B, saw treatment of glycoaldehyde dimer (66) (0.30 g, 2.52 mmol) and *t*-butyl keto ylide (37c) (1.91 g, 5.29 mmol) in CH_2Cl_2 (19 mL) for 4 hours. Irradiation of the enone (67c) solution with benzyl (triphenylphosphoranylidene) acetate (37f) (3.10 g, 7.56 mmol) and benzophenone (0.09 g, 0.49 mmol) for a period of 93 hours, and ensuing chromatography gave a combined (72a) and (72b) yield of 43% (0.59 g). The ratio of isolated *trans:cis* was 3:1.

cis (±) Benzyl 2-[2-(2,2-dimethylpropanoyl)cyclopropyl]acetate (72b)

R_f (10:0.5 hexane:EtOAc)= 0.36; IR (liquid film); 3033(w), 1738(s), 1685(w), 1660(s), 1599(w), 1278(s), 1166(m) cm^{-1}; ^{1}H NMR δ (300 MHz); 7.38-7.30(m, 5, aromatic), 5.09(s,

2, CH$_2$Ph), 2.63(dd, 1, *J* =6.5, 17.3 Hz, CHCH-HCO$_2$), 2.53(dd, 1, *J* =7.7, 17.3 Hz, CHCH-HCO$_2$), 2.36(ddd, 1, *J* =5.9, 7.4, 8.6 Hz, (CH$_3$)$_3$C(O)CCH), 1.74-1.61(m, 1, CHCH$_2$CO$_2$), 1.20-1.05(m, 2, CHCH$_2$CH), 1.15(s, 9, (CH$_3$)$_3$C); **^{13}C NMR** δ (75 MHz); 213.7, 172.7, 136.0, 128.5, 128.3, 128.1, 66.1, 44.5, 31.3, 26.3, 20.3, 19.7, 14.3; **m/z** 274(M$^+$, 1), 217(4), 182(9), 91(100), 57(31); Acc. Mass Calc. for (M$^+$) C$_{17}$H$_{22}$O$_3$ 274.1569; Found 274.1559.

trans (±) 2-(2-Acetylcyclopropyl)acetic acid (74a)

Aqueous potassium hydroxide (10%, 0.45 mL) was added to the *trans* benzyl ester cyclopropane (**69a**) (200 mg, 0.86 mmol) in water (4 mL) and methanol (3 drops). The mixture was allowed to stir at room temperature for 2 days prior to work-up involving; addition of water (*ca.* 5 mL), washing with CH$_2$Cl$_2$ (5 mL), acidification (pH 1) with conc. HCl, extraction with CH$_2$Cl$_2$ (3 x 5 mL), drying over NaSO$_4$ and concentration under reduced pressure. By-product benzyl alcohol was removed from the pale yellow oil with heating (*ca.* 40°C) under high-pressure vacuum (0.2 mmHg). No further purification was required to provide the title acid (**74a**) in 66% (80 mg). **IR** (liquid film); 2630(w), 1712(s), 1670(s), 1404(m), 1359(m), 1182(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 10.36(bs, 1, OH), 2.49(dd, 1, *J* =6.6, 16.5 Hz, CHCH-HCO$_2$), 2.28(dd, 1, *J* =7.0, 16.4 Hz, CHCH-HCO$_2$), 2.27(s, 3, CH$_3$C=O), 1.86(ddd, 1, *J* =4.0, 4.0, 8.1 Hz, CH$_3$(O)CH), 1.74-1.64(m, 1, CHCH$_2$CO$_2$), 1.35(ddd, 1, *J* =4.5, 4.5, 9.0 Hz, CHCH-HCH), 0.89-0.83(m, 1, CHCH-HCH); **^{13}C NMR** δ (75 MHz); 207.8, 177.3, 37.5, 30.3, 28.4, 20.1, 16.8; **m/z** 143(MH$^+$, 12), 125(10), 109(12), 82(36), 43(100); Acc. Mass Calc. for (MH$^+$) C$_7$H$_{11}$O$_3$ 143.0708; Found 143.0715.

cis (±) 2-(2-Acetylcyclopropyl)acetic acid (74b)

Analogously to (**74a**), reaction of the *cis* benzyl ester cyclopropane (**69b**) (150 mg, 0.66 mmol), 10% potassium hydroxide (0.35 mL), water (3 mL) and methanol (3 drops), provided 63 mg, 68%, of the target acid (**74b**). **IR** (liquid film); 2632(m), 1713(s), 1694(s), 1397(m), 1359(m), 1177(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 10.44(bs, 1, OH), 2.72(dd, 1, *J* =5.4, 17.7 Hz, CHCH-HCO$_2$), 2.53(dd, 1, *J* =9.2, 17.6 Hz, CHCH-HCO$_2$), 2.32(s, 3,

$C\underline{H}_3C{=}O$), 2.22(m, 1, $CH_3(O)CC\underline{H}$), 1.70-1.56(m, 1, $C\underline{H}CH_2CO_2$), 1.13-1.08(m, 2, $CHC\underline{H}_2CH$); **^{13}C NMR** δ (75 MHz); 207.5, 178.6, 32.0, 31.1, 25.2, 19.5, 14.3; **m/z** 143(MH$^+$, 3), 125(6), 109(7), 43(100); Acc. Mass Calc. for (MH$^+$) $C_7H_{11}O_3$ 143.0708; Found 143.0710.

S-2-Hydroxypropanal (65a)

To a mixture of protected *S*-(-)-lactaldehyde (**43a**) (1.65 g, 8.84 mmol) in dry acetonitrile (44 mL), was added in a drop wise fashion, aqueous HF (55 drops, 48%) at ambient temperature whilst stirring. After stirring for an additional 15 minutes the reaction mixture was quenched by the addition of solid NaHCO$_3$ (1.65 g) and stirring of the mixture continued until no effervescence was observed (approximately 25 minutes). The solution was then filtered through a short plug of silica and the solids washed with ether (3x 25 mL). Crude deprotected hydroxy aldehyde (**65a**) was provided as a yellow oil in a crude yield of 0.54 g (82 %) by concentration of the combined filtrates. No purification was attempted and the crude product was utilised immediately upon synthesis due to the instability of the hydroxy aldehyde functionality. Analysis of the product was not undertaken due to the complexity of the spectral data, both the monomer and dimer of the product existing in solution, however the aldehyde signal was clearly evident at 9.6 ppm (^{1}H NMR δ (300 MHz)).

S-(*E*)-1-*tert*-Butyl-4-hydroxypent-2-en-1-one (39c)

Under analogous conditions to those described in Method D for (**39a**), protected lactaldehyde (**43a**) (100 mg, 0.54 mmol), acetonitrile (2.7 mL), aqueous HF (4 drops, 48%) and NaHCO$_3$ (*ca.* 100 mg) were employed. Following filtration of the crude mixture and concentration under reduced pressure, the α-hydroxy lactaldehyde (**65a**) was isolated in a crude yield of 85% (28 mg). Dry CH$_2$Cl$_2$ (1 mL) and *tert*-butyl keto ylide (**37c**) (175 mg, 0.48 mmol) were then added and the mixture was maintained under reflux for 5 hours. The target enone was not purified but used immediately for conversion to the cyclopropyl derivatives. Characterisation was achieved by analysis of the crude enone (**39c**). Any attempt at purification resulted in spontaneous decomposition of (**39c**) to the isomeric 1-*tert*-butyl-1,4-pentanedione (**54c**), however, the rearrangement could be slowed by storing

(**39c**) in solution with a minor excess of ylide present. **IR** (liquid film); 3330(m), 1688(s), 1628(s), 1476(s), 1402(m), 1119(s), 1011(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 6.90(dd, 1, J =4.5, 15.3 Hz, CHC$\underline{H}$=CH), 6.72(dd, 1, J =1.5, 15.3 Hz, CHCH=C$\underline{H}$), 4.37(ddq, 1, J =2.0, 4.8, 6.6 Hz, C$\underline{H}$CH=CH), 2.24(s, 1, O$\underline{H}$), 1.20(s, 9, C(C$\underline{H}_3$)$_3$), 1.14(s, 3, C$\underline{H}_3$CH); **^{13}C NMR** δ (150 MHz); 204.6, 149.9, 121.3, 66.9, 43.0, 28.7, 26.1; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 157(M$^+$, 25), 139(21), 111(15), 71(12), 57(24), 43(100).

1-*tert*-Butyl-1,4-pentanedione (**54c**) was identified by comparison with analogous 1,4-diketones (**46/54**) and the literature,[154] and was not isolated for characterisation.

S-(*E*)-1-(4-Bromophenyl)-4-hydroxypent-2-en-1-one (39d)

Applying procedure described for (**39a**) Method D, O-protected lactaldehyde (**43a**) (0.765 g, 4.10 mmol), acetonotrile (20 mL) and aqueous HF (26 drops, 48%) were combined and accordingly quenched with NaHCO$_3$ (*ca.* 0.760 g). Dissolution of the crude α-hydroxy aldehyde (**65a**) (210 mg, 2.83 mmol, 84%) in dry CH$_2$Cl$_2$ (10 mL) was followed by addition of 1-(4-bromophenyl)-2-(1,1,1-triphenyl-1-phosphanylide)-1-ethanone (**37d**) (1.74 g, 4.25 mmol). The mixture was heated under reflux for 5 hours. Removal of the solvent *in vacuo* afforded the crude enone (**39d**), which was partially purified by the removal of the majority of the triphenylphosphine oxide by precipitation with hexane. No further purification was attempted due to the sensitivity of the γ-hydroxy enone (**39d**), hence structural characterisation was performed on the crude mixture. **IR** (liquid film); 3298(m), 1668(m), 1578(s), 1196(s), 1510(s), 1403(s), 1108(s), 1008(s) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.77-7.43(m, 4, aromatic), 7.06(dd, 1, J =1.5, 15.3 Hz, CHCH=C$\underline{H}$), 6.99(dd, 1, J =3.6, 15.6 Hz, CHC$\underline{H}$=CH), 4.41(ddq, 1, J =1.7, 3.8, 15.3 Hz, C$\underline{H}$CH=CH), 2.41(s, 1, O$\underline{H}$), 1.25(d, 3, J =6.6 Hz, C$\underline{H}_3$CH); **^{13}C NMR** δ (150 MHz); 189.6, 152.9, 136.5, 131.7, 130.9, 127.6, 122.2, 66.7, 22.5; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 238(Br^{81}, M$^+$-OH, 100), 236(Br^{79}, M$^+$-OH, 99), 208(2), 185(Br^{81}, 4), 183(Br^{79}, 7), 157(17), 43(22). Concentrated enone (**39d**) slowly decomposed to the isomeric 1,4-diketone (**55d**)

Data for 1-(4-bromophenyl)-1,4-pentanedione (**55d**); **Mp** 85-86 °C; **IR** (Nujol mull); 1707(m), 1675(m), 1584(w), 1354(w) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.86-7.80(m, 2, aromatic), 7.64-7.59(m, 2, aromatic), 3.23(t, 2, J =6.2 Hz, C$\underline{H}_2$), 2.89(t, 2, J =6.2 Hz, C$\underline{H}_2$),

2.26(s, 1, O=CC$\underline{H}_3$); ^{13}**C NMR** δ (75 MHz); 207.0, 197.5, 135.4, 131.9, 129.6, 128.3, 37.0, 32.3, 30.0; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 256(Br^{81}, M$^+$, 9), 254(Br^{79}, M$^+$, 8), 241(Br^{81}, 10), 239(Br^{79}, 11), 185(Br^{81}, 98), 183(Br^{79}, 100), 157(Br^{81}, 22), 155(Br^{79}, 23), 43(52); **Anal. Calc. for** C$_{11}$H$_{11}$O$_2$Br: C: 51.79% H: 4.35%; Found: C: 51.61% H: 4.16%.

S-Methyl (*E*)-4-hydroxypent-2-en-1-oate (39e)

Crude α-hydroxy aldehyde (**65a**) (80 mg, 1.08 mmol) and methyl (triphenylphosphoran-ylidene)acetate (**37e**) (432 mg, 1.30 mmol) were dissolved in dry benzene (3 mL) and heated under reflux for 5.5 hours. Dissolving crude enester (**39e**) in ethyl acetate (1 mL) and hexane (5 mL), followed by filtration of the precipitate accomplished partial removal of triphenylphosphine oxide. Further purification was not possible due to the instability of (**39e**) and as such structural confirmation was achieved by analysis of the crude γ-hydroxyenester (**39e**). **IR** (liquid film); 3408(m), 1722(s), 1658(m), 1439(m), 1176(s) cm^{-1}; ^{1}**H NMR** δ (300 MHz); 6.97(dd, 1, *J* =4.8, 15.6 Hz, CHC$\underline{H}$=CH), 6.04(dd, 1, *J* =1.8, 15.6 Hz, CHCH=C$\underline{H}$), 4.48(m, 1, C$\underline{H}$CH=CH), 3.75(s, 3, OC$\underline{H}_3$), 2.07(bs, 1, O$\underline{H}$), 1.34(d, 3, *J* =6.6 Hz, C$\underline{H}_3$CH); ^{13}**C NMR** δ (75 MHz); 167.1, 151.6, 119.0, 66.9, 51.5, 22.6; **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 131(MH$^+$, 75), 113(74), 99(46), 59(4), 55(54), 43(100); **Anal. Calc. for** C$_6$H$_{10}$O$_3$: C: 69.89% H: 6.84%; Found: C: 69.98% H: 7.03%.

(±)-2-Hydroxy-2-phenylacetaldehyde (36)

To a solution of (±)-O-protected mandelaldehyde (**42**) (300 mg, 1.19 mmol) in dry acetonitrile (2.5 mL) was added aqueous HF (4 drops, 48%) at ambient temperature. The procedure was analogous to that for (**65a**) except that a reaction time of 3.5 hours was required and no work-up was performed. Reaction completion was confirmed by concentration of the crude solution *in vacuo* and ^{1}H NMR analysis displaying a signal at 9.64 ppm corresponding to the aldehyde proton (^{1}H NMR δ (300 MHz)). Due to the complexity of the spectrum (mono/dimeric mixture) and the instability of the title compound (**36**), no further characterisation was achieved and (**36**) was employed immediately for further synthesis with no purification.

(*E*)-1-*tert*-Butyl-4-hydroxy-4-phenylbut-2-en-1-one (17c)

α-Hydroxy mandelaldehyde (36) (0.60 mmol) was generated identically to that reported in Method D for (17a). Treatment of (36) with *t*-butyl keto ylide (37c) (205 mg, 0.57 mmol) provided γ-hydroxy enone (17c) as a crude mixture unstable to purification. Structural characterisation of (17c) was performed on the crude product. **IR** (liquid film); 3356(m), 1699(s), 1626(m), 1597(w), 1119(s) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.67-7.46(m, 5, aromatic), 7.00(dd, 1, J =4.8, 15.0 Hz, CHC$\underline{H}$=CH), 6.88(dd, 1, J =1.5, 15.3 Hz, CHCH=C$\underline{H}$), 5.36(dd, 1, J =1.8, 4.2 Hz, C$\underline{H}$CH=CH), 4.19(bs, 1, O$\underline{H}$), 1.21(s, 9, C(C$\underline{H}_3$)$_3$); **^{13}C NMR** δ (150 MHz); 204.3, 146.3, 141.7, 126.1, 73.4, 45.2, 26.1. Incomplete ^{13}C NMR data is quoted for enone (17c) due to inconclusive assignment of aromatic and alkene signals. **mass spectrum** (GC-MS, CDCl$_3$) m/z 217(M$^+$-H$^+$, 4), 201(1), 161(100), 133(34), 105(50), 77(17), 57(5). Enone (17c) decomposed on attempted purification to 1,4-diketone (46c), identified by comparison with the literature.[148]

trans (-) Benzyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl]acetate (16a)

Method A:

O-protected lactaldehyde (43a) (1.65 g, 8.84 mmol) in dry acetonitrile (44 mL) was treated with aqueous HF (48%) (55 drops, *ca.* 45 mL) for 15 minutes prior to quenching with NaHCO$_3$ (*ca.* 1.65 g). Work-up was performed following an analogous procedure as for (65a), providing 0.54 g (83 %) of crude α-hydroxy aldehyde (65a). The crude oil (65a) (7.26 mmol) was then dissolved in dry CH$_2$Cl$_2$ (20 mL), phenyl keto ylide (37b) (2.90 g, 7.62 mmol) added, and the mixture was heated under reflux following the conditions set out for (39b), Method D. No purification of intermediate γ-hydroxy enone (39b) was performed and benzyl (triphenylphosphoranylidene)acetate (37f) (4.47 g, 10.89 mmol) was added directly to the reaction vessel. Heating under reflux with stirring was continued until reaction completion (confirmed by ^{1}H NMR) after 180 hours. Removal of the solvent *in vacuo* provided a crude oil to which hexane (50 mL) was added to precipitate out by-product triphenylphosphine oxide. The filtrate was concentrated under reduced pressure affording an oil which was partially purified on a squat chromatography column (10:2 hexane:EtOAc) packed with tlc silica. The major products were collected as a group

exhibiting R_f values in the range between 0.40 and 0.33. The resultant oil contained a mixture of the title cyclopropane (**16a**) and enolene product (**16c**). *trans*-Benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (**16a**) was obtained as a pure white crystalline solid by recrystallisation from heptane in a yield of 0.637 g (29%). **Mp** 54-55 °C (heptane); **R_f** (10:1 CH_2Cl_2:hexane)=0.39; $[\alpha]_D^{23}$ = -39.6° (*c* 1.15, $CHCl_3$); **IR** (Nujol mull); 1729(s), 1660(s), 1598(m), 1581(w), 1455(s), 1171(s), 964(m) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.95-7.92(m, 2, aromatic), 7.47-7.29(m, 8, aromatic), 5.12(s, 2, C$\underline{H}_2$Ph), 2.62(dd, 1, J =7.1, 16.1 Hz, CHC$\underline{H}$-HCO$_2$), 2.52(dd, 1, J =8.1, 16.2 Hz, CHCH-$\underline{H}$CO$_2$), 2.26(dd, 1, J =4.5, 4.5 Hz, Ph(O)CC$\underline{H}$), 2.12-2.03(m, C$\underline{H}$CH$_2$CO$_2$), 1.92-1.81(m, 1, C$\underline{H}$CH$_3$), 1.21(d, 3, J =6.3 Hz, CHC$\underline{H}_3$); **^{13}C NMR** δ (75 MHz); 199.0, 172.0, 138.0, 135.7, 132.6, 128.5, 128.4, 128.2, 128.1, 128.0, 66.5, 32.9, 32.6, 26.5, 24.5, 12.4; **m/z** 308(M$^+$, 0.5), 217(30), 159(10), 105(82), 91(100), 43(6); Anal. Calc. for $C_{20}H_{20}O_3$: C: 77.90% H: 6.54%; Found: C: 78.04% H: 6.52%.

Subsequent chromatography (10:1 CH_2Cl_2:hexane) of the residual oil provided 0.08 g (4%) of pure benzyl (*E*)-4-methyl-6-oxo-6-phenyl-2-hexenoate (**16c**) as a clear colourless oil.

Method B:

Similarly to Method A, protected lactaldehyde (**43a**) (400 mg, 2.13 mmol), dry CH_2Cl_2 (10 mL), 48% aqueous HF (14 drops, *ca.* 11 mmol), and NaHCO$_3$ (*ca.* 400 mg) were employed to produce deprotected lactaldehyde (**65a**), 74%. Intermediate (**65a**) (117 mg, 1.57 mmol) was subsequently heated under reflux in dry CH_2Cl_2 (4.5 mL) in the presence of phenyl keto ylide (**37b**) (628 mg, 1.65 mmol). The procedural exception to Method A was the irradiation of the enone (**39b**) and CH_2Cl_2 solution with 2 x 300 W sun lamps following the addition of benzyl (triphenylphosphoranylidene)acetate (**37f**) (966 mg, 2.36 mmol) and benzophenone (25 mg, 0.14 mmol). ^{1}H NMR confirmed reaction completion after 40 hours irradiation. Standard product isolation (Method A) yielded 219 mg (50%) of *trans* cyclopropane (**16a**), approximately 10% (44 mg) of *cis* cyclopropane (**16b**) and 2% (14 mg) of enolene (**16c**).

cis Benzyl 2-[(1*S*,2*R*,3*R*)-2-benzoyl-3-methylcyclopropyl]acetate (16b)

cis Cyclopropane (16b) decomposed slowly at ambient temperature, undergoing an enolene rearrangement to the observed enolene (16c). Complete characterisation of (16b) was not possible due to this instability. R_f (10:1 CH_2Cl_2:hexane)=0.54; ^1H NMR δ (600 MHz); 7.94-7.90(m, 2, aromatic), 7.56-7.40(m, 3, aromatic), 7.33-7.28(m, 5, aromatic), 5.10 and 5.08(AB_q, 2, J =12.6 Hz, CH_2Ph), 2.99(dd, 1, J =7.8, 17.6 Hz, CHC$\underline{H}$-HCO_2), 2.91(dd, 1, J =6.8, 17.6 Hz, CHCH-$\underline{H}CO_2$), 2.80(dd, 1, J =8.8, 8.8 Hz, Ph(O)CC$\underline{H}$), 1.93(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.83(m, 1, C$\underline{H}$CH$_3$), 1.21(d, 3, J =6.0 Hz, CHC$\underline{H}_3$).

Heating (16b) in $CDCl_3$ at 55°C for 3 days resulted in complete transformation to (16c).

(+)-Benzyl (*E*)-4-methyl-6-oxo-6-phenylhex-2-enoate (16c)

R_f (10:1 CH_2Cl_2:hexane)=0.56; $[α]_D^{24}$ = +8.2° (*c* 0.95, $CHCl_3$); IR (liquid film); 1719(s), 1685(s), 1654(w), 1597(w), 1169(m), 977(m) cm^{-1}; ^1H NMR δ (600 MHz); 7.95-7.57(m, 2, aromatic), 7.56-7.25(m, 8, aromatic), 7.03(dd, 1, J =6.6, 15.6 Hz, CH=C$\underline{H}$CH), 5.91(dd, 1, J =1.2, 15.6 Hz, C$\underline{H}$=CHCH), 5.17(s, 2, C$\underline{H}_2$Ph), 3.14-3.07(m, 2, CHC$\underline{H}$(CH$_3$)C$\underline{H}$-H), 3.00-2.96(m, 1, CHCH-$\underline{H}CO_2$), 1.15(d, 3, J =6.6 Hz, CHC$\underline{H}_3$); ^{13}C NMR δ (150 MHz); 197.93, 166.44, 153.29, 136.90, 136.03, 133.19, 128.63, 128.52, 128.23, 128.16, 128.00, 119.81, 66.13, 44.11, 31.96, 19.09; m/z 308(M$^+$, 0.3), 262(1), 217(14), 105(100), 91(95), 82(49), 77(36), 43(37); Acc. Mass Calc. for (MH$^+$) $C_{20}H_{20}O_3$ 309.1491; Found 309.1485.

trans (+) Benzyl 2-[(1*S*,2*S*,3*R*)-2-acetyl-3-methylcyclopropyl]acetate (76a)

Method A:

The following reagents; TBDMSO-protected lactaldehyde (43a) (1.50 g, 8.03 mmol), acetonitrile (40 mL), aqueous HF (50 drops, *ca.* 40 mmol) and $NaHCO_3$ (*ca.* 1.50 g), were combined as described for (16a) with the exception that hydroxy aldehyde (65a) (0.375 g, 5.05 mmol, 65 %) in CH_2Cl_2 (15 mL) was treated with 1-triphenylphosphoranylidene-2-propanone (37a) (1.69 g, 5.31 mmol). Synthesis of γ-hydroxy enone (39a) *in situ* was followed by the addition of benzyl (triphenylphosphoranylidene)acetate (37f) (3.11 g, 7.58 mmol). Heating this mixture under reflux for 448 hours provided an optimal yield 21% (0.25 g) of *trans* cyclopropane (76a), as a colourless oil. After cessation of the reaction a

portion of enone (**39a**) remained in the reaction mixture (determined by ^{1}H NMR), however, no further consumption appeared to be occurring. R_f (10:2 CH_2Cl_2:EtOAc)= 0.63; $[\alpha]_D{}^{23}$ = +26.9 (*c* 0.95, $CHCl_3$); **IR** (liquid film); 3050(w), 1738(s), 1694(s), 1498(w), 1456(m), 1169(s), 752(m) cm^{-1}; ^{1}**H NMR** δ (300 MHz); 7.38-7.33(m, 5, aromatic), 5.14(s, 2, C$\underline{H}_2$Ph), 2.51(dd, 1, *J* =6.9, 16.5 Hz, CHC$\underline{H}$-HCO$_2$), 2.41(dd, 1, *J* =8.0, 16.4 Hz, CHCH-$\underline{H}$CO$_2$), 2.16(s, 3, C$\underline{H}_3$C=O), 1.87-1.77(m, 1, CHC$\underline{H}$CH$_2$), 1.70-1.58(m, 1, CH$_3$C$\underline{H}$CH), 1.52(dd, 1, *J* =4.2, 4.2 Hz, CH$_3$(O)CC$\underline{H}$), 1.12(d, 3, *J* =6.6 Hz, C$\underline{H}_3$CH); ^{13}**C NMR** δ (75 MHz); 207.0, 171.9, 135.8, 128.5, 128.2, 128.1, 66.4, 36.4, 32.6, 30.3, 25.6, 23.2, 12.2; **m/z** 246(M$^+$, 2), 203(2), 186(4), 155(9), 91(100), 43(32); Anal. Calc. for $C_{15}H_{18}O_3$: C: 73.15% H: 7.37%; Found: C: 73.34% H: 7.20%.

Due to the lengthy reaction time and conditions of continuous reflux, no isomeric *cis*-cyclopropane was observed, only the acyclic enolene isomer (**76c**) (115 mg, 9%) was isolated from subsequent chromatography.

Method B:

Under analogous conditions to Method B for cyclopropane (**16a**), irradiation of γ-hydroxy enone (**39a**) for 3 days with increasing equivalents of benzophenone sensitiser, provided no cyclopropyl derivatives. Unreacted enone (**39a**), unidentified products and 1,4-diketone (**46a**) were the only compounds identified in the crude reaction mixture by ^{1}H NMR.

Benzyl (*E*)-4-methyl-6-oxo-6-methylhex-2-enoate (76c)

R_f (10:2 CH_2Cl_2:EtOAc)= 0.78; **IR** (liquid film); 1736(s), 1716(s), 1691(m), 1653(w), 1169(m), 997(w), 740(w) cm^{-1}; ^{1}**H NMR** δ (600 MHz); 7.38-7.31(m, 5, aromatic), 6.93(dd, 1, *J* =7.2, 15.6 Hz, CH=C$\underline{H}$CH), 5.85(dd, 1, *J* =1.5, 15.9 Hz, C$\underline{H}$=CHCH), 5.17(s, 2, C$\underline{H}_2$Ph), 2.95-2.88(m, 1, CHC$\underline{H}$(CH$_3$)CH$_2$), 2.55(dd, 1, *J* =6.3, 17.1 Hz, CHC$\underline{H}$-HCO$_2$), 2.44(dd, 1, *J* =7.5, 17.1 Hz, CHCH-$\underline{H}$CO$_2$), 2.13(s, 3, O=CC$\underline{H}_3$), 1.07(d, 3, *J* =7.2 Hz, CHC$\underline{H}_3$); ^{13}**C NMR** δ (150 MHz); 206.5, 166.4, 153.0, 136.0, 128.5, 128.3, 128.2, 119.8, 66.2, 49.1, 31.7, 30.5, 18.9; **m/z** 246(M$^+$, 1), 155(4), 91(100), 82(27), 43(59); Acc. Mass Calc. for (MH$^+$) $C_{15}H_{19}O_3$ 247.1334; Found 247.1312.

trans (+) Benzyl 2-[(1*R*,2*R*,3*S*)-2-benzoyl-3-methylcyclopropyl]acetate (78a)

A solution of dry acetonitrile (17 mL) containing R-(+)-lactaldehyde (43b) (0.633 g, 3.39 mmol) and 48% aqueous HF (22 drops, *ca.* 17 mmol) was quenched with $NaHCO_3$ (*ca.* 0.640 g) as for Method A of (16a). α-Hydroxy lactaldehyde (65b) (0.254 g, 3.29 mmol), 100%) was likewise heated under reflux with phenyl keto ylide (37b) (1.32 g, 3.29 mmol) in dry CH_2Cl_2 (10 mL). Addition of benzyl (triphenylphosphoranylidene)acetate (37f) (2.03 g, 4.95 mmol) and continuing heating under reflux for 120 hours afforded cyclopropane (78a). Column chromatography and recrystallistion provided pure (78a) in a yield of 34% (0.354 g). Chromatography also provided approximately 2% (0.021 g) of a compound (78c) assigned as the opposite enantiomer of enolene (16c), by comparison of NMR spectra. An analytically pure sample of (78c) was not recovered, hence analysis of was not undertaken. **Mp** 54-57 °C (heptane); $[\alpha]_D^{23}$ = +41.5 (*c* 1.15, $CHCl_3$); **^{1}H NMR** δ (300 MHz); 7.96-7.93(m, 2, aromatic), 7.58-7.42(m, 8, aromatic), 5.12(s, 2, C$\underline{H}_2$Ph), 2.62(dd, 1, *J* =7.2, 16.2 Hz, CHC$\underline{H}$-HCO$_2$), 2.52(dd, 1, *J* =7.7, 16.1 Hz, CHCH-$\underline{H}$CO$_2$), 2.26(dd, 1, *J* =4.4, 4.4 Hz, Ph(O)CC$\underline{H}$), 2.13-2.03(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.92-1.81(m, 1, C$\underline{H}$CH$_3$), 1.21(d, 3, *J* =6.6 Hz, CHC$\underline{H}_3$); **^{13}C NMR** δ (75 MHz); 199.02, 171.97, 137.99, 135.77, 132.56, 128.51, 128.45, 128.19, 128.10, 127.97, 66.46, 32.87, 32.61, 26.48, 24.49, 12.43. Remaining physical data was analogous to that obtained for the opposite enantiomer (-)-(16a).

trans (-) Benzyl 2-[(1*S*,2*S*,3*R*)-2-(2,2-dimethylpropanoyl)-3-methylcyclopropyl]acetate (80a)

Method A:

Following the procedure for (16a) in Method A, generation of hydroxy enone (39c) was achieved through utilisation of O-protected lacetaldehyde (43a) (475 mg, 2.57 mmol), aqueous HF (16 drops, *ca.* 13 mmol, 48%), acetonitrile (13 mL) and $NaHCO_3$ (*ca.* 480 mg), and subsequently, α-hydroxy lactaldehyde (65a) (150 mg, 2.03 mmol, 79%), CH_2Cl_2 (6.5 mL) and *t*-butyl keto ylide (37c) (766 mg, 2.13 mmol). Benzyl (triphenylphosphoranylidene)acetate (37f) (1.25 g, 3.05 mmol) was added to the enone (39c) solution and the mixture was heated under reflux and maintained for 358 hours. Squat and column chromatography (10:2 hexane:EtOAc) provided the target *trans*

cyclopropane (**80a**) in 13% (78 mg) and the structural enolene isomer (**80c**) in a yield of 5%, 30 mg. Despite the long reaction time, ^{1}H NMR analysis showed the reaction to be less than 50% complete. As no further cyclopropanation was apparent through monitoring by ^{1}H NMR, heating under reflux was discontinued. In fact, decomposition of enone (**39c**) to 1,4-diketone (**46c**) was the predominant reaction occurring. R_f (10:2 hexane:EtOAc)= 0.39; $[\alpha]_D^{24}$ = -11.4 (*c* 1.75, CHCl$_3$); **IR** (liquid film); 1736(s), 1685(s), 1653(w), 1458(m), 1263(m), 1167(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.36-7.34(m, 5, aromatic), 5.12(s, 2, C$\underline{H}_2$Ph), 2.53(dd, 1, *J* =7.1, 16.1 Hz, CHC$\underline{H}$-HCO$_2$), 2.39(dd, 1, *J* =8.0, 16.1 Hz, CHCH-$\underline{H}$CO$_2$), 1.85-1.75(m, 1), 1.70(dd, 1, *J* =4.7, 4.7 Hz, (CH$_3$)$_3$C(O)CC$\underline{H}$), 1.61-1.52(m, 1), 1.14(s, 9, C(C$\underline{H}_3$)$_3$), 1.11(d, 3, CHC$\underline{H}_3$); **^{13}C NMR** δ (75 MHz); 213.6, 172.0, 135.8, 128.5, 128.1, 66.4, 43.6, 32.7, 31.3, 26.1, 25.5, 23.6, 12.2; **m/z** 288(M$^+$, 2), 231(8), 197(3), 91(100), 57(13); Acc. Mass Calc. for (M$^+$) C$_{18}$H$_{25}$O$_3$ 289.1804; Found 289.1790.

Method B:

Irradiation of enone (**39c**) *in situ*, under standard reaction conditions and reagent ratios ((**16a**), Method B), provided no cyclopropane derivatives. After 22 hours of irradiation the only observable reaction was decomposition of (**39c**) to the corresponding furan (**54c**) (<5%) and diketone (**46c**).

Benzyl (*E*)-4,7,7-trimethyl-6-oxo-oct-2-enoate (80c)

R_f (10:2 hexane:EtOAc)= 0.45; **IR** (liquid cell, CDCl$_3$); 1704(s), 1653(w), 1456(w), 1271(m), 1174(m), 982(w) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.38-7.34(m, 5, aromatic), 6.95(dd, 1, *J* =7.1, 15.8 Hz, CH=C$\underline{H}$CH), 5.86(dd, 1, *J* =1.5, 15.9 Hz, C$\underline{H}$=CHCH), 5.17(s, 2, C$\underline{H}_2$Ph), 2.96(dseptet, 1, *J* =1.5, 7.4 Hz, CHC$\underline{H}$(CH$_3$)CH$_2$), 1.12(s, 9, C(C$\underline{H}_3$)$_3$), 1.04(d, 3, *J* =6.6 Hz, CHC$\underline{H}_3$); **^{13}C NMR** δ (75 MHz); 213.4, 166.5, 153.6, 136.1, 128.5, 128.19, 128.15, 119.6, 66.1, 44.1, 42.3, 31.5, 26.2, 18.8; **mass spectrum** (LSIMS) **m/z** 289(MH$^+$), 42), 288(M$^+$, 5), 231(5), 181(100), 153(13); Acc. Mass Calc. for (MH$^+$) C$_{20}$H$_{25}$O$_3$ 289.1804; Found 289.1796.

trans (-) Benzyl 2-[(1*S*,2*S*,3*R*)-2-(4-bromobenzoyl)-3-methylcyclopropyl]acetate (81a)

<u>Method A</u>: Similarly to the synthesis of (**16a**, Method A), lactaldehyde (**43a**) (0.765 g, 4.10 mmol), aqueous HF (26 drops, *ca.* 20 mmol, 48%), acetonitrile (20 mL) and NaHCO₃ (*ca.* 0.760 g) were combined to form hydroxy acetaldehyde (**65a**) in a yield of 0.220 g, 70% (2.83 mmol). Dry CH_2Cl_2 (10 mL), *p*-bromophenyl keto ylide (**37d**) (1.36 g, 2.97 mmol) and benzyl (triphenylphosphorylidene)acetate (**37f**) (1.74 g, 4.25 mmol) were then added and the mixture was heated under reflux for 144 hours. Work-up afforded 48% (0.518 g) of the titled cyclopropane (**81a**) as white crystalline needles. **Mp** 87-89 °C (heptane); **R**f (10:1 CH_2Cl_2:hexane)= 0.30; $[\alpha]_D^{24}$ = -42.6 (*c* 2.35, CHCl₃); **IR** (Nujol mull); 3051(w), 1728(s), 1660(s), 1584(w), 1224(m), 1174(s), 750(w) cm⁻¹; **¹H NMR** δ (300 MHz); 7.80-7.77(m, 2, aromatic), 7.58-7.55(m, 2, aromatic), 7.29(bs, 5, aromatic), 5.11(s, 2, C$\underline{H}_2$Ph), 2.63(dd, 1, *J* =6.5, 16.1 Hz, CHC$\underline{H}$-HCO₂), 2.48(dd, 1, *J* =8.3, 16.1 Hz, CHCH-$\underline{H}$CO₂), 2.19(dd, 1, *J* =4.4, 4.4 Hz, BrPh(O)CC$\underline{H}$), 2.10-2.00(m, 1), 1.93-1.82(m, 1), 1.21(d, 3, *J* =6.3 Hz, CHC$\underline{H}_3$); **¹³C NMR** δ (75 MHz); 198.0, 171.9, 136.6, 135.7, 131.7, 129.5, 128.5, 128.3, 128.1, 127.7, 66.5, 32.8, 32.5, 27.0, 24.6, 12.4; **m/z** 389(MH⁺, ⁸¹Br, 1), 387(MH⁺, ⁷⁹Br, 1), 309(⁸¹Br, 17), 307(⁷⁹Br, 16), 204(⁸¹Br, 34), 202(⁷⁹Br, 33), 91(100); Anal. Calc. for $C_{20}H_{19}O_3Br$: C: 62.03% H: 4.95%; Found: C: 62.25% H: 5.01%.

A trace of enolene by-product (**81c**) was noted in the crude reaction mixture (identified by comparison with a later sample), however none was isolated after column chromatography.

<u>Method B</u>:

Procedure 16a, Method B was modified to accommodate for the synthesis of hydroxy enone (**39d**). *S*-(-)-lactaldehyde (**43a**) (250 mg, 1.35 mmol), aqueous HF (7 drops, *ca.* 7 mmol, 48%), dry acetonitrile (6.7 mL) and NaHCO₃ (*ca.* 250 mg) provided 67 mg of α-hydroxy aldehyde (**65a**) (0.83 mmol, 68%) Treatment of (**65a**) in CH_2Cl_2 (3 mL) with *p*-bromophenyl keto ylide (**37d**) (425 mg, 0.92 mmol) and finally irradiation with benzyl(triphenylphosphorylidene)acetate (**37f**) (541 mg, 1.32 mmol) and benzophenone (20 mg, 0.11 mmol) for 27 hours, completed the synthesis. After standard work-up and purification, 65% of crystalline *trans* (**81a**), 209 mg, and 21 mg of oil *cis* cyclopropane

(**81b**), 6%, were afforded. An analytically pure sample of (**81b**) required sequential chromatography, which also resulted in the isolation of enolene (**81c**), 8mg in 2% yield.

cis Benzyl 2-[(1S,2R,3R)-2-(4-bromobenzoyl)-3-methylcyclopropyl]acetate (81b)

Subsequent chromatography of the residual oil from recrystallisations afforded a further 3% (32mg) of product, characterised as *cis* cyclopropane (**81b**), recovered as a pale yellow oil. **R$_f$** (10:1 CH$_2$Cl$_2$:hexane)= 0.43; **IR** (liquid cell, CDCl$_3$); 1730(s), 1664(s), 1585(m), 1218(m), 1172(s) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.78-7.74(m, 2, aromatic), 7.60-7.55(m, 2, aromatic), 7.33-7.28(m, 5, aromatic), 5.10(s, 2, C$\underline{H}_2$Ph), 2.96(dd, 1, J =8.1, 17.7 Hz, CHC$\underline{H}$-HCO$_2$), 2.88(dd, 1, J =6.6, 17.4 Hz, CHCH-$\underline{H}$CO$_2$), 2.73(dd, 1, J =8.4, 8.4 Hz, BrPh(O)CC$\underline{H}$), 1.97-1.91(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.87-1.80(m, 1, C$\underline{H}$CH$_3$), 1.21(d, 3, J =6.6 Hz, CHC$\underline{H}_3$); **^{13}C NMR** δ (150 MHz); 198.5, 173.1, 138.5, 136.0, 132.0, 129.6, 129.3, 128.5, 128.1, 127.4, 66.2, 27.7, 24.2, 23.4, 22.2, 7.2; **mass spectrum** (LSIMS) **m/z** 389(MH$^+$, ^{81}Br, 96), 387(MH$^+$, ^{79}Br, 99), 297(^{81}Br, 9), 295(^{79}Br, 19), 281(^{81}Br, 33), 279(^{79}Br, 38), 185(^{81}Br, 65), 183(^{79}Br, 68); Acc. Mass Calc. for (MH$^+$) C$_{20}$H$_{20}$O$_3$Br 387.0596; Found 387.0583. At room temperature a solution of *cis* cyclopropane (**81b**) in CDCl$_3$ very slowly decomposed through an enolene rearrangement mechanism to give isolated enolene (**81c**).

Benzyl (E)-6-(4-bromophenyl)-4-methyl-6-oxohex-2-enoate (81c)

R$_f$ (10:1 CH$_2$Cl$_2$:hexane)= 0.40; **IR** (liquid cell, CDCl$_3$); 1714(s), 1689(m), 1585(m), 1272(m), 1173(m), 1007(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.80-7.78(m, 2, aromatic), 7.61-7.59(m, 2, aromatic), 7.37-7.32(m, 5, aromatic), 7.01(dd, 1, J =7.2, 15.6 Hz, CH=C$\underline{H}$CH), 5.90(dd, 1, 1.5, 15.9 Hz, C$\underline{H}$=CHCH), 5.17(s, 2, C$\underline{H}_2$Ph), 3.14-3.03(m, 2, CHC$\underline{H}$-HCO$_2$), 2.94(dd, 1, J =6.9, 16.3 Hz, CHCH-$\underline{H}$CO$_2$), 1.15(d, 3, J =6.6 Hz, CHC$\underline{H}_3$); **^{13}C NMR** δ (150 MHz); 197.0, 166.5, 153.1, 136.1, 135.7, 132.0, 129.6, 128.6, 128.5, 128.3, 128.1, 120.0, 66.2, 44.1, 31.9, 19.1; **mass spectrum** (LSIMS) **m/z** 389(MH$^+$, ^{81}Br, 97), 387(MH$^+$, ^{79}Br, 93), 281(^{81}Br, 68), 279(^{79}Br, 71), 253(^{81}Br, 11), 251(^{79}Br, 14), 185(^{81}Br, 97), 183(^{79}Br, 100); Acc. Mass Calc. for (MH$^+$) C$_{20}$H$_{20}$O$_3$^{79}Br 387.0596; Found 387.0588.

R-(+)-Methyl 2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-propanoate (41b)

Following the standard experimental procedure as described for compound (40), R-(+)-protected methyl lactate (41b) was synthesised from the reaction of R-(+)-methyl lactate (38b) (5.00 g, 0.048mol), imidazole (4.90 g, 0.072 mol) and *tert*-butyldimethylsilyl chloride (8.74 g, 0.058 mol) in dry dimethyl formamide (25 mL). $[\alpha]_D^{21}$ = +30.6° (*c* 2.36, CHCl$_3$); IR (liquid film); 1760(s), 1257(s), 1149(s), 1063(m), 838(s);^{1}H NMR δ (300 MHz); 4.34(q, 1, *J* =6.7 Hz, CH$_3$CH), 3.72(s, 3, CO$_2$CH$_3$), 1.40(d, 3, *J* =6.9 Hz, CH$_3$CH), 0.90(s, 9, C(CH$_3$)$_3$), 0.100(s, 3, SiCH$_3$), 0.07(s, 3, SiCH$_3$); ^{13}C NMR δ (75 MHz); 174.5, 68.4, 51.8, 25.7, 21.3, 18.3, -5.0, -5.3; m/z 219(MH$^+$, 12), 203(20), 161(65), 133(35), 59(38); Anal. Calc. For C$_{10}$H$_{22}$O$_3$Si: C: 55.00% H: 10.15%; Found: C: 54.83% H: 10.02%.

R-(+)-2-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-propanal (43b)

Similarly to the synthesis of (43a), protected R-(+)-methyl lactate (41b) (3.00 g, 14.0 mmol), dry ether (30 mL) and DIBAL-H (14.7 mL, 15.0 mmol, 1M in hexanes) were combined to induce reduction to the titled compound (43b). The reaction was likewise quenched with methanol (1 mL) and water (*ca.* 2 mL) prior to work-up. Purified aldehyde (43b) was obtained in a yield of 0.910 g (62%) with identical spectral and physical data to the opposite *S*-enantiomer (43a). $[\alpha]_D^{20}$ = +11.9° (*c* 1.5, CHCl$_3$); ^{1}H NMR δ (300 MHz); 9.61(d, 1, *J* =1.8 Hz, CH=O), 4.07(dq, 1, *J* =1.8, 10.2 Hz, CH$_3$CH), 1.27(d, 3, *J* =10.2 Hz, CH$_3$CH), 0.91(s, 9, C(CH$_3$)$_3$), 0.09(s, 3, SiCH$_3$), 0.08(s, 3, SiCH$_3$).

R-2-Hydroxypropanal (65b)

Deprotection of R- (+)-2-[1-(*tert*-butyl)-1, 1-dimethylsilyl]-2-lactaldehyde (43b) (633 mg, 3.39 mmol) was achieved in dry acetonitrile (17 mL) with aqueous HF (22 drops, 48%) following the model procedure as for (65a). Following work-up and concentration, 254 mg of crude yellow oil (65b) was afforded in a yield of 97 %. Analysis of the aldehyde was not undertaken other than the ^{1}H NMR δ (300 MHz) of 9.6 for the monomeric aldehyde proton. The hydroxy aldehyde (65b) was used directly following synthesis.

Benzyl (*E*)-4-hydroxy-4-phenylbut-2-en-1-oate (84)

Enester (84) was isolated from column chromatography of the alternate product (83a) as a result of minor amounts of unreacted hydroxy aldehyde (36a) remaining in solution on addition of benzyl (triphenylphosphoranylidene)acetate (37f). Alkene (84) was unstable to prolonged exposure to silica therefore a sample of greater than *ca.* 85% purity was unobtainable. **R$_f$** (10:2 hexane:EtOAc)= 0.10; **IR** (liquid film); 3462(m), 1721(s), 1682(s), 1594(m), 1376(m), 1163(s), 999(m) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.59-7.27(m, 10, aromatic), 7.09(dd, 1, *J* =4.8, 15.6 Hz, CHC$\underline{H}$=CH), 6.21(dd, 1, *J* =1.5, 15.3 Hz, CHCH=C$\underline{H}$), 5.36(dd, 1, *J* =1.5, 5.1 Hz, C$\underline{H}$CH=CH), 5.18(s, 2, C$\underline{H}_2$Ph), 2.18(bs, 1, O$\underline{H}$); **^{13}C NMR** δ (150 MHz); 166.2, 149.1, 120.0, 73.6, 66.3. Incomplete ^{13}C NMR data is quoted for enester (84) due to inconclusive assignment of aromatic and alkene signals. **mass spectrum** (GC-MS, CDCl$_3$) **m/z** 252(MH$^+$-OH, 2), 161(17), 133(15), 105(100), 91(78), 77(51).

trans (±) Methyl 2-(2-benzoylcyclopropyl)acetate (86a)

Method A:

Under analogous conditions to Method A for (71a), with the exception that enone (67b) was treated with methyl (triphenylphosphoranylidene)acetate (37e), no cyclopropyl products were obtained throughout a period of heating under reflux for 240 hours. Reduction of (67b) was noted by ^{1}H NMR analysis, however no identifiable products were isolated.

Method B:

Hydroxy enone (67b) was formed as for (71a) in Method B, from glycoaldehyde dimer (66) (0.25 g, 2.10 mmol), 1-phenyl-2-(1,1,1-triphenyl-1-phosphanylide)-1-ethanone (37b) (1.68 g, 4.41 mmol) and dry CH$_2$Cl$_2$ (16 mL). The solution was treated with methyl (triphenylphosphoranylidene)acetate (37e) (1.83 g, 5.46 mmol) and benzophenone (0.08 mg, 0.41 mmol), and the mixture subjected to irradiation for 30 hours. A squat column provided the crude product consisting of a 6:1 mix of (86a):(86c) (R$_f$ (10:2 hexane:EtOAc) =0.23). Subsequent flash chromatography (10:1 benzene:EtOAc) provided the pure colourless oil of cyclopropane (86a) in 578 mg (64%) and 15 mg (2%)

of isomeric enolene (**86c**). Both products appeared to decompose on silica as indicated by the presence of methanol (by-product of hydrolysis). R_f (10:1 benzene:EtOAc)= 0.33; **IR** (liquid film); 3059(w), 1738(s), 1668(s), 1598(m), 1450(m), 1127(m), 753(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 8.01-8.00(m, 2, aromatic), 7.58-7.46(m, 3, aromatic), 3.68(s, 3, CH$_3$O), 2.60(ddd, 1, J =4.2, 4.2, 8.4 Hz, Ph(O)CC<u>H</u>), 2.55(dd, 1, J =6.6, 15.6 Hz, CHCH-<u>H</u>CO$_2$), 2.36(dd, 1, J =7.8, 15.6 Hz, CHCH-<u>H</u>CO$_2$), 1.91-1.85(m, 1, C<u>H</u>CH$_2$CO$_2$), 1.56(ddd, 1, J =4.5, 4.5, 8.7 Hz, CHC<u>H</u>-HCH), 1.01-0.98(m, 1, CHCH-<u>H</u>CH); **^{13}C NMR** δ (150 MHz); 199.1, 172.2, 137.8, 132.8, 128.7, 128.0, 51.8, 37.9, 24.4, 21.4, 17.6; **m/z** 219(MH$^+$, 21), 187(10), 159(17), 144(98), 105(100), 77(57); Acc. Mass Calc. for (M$^+$) C$_{13}$H$_{14}$O$_3$ 218.0943; Found 218.0932.

Methyl (*E*)-6-oxo-6-phenylhex-2-enoate (86c)

R_f (10:1 benzene:EtOAc)= 0.38; **^{1}H NMR** δ (600 MHz); 7.98-7.94(m, 2, aromatic), 7.59-7.47(m, 3, aromatic), 7.04(dt, 1, J = 6.9, 15.4 Hz, CH$_2$C<u>H</u>=CH), 5.91(dt, 1, J = 1.8, 15.6 Hz, CH$_2$CH=C<u>H</u>), 3.73(s, 3, OC<u>H</u>$_3$), 3.15(t, 2, O=CC<u>H</u>$_2$), 2.76-2.62(m, 2, CH$_2$C<u>H</u>$_2$CH=); **^{13}C NMR** δ δ (150 MHz); 198.2, 167.8, 137.1, 147.7, 133.3, 128.7, 128.0, 122.0, 51.2, 36.6, 26.3. Complete characterisation of enolene (**86c**) was not obtained due to decomposition of the small sample recovered, however, the ^{1}H and ^{13}C NMR spectral data was consistent with the analogous (**71c**).

trans (±) Adamantyl 2-(2-benzoylcyclopropyl)acetate (87a)

<u>Method A:</u>

Heating a CH$_2$Cl$_2$ solution containing enone (**67b**) and adamantyl (triphenylphosphoranylidene)acetate[117] (**37g**) under reflux showed no reaction after 264 hours.

<u>Method B:</u>

In a procedure analogous to Method B for (**71a**), γ-hydroxy enone (**67b**) (234 mg, 1.45 mmol) in CH$_2$Cl$_2$ (4 mL) was irradiated in the presence of adamantyl (triphenylphosphoranylidene) acetate[117] (**37g**) (760 mg, 1.73 mmol). After 9 hours of irradiation no (**37b**) remained and the crude oil was run through a squat column (10:2 hexane:EtOAc), collecting the major products with R_f = *ca.* 0.43. Subsequent flash

chromatography afforded pure samples of the oils, *trans* cyclopropane (87a) in 56% (288 mg) and enolene (87c) in 4% (18mg). R_f (10:0.25 CH$_2$Cl$_2$:EtOAc)= 0.61; **IR** (liquid film); 3057(w), 1732(s), 1668(s), 1596(m), 1779(w), 1455(m), 1054(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 8.02-7.99(m, 2, aromatic), 7.59-7.47(m, 3, aromatic), 2.61-2.55(m, 1, Ph(O)CC$\underline{H}$), 2.47(dd, 1, *J* =6.3, 15.3 Hz, CHC$\underline{H}$-HCO$_2$), 2.23(dd, 1, *J* =8.0, 15.2 Hz, CHCH-$\underline{H}$CO$_2$), 2.12(bs, 3), 2.05-2.04(m, 6), 1.90-1.80(m, 1, C$\underline{H}$CH$_2$CO$_2$), 1.62(bt, 6, J =3.0 Hz), 1.59-1.53(m, CHC$\underline{H}$-HCH), 0.99(ddd, 1, *J* =3.9, 6.3, 7.8 Hz, CHCH-$\underline{H}$CH); **^{13}C NMR** δ (75 MHz); 199.4, 170.8, 138.0, 132.7, 128.5, 128.1, 80.9, 41.3, 39.7, 36.2, 30.8, 24.4, 22.2, 17.5; **m/z** 338(M$^+$, 7), 203(8), 135(100), 105(21), 77(13); Acc. Mass Calc. for (MH$^+$) C$_{22}$H$_{27}$O$_3$ 339.1960; Found 339.1963.

The corresponding *cis* cyclopropane (87b) was observed as a minor component in the crude mixture (^{1}H NMR) but isolated only as a mixture with enolene (87c). Conversion to 100% (87c) was accomplished after heating for 6 days in CDCl$_3$ at 55°C.

Adamantyl (E)-6-oxo-6-phenylhex-2-enoate (87c)

R_f (10:0.5 CH$_2$Cl$_2$:EtOAc)= 0.66; **IR** (liquid film); 1705(s), 1687(s), 1597(w), 1518(w), 1201(m), 1057(m) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.97-7.95(m, 2, aromatic), 7.59-7.56(m, 1, aromatic), 7.48-7.46(m, 2, aromatic), 6.92(dt, 1, *J* =6.9, 15.6 Hz, CH$_2$C$\underline{H}$=CH), 5.82(dt, 1, *J* =1.8, 15.6 Hz, CH$_2$CH=C$\underline{H}$), 3.14(t, 2, *J* =7.4 Hz, O=CC$\underline{H}_2$), 2.65-2.61(m, 2, CH$_2$C$\underline{H}_2$CH), 2.17-2.16(m, 9), 1.70-1.62(m, 6); **^{13}C NMR** δ (150 MHz); 198.5, 165.6, 146.0, 136.7, 133.3, 128.7, 128.0, 124.0, 80.3, 41.4, 36.7, 36.2, 30.8, 26.1; **mass spectrum** (LSIMS) **m/z** 339(MH$^+$, 12), 187(8), 135(100), 105(16); Acc. Mass Calc. for (MH$^+$) C$_{22}$H$_{27}$O$_3$ 339.1960; Found 339.1945.

trans (-)Methyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl]acetate (79a)

Method A:

Employing reagent ratios and conditions as for (16a), no cyclopropyl derivatives were generated from enone (39b) after 20 days heating under reflux (as seen by ^{1}H NMR).

Method B:

Under the conditions described for (**16a**), aldehyde (**43a**) (275 mg, 1.49 mmol), 48% aqueous HF (9 drops, *ca.* 7.5 mmol), acetonitrile (7.5 mL), and NaHCO$_3$ (*ca.* 280 mg) provided 85 mg (77%, 1.15 mmol) of α-hydroxy aldehyde (**65a**). Dry CH$_2$Cl$_2$ (4 mL) and ylide (**37b**) (459 mg, 1.21 mmol) generated γ-hydroxy enone (**39b**) *in situ*. Irradiation of the solution containing enone (**39b**) (1.15 mmol), methyl (triphenylphosphoranylidene) acetate (**37e**) (578 mg, 1.73 mmol) and benzophenone (20 mg, 0.11 mmol) was continued for 27 hours. Isolation procedures were as for (**16a**) providing 41% (140 mg) of the title cyclopropane (**79a**) as a white crystalline solid along with 31 mg, 9%, of isomeric (**79b**). **Mp** 64.5-65.5°C (heptane); **R$_f$** (4:1 hexane:EtOAc)=0.35; $[\alpha]_D^{24}$ = -100.9 (*c* 0.65, CHCl$_3$); **IR** (Nujol mull); 3060(w), 1739(s), 1666(s), 1598(m), 1580(m), 1450(s), 1170(s) 696(m) cm^{-1}; **^{1}H NMR** δ (300 MHz); 7.98-7.96(m, 2, aromatic), 7.56-7.44(m, 3, aromatic), 3.68(s, 3, OC<u>H</u>$_3$), 2.57(dd, 1, *J* =7.4, 16.1 Hz, CHC<u>H</u>-HCO$_2$), 2.48(dd, 1, *J* =7.4, 16.1 Hz, CHCH-<u>H</u>CO$_2$), 2.26(dd, 1, *J* =4.4, 4.4 Hz, Ph(O)CC<u>H</u>),2.09-1.99(m, 1, C<u>H</u>CH$_2$CO$_2$), 1.91-1.84(m, 1, CHC<u>H</u>(CH$_3$)CH), 1.23(d, 3, *J* =6.6 Hz, CHC<u>H</u>$_3$); **^{13}C NMR** δ (75 MHz); 199.0, 172.5, 138.0, 132.6, 128.4, 127.9, 51.7, 32.6, 32.5, 26.4, 24.3, 12.3; **m/z** 232(M$^+$, 5), 217(7), 200(18), 159(83), 115(13), 105(100), 77(88); Anal. Calc. for C$_{14}$H$_{16}$O$_3$: C: 72.39% H: 6.94%; Found: C: 72.18% H: 6.94%.

cis Methyl 2-[(1*S*,2*R*,3*R*)-2-benzoyl-3-methylcyclopropyl]acetate (79b)

cis Cyclopropane (**79b**) was isolated in approximately 95% purity with 5% contamination by the structural enolene isomer (**79c**), following chromatographic separation of the residual oil from the recrystallisation of *trans* (**79a**). **R$_f$** (4:1 hexane:EtOAc)=0.40; **^{1}H NMR** δ (300 MHz); 7.96-7.91(m, 2, aromatic), 7.53-7.42(m, 3, aromatic), 3.64(s, 3, OC<u>H</u>$_3$), 2.92(dd, 1, *J* =7.2, 17.4 Hz, CHC<u>H</u>-CHCO$_2$), 2.85(dd, 1, *J* =7.1, 17.6 Hz, CHCH-CHCO$_2$), 2.81(dd, 1, *J* =8.6, 8.6 Hz, Ph(O)CC<u>H</u>), 1.97-1.80(m, 2, CH$_3$C<u>H</u>C<u>H</u>CH$_2$), 1.22(d, 3, *J* =6.3 Hz, CHC<u>H</u>$_3$); **^{13}C NMR** δ (75 MHz); 199.5, 173.7, 139.9, 133.2, 128.4, 127.7, 51.5, 27.5, 24.4, 23.1, 21.9, 7.3.

Cyclopropane (**79b**) was found to be unstable gradually undergoing an enolene rearrangement at room temperature to (**79c**). After 9 months standing of the concentrated sample, no *cis* cyclopropane (**79b**) remained.

Methyl (*E*)-4-methyl-6-oxo-6-phenylhex-2-enoate (79c)

R$_f$ (4:1 hexane:EtOAc)=0.40; **IR** (liquid cell,CDCl$_3$) 1718(s), 1687(s), 1660(m), 1598(w), 1438(m), 1281(m), 1003(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.97-7.93(m, 2, aromatic), 7.59-7.56(m, 1, aromatic), 7.48-7.45(m, 2, aromatic), 6.99(dd, 1, *J* =6.9, 15.9 Hz, C<u>H</u>=CHCH), 5.87(dd, 1, *J* =1.2, 15.6 Hz, CH=C<u>H</u>CH), 3.72(s, 3, OC<u>H</u>$_3$), 3.18-3.05(m, 2, C<u>H</u>(CH$_3$)CH-HCO$_2$), 3.01-2.96(m, 1, CHCH-<u>H</u>CO$_2$), 1.16(d, 3, *J* =6.6 Hz, CHC<u>H</u>$_3$); **^{13}C NMR** δ (150 MHz); 198.1, 167.2, 153.0, 137.0, 133.3, 128.6, 128.1, 125.7, 122.4, 119.8, 51.4, 44.1, 31.9, 19.1; **m/z** 232(M$^+$, 0.4), 200(7), 127(12), 105(100), 77(13), 59(2); Acc. Mass Calc. for (M$^+$) C$_{14}$H$_{16}$O$_3$ 232.1099; Found 232.1098. All data was consistent with the literature reported values.[155]

trans (-)-[(1*R*,2*S*,5*R*)-Menthyl] 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-methylcyclopropyl] acetate (88a)

Lactaldehyde (**43a**) (475 mg, 2.57 mmol), acetonitrile (13 mL), 48% aqueous HF (16 mL) and NaHCO$_3$ (*ca.* 480 mg) were allowed to react (Method B (**16a**)) to form hydroxy lactaldehyde (**65a**) in a crude yield of 76% (150 mg, 1.95 mmol). Further treatment with keto ylide (**37b**) (809 mg, 2.13 mmol) in CH$_2$Cl$_2$ (6.5 mL), followed by 27 hours of irradiation in the presence of (1*R*,2*S*,5*R*)-menthol (triphenylphosphoranylidene)acetate[117] (**37h**) (1.30 g, 3.05 mmol) and benzophenone (35 mg, 0.19 mmol) completed the experimental procedure. At 27 hours some unreacted enone (**39b**) remained however no further consumption of (**39b**) was taking place, as seen by ^{1}H NMR. Successive column chromatography (10:1 CH$_2$Cl$_2$:hexane) provided the two major products *trans* cyclopropane (**88a**) (280 mg, 40%) and *cis* cyclopropane (**88b**) (70 mg, 10%). **R$_f$** (10:1 CH$_2$Cl$_2$:hexane)= 0.23; [α]$_D^{24}$ = -73.9 (*c* 1.70, CHCl$_3$); **IR** (liquid film); 3060(w), 1731(s), 1667(s), 1599(w), 1440(s), 1227(s), 695(w) cm^{-1}; **^{1}H NMR** δ (600 MHz); 7.98-7.97(m, 2, aromatic), 7.55-7.45(m, 3, aromatic), 4.68(dt, 1, *J* =4.4, 11.0 Hz, CH$_2$CO$_2$C<u>H</u>), 2.54(dd, 1, *J* =6.6, 15.6 Hz, CHC<u>H</u>-HCO$_2$), 2.44(dd, 1, *J* =7.8, 15.6 Hz, CHCH-<u>H</u>CO$_2$), 2.25(dd, 1, *J* =4.5, 4.5 Hz, Ph(O)CC<u>H</u>), 2.07-2.02(m, 1, C<u>H</u>CH$_2$CO$_2$), 1.91-1.85(m, 2, CHC<u>H</u>(CH$_3$)CH + C<u>H</u> of Mn), 1.85-1.77(m, 1, Mn), 1.67-1.59(m, 2, Mn), 1.47-1.40(m, 1, Mn), 1.30-1.25(m, 1, Mn), 1.30-1.25(m, 1, Mn), 1.23(d, 3, *J* =6.6 Hz, CHCH(C<u>H</u>$_3$)CH), 1.04-0.97(m, 1, Mn), 0.94-0.91(m, 1, Mn), 0.89-0.83(m, 1, Mn), 0.82(d, 3, *J* =6.6 Hz, C<u>H</u>$_3$ of Mn),

0.80(d, 3, J =7.2 Hz, C$\underline{H}_3$ of Mn), 0.71(d, 3, J =6.6 Hz, C$\underline{H}_3$ of Mn); ^{13}C NMR δ (150 MHz); 199.1, 171.8, 138.0, 132.6, 128.4, 128.0, 74.5, 46.9, 40.8, 34.5, 34.2, 33.3, 32.6, 31.3, 26.2, 24.6, 23.3, 21.9, 20.6, 16.2, 12.4; m/z 356(M$^+$, 37), 218(85), 159(93), 105(100), 77(29), 43(32); Acc. Mass Calc. for (MH$^+$) C$_{23}$H$_{33}$O$_3$ 357.2430; Found 357.2419.

cis   [(1*R*,2*S*,5*R*)-Menthyl]   2-[(1*S*,2*R*,3*R*)-2-benzoyl-3-methylcyclopropyl]acetate (88b)

R$_f$ (10:1 CH$_2$Cl$_2$:hexane)= 0.35; IR (liquid film); 3057(w), 1729(s), 1664(m), 1596(w), 1447(m), 1178(s), 689(w) cm^{-1}; ^{1}H NMR δ (300 MHz); 7.94-7.91(m, 2, aromatic), 7.47-7.44(m, 3, aromatic), 4.64(dt, 1, J =4.3, 11.1 Hz, CH$_2$CO$_2$C$\underline{H}$), 2.90(dd, 1, J =7.8, 15.6 Hz, CHC$\underline{H}$-HCO$_2$), 2.77(dd, 1, J =6.9, 15.9 Hz, CHCH-$\underline{H}$CO$_2$), 1.96-1.82(m, 3), 1.66-1.57(m, 3), 1.54-1.35(m, 2), 1.24(d, 3, J =6.3 Hz, CHCH(C$\underline{H}_3$)CH), 1.18-0.78(m, 4), 0.86(d, 3, J =6.6 Hz, C$\underline{H}_3$ of Mn), 0.83(d, 3, J =6.9 Hz, C$\underline{H}_3$ of Mn), 0.65(d, 3, J =6.9 Hz, C$\underline{H}_3$ of Mn); ^{13}C NMR δ (75 MHz); 199.3, 172.8, 139.8, 132.2, 128.3, 127.7, 74.0, 46.9, 40.8, 34.2, 31.3, 28.0, 26.0, 24.2, 23.4, 23.2, 22.1, 22.0, 20.7, 16.1, 7.3; m/z 358(MH$^+$, 2), 357(M$^+$, 2), 218(58), 159(23), 105(100), 77(34), 43(21). *cis* Cyclopropane (88b) gradually decayed through an enolene rearrangement at room temperature to the acyclic product (88c). Full conversion to (88c) was accompanied by heating in CDCl$_3$ at 55 °C for 12 days.

[(1*R*,2*S*,5*R*)-Menthyl] (*E*)-4-methyl-6-oxo-6-phenylhex-2-enoate (88c)

R$_f$ (10:1 CH$_2$Cl$_2$:hexane)= 0.35; IR (liquid cell, CDCl$_3$); 1705(s), 1691(s), 1597(w), 1275(m), 1210(w), 1147(m), 1039(w) cm^{-1}; ^{1}H NMR δ (600 MHz); 7.94(dd, 2, J =1.5, 8.1 Hz, aromatic), 7.59-7.45(m, 3, aromatic), 6.97(dd, 1, J =6.3, 15.9 Hz, CH=C$\underline{H}$CH), 5.84(dd, 1, J =1.2, 15.6 Hz, C$\underline{H}$=CHCH), 4.74(dt, 1, J =4.2, 10.8 Hz, CH$_2$CO$_2$C$\underline{H}$), 3.13-3.09(m, 1, CHC$\underline{H}$-HCO$_2$), 2.97(dd, 1, J =9.0, 18.0 Hz, CHCH-$\underline{H}$CO$_2$),2.02-1.99(m, 1, Mn), 1.87(dpentet, 1, J =2.6, 7.0 Hz, Mn), 1.70-1.65(m, 2, Mn), 1.64-1.56(m, 1, Mn), 1.54-1.46(m, 1, Mn), 1.42-1.37(m, 1, Mn), 1.16(d, 3, J =10.8 Hz, CHC$\underline{H}_3$), 1.10-1.04(m, 1, Mn), 0.98(q, 1, J =11.6 Hz, Mn), 0.90(d, 3, J =4.2 Hz, C$\underline{H}_3$ of Mn), 0.89(d, 3, J =4.8 Hz, C$\underline{H}_3$ of Mn), 0.77(d, 3, J =7.2 Hz, C$\underline{H}_3$ of Mn); ^{13}C NMR δ (150 MHz); 198.2, 166.4, 152.4, 137.1, 133.2, 129.6, 128.7, 120.5, 74.1, 47.1, 44.2, 40.9, 34.3, 31.9, 31.3, 26.2, 23.5, 22.0,

20.7, 19.0, 16.4; **mass spectrum** (LSIMS) m/z 357(MH+, 19), 219(87), 201(100), 173(20), 105(70); Acc. Mass Calc. for (MH$^+$) $C_{23}H_{33}O_3$ 357.2430; Found 357.2433.

S-(+)-Ethyl-2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-phenylacetate (40a)

The procedure was analogous to that for (**40**) using S-(+)-ethyl mandelate (**35a**) (10.0g, 56 mmol) and treating with imidazole (5.65 g, 83 mmol), *tert*-butyldimethylsilyl chloride (9.95 g, 66 mol) in dimethyl formamide (63 mL). Following stirring overnight and work-up, the title mandelate (**40a**) was obtained in a 98% yield of 16.05 g. $[\alpha]_D^{27} = +39.7°$ (*c* 3.05, CHCl$_3$); Lit. $[\alpha]_D^{25} = +41.2°$ (*c* 1.5, CHCl$_3$);[145] **^{1}H NMR** δ (300 MHz); 7.50-7.27(m, 5, aromatic), 5.22(s, 1, C<u>H</u>CO$_2$CH$_2$CH$_3$), 4.15(q, 2, *J* =7.2 Hz, CHCO$_2$C<u>H</u>$_2$CH$_3$), 1.22(t, 3, *J* =7.2 Hz, CO$_2$CH$_2$C<u>H</u>$_3$), 0.92(s, 9, C(C<u>H</u>$_3$)$_3$), 0.11(s, 3, SiC<u>H</u>$_3$), 0.04(s, 3, SiC<u>H</u>$_3$); **m/z** 293(M$^+$-H$^+$, 10), 237(81), 221(100), 163(95), 131(45), 75(38). Spectral data was consistent with that obtained for the racemate (**40**) and the literature.[145]

S-(+)-2-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-2-phenylacetaldehyde (42a)

Following an analogous procedure to that for (**42**), *S*-(+)-protected ethyl mandelate (**40a**) (3.61 g, 12.3 mmol), DIBAL-H (8.20 mL, 12.3 mmol, 1.5 M in toluene) and dry toluene (55 mL) were combined. After work-up the target aldehyde (**42a**) was obtained in 3.08 g (80%) as a clear colourless oil. $[\alpha]_D^{27} = +8.9°$ (*c* 3.0, CHCl$_3$); Lit. $[\alpha]_D^{25} = +5.5°$ (neat);[145] **^{1}H NMR** δ (200 MHz); 9.51(d, 1, *J* =2.2 Hz, CHC<u>H</u>=O), 7.40-7.26(m, 5, aromatic), 5.01(d, 1, *J* =2.2 Hz, C<u>H</u>CH=O), 0.95(s, 9, C(C<u>H</u>$_3$)$_3$), 0.12(s, 3, SiC<u>H</u>$_3$), 0.04(s, 3, SiC<u>H</u>$_3$). Spectral data was consistent with that obtained for the racemate (**42**) and the lierature.[145]

S-2-Hydroxy-2-phenylacetaldehyde (36a)

To a solution of *S*-(+)-O-protected mandelaldehyde (**42a**) (300 mg, 1.19 mmol) in dry acetonitrile (2.5 mL) was added aqueous HF (4 drops, 48%) at ambient temperature. The scale and procedure followed was analogous to that for the racemate (**36**). A signal at 9.64 ppm for the aldehyde proton in the 300 MHz ^{1}H NMR spectrum, confirmed reaction completion. No further characterisation was carried out and (**36**) was employed immediately.

trans (-) Benzyl 2-[(1*S*,2*S*,3*R*)-2-benzoyl-3-phenylcyclopropyl]acetate (83a)

<u>Method A:</u>

Treatment of a CH_2Cl_2 solution of the hydroxy enone (**17b**) and 1.5 equivalents of benzyl ester ylide (**37f**) for extended periods did not afford any of the target cyclopropane (**83a**). The major product of the reaction was the decomposition product 1,4-diketone (**46b**) along with a trace of the cyclic furan (**54b**) and benzyl (*E*)-4-hydroxy-4-phenylbutenoate (**84**).

<u>Method B:</u>

Formation of hydroxy enone (**17b**) was achieved following the methodology of Method D for (**17b**) with *S*-(+)-*O*-protected mandelaldehyde (**42a**) (400 mg, 1.59 mmol) and aqueous HF (5 drops, *ca*. 8 mmol, 48%) in acetonitrile (3.3 mL). Phenyl keto ylide (**37b**) (514 mg, 1.35 mmol) was added to the α-hydroxy mandelaldehyde (**36a**) solution and heating to 55°C was maintained for 2 hours. Analysis of the R-enone (**17b**) solution by ^{1}H NMR showed significant diketone (**46b**) formation. Concentrated (**17b**) was taken up in CH_2Cl_2 (4 mL), benzyl (triphenylphosphoranylidene)acetate (**37f**) (738 mg, 1.91 mmol) and benzophenone (25 mg, 0.14 mmol) were added and the stirred solution was subjected to irradiation with 2 x 300 W sunlamps for 17.5 hours. ^{1}H NMR analysis of the crude reaction mixture showed the major product to be 1,4-diketone (**46b**). Squat chromatography removed the bulk of impurities and subsequent flash chromatography enabled the isolation of pure white crystalline *trans* cyclopropane (**83a**) in a 10% yield of 56 mg. **Mp** (heptane) 76-79°C; **R$_f$** (4:1 hexane:EtOAc)= 0.50; $[\alpha]_D^{24}$ = -60.7° (*c* 0.75, CHCl$_3$); **IR** (Nujol mull); 1727(s), 1663(s), 1598(m), 1164(m) cm^{-1}; **^{1}H NMR** δ (600 MHz, CDCl$_3$); 8.07-8.04(m, 2, aromatic), 7.62-7.58(m, 1, aromatic), 7.51-7.48(m, 2, aromatic), 7.32-7.21(m, 10, aromatic), 5.07 and 5.04(AB$_q$, 2, *J* =12.6 Hz, C$\underline{H}_2$Ph), 3.13(dd, 1, *J* =4.9, 9.3 Hz, C$\underline{H}$-HCO$_2$), 3.10(dd, 1, *J* =4.9, 4.9 Hz, CH-$\underline{H}$CO$_2$), 2.44(dd, 1, *J* =6.4, 16.1 Hz, C$\underline{H}$Ph), 2.35(dddd, *J* =4.9, 6.4, 8.3, 9.3 Hz, C$\underline{H}$CH$_2$CO$_2$), 2.20(dd, 1, *J* =8.3, 16.1 Hz, C$\underline{H}$C(O)Ph); **^{13}C NMR** δ (150 MHz, CDCl$_3$); 198.6, 172.0, 137.8(one aromatic carbon masked), 137.82, 135.88, 135.71, 133.08, 128.98, 128.72, 128.57, 128.30, 128.24, 128.21, 127.07, 66.41, 33.48, 33.12, 29.33, 27.11; **m/z** 372(MH$_2^+$, 1), 312(0.5), 105(100), 91(36), 77(49); Anal. Calc. for C$_{25}$H$_{22}$O$_3$: C: 81.06% H: 5.99%; Found: C: 80.62% H: 5.98%.

4-Hydroxy-1-phenyl-3-(phenylsulfanyl)-1-pentanone (90)

A solution of *trans* 1-phenyl-4-hydroxy-2-pentenone (**39b**) (120 mg, 0.68 mmol) in CH_2Cl_2 (2.2 mL), was irradiated by two 300 W sunlamps in the presence of diphenyl disulphide (741 mg, 3.4 mmol) and benzyl (triphenylphosphoranylidene)acetate (**37f**) (418 g, 1.02 mmol) for 5 hours. The solution was concentrated under reduced pressure and the crude product was subjected to column chromatography. The major product isolated was the decomposition product 1,4-diketone (**46a**) in approximately 50%, estimated by ^1H NMR analysis of the crude product mixture. The titled compound (**90**) was isolated in a yield of 34%, 65 mg, and was shown to decompose over *ca.* 1 week in a $CDCl_3$ solution at ambient temperature. **R_f** (10:1 CH_2Cl_2:EtOAc)= 0.65; **IR** (liquid film); 3413(s), 1679(m), 1612(m), 1598(w), 1581(s), 1262(s), 1102(m), 691(s) cm^{-1}; **^1H NMR** δ (600 MHz, $CDCl_3$); 7.95-7.93(m, 2, aromatic), 7.54-6.96(m, 8, aromatic), 4.01(dq, 1, *J* =4.2, 6.2 Hz, C$\underline{H}_3$CHOH), 3.87(dt, 1, *J* =4.2, 6.6 Hz, C$\underline{H}$SPh), 3.41(dd, 1, *J* =6.6, 17.4 Hz, $\underline{H}$-CHC(O)), 3.35(dd, 1, *J* =6.9, 17.7 Hz, H-C$\underline{H}$C(O)), 1.61(bs, 1, CHO$\underline{H}$), 1.31(d, 3, *J* =6.0 Hz, C$\underline{H}_3$CH); **^{13}C NMR** δ (150 MHz, $CDCl_3$); 198.3, 69.3, 52.0, 40.7, 20.5, -0.1 Incomplete ^{13}C NMR data is quoted for (**90**) due to inconclusive assignment of aromatic signals.; **mass spectrum** (LSIMS) m/z 286(M$^+$, 11), 242(10), 133(36), 119(26), 105(100), 77(49), 43(23); Acc. Mass Calc. for (M$^+$) $C_{17}H_{18}O_2S$ 286.1044; Found 286.1029.

(-) Methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate (97)

As described in the literature,[132,133] D-glucono-1,5-lactone (**91**) (11.87 g, 0.07 mmol) was allowed to react with 2,2-dimethoxy-propane (20 mL, 0.16 mmol) and p-toluenesulphonic acid (133 mg, 0.71 mmol) in a solution of acetone (6.7 mL) and methanol (2 mL), at ambient temperature under a nitrogen atmosphere for 48 hours. Solid $NaHCO_3$ (*ca.* 3 g) was added to the solution and the resultant white precipitate was removed by filtration. Concentration of the filtrate *in vacuo* provided a viscous oil, which was purified by column chromatography. The titled compound (**97**) was provided in a 65% yield (12.75 g) along with 13% (2.52 g) of isomeric (**98**). **R_f** (10:4 hexane:EtOAc)= 0.22; [α]$_D^{20}$ = -8.2° (*c* 3.25, CHCl$_3$); Lit. [α]$_D^{20}$ = -6.0° (1% in CHCl$_3$);[132] **^1H NMR** δ (300 MHz, $CDCl_3$); 4.37-3.98(m, 6, C$\underline{H}_2$(C$\underline{H}$)$_4$OH), 3.84(s, 3, $CO_2C\underline{H}_3$), 3.01(d, 1, *J* =9.3 Hz, O$\underline{H}$), 1.43, 1.39, 1.37

and 1.35(4 x s, 12, 4 x C$\underline{H}_3$C); ^{13}C NMR δ (75 MHz, CDCl$_3$); 172.9, 110.0, 109.8, 80.9, 77.2, 76.5, 69.4, 67.8, 52.6, 27.1, 26.6, 26.5, 25.2.

Methyl 2,3:5,6-di-*O*-isopropylidene-D-gluconate[133] (98)

R$_f$ (10:4 hexane:EtOAc)= 0.10; ^{1}H NMR δ (300 MHz, CDCl$_3$); 4.57(d, 1, J =7.5 Hz, C$\underline{H}$CO$_2$CH$_3$), 4.42(dd, 1, J =2.0, 7.7 Hz C$\underline{H}$CHCO$_2$), 4.11-4.00(m, 3, C$\underline{H}_2$C$\underline{H}$CH), 3.80(s, 3, CO$_2$C$\underline{H}_3$), 3.67(ddd, 1, J =1.8, 8.0, 9.8 Hz, C$\underline{H}$OH), 2.15(d, 1, J =9.6 Hz, CHO$\underline{H}$), 1.49, 1.46, 1.42 and 1.35(4 x s, 12, 4 x C$\underline{H}_3$C); ^{13}C NMR δ (75 MHz, CDCl$_3$); 170.9, 111.4, 109.3, 78.0, 76.0, 75.0, 70.5, 66.8, 52.1, 26.7, 26.5, 25.6, 25.1.

(+) Methyl 3,4:5,6-di-*O*-isopropylidene-2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-D-gluconate (99)

3,4:5,6-Protected gluconoate (**97**) (14.0 g, 48.1 mmol) was dissolved in dry dimethyl formamide (54 mL) and the solution was treated with imidazole (4.85 g, 71.9 mmol) and *tert*-butyldimethylsilyl chloride (8.54, 57.7 mmol). The mixture was allowed to stir overnight at ambient temperature and under an atmosphere of nitrogen. The work-up and purification procedure was completed as described for (**40**). The TBDMS-ether (**99**) (14.79 g) was afforded in a 76% yield. [α]$_D^{20}$ = +49.4° (*c* 3.15, CHCl$_3$); IR (liquid film); 1766(s), 1736(m), 1369(s), 1254(s), 1157(s), 1076(s), 839(s) cm^{-1}; ^{1}H NMR δ (300 MHz, CDCl$_3$); 4.37-3.78(m, 6, C$\underline{H}_2$(C$\underline{H}$)$_4$O), 3.77(s, 1, OC$\underline{H}_3$), 1.41, 1.40, 1.37 and 1.35(4 x s, 12, 4 x C$\underline{H}_3$C), 0.94(s, 9, C(C$\underline{H}_3$)$_3$), 0.13(s, 3, SiC$\underline{H}_3$), 0.07(s, 3, SiC$\underline{H}_3$); ^{13}C NMR δ (75 MHz, CDCl$_3$); 171.9, 110.4, 109.7, 82.0, 77.3, 77.1, 71.9, 68.1, 52.0, 27.5, 26.7, 25.8, 25.2, 18.4, -4.7, -5.2; m/z 405(M$^+$, 28), 346(100), 289(50), 101(67), 73(31), 43(55); Anal. Calc. for C$_{19}$H$_{36}$O$_7$Si: C: 56.41% H: 8.97%; Found: C: 56.71% H: 8.70%.

(+) 3,4:5,6-Di-*O*-isopropylidene-2-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-D-glucose (100)

Under similar conditions to that stated for the synthesis of (**43a**), the protected sugar (**99**) (3.00 g, 7.40 mmol) in dry ether (22.2 mL) was treated with DIBAL-H (11.1, mL, 11.11

mmol, 1 M in hexanes) at −78°C. The mixture was allowed to stir for 1.5 hours prior to quenching with methanol (0.5 mL) and water (*ca.* 1 mL). An analogous work-up procedure was followed and the crude product was purified by reduced pressure distillation (bp 115°C, 0.2 mmHg) in a yield of 62%, 1.74 g. $[\alpha]_D^{20}$ = +45.8° (*c* 3.25, CHCl₃); **IR** (liquid film); 1738(s), 1473(w), 1381(s), 1255(s), 1154(s), 1077(s), 840(s) cm⁻¹; **¹H NMR** δ (300 MHz, CDCl₃); 9.62(d, 1, *J* =1.2 Hz, C$\underline{H}$=O), 4.26-3.75(m, 6, C$\underline{H}_2$(CH)₄O), 1.34, 1.33, 1.29 and 1.27(4 x s, 12, 4 x C$\underline{H}_3$C), 0.90(s, 9, C(C$\underline{H}_3$)₃), 0.06(s, 3, SiC$\underline{H}_3$), 0.04(s, 3, SiC$\underline{H}_3$); **¹³C NMR** δ (75 MHz, CDCl₃); 202.4, 110.3, 109.6, 81.2, 77.3, 77.2, 76.8, 68.2, 27.2, 26.5, 26.4, 25.7, 25.0, 18.2, -4.4, -5.0; **m/z** 376(M-H⁺, 2), 288(5), 201(24), 143(48), 101(50), 43(100).

(+) 1-Phenyl-2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-4-{[1-(*tert*-butyl)-1,1-dimethyl silyl]oxy}-D-*glucono*-oct-2-enone (93)

A solution of aldehyde (**100**) (600 mg, 1.59 mmol) and phenyl keto ylide (**37b**) (634 mg, 1.67 mmol) in dry CH₂Cl₂ (3 mL) was heated under reflux for two days in a nitrogen atmosphere. Concentration of the solution under reduced pressure was followed by the addition of hexane (*ca.* 20 mL) and removal of the precipitated triphenylphosphine oxide by gravity filtration. The γ-hydroxy enone (**93**) was afforded in greater than 95 % purity and in a yield of 95%, 719 mg. **R**ₜ (10:2 hexane:EtOAc)= 0.33; $[\alpha]_D^{23}$ = +9.2° (*c* 2.05, CHCl₃); **IR** (liquid film); 1752(w), 1675(s), 1629(m), 1599(m), 1371(s), 1251(s), 1073(s), 838(s) cm⁻¹; **¹H NMR** δ (300 MHz, CDCl₃); 7.96-7.93(m, 2, aromatic), 7.58-7.46(m, 3, aromatic), 7.14(d, 2, *J* = 1.8 Hz, C$\underline{H}$=C$\underline{H}$), 4.59(ddd, 1, *J* =1.6, 1.6, 3.2 Hz, C$\underline{H}$CH=CH), 4.18-3.88(m, 5, C$\underline{H}_2$(C$\underline{H}$)₃), 1.42(s, 6, 2 x C$\underline{H}_3$C), 1.38 and 1.35(2 x s, 6, 2 x C$\underline{H}_3$C), 0.97(s, 9, C(C$\underline{H}_3$)₃), 0.13(s, 3, SiC$\underline{H}_3$), 0.10(s, 3, SiC$\underline{H}_3$); **¹³C NMR** δ (75 MHz, CDCl₃); 190.1, 147.2, 137.8, 132.7, 128.5(2 masked signals), 125.9, 110.0, 109.5, 82.5, 77.5, 77.0, 72.3, 67.0, 27.4, 26.9, 26.4, 25.8, 25.2, 18.2, -4.4, -4.8; **m/z** 478(MH⁺, 2), 462(4), 276(100), 143(65), 105(35), 101(42); Acc. Mass Calc. for (MH⁺) C₂₆H₄₁O₆Si 477.2672; Found 477.2649.

(+) 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-gluconate (102)

As described in the literature,[134] sulfuric acid (*ca.* 0.2 mL, 0.40 g) was added dropwise to a solution of freshly melted zinc chloride (23 g) in acetone (120 mL) and the mixture was stirred at ambient temperature for 10 minutes. D-glucono-1,5-lactone (91) (10.50 g, 59.0 mmol) was added and the solution was allowed to stir overnight before being poured into toluene/saturated sodium chloride (250/50 mL). The organic phase was washed with brine (4 x 50 mL), followed by washings with aqueous sodium hydroxide and sodium hydrogen carbonate, until the solution reached neutrality (only saturated brine was noted in the literature). Desiccation (MgSO$_4$), concentration *in vacuo* and recrystallisation from methanol provided a total yield of 11.86 g of the titled compound (102), 64%, a combined yield of three successive crops of crystals. R_f (10:3 hexane:EtOAc)= 0.45; **Mp** 109-111°C (lit. **Mp** 110°C);[134] $[\alpha]_D^{21}$ = +27.8° (*c* 2.00, CHCl$_3$); Lit. $[\alpha]_D^{20}$ = +34.0° (2.00, CHCl$_3$);[156] **^{1}H NMR** δ (300 MHz, CDCl$_3$); 4.62(d, 1, *J* =1.8 Hz, C*H*C=O), 4.27(dd, 1, *J* =1.4, 8.3 Hz, C*H*CHC=O), 4.17-3.91(m, 4, C*H$_2$*C*H*C*H*), 1.65, 1.57, 1.42, 1.40, 1.39 and 1.33(6 x s, 18, 6 x C*H$_3$*C); **^{13}C NMR** δ (75 MHz, CDCl$_3$); 170.5, 111.3, 110.2, 109.7, 78.6, 77.1, 76.3, 73.6, 67.7, 27.1, 26.9, 26.8, 26.6, 26.4, 25.1.

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-glucose (103)

Triacetonilide (102) (5.59 g, 17.65 mmol) was taken up in dry CH$_2$Cl$_2$ (196 mL), cooled to -78°C under a nitrogen atmosphere and treated with DIBAL-H (14.1 mL, 21.19 mmol, 1.5 M in toluene). After stirring for approximately 1 hour, EtOAc (20 mL) was added to quench the excess DIBAL-H and the mixture was left to stir for an additional 10 minutes at -78°C. The cold bath was removed and the mixture was allowed to warm to 0°C prior to the addition of water (50 mL) and CH$_2$Cl$_2$ (100 mL). Once at ambient temperature, the solution was filtered through a pad of kenite using CH$_2$Cl$_2$ to wash residual products through the filter. The organic phase was dried over Na$_2$SO$_4$ and the solvent removed to afford the crude colourless oil. Purification by column chromatography provided 33% (1.85 g) of hemiacetal (103), 7% (0.34 g) of the free aldehyde (101) and 32% (1.80 g) of unreacted triacetonilide (102). R_f (103) (10:3 hexane:EtOAc)= 0.24. The titled hemiacetal (103) was characterised in the literature as the corresponding acetate derivative,[134] characterisation of (103) was not performed.

3,4:5,6-Di-*O*-isopropylidene-*aldehydo*-D-glucose (101)

Under similar conditions to the literature,[134] hemiacetal (103) (1.85 g, 5.82 mmol) in benzene (61 mL), was treated with methanol (2 mL), water (2 mL) and triethylamine (2 mL). The mixture was stirred at ambient temperature overnight and then partitioned between toluene (75 mL) and water (20 mL). The organic phase was separated, dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude oil (101) in a yield of 78%, 1.19 g. The aldehyde (101) was used for the next step without purification and was unable to be characterised, however, the ^1H NMR spectrum of (101) clearly displayed a signal at 9.77 ppm due to the aldehyde proton.

(-) 1-Phenyl-2,3-dideoxy-5,6:7,8-di-*O*-isopropylidene-D-*gluco*-oct-2-enone (96)

Phenyl keto ylide (37b) (1.87 g, 4.93 mmol) was added to a solution of crude 3,4:5,6-Di-*O*-isopropylidene-D-glucose (101) (1.19 g, 4.49 mmol) in dry CH_2Cl_2 (25 mL), and the reaction mixture was heated under reflux in a nitrogen atmosphere for 4 hours. The mixture was concentrated *in vacuo* and purification was achieved by column chromatography, which provided 801 mg of the white crystalline solid (96), 49%. R_f (9:6 EtOAc:hexane)= 0.76; **Mp** 144-147°C; $[\alpha]_D^{21}$ = -4.76° (*c* 1.40, CHCl₃); **IR** (Nujol mull); 3430(m), 1722(w), 1670(m), 1614(s), 1595(w), 1072(s) cm⁻¹; **^1H NMR** δ (600 MHz, CDCl₃); 7.97-7.96(m, 2, aromatic), 7.58-7.55(m, 1, aromatic), 7.48-7.46(m, 2, aromatic), 7.26(dd, 1, *J* =1.8, 15.6 Hz, CHCH=CH̲), 7.18(dd, 1, *J* =3.6, 15.6 Hz, CHCH̲=CH), 4.40(dddd, 1, *J* =2.0, 2.0, 3.3, 9.8 Hz, CH̲OH), 4.17(dd, 1, *J* =6.0, 9.0 Hz, H̲-CHCH), 4.12(dd, 1, *J* =3.6, 7.8 Hz, CH̲CHOH), 4.06(ddd, 1, *J* =4.7, 6.3, 8.9 Hz, CH₂CH̲CH), 3.98(dd, 1, *J* =4.5, 8.7 Hz, H-CH̲CH), 3.81(dd, 1, *J* =7.8, 8.0 Hz, CH₂CHCH̲), 3.12(d, 1, *J* =10.2 Hz, CHOH̲), 1.42(s, 6, 2 x CH₃C), 1.39 and 1.36(2 x s, 6, 2 x CH₃C); **^{13}C NMR** δ (75 MHz, CDCl₃); 190.04, 147.10, 137.67, 132.88, 128.60, 128.56, 125.42, 110.12, 109.90, 81.97, 77.41, 76.75, 69.93, 67.91, 26.99, 26.85, 26.54, 25.08; **m/z** 363(MH⁺, 2), 347(4), 143(12), 105(19), 77(12), 43(100); Anal. Calc. for $C_{20}H_{26}O_6$: C: 66.28% H: 7.23%; Found: C: 66.29% H: 7.46%.

trans (+) Benzyl 2-{(1*R*,2*S*,3*S*,4*R*,5*R*,9*R*)-2-benzoyl-3-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropyl}acetate (92)[#]

A solution of *trans* γ-hydroxy enone (96) (330 mg, 0.91 mmol) was prepared in CH_2Cl_2 (20 mL), to which benzyl (triphenylphosphoranylidene)acetate (37f) (560 mg, 1.37 mmol) and dicyanoanthracene (21 mg, 0.09 mmol) were added. The solution was irradiated with two 300 W sunlamps with stirring for 15 hours, at which time ^1H NMR indicated no enone (96) remained. The solution was concentrated *in vacuo* and the crude oil was subjected to column chromatography. The titled cyclopropane (92) was afforded as pure white crystals in a yield of 18%, 81 mg, along with 13% (43 mg) of the 1,4-diketone by-product (94). Crystals of x-ray quality were obtained by recrystallisation of the cyclopropane (92) from a 10:1 mixture of EtOAc and toluene, by slow diffusion with hexane. R_f (10:1 CH_2Cl_2:EtOAc)= 0.51; **Mp** 138-140°C; $[\alpha]_D^{21}$ = +56.7° (*c* 1.90, CHCl$_3$); **IR** (Nujol mull); 3065(m), 1732(s), 1688(m), 1660(s), 1597(m), 1069(s), 699(m) cm^{-1}; **^1H NMR** δ (300 MHz, CDCl$_3$); 8.01-7.98(m, 2, aromatic), 7.56-7.42(m, 3, aromatic), 7.28(s, 5, C$\underline{H}_2$P$\underline{h}$), 5.11 and 5.09(ABq, 2, *J* =12.0 Hz, C$\underline{H}_2$Ph), 4.09(dd, 1, *J* =6.0, 8.1 Hz, $\underline{H}$-CHCH), 3.98-3.91(m, 1), 3.85(dd, 1, *J* =5.3, 8.6 Hz, H-C$\underline{H}$CH), 3.75-3.67(m, 2), 2.95(dd, 1, *J* =4.8, 16.2 Hz, C$\underline{H}$-HCO$_2$Bn), 2.73(dd, 1, *J* =4.7 Hz, C$\underline{H}$C(O)Ph), 2.50(dd, 1, *J* =9.2, 16.4 Hz, CH-$\underline{H}$CO$_2$Bn), 2.15-2.02(m, 2, CH$_2$C$\underline{H}$C$\underline{H}$CHC(O)), 1.42, 1.32, 1.08, 0.91 (4 x s, 12, 4 x C$\underline{H}_3$C) The multiplets at 3.98-3.91 and 3.75-3.67 ppm in the ^1H NMR spectrum are due to CH$_2$(C$\underline{H}$)$_3$ of the 'sugar arm', however, assignment of the specific protons could not be conclusively determined.; **^{13}C NMR** δ (75 MHz, CDCl$_3$); 198.1, 171.8, 137.7, 135.8, 132.8, 128.5, 128.4, 128.3, 128.2, 128.1, 109.7, 109.3, 81.9, 80.0, 67.9, 66.5, 33.5, 30.3, 29.7, 27.1, 26.9, 26.2, 26.1, 25.1; **m/z** 495(MH$^+$, 0.1), 480(8), 335(6), 105(50), 101(27), 91(100), 43(26); Acc. Mass Calc. for (MH$^+$) C$_{29}$H$_{35}$O$_7$ 495.2383; Found 495.2357.

1-[5-(2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-1,3-dioxolan-4-yl]-4-phenyl-1,4-butanediol (94)

R_f (10:1 CH_2Cl_2:EtOAc)= 0.60; **Mp** 68-71°C; **IR** (Nujol mull); 1734(s), 1682(s), 1596(w), 1580(w), 1080(s), 692(m) cm^{-1}; **^1H NMR** δ (600 MHz, CDCl$_3$); 7.98-7.97(m, 2, aromatic),

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[#] Numbering of the carbons in the absolute configuration refer to Figure 32, the molecular structure of (92).

7.57-7.55(m, 1, aromatic), 7.47-7.44(m, 2, aromatic), 4.47(d, 1, J =6.0 Hz, C$\underline{H}$C(O)), 4.32(dd, 1, J =6.3, 6.3 Hz, C$\underline{H}$CHC(O)), 4.23(dt, 1, J =5.4, 6.6 Hz, CH$_2$C$\underline{H}$), 4.12(dd, 1, J =6.3, 8.7 Hz, C$\underline{H}_2$CHCH), 3.99(dd, 1, J =5.4, 9.0 Hz, C$\underline{H}_2$CHCH), 3.35(ddd, 1, J =5.4, 7.2, 18.0 Hz, PhC(O)C$\underline{H}$-H), 3.28(ddd, 1, J =5.3, 6.8, 18.0 Hz, PhC(O)CH-$\underline{H}$), 3.15(ddd, 1, J =5.4, 7.2, 18.6 Hz, $\underline{H}$-CHC(O)CH), 3.06(ddd, 1, J =5.4, 6.9, 19.2 Hz, H-C$\underline{H}$C(O)CH), 1.48, 1.44, 1.44 and 1.36(4 x s, 12, 4 x C$\underline{H}_3$C); **^{13}C NMR** δ (75 MHz, CDCl$_3$); 208.5, 198.1, 136.6, 133.2, 128.6, 128.1, 111.4, 109.9, 82.9, 78.2, 76.5, 66.5, 33.0, 32.0, 27.0, 26.4, 26.2, 25.1; **m/z** 363(MH$^+$, 0.5), 229(54), 161(80), 143(100), 105(54), 77(21); Acc. Mass Calc. for (MH$^+$) C$_{20}$H$_{27}$O$_6$ 363.1807; Found 363.1799.

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(51)   Since this early mechanistic report much work has been conducted towards the full establishment of the mechanism, including the research presented within this thesis, unpublished results and work reported in the later publication of Taylor *et al*, *J. Org. Chem.*, **2000**, *65*, 5531. See Chapter 6 for a complete synopsis of the corrected mechanism.

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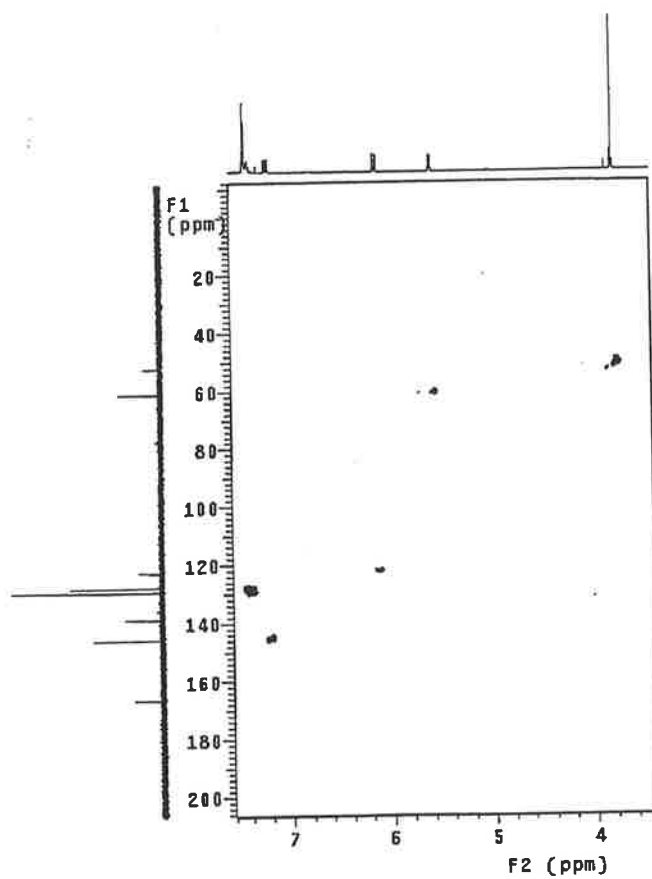
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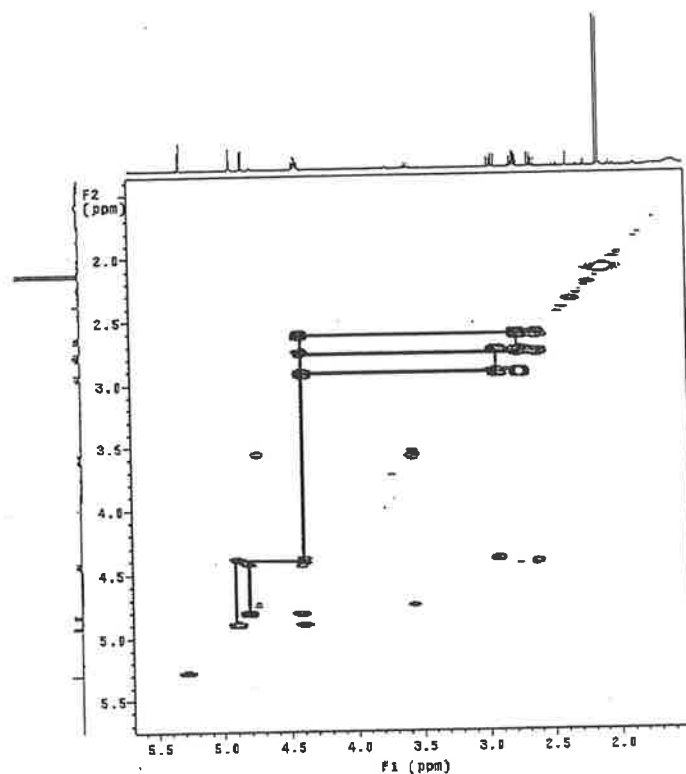
An expansion of the COSY spectrum at 600 MHz of 4-chloro-5[{1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-5-phenylpentan-2-one (**56a**).
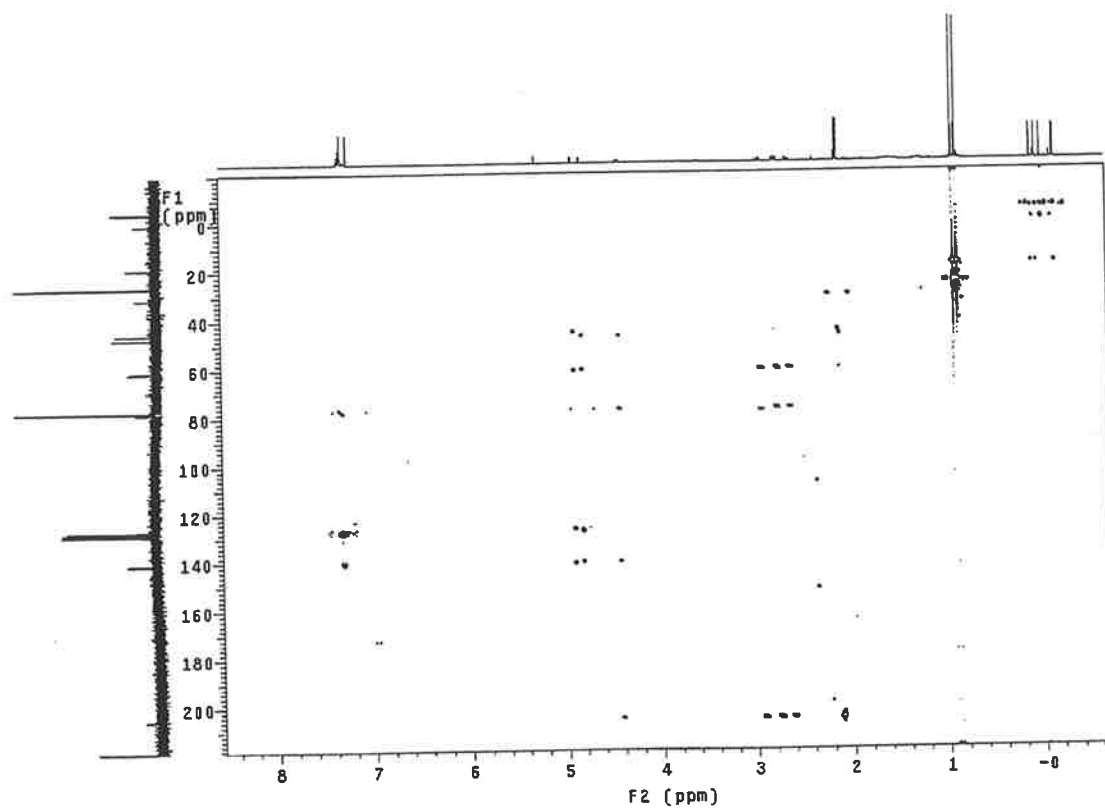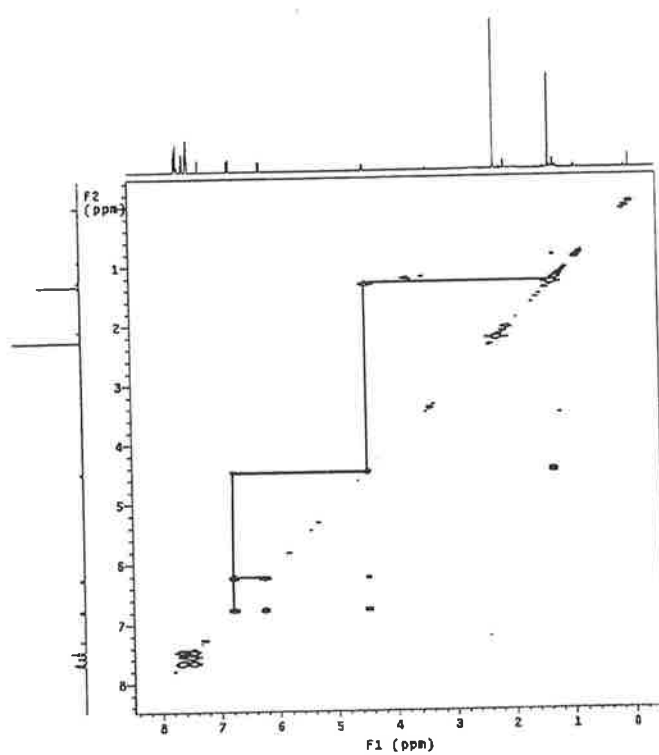

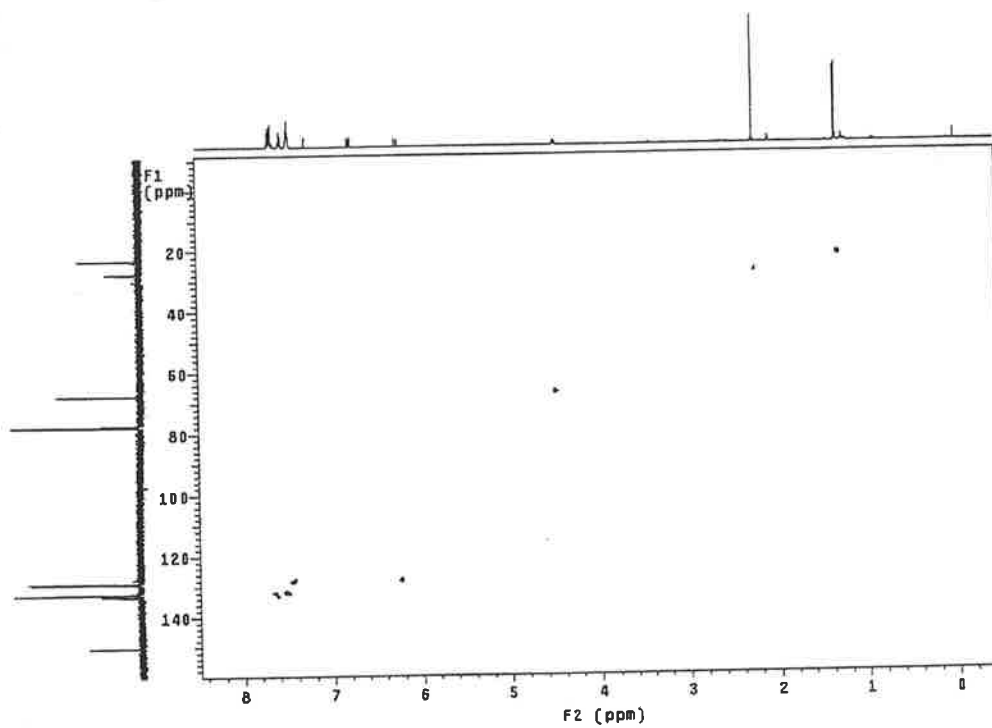The HMBC spectrum at 600 MHz of (**56a**).
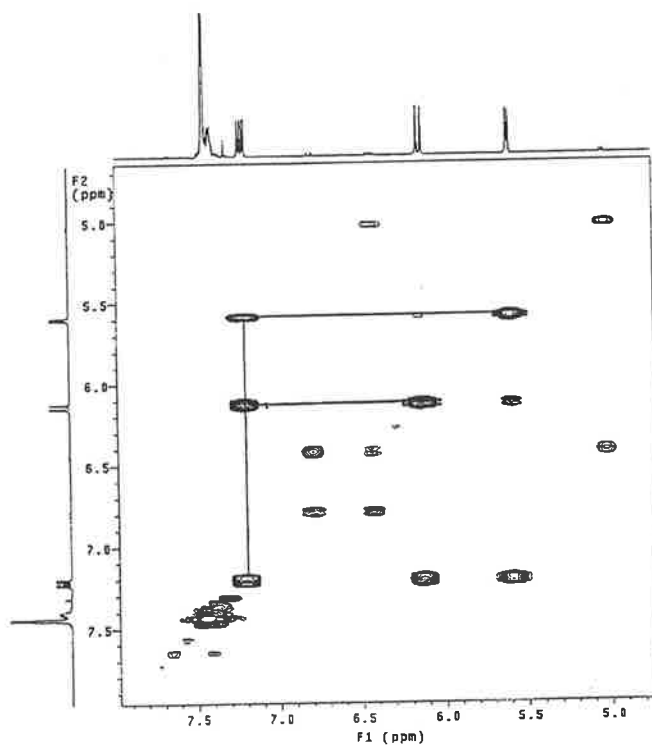
The COSY spectrum at 600 MHz of methyl (*E*)-4-chloro-4-phenylbutenoate (**60**).
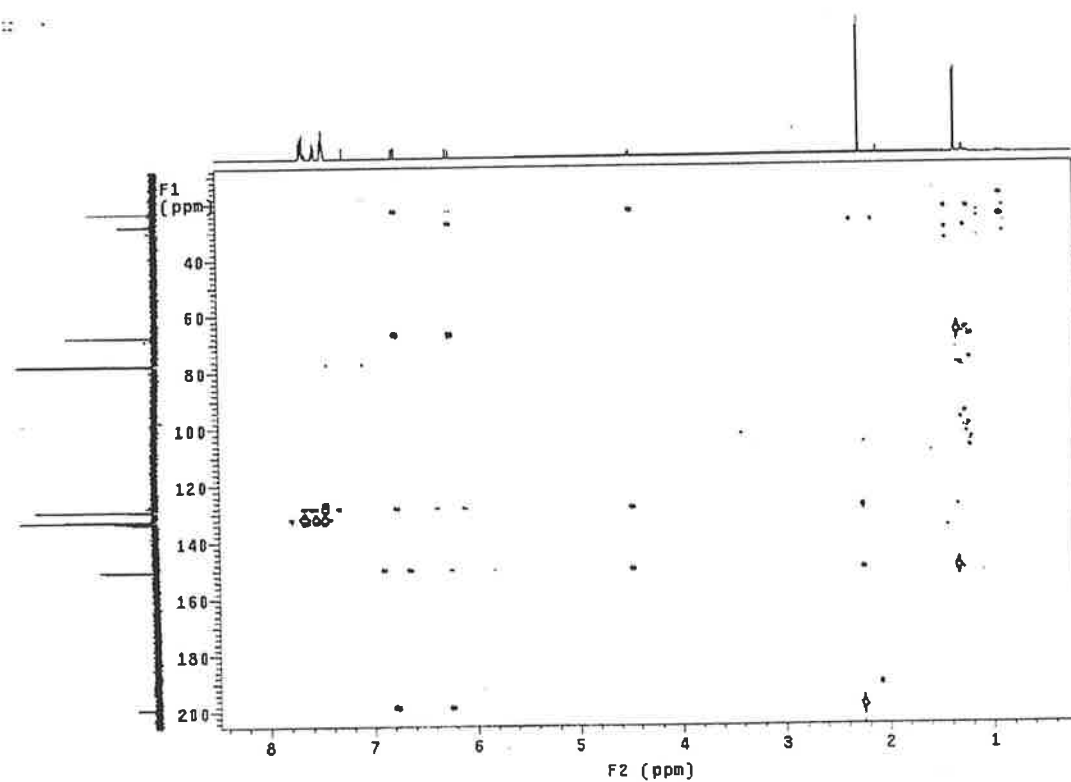

The HMQC spectrum at 600 MHz of (**60**).

The COSY spectrum at 600 MHz of (*E*)-hydroxyhex-3-en-2-one (**39a**).

The HMQC spectrum of (**39a**).

The HMBC spectrum at 600 MHz of (**39a**).

The first practical approach to optically pure cyclopropanes derived from *trans* γ-hydroxy enones

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A new approach for the synthesis of optically pure cyclopropanes from *trans* γ-hydroxy enones and stabilised phosphorus ylides is presented; the use of light and a triplet sensitiser leads to a dramatic increase in reaction rate and isolated yield.
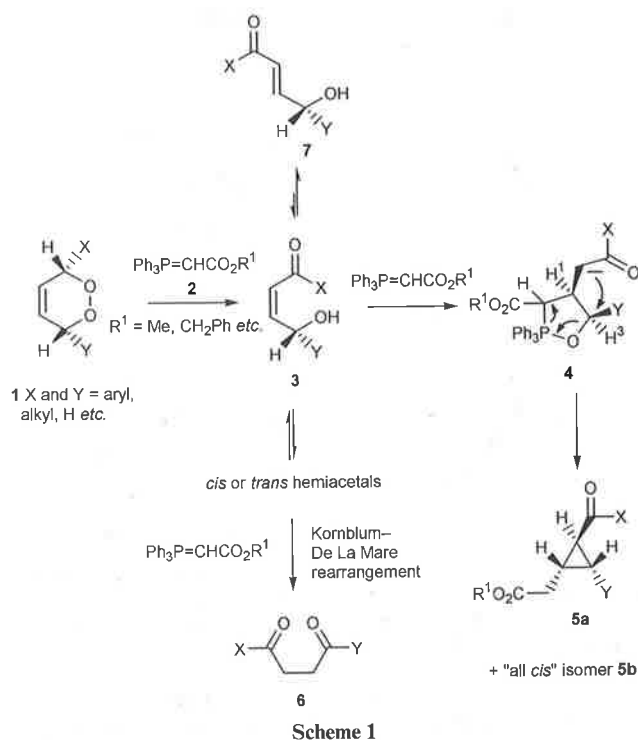
The most noticeable current strategies for the construction of the cyclopropyl motif include, i) the direct carbene transfer (both stoichiometric and catalytic) from a diazo precursor to an olefin utilising transition metals (Rh, Cu, Zn and Pd)[1] and ii) Michael addition of nucleophiles (usually sulfur ylides) to α,β-unsaturated ketones and esters followed by intramolecular cyclisation.[2] Despite the great advances in these areas, the efficient synthesis of diversely functionalised enantiopure cyclopropanes containing greater than di-substitution still remains a considerable challenge. We recently reported on a new approach to diastereomerically pure diversely functionalised cyclopropanes **5a** which utilised 1,2-dioxines **1** and stabilised phosphorus ester ylides as the key precursors (Scheme 1).[3] Key features of the cyclopropanation sequence

Scheme 1

included the ylide acting as a mild base inducing ring opening of the 1,2-dioxines **1** to their isomeric *cis* γ-hydroxy enones **3**, Michael addition of the ylide to the *cis* γ-hydroxy enones **3** and attachment of the electrophilic phosphorus pole of the ylide to the hydroxy moiety afford the intermediate 1,2λ[5]-oxaphospholanes **4** and sets up the observed *cis* stereochemistry between H1 and H3. Cyclisation of the resultant enolate, expul-

sion of triphenylphosphine oxide and proton transfer from the reaction manifold afford the observed cyclopropanes in excellent diastereomeric excess. A minor amount of the "all *cis*" isomer **5b** is occasionally formed. While cyclopropanation is favored by the use of ester stabilised ylides **2**, the use of keto or aldo stabilised ylides results in a preference for 1,4-dicarbonyl **6** formation through a competing Kornblum–De La Mare rearrangement of the intermediate hemiacetals.[4] The *trans* γ-hydroxy enones **7** were also shown to be a possible entry point into the cyclopropanation manifold, however, reaction times were excessive (weeks at ambient temp.) and yields were poor due to the position of the *cis–trans* equilibrium favoring the *trans* form.
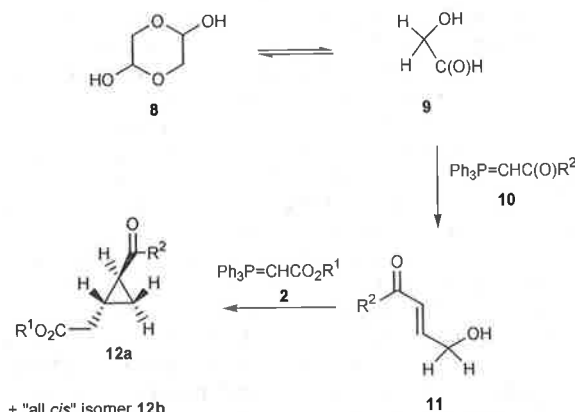
According to Scheme 1, in order to allow for the preparation of enantiomerically pure cyclopropanes one would need to prepare either the *cis* or *trans* γ-hydroxy enones in an optically pure form. Synthesis of optically pure *cis* γ-hydroxy enones is unattractive as they are highly sensitive to acid and base, rearranging rapidly to furan or 1,4-diketone **6** respectively.[3] Therefore, we decided to embark on developing a practical strategy for the synthesis of optically pure *trans* γ-hydroxy enones **7**, which could be utilised for the construction of optically pure cyclopropanes. Additionally, we report herein the first practical approach to the shifting of the *cis–trans* γ-hydroxy enone equilibrium which allows for a dramatic acceleration in the rate of the cyclopropanation sequence along with an increase in overall yield.

Retrosynthetically, we envisaged that the *trans* γ-hydroxy enones **7** could be prepared from reaction of stabilised keto ylides on optically pure α-hydroxy aldehydes. The latter aldehydes themselves could be prepared from reduction of optically pure α-hydroxy esters. In order to test this general approach we first utilised the commercially available glycolaldehyde dimer **8**, which being optically inactive would result in the formation of only diastereomerically pure cyclopropanes (Scheme 2).†

Reaction of the glycolaldehyde dimer **8** with keto ylides **10** resulted in the smooth generation of the *trans* γ-hydroxy enones **11** which were judged to be of >90% purity by ^{1}H NMR. Direct

Scheme 2

Table 1 Formation of cyclopropanes from glycolaldehyde dimer **8** under thermal and photolytic conditions[a]

Entry	R¹	R²	Thermal conditions Cyclopropane (yield, %)	Time/h	Photolytic conditions Cyclopropane (yield, %)	Time/h
1	CH₂Ph	Ph	**12a** (35) **12b** (0)	120	**12a** (68) **12b** (0)	30
2	CH₃	Ph	—[b]	—	**12a** (64) **12b** (0)	30
3	CH₃	CH₃	**12a** (26) **12b** (6)	192	**12a** (41) **12b** (3)	96

[a] Yields quoted refer to isolated yields starting from **8**. The *trans* γ-hydroxy enones **11** were prepared under an inert atmosphere by heating a mixture of glycolaldehyde dimer **8** in CH₂Cl₂ (0.5 g in 32 mL) with ylide **10** (1.05 equiv.) under reflux. After 4 hours ylide **2** (1.5 equiv.) was then introduced and the mixture heated under reflux for the time indicated. The volatiles were then removed *in vacuo* and the residue subjected to column chromatography. The reactions performed under photolytic conditions were carried out in an identical manner except after the introduction of ylide **2**, the mixture was irradiated with light from 2 sun lamps (300 W) at a distance of 10 cm in the presence of benzophenone (10 mol%). [b] Complex mixture of unidentified products.

Table 2 Formation of enantiomerically pure cyclopropanes **18** from optically pure ethyl lactate **13**[a]

Entry	R¹	R²	Ent.[b]	Thermal conditions Cyclopropane (yield, %)	Time/h	Photolytic conditions Cyclopropane (yield, %)	Time/h
1	CH₂Ph	Ph	−	**18a** (29) **18b** (4)	180	**18a** (50) **18b** (12)	40
2	CH₂Ph	Ph	+	**18a** (34) **18b** (2)	120	—[e]	—
3	CH₃	Ph	−	—[d]	—	**18a** (41) **18b** (9)	27
4	(−)-Menthol	Ph	−	—[c]	—	**18a** (40) **18b** (10)	27
5	CH₂Ph	p-Br-Ph	−	**18a** (48) **18b** (3)	144	**18a** (65) **18b** (6)	27
6	CH₂Ph	CH₃	−	**18a** (21) **18b** (0)	448	—[c]	—
7	CH₂Ph	t-Bu	−	**18a** (13) **18b** (5)	358	—[c]	—
8[a]	CH₂Ph	Ph	−	—[c]	—	**18a** (54) **18b** (8)	25

[a] Yields quoted refer to isolated yields starting from **16**. Time refers to overall reaction time. Both the *trans* γ-hydroxy enones **17** and the cyclopropanes **18** were prepared in an analogous manner to those described within Table 1 except the reaction time for enone formation was 5 hours. [b] Refers to the enantiomer of **13** utilised. [c] Not attempted. [d] Complex mixture of unidentified products. [e] DCA utilised as sensitiser.

addition of the ester stabilised ylides **2** to the reaction mixture resulted in the formation of the desired cyclopropanes **12** (entries 1–3, Table 1). Under thermal conditions the formation of the desired cyclopropanes was extremely slow due to the *cis–trans* γ-hydroxy enone equilibrium favouring the thermodynamically more stable *trans* isomers. Furthermore, the isolated yields were poor due to base induced Kornblum–De La Mare competing rearrangement of the resultant hemiacetals in solution and the formation of unidentified decomposition products. Previous studies showed that the cyclopropane yield is essentially quantitative when starting from the *cis* γ-hydroxy enones **3**.[3] Therefore, it seemed only reasonable to expect that if we could in some way shift the equilibrium away from the *trans* γ-hydroxy enones **11** and towards the *cis* γ-hydroxy enones, then we would expect an increase in overall cyclopropane yield coupled with an increase in reaction rate. Thus, we repeated the same three experiments in Table 1 under photolytic conditions utilising benzophenone as the sensitiser. As can be seen, not only did the yield of desired cyclopropane dramatically increase but also the overall reaction rate.

With the validity of this new approach to cyclopropane formation now established, we turned our attention to the preparation of optically pure cyclopropanes utilising optically pure α-hydroxy aldehydes (Scheme 3). Thus, protection of (−)-ethyl lactate **13** as the TBDMS ether proceeded in 89% yield. DIBAL-H reduction afforded aldehyde (−)-**15** in 81% yield which was deprotected with aqueous HF to afford (−)-**16**. This α-hydroxy aldehyde was immediately treated with keto ylides **10** to afford the intermediate optically pure *trans* γ-hydroxy enones (−)-**17**. Subsequent addition of ester ylides **2** gave rise to optically pure cyclopropanes, (Table 2) which were determined to be of >98% ee by ¹H NMR analysis in the presence of [Eu(hfc)₃].‡§ In a similar fashion, the opposite enantiomeric series (+)-**17** was prepared from (+)-methyl lactate. As can be seen by inspection of the data collated in Table 2, the yields are poor and reaction times excessive under thermal conditions. However, under photolytic conditions the overall reaction rate was once again dramatically accelerated, while the isolated yields of optically pure cyclopropanes were extremely good considering
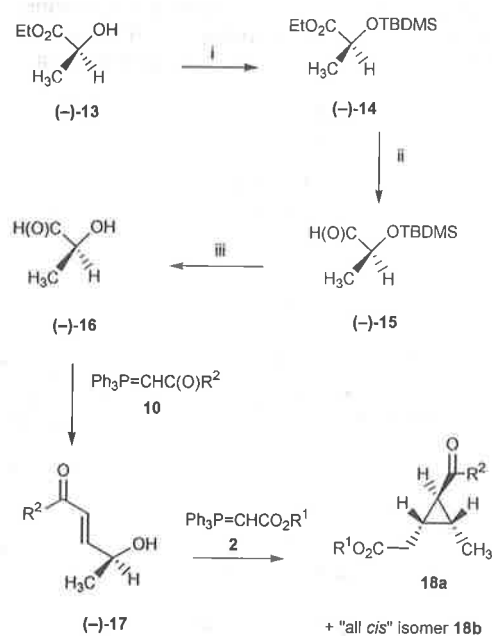
Scheme 3 *Reagents and conditions*: i, TBDMSCl, imidazole (1.5 equiv.), DMF, 25 °C, 1.5 h, 98%; ii, DIBAL-H (1.5 equiv.), ether, −78 °C, 10 min, then MeOH–H₂O (dropwise) to 25 °C, 1 h, 81%; iii, aq. HF (48%), CH₃CN, 15 min, 82%.

they represent several synthetic transformations (*i.e.* **16** to **18**). Finally, we report that the use of benzophenone as the sensitiser in these reactions can be exchanged for dicyanoanthracene (DCA). While the use of DCA failed to dramatically increase cyclopropane yield, comparison of entries 1 and 8 within Table 2 reveals that it was effective in lowering the overall reaction time.

As the cyclopropanation can accommodate a wide range of substituents (*e.g.* H, alkyl and aryl) at the hydroxy terminus of the *trans* γ-hydroxy enones, we envisage that the approach

highlighted here will find application in the construction of a wide range of diversely functionalised optically pure cyclopropanes. We are currently evaluating the use of optically pure α-hydroxy aldehydes derived from ethyl mandelate and also from the sugar chiral pool which will be reported in due course along with a more thorough investigation of how other types of sensitisers influence the cyclopropanation sequence.

Acknowledgements

Notes and references

† All new compounds have been fully characterised by elemental analysis, spectroscopy and mass spectrometry.
‡ (+)-Camphorate utilised.
§ hfc = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

1 See for example: S. E. Denmark, B. L. Christenson, S. P. O'Conner and N. Murase, *Pure Appl. Chem.*, 1996, **68**, 23; S. Boverie, F. Simal, A. Demonceau, A. F. Noels, I. L. Eremenko, A. A. Sidorov and S. E. Nefedov, *Tetrahedron Lett.*, 1997, **38**, 7543; A. Demonceau, F. Simal, A. F. Noels, C. Viñas, R. Nunez and F. Teixidor, *Tetrahedron Lett.*, 1997, **38**, 7879; V. K. Singh, A. DattaGupta and G. Sekar, *Synthesis*, 1997, 137; T. Ichiyanagi, M. Shimizu and T. Fujisawa, *Tetrahedron*, 1997, **53**, 9599; H.-U. Reissig, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 971; H. M. L. Davies and S. A. Panaro, *Tetrahedron Lett.*, 1999, **40**, 5287.
2 See for example: J. Salaun, *Chem. Rev.*, 1989, **89**, 1247; M. Calmes, J. Daunis and F. Escale, *Tetrahedron: Asymmetry*, 1996, **7**, 395; A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341 and references cited therein; A. Krief, L. Provins and A. Froidbise, *Tetrahedron Lett.*, 1998, **39**, 1437.
3 T. D. Avery, T. D. Haselgrove, T. J. Rathbone, D. K. Taylor and E. R. T. Tiekink, *Chem. Commun.*, 1998, 333; T. D. Avery, D. K. Taylor and E. R. T. Tiekink, *J. Org. Chem.*, 1999, *submitted.*
4 N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, 1951, **73**, 881; M. E. Sengül, Z. Ceylan and M. Balci, *Tetrahedron*, 1997, **53**, 10401 and references cited therein.

Addendum:

Page 12 of Chapter 1 highlights the terminology employed for naming the trisubstituted cyclopropane products (**16**). The all *cis* cyclopropane (**16b**) was assigned on the basis of H^1, H^2 and H^3 all being *cis* to one another. The *trans* isomer (**16a**) refers to the orientation of H^2, i.e. H^2 is in a *trans* orientation to both H^1 and H^3.
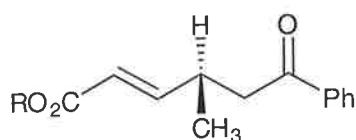
In Section 5.2.1, the by-products formed from an enolene rearrangement of a *cis* cyclopropane have been referred to throughout this thesis as 'enolene' compounds. This assignment is incorrect. A more accurate name would be 'α, β-unsaturated carbonyl' compounds. Similarly, by convention of the research group, compound (**47**) was described as a 'conjugate base', see Chapter 2. The by-product (**47**) should have been referred to as an 'alkoxide'.

With the exception of those noted on pages 156 and iv, IUPAC nomenclature has been employed for the naming of all synthesised compounds and confirmed using the ACD Labs naming program.

For simplicity, incomplete structural fragments have been used in the assignment of ^1H NMR data to indicate the relevant proton(s). However, a more correct method should show the complete structural fragment. E.g. CH_2CHCH should be written $CH_2CH(O)CH$, and similarly $CHC\underline{H}$-$CHCO_2$ should be written $CHC\underline{H}_AH_BCO_2$.

Compounds (**39c**) and (**41a**) displayed unusual ^1H NMR couplings, this has been noted in the thesis, however, further study into these anomalies was not conducted.

Structures omitted from the thesis body:
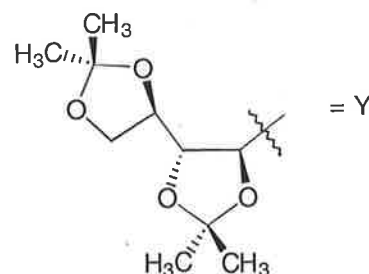

(**86c**)   R = CH_3
(**87c**)   R = Ad

(**94**)

(**95**)