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Metal Carbenes in Natural Product Synthesis

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ABSTRACT

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METAL CARBENES IN NATURAL PRODUCT SYNTHESIS

by Jeremy David Hinks

Two unrelated classes of natural products were targeted as challenges for the application of new synthetic methodology. The unifying theme was the prospective involvement of metal stabilised carbenes as pivotal reactive intermediates in each case.

A study of the application of rhodium stabilised carbene intermediates in the preparation of furofuran lignans, products of biosynthesis in all lignin containing plants, resulted in the development of a new strategy for the synthesis of these compounds. After the successful preparation of a model series of compounds proved the viability of the process it was applied to the synthesis of (±)-asarinin with efficiency comparable to previously employed synthetic approaches. In addition, (±)-epimagnolin A, a non-symmetrical furofuran lignan, was prepared by total synthesis for the first time.

En route to the target compounds an efficient method for the preparation of electron rich, aromatic substituted cyclobutanones and a reliable way of preparing α-diazo-γ-butyrolactones were each investigated. In both cases the results suggest that the methodology might well find a more general rôle in organic synthesis.

A more brief investigation into a new synthetic route towards laurencin, a medium ring ether of marine origin, failed to produce convincing results. The preparation of the substrates for the pivotal ruthenium(II) catalysed metathesis reaction proved difficult to the extent that a wide survey of the catalysts available for ring closing metathesis was not possible. Nonetheless, the preparation of suitable 1,2,4-triols was ultimately achieved and future investigations in this area will be facilitated by the early results described herein.

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Acknowledgements

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Finally, the author is indebted to the Department of Chemistry that has provided tuition fees for the duration of this research programme.

My thanks are due to Richard Brown, supervisor and colleague, who managed the difficulties attendant in overseeing the work of a colleague, and a part-time one at that, with the relaxed efficiency that typifies his approach to all that he does. Likewise, thanks to all his post-graduate group for whom working with someone who at one moment was a student and the next a member of staff must have been occasionally as unnerving as it was for me. Overall, there is no question that having friends and colleagues from both communities for the duration of this project, and hopefully beyond, has been a benefit and a rewarding experience.

It goes without saying that I am grateful to all my colleagues for the willingness to impart advice and comment, particularly to those who provided comment on the thesis itself.

Also, thanks to family and friends who have been unerringly interested in my progress even in the light of sometimes terse responses to questions concerning progress. Most particularly, to Derryn who has never questioned my wish, perhaps need, to do things my way.

Abbreviations

Ac	acetyl-	**m**	multiplet
acam	acetamide	***m*-CPBA**	*m*-chloroperoxy benzoic acid
AIBN	2,2'-azobis*iso*butyro-nitrile	**Me**	methyl
app.	apparent	**MEM**	methyoxymethyl-
Ar	aryl	**MEPY**	methyl 2-oxapyrrolidine-5-carboxylate
ATR	attenuated total reflectance	**NADP(H)**	Nicotinamide adenine dinucleotide phosphate (H)
Bn	benzyl-	**Nap**	napthalenyl-
Boc	butoxycarbonyl-	**NMR**	nuclear magnetic resonance
BOM	benzyloxymethyl-	**P**	generic protecting group
br	broad	**PAL**	phenylalanine ammonia-lyase
cap	caprolactam	**pfb**	perfluorobutyrate
cat.	catalyst	**PMB**	*p*-methoxybenzyl-
CI	chemical ionisation	**PMP**	*p*-methoxyphenyl-
CoA	co-enzyme A	**q**	quartet
Cy	cyclohexyl-	**quint**	quintet
d	doublet	**s**	singlet
DCC	dicyclohexylcarbodiimide	**SAMP**	(S)-1-amino-2-methoxy-pyrollidine
DIBAL	di*iso*butylaluminium hydride	**t**	triplet
DMAP	dimethylaminopyridine	**TAL**	tyrosine ammonia-lyase
DMF	dimethylformamide	**TBDMS**	*tert*-butyldimethylsilyl-
DMSO	dimethylsulfoxide	**TES**	triethylsilyl-
e.e.	enantiomeric excess	**Tf**	trifluoromethanesulfonyl-
EI	electron impact	**tfa**	trifluoroacetate
ES	electrospray	**THF**	tetrahydrofuran
FT	Fourier transform	**TLC**	thin layer chromatorgraphy
HMDS	hexamethyldisilazane	**TMS**	trimethylsilyl-
IR	infra red	**TBDPS**	*tert*-butyldiphenylsilyl-
LDA	lithium di*iso*propylamide	**TPS**	triphenylsilyl-

Chapter 1

Introduction

The preparation of natural products by total synthesis remains a significant challenge to the world-wide community of synthetic organic chemists. The justification for such enterprise may be described in one, or more, of several different objectives: to expand the understanding of biochemical processes in the plant and animal kingdom; to assist in the evaluation of a given natural product for use in a specified application; to produce a compound more efficiently than nature, possibly as dictated by market forces; to submit a new synthetic strategy to the challenge of a natural product synthesis.

Recently the chemical industry (the pharmaceutical sector in particular) has turned away from natural product chemistry. No longer is it a core strategy for the discovery of new chemical entities of defined activity. At the same time there has been a downturn in the level of target based natural product syntheses. The importance of a new method of preparing a complex natural product started to take second place to the importance of understanding its function and activity. Even in the face of this the testing of new chemical strategies through either synthesising compounds from nature for the first time, or by making known compounds more efficiently, remains a mainstay of the chemical community. The evolution of new methods and their assimilation into the synthetic lexicon is the greatest legacy of natural product synthesis.

The myriad new chemistries developed in recent times have all aimed to provide the chemist with conditions that give products selectively and efficiently. Each new strategy provides a means of controlling a reactive intermediate such that it interacts with a substrate in an unambiguously defined fashion. This control of reactivity, sometimes predicted but often arrived at serendipitously, is the essence of reaction development.

Some of the most dramatic recent developments have taken place in the area of transition metal stabilisation of reactive intermediates. In particular, their capacity to stabilise carbenes has ensured that the latter have moved from the fringes of synthetic methodology to centre stage.

Only three decades ago carbene chemistry was associated with interesting but indiscriminate chemistries linked to its high degree of reactivity. Now it is commonly employed within synthetic chemistry in reactions with defined selectivities, both in terms of reaction centre and stereoisomerism. It is interesting to note that Seebach [1] predicted

both a change away from natural product research and the likely utility of new transition metal mediated methodology over a decade ago.

1.1 From Carbenes to Carbenoids

Carbenes [2] are species that contain only 6 electrons on carbon. There are two possible electronic configurations of this highly reactive state. The singlet form has three pairs of electrons and an empty p orbital whilst the triplet form has two paired and two unpaired electrons. A consequence of this is that the more reactive singlet form is planar, with the empty orbital extending above and below the plane of the electron containing orbitals, and the triplet form is tetrahedral (Figure 1.1).

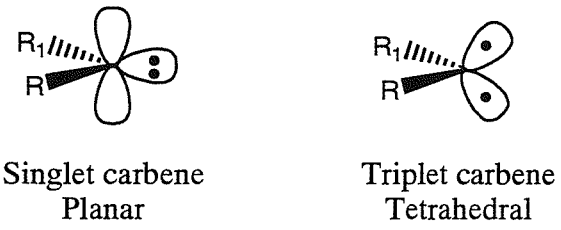


Figure 1.1 The two electronic configurations of free carbenes

The stabilisation to be gained in acquiring a stable octet of electrons means that both forms of carbenes, particularly the singlet form, are highly reactive towards nucleophiles. Indeed they are so reactive that they can induce normally unactivated functionality to undergo reactions as nucleophiles.

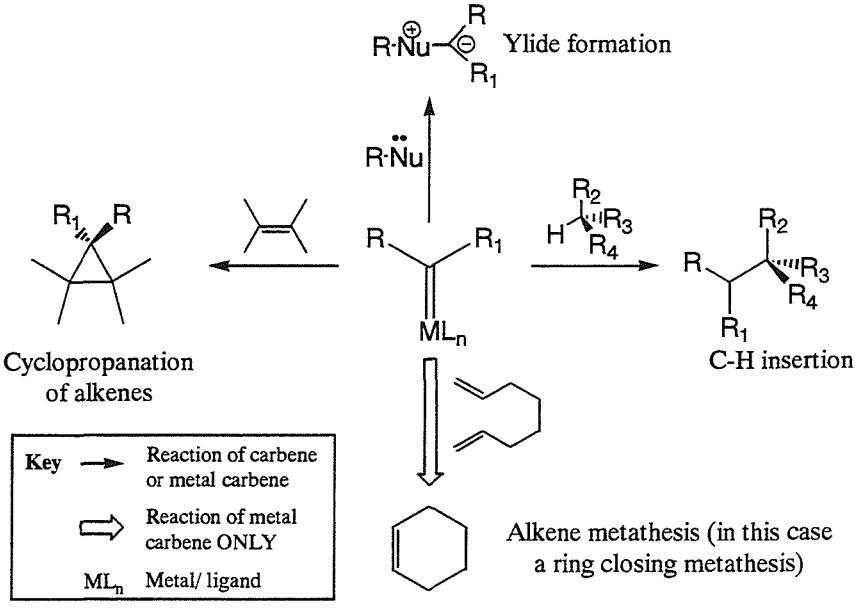


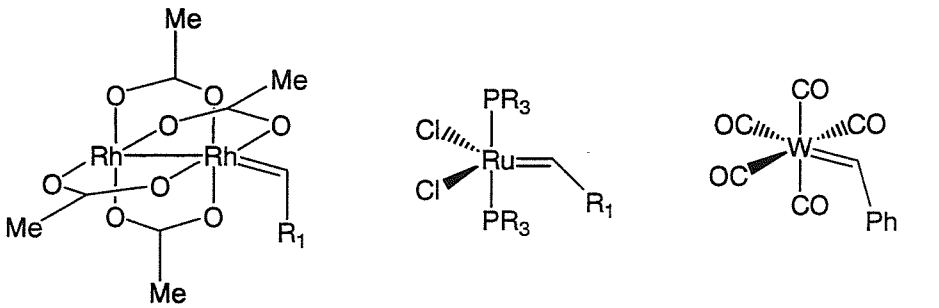
Figure 1.2 Reactions of carbenes and metal carbenes

These extremely interesting reactions [3], particularly carbene insertion into either heteroatom-hydrogen or carbon-hydrogen single bonds, were only compromised by the lack of selectivity in the transformations (Figure 1.2) .

Efficient transformations using carbene intermediates could only be achieved by ensuring the substrate was bereft of any potentially nucleophilic functionality, apart from that at the reaction centre. Whilst many reactions could be achieved in this fashion the general applicability to synthesis was obviously self-limiting.

The reactivity of a carbene may be controlled to a significant extent by the electronic properties of the functionality attached directly to it. For instance, heteroatoms in these positions can stabilise its electron deficiency and thereby modulate its reactivity. Indeed diaminocarbenes are isolable intermediates and have found utility as stabilising ligands associated with transition metal metathesis catalysts (*vide supra*). A more effective way of stabilising carbenes, and the cornerstone of their relatively recent development as useful reactive intermediates, is their complexation by transition metals. The development of these synthetically useful intermediates has been extensively described in the literature and relevant references to this body of work are included in Chapter 2.

Transition metals stabilise carbenes through a co-operative σ- and π- bonding framework. Interaction through σ- donation from the carbene to the metal is augmented by π- back donation from the metal d-orbitals into the vacant p-orbital of the carbene. These relatively stabilised complexes are known as metal carbenes (or carbenoids) (Figure 1.3) [4]. Metals for which the σ-acceptor capability dominates the π- back donation give rise to carbenoids that react as electrophiles in the first instance (Fischer type). Alternatively, metals in which the π-back donation is more effective than its σ-acceptor capability have electron density at the carbenoid centre heightened and it is nucleophilic in character (Schrock type).



Rhodium(II) carbenoid

Ruthenium(II) metathesis catalyst

Tungsten(0) carbenoid - stoichiometric use

Figure 1.3 Some examples of different metal carbenes

Both kinds of complex undergo reactions typical of carbenes but show much greater selectivity than their uncomplexed analogues under appropriate conditions. In addition, different transition metals result in different reactivity profiles of the metal carbenes and reactivity may be further influenced by varying the attached ligands. In one very important instance the metal carbene can undergo reactions atypical of the free carbene, namely olefin metathesis.

Examples of the use of metal carbenes in complex natural product syntheses became commonplace within a relatively short space of time. Representative examples demonstrating each of the reactivities of carbenes/ metal carbenes is outlined in the following section.

1.2 Carbenoids in Natural Product Synthesis

Cyclopropanation of alkenes with metal carbenes is one of the oldest reactions of this class of compounds. Its use in natural product synthesis demonstrates how selectivity of cyclopropanation over C–H insertion (into the β-Me group) is achieved through appropriate choice of metal. For example, copper catalysed decomposition of a diazo-compound (**1.1**) chemoselectively provides an intermediate (**1.2**) in the formal synthesis of pinguisenol (**1.3**) described by Srikrishna [5] (Figure 1.4).

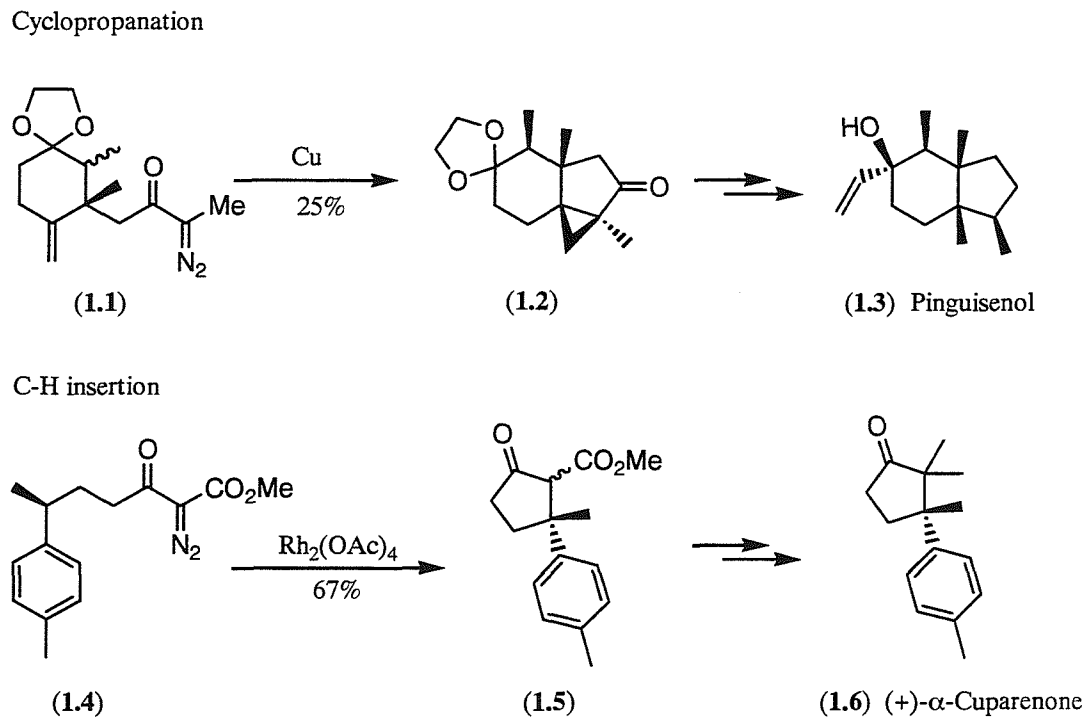
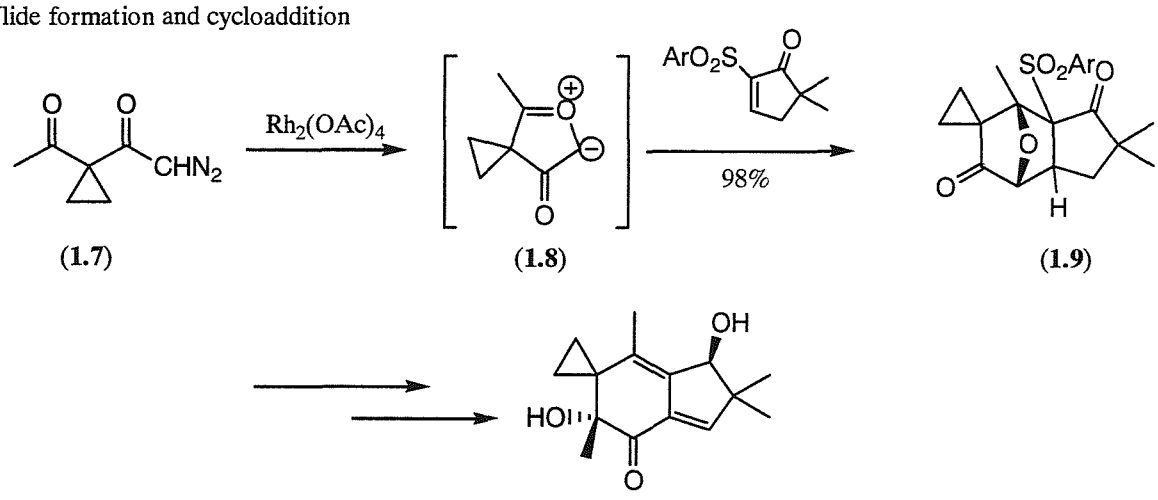


Figure 1.4 Cyclopropanation and C–H insertion

Metal carbenes derived from rhodium(II) have been used in the conversion of diazo-ester (**1.4**) to cyclopentanone (**1.5**) *en route* to (+)-α-cuparenone (**1.6**) [6] (Figure 1.4). The reaction demonstrated the preference of 5- over 6-membered ring formation.

Ylide formation from metal carbenes has proved to be a rapid and effective way of increasing structural complexity through a cascade of reactions initiated by the carbenoid formation. An example of this, described by Padwa [7], is to be found in a preparation of the sesquiterpene illudin M (Scheme 1.5). Thus, diazoketone (**1.7**) forms a cyclic oxonium ylide (**1.8**) on treatment with Rh(II) which immediately undergoes a [3 + 2] cycloaddition with the electron deficient olefin to produce a tetracyclic intermediate (**1.9**) in one step. Elaboration into illudin M (**1.10**) is completed in 5 steps.

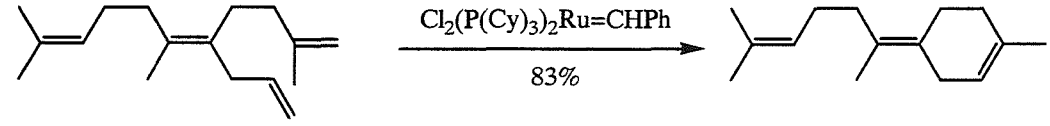
Ylide formation and cycloaddition



(**1.7**) (**1.8**) (**1.9**)

(**1.10**) Illudin M

Olefin metathesis



(**1.11**) (**1.12**) (*E*)-χ-Bisabolene

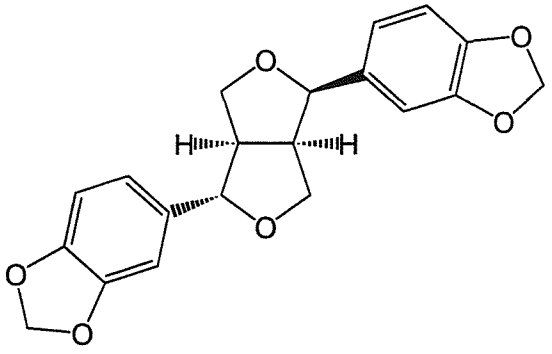
Figure 1.5 Ylide formation and olefin metathesis

Without question the most utilised metal carbene based strategy in natural product synthesis involves catalysts that mediate alkene metathesis. A recent example, described by Negishi *et al.* [8], demonstrates both its utility in the conversion of tetraene (**1.11**) to the tri-substituted olefin (**1.12**) and its mildness in allowing access to the unconjugated product (Figure 1.5).

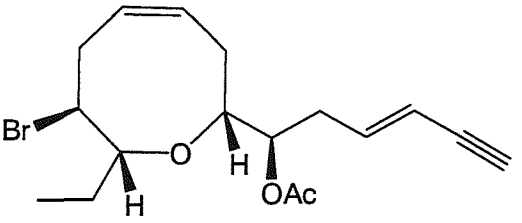
This thesis describes research carried out in the traditional style of natural product chemistry – that is the synthesis was target dominated. Two unrelated classes of natural products, furofuran lignans and laurencin, were investigated during the programme.

These different targets had a shared synthetic theme – the rationale for both syntheses hinged on successful use of metal carbene intermediates. The next chapter will expand on this commonality by describing the background and chemistry of each of the metal carbenes involved: rhodium stabilised carbenes in the preparation of furofurans and ruthenium centred metathesis catalysts in the preparation of laurencin. From thence forward work on each target compound, in terms of both reviewing pertinent literature and describing current results, will be described in separate chapters.

The research described herein confirms that the challenge of preparing natural products remains as significant as it always has been. It provides an unparalleled opportunity for a researcher to develop their skills whilst producing results that might either increase the scope of a method or produce a compound that might be of interest to the scientific community.



A furofuran lignan - Asarinin



Laurencin

Figure 1.6 The target compounds

Chapter 2

Rhodium and Ruthenium Complexation of Carbenes: Structure, Mechanism and Selectivity

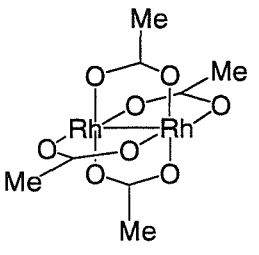
The metals rhodium (s^2d^7) and ruthenium (s^2d^6) are neighbours in the second period of transition metal elements. Their organometallic derivatives are much used in both organic and inorganic synthesis [9, 10]. Most significant is their contribution in the area of homo- and heterogeneous catalysis of oxidation [11] and reduction [12] reactions in which both metals have found use in both small and large scale processes. The following chapter will take this general utility as read and focus on a different aspect of each metal's synthetic use. In the case of rhodium its application to metal carbene insertion into unactivated C–H bonds will be discussed and for ruthenium its ability to mediate metathesis between two alkenes.

2.1 Rhodium(II) carboxylates as catalysts in C–H insertion reactions

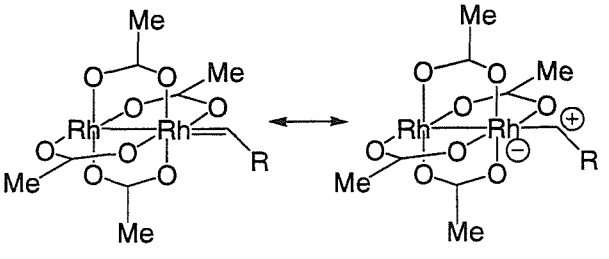
The last 30 years have seen a great deal of research investigating all aspects of rhodium carbene mediated C–H insertion reactions. The story of the development of mechanistic theories is one in which many years of experimentation, observation and analysis led to the proposal of a number of mechanisms. The proposals were then supported or refuted by more recent work. This sequence of events is reflected in the discussion throughout this section.

2.1.1 Formation and Structure of the Rhodium Carbene Complex

The first reports of rhodium(II) acetate (Figure 2.1) as a catalyst in the controlled decomposition of diazo-compounds [13] paved the way for metal carbene chemistry to become a standard methodology in the chemistry community. Whilst there are many different Rh(II) carboxylates known today the following discussion will primarily focus on the prototypical acetate complex (**2.1**).



(**2.1**) Dirhodium(II) tetraacetate



(**2.2**) Rhodium(II) metal carbene

Figure 2.1

The complex contains two rhodium(II) atoms bound together by four bridging acetate ligands in a cage like structure, a shape for which the term paddlewheel motif was coined [14]. The acetates occupy all the equatorial positions leaving a single vacant axial co-ordination site at each metal. The complex also involves a single bond between the two rhodium atoms. The structural rigidity of this D_{4h} complex [15] is one of the facets that make the complex so useful in synthesis. Under normal reaction conditions the ligands are not interchangeable although under more forcing protocols they may be exchanged with other carboxylates, an essential feature in the design of the later generation of chiral rhodium carboxylates (*vide supra*).

There are several other factors that were critical the successful development of the rhodium(II) carboxylates. Firstly, they do not undergo redox reactions with diazo-compounds. Secondly, they do not associate with alkenes (with the exception of the complexes bearing strongly electron withdrawing ligands) which is of importance given that alkene cyclopropanation is one major reaction mediated by these catalysts. Finally, the diazo- compounds which form the metal carbene with rhodium(II) acetate are readily available by a number of different synthetic methods [16].

The interaction of the complex with diazo- compounds is initiated through the co-ordinative unsaturation at rhodium. The metal acts as an electrophile at the carbon of the diazo- species. Nitrogen is extruded from the resulting ylide to produce an electrophilic metal carbene complex that was first invoked by Yates in 1952 [17] (Figure 2.2). The vacant co-ordination site on rhodium may also interact with any other Lewis base present in the reaction system. Provided this interaction is reversible the chemical outcome of the transformation (with substrate S) is not effected. However some irreversibly complexing functional groups, such as amines, sulfides and nitriles, can poison the catalyst.

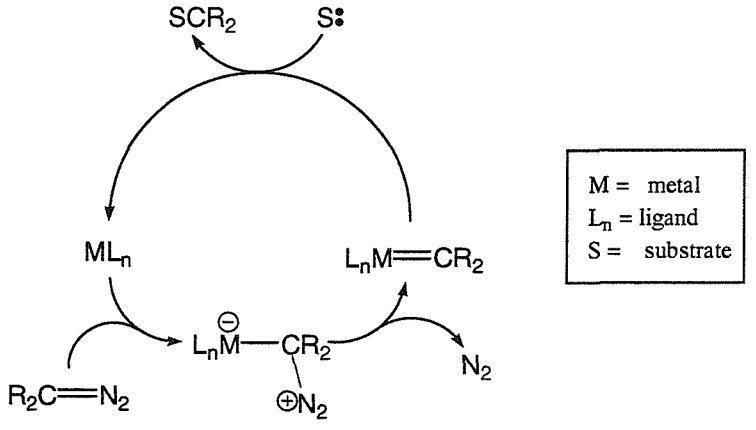


Figure 2.2 The catalytic cycle of metal carbene formation and regeneration

The metal carbene species (**2.2**) implicated in the mechanistic cycle and illustrated above (Figure 2.1) has never been isolated but its intermediacy is strongly implied by comparison with the reactivity of stable metal carbene complexes with similar substrates [18].

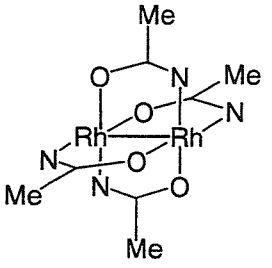
Given the absence of any direct data on rhodium carbenes all the mechanistic proposals are based upon the outcomes of reactions in which they are involved or from molecular modelling studies. The former strategy has clearly demonstrated that the ligands have a profound effect on the reactivity of the metal carbene. The latter strategy, once its efficacy had been proven, has made some interesting observations on the reactivity of such complexes. For instance, Snyder's work [19] confirmed the proposed bond order of one for the Rh–Rh bond in the unsubstituted complex but suggested that on complexation of methylene carbene the metal/ metal bond weakens to a bond order of 0.5. This results from the *trans*- effect of the complexed methylene which itelf has a single bond to the metal centre.

The polarisation of the metal-carbon bond was shown to be such that the carbon held a partial negative charge. This is not in accord with the perceived reactivity of rhodium carbenes that are normally depicted with a positive charge residing on carbon (Figure 2.1). Snyder suggested that this was not as contradictory as seemed at first inspection. Although the ground state polarisation is not in accord with observed reactivity it is possible that the incoming nucleophile could avoid electron-electron repulsion by interaction with the p*-orbital at the carbene's carbon centre. This would cause a π-electron redistribution onto the metal resulting in the polarisation of the metal carbene that is implied by its reactivity. The role of the second rhodium atom is to shoulder some of the charge that is redistributed during carbene complexation, a co-operative effect that is slightly compromised if it is coordinated to a Lewis base.

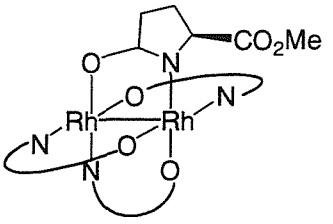
2.1.2 Variation of Ligands on Rhodium and their Influence on Reactivity

In Section 2.1.1 it was appropriate to focus the discussion on dirhodium tetraacetate. However, the complexities of the mechanism of C–H insertion have largely become apparent through observation of the experimental outcomes of reactions involving Rh(II) complexed to different acetate ligands. Conveniently these catalysts are easily accessible [20] either from dirhodium tetraacetate itself, by acetate exchange under fairly forcing conditions, or through treatment of rhodium chloride with the appropriate acetate. The available acetate ligands in common use today can be classified in four broad categories.

1. The acetamide ligands [21] that ligate to the binuclear rhodium core through one oxygen atom and one nitrogen atom. The two most commonly used are dirhodium(II) tetraacetamide ($Rh_2(acam)_4$) (**2.3**) (Figure 2.3) and rhodium(II) tetracaprolactam ($Rh_2(cap)_4$).
2. The alkyl substituted acetate ligands, for instance the parent system of dirhodium(II) tetraacetate (**2.1**).
3. The electron withdrawing acetate ligands [22], for instance dirhodium(II) tetrakisperfluorobutyrate ($Rh_2(pfb)_4$) and dirhodium(II) tetrakistrifluoroacetate ($Rh_2(tfa)_4$).
4. Chiral ligands [23] which may come from any one of the classes outlined above but which tend to be chiral versions of the acetamide ligands, for example, Rh_2(5S-MEPY)$_4$ (**2.4**) (Figure 2.3).



(**2.3**) Dirhodium(II) tetraacetamide



For the sake of clarity only one of the ligands has been drawn in full

(**2.4**) Rh_2(5S-MEPY)$_4$

Figure 2.3 Structures of some representative Rh (II) acetamide complexes

The first three classes mentioned above cover the spectrum of electronic influence of ligand on metal; going from the least to the most electron withdrawing. In many of the early studies the efficacy of ligands from each class 1 to 3 were compared as a means of understanding the mechanism of the insertion process.

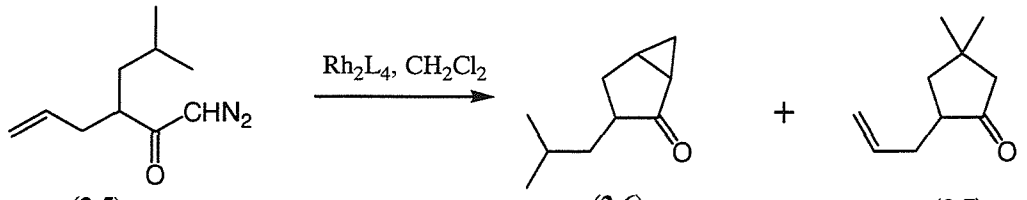
2.1.3 Observations on Chemo- and Regioselectivity during C–H Insertion reactions

Given that isolation of the intermediate metal carbene species has not proved possible it has been necessary to base mechanistic proposals on the outcomes of carefully designed experiments designed to evaluate the impact of (a) different ligands (b) steric congestion in the substrate and (c) electronic effects in the substrate on the mechanism. Before discussing the proposals for the mechanism that have been put forward it is appropriate to describe some of the experimental results on which they are based.

2.1.3.1 Chemoselectivity

A wide variety of experiments have been described in the literature in which substrates have been assembled that present metal carbenes derived from them with at least two different reaction pathways. These have been reviewed recently [24] and two examples are outlined below (Figure 2.4).

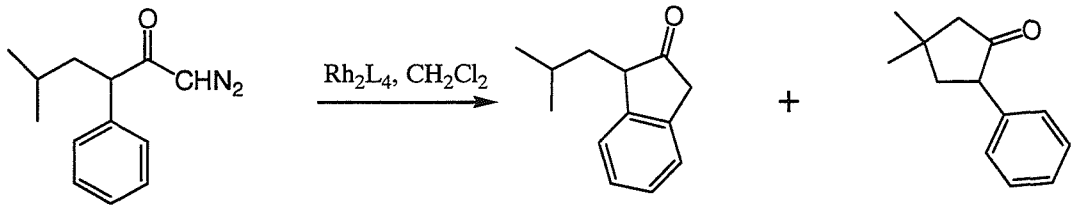
Cyclopropanation *vs.* C-H insertion



(2.5) (2.6) (2.7)

Rh_2L_4	% yield	(2.6)	(2.7)
$Rh_2(pfb)_4$	56	0	100
$Rh_2(OAc)_4$	97	44	55
$Rh_2(cap)_4$	76	100	0

Aromatic substitution *vs.* C-H insertion



(2.8) (2.9) (2.10)

Rh_2L_4	% yield	(2.9)	(2.10)
$Rh_2(pfb)_4$	96	100	0
$Rh_2(OAc)_4$	97	65	35
$Rh_2(cap)_4$	64	59	41

Figure 2.4 Investigation of chemoselectivity through competition experiments

The observation that the dominance of C–H insertion over cyclopropanation (**2.5→2.7** *vs.* **2.5→2.6**) [25] could be completely reversed by using a less electron withdrawing ligand (*e.g.* caprolactam) was the first of many results that showed the influence that ligands have on the course of reactions. Whilst this result was not easy to explain the capacity of an electron withdrawing ligand (*e.g.* perfluorobutyrate) to favour aromatic C–H insertion over aliphatic C–H [26] insertion did fit into a developing model. Removal of electron density from the metal centre effectively favours the formation of the metal stabilised carbocation

resonance form of the metal carbene (see **2.2**). Thus, formal electrophilic aromatic substitution would be envisaged to be more favoured than insertion into an aliphatic C–H (**2.8**→**2.9** *vs.* **2.8**→**2.10**) than when the metal is complexed with a less electron withdrawing ligand.

2.1.3.2 Regioselectivity

The propensity of metal carbenes to undergo intramolecular C–H insertion to give cyclopentane derivatives was first discovered by Wenkert *et al.* [27] The area was more thoroughly investigated by Taber who confirmed the original observation in a study involving metal carbenes derived from α-diazo-β-ketoesters [28] (*e.g.* **2.11** to **2.12**) (Figure 2.5). It is also noteworthy that in all his examples the relative stereochemistry at the newly formed C–C bond was always found to be *trans*-. Taber challenged his developing methodology with the synthesis of (±)-pentalenolactone E methyl ester wherein the critical conversion of **2.13** was effected to give a single diastereoisomer (**2.14**) in unspecified yield.

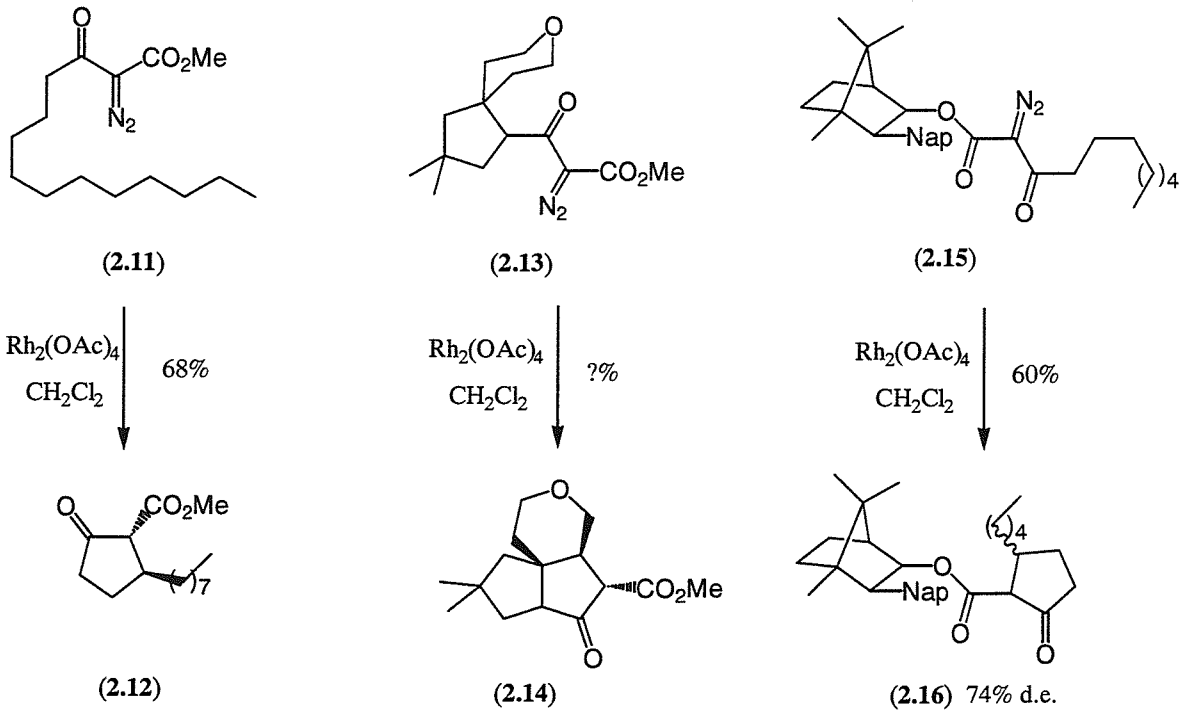


Figure 2.5 Preferential 5-membered ring formation during C-H insertion

Their interpretation of facile five membered ring formation was that the transition state, even from freely rotating alicyclic substrates, must be highly ordered. An attempt to exploit this by undertaking a enantiospecific synthesis of cyclopentanes [29] by utilising a substrate functionalised with a chiral auxiliary (*e.g.* **2.15** to **2.16**) met with limited success

although Taber did successfully prepare (+)-estrone methyl ether [30] in 91% e.e. Its development as a general method was halted with the discovery of the rhodium catalysts with chiral ligands (*vide supra*).

Another important observation during this early work was that insertion into a C–H bond at a chiral centre occurs with retention of configuration. This was identified during the preparation of (+)-α-cuparenone [31] (see Figure 1.4), the first enantioselective synthesis to use C–H insertion methodology.

The influence of the electronic characteristics of the substrate was demonstrated by two separate studies. Stork and Nagatani [32] showed that electron withdrawing groups deactivate methylene groups towards C–H insertion. This was demonstrated effectively in experiments in which there were two possible 5-membered ring insertion products, one that would result from insertion α- to an ester carbonyl and one at a remote C–H. They demonstrated that insertion was prevented at not only α- but also the β-position relative to the ester (Figure 2.6). Conversely, investigation into the effect of an α-sp^3 hybridised heteroatom on C–H insertion by Adams and Poupart [33, 34] showed that insertion was activated at these positions (Figure 2.6). Both of these results indicate that the first interaction between the metal carbene and the substrate requires that the latter react as a nucleophile.

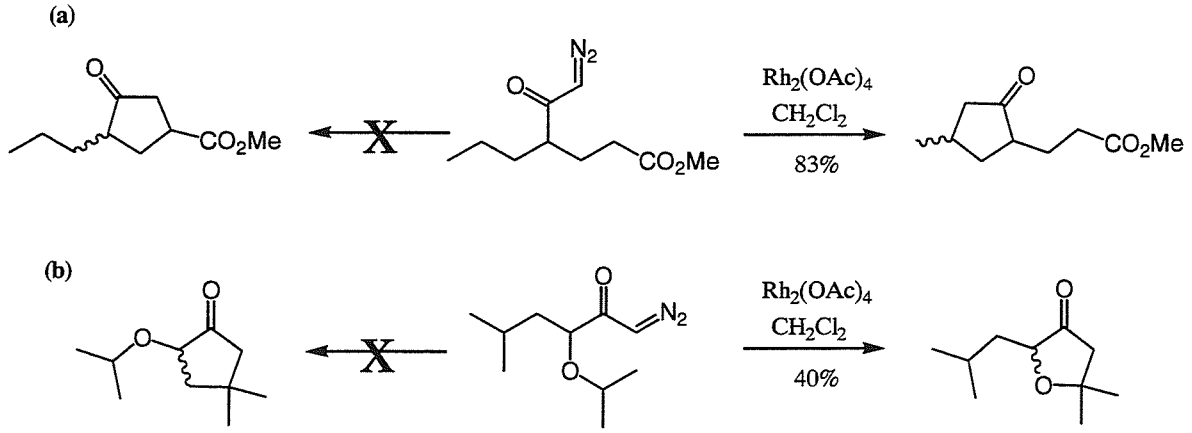


Figure 2.6 Electronic effects in the substrate on C–H insertion: (a) the influence of electron withdrawal and (b) the influence of electron donation

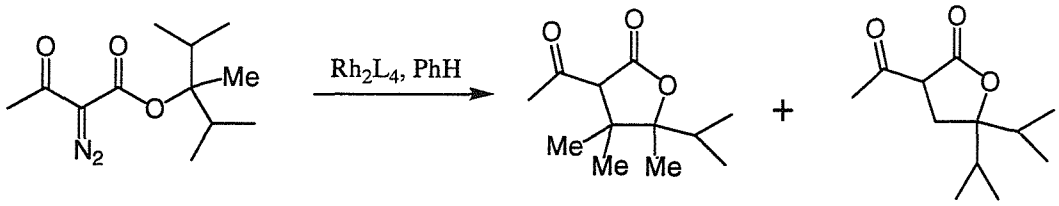
These results were reinforced by later experiments whose aim was to demonstrate the impact of the degree of branching at the C–H insertion site. Taber *et al.* [35] showed that the preference for C–H insertion increased along the series of methyl to methylene to methine.

These findings are in accord with the observations that insertions are favoured at electron rich C–H bonds and are the same trends observed for the insertion of free carbenes into C–H bonds [36].

This relationship between metal stabilised and free carbenes with respect to ease of insertion breaks down when considering insertion into allylic and benzylic methylene C–Hs. For metal stabilised carbenes insertion at these centres is less favoured than for an isolated methylene C–H bonds whilst free carbene insertion at these centres is a facile process. This may be taken as further evidence for the fact that metal stabilised carbenes react with the most electron rich C–H bonds.

2.1.3.3 Effect of Ligands on Rhodium

Doyle and coworkers [37] undertook a series of experiments in which they also investigated the relative ease of insertion of a doubly stabilised metal carbene into methyl, methylene, and methine C–H bonds. Their focus was to investigate the influence of the electronic characteristics of the metal centre that was modified by the ligands attached to it. Through an extensive series of experiments they identified two different influences on the regioselectivity of insertion.



(2.17) (2.18) (2.19)

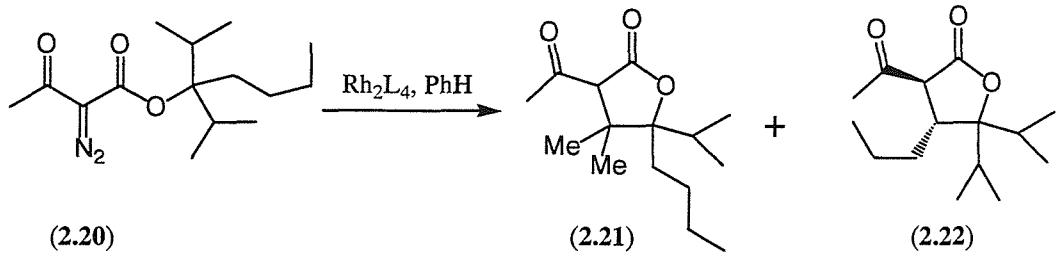
Rh_2L_4	% yield	(2.18)	(2.19)
$Rh_2(pfb)_4$	61	39	61
$Rh_2(OAc)_4$	97	90	10
$Rh_2(cap)_4$	89	99	1

Figure 2.7 The influence of the ligand on regioselectivity I

Firstly, there were those reactions in which the regioselectivity was influenced by the electronic effects of the ligand (Figure 2.7). For instance, the diazo- compound **(2.17)** would be predicted to undergo insertion into one of the secondary centres to give **2.18** or the primary centre to give **2.19**, both assuming that the predisposition for 5-membered ring formation would hold true. With the prototypical acetate ligand Taber's results were supported in that insertion into the more electron rich secondary centre was favoured. This preference is magnified with the less electron withdrawing caprolactam ligand complex,

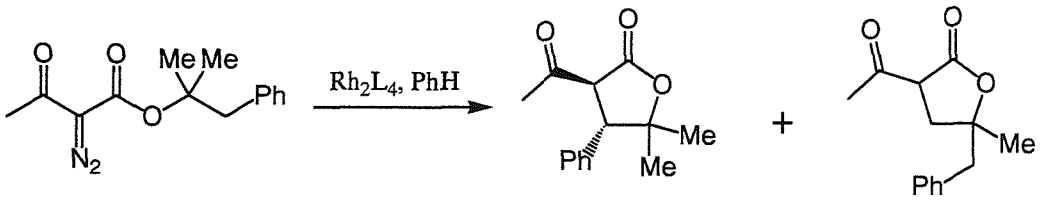
whilst the strongly electron withdrawing perfluorobutyrate ligands give a statistical product distribution. Several other examples demonstrated this same dependence of reaction selectivity on the balance of electronic effects within the substrate and the ligand coordination sphere. The original observation that the products containing 3,4-disubstitution had the pendant functional groups in a *trans*- configuration across the newly formed bond was upheld by the results of this work.

A second group of reactions showed anomalous results indicating that electronic effects did not dominate all insertion reactions (Figure 2.8).



(2.20) **(2.21)** **(2.22)**

Rh_2L_4	% yield	(2.21)	(2.22)
$Rh_2(pfb)_4$	74	5	95
$Rh_2(OAc)_4$	78	3	97
$Rh_2(cap)_4$	89	4	96



(2.23) **(2.24)** **(2.25)**

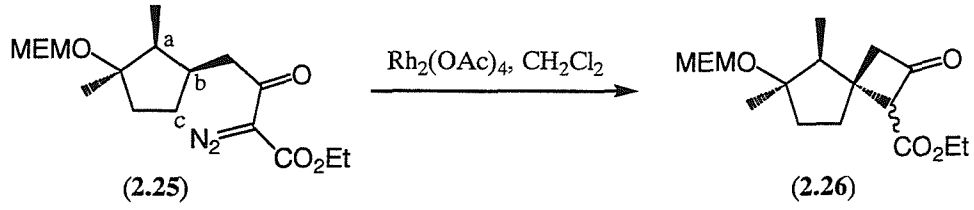
Rh_2L_4	% yield	(2.24)	(2.25)
$Rh_2(pfb)_4$	31	26	74
$Rh_2(OAc)_4$	84	29	71
$Rh_2(cap)_4$	71	30	70

Figure 2.8 The influence of the ligand on regioselectivity II

Diazo- compounds **2.20** and **2.23** show a tendency to insert into the least electron rich C-H bond. In the case of **2.20** insertion into the secondary position to give **2.22** was favoured over insertion into a tertiary C-H (**2.21**). For **2.23** the predicted insertion into the benzylic methylene to give **2.24,** instead of reaction at the primary to centre to give **2.25,** was not supported by the results. In both cases the influence of changing the ligand was negligible

and in one case (insertion of **2.23**) changing of the solvent (to CH_2Cl_2) had no influence on the product ratio.

Doyle's conclusion was that for this second class of reactions the main influence on regioselectivity was the ability of the compound to adopt a conformation that held a particular insertion site proximate to the metal carbene centre. He supported his comments with the results of molecular modelling studies on the transition states proposed for C–H insertions leading to formation of **2.21** and **2.22**. The latter was calculated to be the more stable by 3.2 kcal/ mol^{-1}, a result which was also reflected in the relative stabilities of the most favourable conformation of the products. This interplay between steric, conformational and electronic influences is illustrated effectively by an example taken from the work of Cane and co-workers [38] (Figure 2.9)



(2.25) (2.26)

Figure 2.9 Steric and electronic influences in C-H insertions

The favourability of 5-membered ring formation would predispose diazo- compound (**2.25**) towards insertion at either at positions C_a or C_c. The product isolated arises through insertion at C_b to give a 4-membered ring (**2.26**). Insertion at the α-C–H at C_a or C_c is disfavoured by the strain imposed by forming a *trans-* ring junction as well as the fact that the α-methyl group shields the two insertion sites on the α- face of the ring. Similarly, the the β-Me group at C_a prevents insertion into the β-H at C_c. Thus, steric and conformational issues prevent 5-membered ring formation whilst the tertiary centre at C_b is favourably disposed towards insertion and a conformational preference that places the two reacting centres close to each other for what is normally an ineffective reaction.

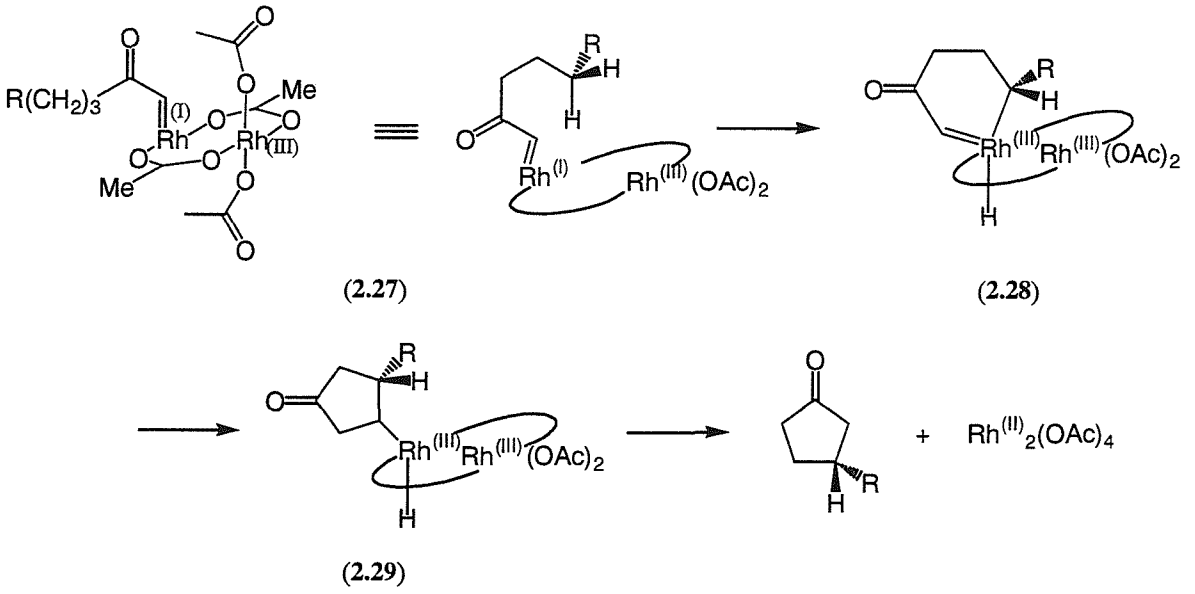
2.1.4 The Early Mechanistic Proposals

The observations that formed the basis of early mechanistic proposals were that -

- correlation with stoichiometric carbene reactions implied that the reaction mediated by rhodium went by a metal carbene;
- selectivity (in a number of different guises) implied a highly ordered transition state;

- the retention of configuration after insertion into a chiral C-H with an achiral catalyst implied a concerted process in the formation of the transition state;
- the electronic effect of ligands and substrate showed the metal carbene to be electrophilic.

With these observations in mind two proposals were published. The first, by Taber [35] was made as a footnote in a publication at the request of a referee. It involved a process where the metal carbene was formed at one rhodium atom that disassociated from two of the bridging ligands at the same time to provide **2.27** (Figure 2.10).



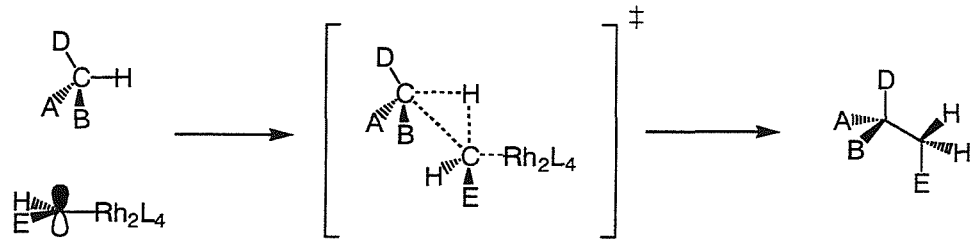
(2.27) (2.28) (2.29)

Figure 2.10 The original Taber proposal

During this process the Rh–Rh bond effectively undergoes a disproportionative bond cleavage and the remote rhodium remains associated with all four acetate ligands, with only two of them bridging both metal atoms. The proposal suggests that a sequence of oxidative addition (to give **2.28**), rearrangement (to give **2.29**), reductive elimination and bridging ligand reassociation complete the cycle.

Taber put out the proposal in the spirit of inviting debate in the area. No supporting evidence for his suggestions were forthcoming subsequently and he only revisited the proposal in a review publication a few years later [39]. His outline proposal was difficult to support even at the time given the observation of retention of configuration and that a highly ordered transition state was implied by reaction specificities. The suggestion that the two rhodium atoms do not form a formal bond in the metal carbene has also been refuted by the molecular modelling studies alluded to in Section 2.1.1.

Doyle's group outlined their own proposals some years later in the same study that produced the results shown in Figure 2.7 and 2.8. In addition, he had just completed work on a series of insertion reactions into enantiotopic methylene compounds using chiral carboxamide ligands which demonstrated remarkable stereoselectivity [40]. His view was that stereoselective nature of reactions involving chiral catalysts strongly supported the idea that the rhodium/ ligand assembly retained its structural integrity throughout the reaction. He had proposed this aspect of the mechanism as early as 1986 [41] and was supported by the observations on the rigidity of rhodium carboxylate complexes [15].



(2.30)

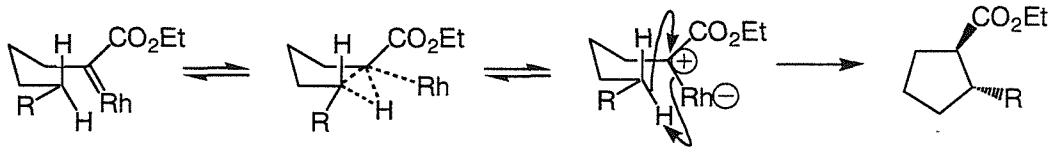
Figure 2.11 The Doyle mechanism

The formation of the rhodium carbenoid itself occurred, in his scheme, according to the mechanism outlined in Section 2.1.1. The resultant metal carbene's empty p-orbital overlaps with the σ-C–H orbital at the insertion locus to provide a 3-centre-2-electron bond (**2.30**) which rapidly undergoes insertion with simultaneous loss of the rhodium complex (Figure 2.11). The mechanism accounts for the observed regioselectivity of bond insertion reactions. Equally, it provides an explanation for the ligand dependent changes in selectivity observed in reactions of the type illustrated in Figure 2.7. A more electron withdrawing ligand (*e.g.* perfluorobutyrate) would facilitate formation of an 'earlier transition state' with a corresponding decrease in selectivity and increase in reactivity. This is in accord with experimental observations which show that catalysts with strongly electron withdrawing ligands give product profiles more akin to those anticipated for a free carbene.

Doyle's explanation for the results of reactions of the type illustrated in Scheme 2.8 was less detailed. Any reaction that was not responsive to changes in electrophilicity of the carbene was described as being driven by conformational issues that dictated the ease of presenting the insertion centre to the rhodium carbene. In these instances he found that the outcome of the reaction could be predicted on the basis of the energy of the products, a fact that implies that the transition state occurs late in the reaction co-ordinate.

2.1.5 Later Developments

Some years after his original proposal Taber accepted that the better mechanistic model for the insertion process was the one being developed by Doyle. He investigated it further and added an embellishment of his own with regard to the formation of the transition state (Figure 2.12) [42, 43]. He proposed that the reaction proceeded *via* an intermediate of the type proposed by Doyle (**2.31**), but that this was not the transition state. Instead, he suggested that **2.31** was in rapid equilibrium with intermediate (**2.32**) in which the C–H insertion centre and the C–Rh bond are coplanar. This would dispose the empty p-orbital of the carbene (drawn in its ylide form) at 90° relative to the C–H bond. A rapid collapse of **2.32** to products completes the reaction.



(2.31) (2.32)

Figure 2.12 Taber's later mechanism

Taber's contention was that the two diastereoisomeric transition states of **2.32** could be modelled, as could the compounds derived from them. He was aiming ultimately for a predictive algorithm to support synthetic design using this chemistry. With his modelling protocol he did find that the isolated products corresponded to those with the low energy transition states identified through his modelling of each diastereoisomer. In addition, he found that whilst the energies of the transition states did correspond to observed product ratios the energy of the products did not.

This author's view is that Taber's argument about the diastereoisomeric transition states could just as well apply to the Doyle intermediate. The proposal about the alignment of the bonds as a prerequisite for reaction led to a system that was feasible to model but whose reason for existence was not clear and offered no better solution to the problem of the nature of the mechanism that Doyle's proposal.

A number of different groups began using the Doyle mechanism as an explanation for the results that they observed. Examples (Figure 2.13) include work by Fernandez Mateos *et al.* [44] in the preparation of 6,5-fused ring systems (**2.33**) and Ikeda during the stereoselective synthesis of highly functionalised cyclopentanones (**2.34**) [45, 46].

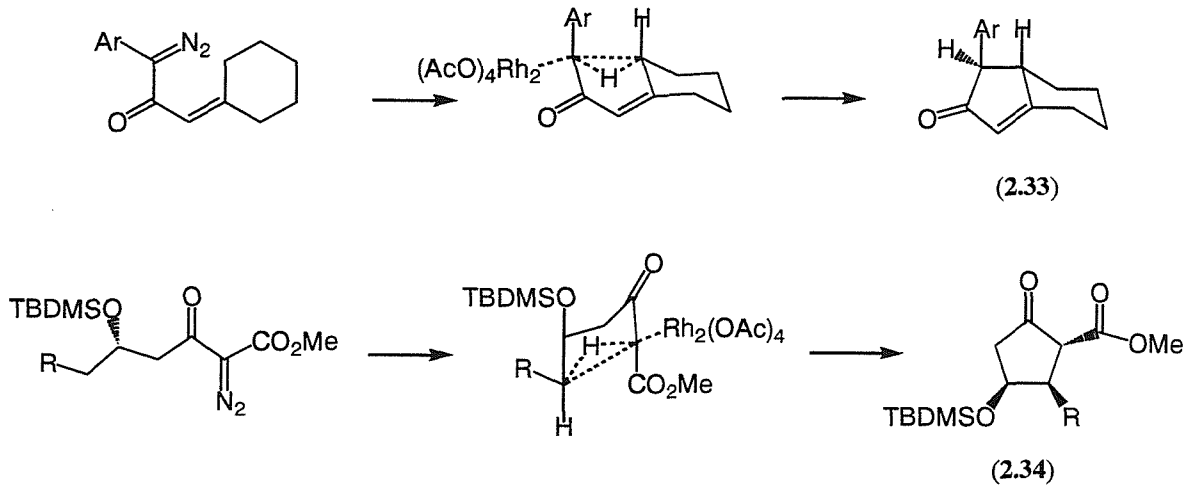


Figure 2.13 Examples of explanation for stereoselectivity by Doyle's mechanism for insertion

Doyle's mechanism supposed that there was little or no backbonding between the metal centre and the carbenic carbon atom, thereby implying that the complexes behave as a metal stabilised carbocation (see Figure 2.1). The issue of the absence of back bonding in metal carbenes was called into question by the work of Pirrung *et al.* [47] They studied rhodium(II) carboxylate / C≡O complexes and analysed them by IR spectroscopy. Inspection of the C≡O stretching frequencies revealed that they moved to higher energy with increasing electron withdrawal from the ligands.

The implication of this is that the ligand's capacity for electron withdrawal inhibits the metal's ability to back bond which, in turn, implies that less electronegative ligands supplement the σ-bonding interaction with a degree of π-back bonding (that weakens the complexed C≡O bond). Given the metal carbene's obvious ability to act as a π-acceptor it was assumed that the above studies with carbon monoxide would serve as a genuine model for the bonding interactions between metal and carbene.

In an attempt to throw more light on the nature of the metal carbene intermediate Pirrung undertook an investigation of the fate of the reactive species derived from **2.35** by reacting it in the presence of a wide range of different Rh(II) carboxylate ligands (Figure 2.14).

Firstly, they tested assumption that the electrophilicity of the metal carbene could be attenuated by electron withdrawing effect of the ligands. If this was so the relative proportions of tetrahydropyran (**2.36**) (produced *via* ylide formation) and cyclopentenone (**2.37**) (arising from C-H insertion) were predicted to vary depending on the ligand on rhodium. Their assumption was that the more electron withdrawing the ligand (or the lower the pKa of its conjugate acid) the greater its affinity for initial association with the

Lewis basic sp^3 oxygen (resulting in formation of **2.36**) as compared to insertion at the more weakly nucleophilic C–H (which would provide **2.37**). Observations did not bear this out nor did any other simplistic single parameter model.

As a consequence they undertook a multiparameter regression analysis involving the impact of field (dipole-dipole interactions), resonance (delocalisation), polarisability (induced dipoles) and electronegativity factors of each ligand on the product composition resulting from decomposition of **2.35**. From this they determined that the product composition had a significant dependence on the polarisability and field effects and these results were reproduced in a similar study of competitive secondary *vs.* tertiary C–H insertion.

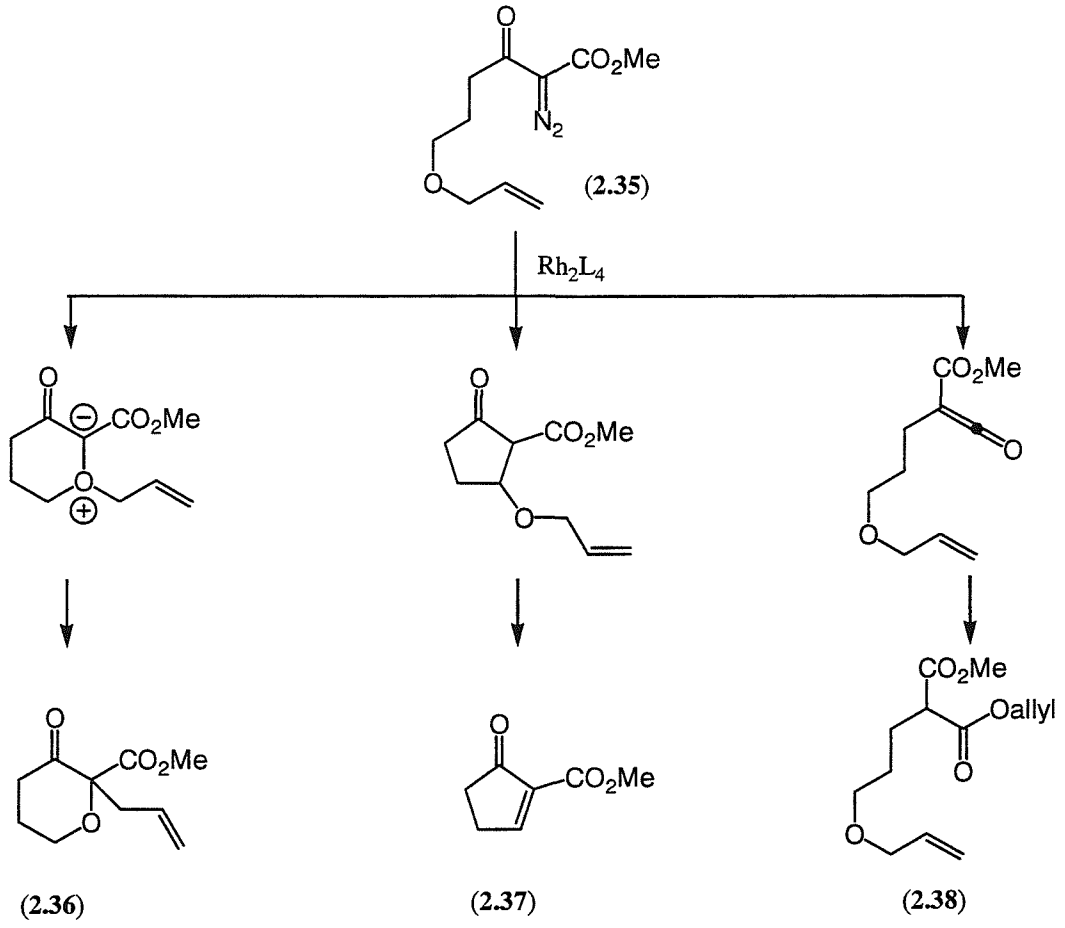


Figure 2.14 Comparison of product compositions from ylide formation, C–H insertion and Wolff rearrangement for different Rh(II) carboxylates

If the metal stabilised carbocation form of the reactive intermediate (Figure 2.1) was correct the only means of ligand stabilisation would operate through an electron withdrawing field effect that would stabilise the σ-interaction by enhancing the positive charge on carbon. If the stability of the intermediate were to be enhanced in this way the

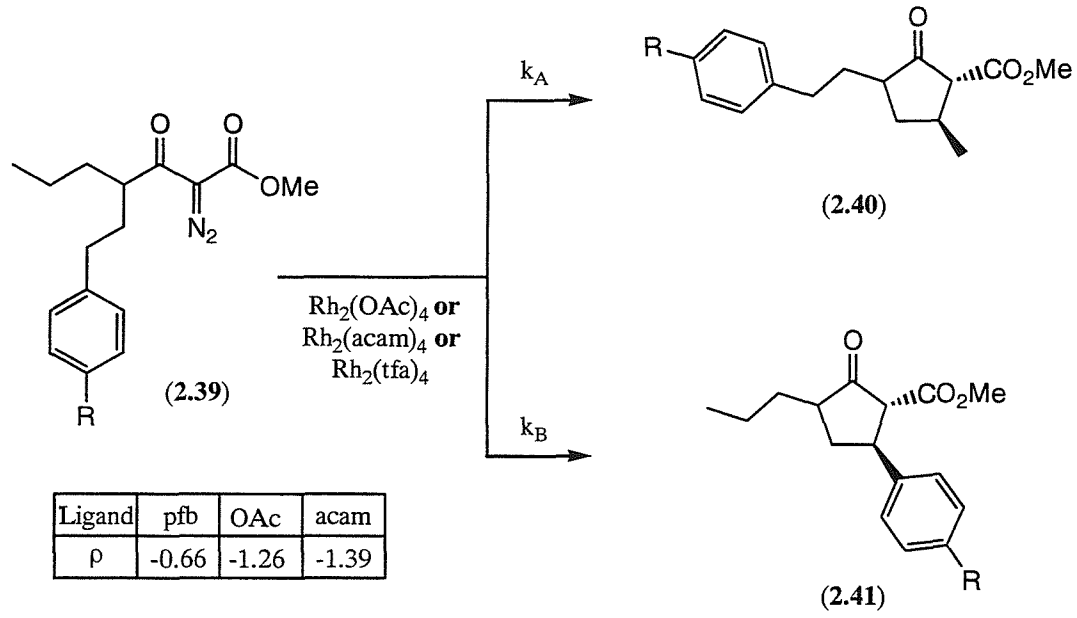
metal carbenes with the *most* electron withdrawing ligands would be predicted to be the most selective, assuming that stability correlated with selectivity.

The fact that the converse was found to be true led Pirrung to suggest that an alternative stabilisation effect was in operation that would account for the fact that the *most* polarisable and *least* electronegative ligands (*e.g.* acetamide) were the most selective. His proposal was that whilst these ligands might be less effective in stabilising the σ-interaction but they would promote effective back-bonding. This, along with the IR results above, were taken as some evidence in favour of the intermediate not being equivalent to a metal stabilised carbocation.

The most strongly electron withdrawing ligands did not fit into any of Pirrung's developing models. In the laboratory their use resulted in the formation of both **2.36** and **2.37** and a third product arising from Wolff rearrangement (**2.38**) and subsequent quenching with allyl alcohol produced during formation of **2.37** (Figure 2.14). Their deviation from the norm was explained by suggesting that they operated by two different mechanisms. One *via* a metal carbene to produce either **2.36** or **2.37** and one *via* a free carbene that decomposed by a reaction typical of such intermediates to produce **2.38.** A mixed mechanism as an explanation for a complex product profile arising from a metal carbene decomposition has also been invoked by Demonceau and co-workers [48].

Once again this was taken as support for the correlation of back bonding in metal carbenes as being necessary for stability and selectivity. The fact that free carbenes are invoked in reactions involving strongly electron withdrawing ligand complexes suggests that the metal carbene bond involving σ-character only is very weak. Therefore, by association the ylide form of the metal carbene (Figure 2.2) is not a major contributor in explaining the selectivity of rhodium carbenes.

More recent work by Wang *et al.* [49] attempted to develop understanding further by trying to isolate the electronic influence of the substrate on the insertion site from conformational and/ or steric influences. To achieve this they investigated α-diazo-β-ketoester (**2.39**), a substrate already employed by Taber in the past [35] during an investigation on the relative ease of insertion into either secondary or benzylic C–H (Figure 2.15). They varied the *para*-substituent (R) on the aromatic ring and made the assumption that it would have no conformational or steric effect on either of the potential insertion sites and would only have an electronic influence on the benzylic centre.



Ligand	pfb	OAc	acam
ρ	-0.66	-1.26	-1.39

Figure 2.15 A Hammett study on C–H insertion at secondary or benzylic centres

On completion of the experiments the rates were determined and the ratios k_A/ k_H and k_B/ k_H calculated (k_H is the rate of insertion when R = H). Hammett analyses relating the reaction rates to the substituent constants (σ) generated reaction constants (ρ) that were all negative, implying development of a positive charge at the reaction centre in the transition state. They were largest for the least electron withdrawing ligands (*i.e.* $Rh_2(acam)_4$).

A general observation that electron releasing substituents on the aromatic ring favoured benzylic insertion supported the fact that the metal carbene acts as an electrophile. What was surprising was that in these reactions the pfb ligand was the most selective, suggesting that the free carbene mechanism, alluded to above, is not involved in this particular system.

The lowest reaction constant associated with the pfb ligand demonstrates the smaller the influence of the aromatic substituents on the reaction involving this complex. Thus, for the pfb ligand this small influence is consistent with the associated metal carbene forming an early transition state in which development of the positive charge on carbon is minimal. In this case the substituents will have a limited impact on promoting or inhibiting benzylic C–H insertion relative to the 'control' insertion at the secondary C–H. Conversely, the metal carbenes associated with electron rich ligands form a late transition state in which the partial positive charge at the benzylic carbon is more developed and thus more susceptible to the electronic influence of the *para*-substituent.

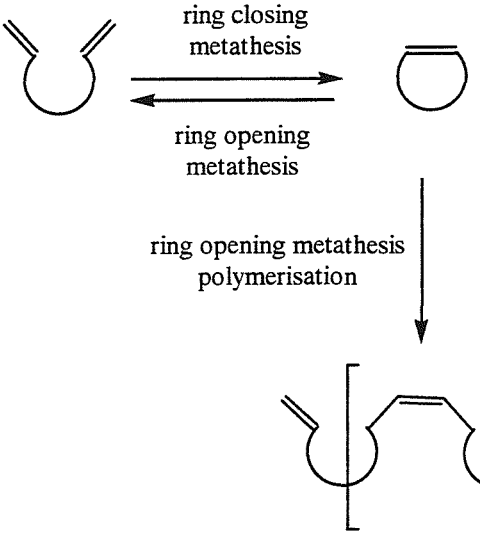
2.1.6 Concluding Comments

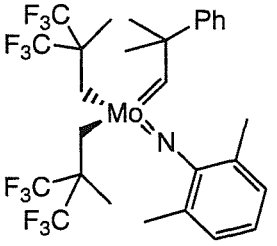
The development of a rationale to partially predict the specificity of rhodium carbenoid mediated reactions has benefited the synthetic chemistry community at large. This is particularly true in the area of chiral catalysts [50] which has not formed an extensive part of the discussion in this section but whose utility stems from the results contained herein. What is equally attractive is the ability to manipulate the outcome of the reaction (at least in some cases) to fit the needs of a given synthesis. Even given these developments the chemistry of rhodium carbenoids still has the capacity to surprise.

The work described in Chapter 4 depended on the chemoselective reaction of rhodium carbenoids in a system that could have reacted through up to 4 different pathways. Having identified conditions to provide only one regioisomer we hoped to exploit the possibility of changing the electronic and steric demand at rhodium to provide diastereoselection and ultimately to use the chemistry to produce an enantioselective C–H insertion. As commented on above not all aspects of our results were easy to explain!

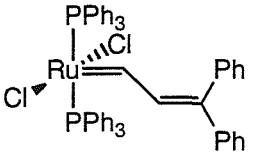
2.2 Ruthenium (II) Aikylidene Complexes as Metathesis Catalysts

The use of metal carbenes as catalysts in metathesis reactions has a slightly more recent history than that described for the metal carbene mediated C–H insertion reactions outlined in the previous section. Nonetheless, its development has accelerated faster because of the greater generality of its application in synthesis.





(2.42) The Schrock prototype



(2.43) The Grubbs prototype

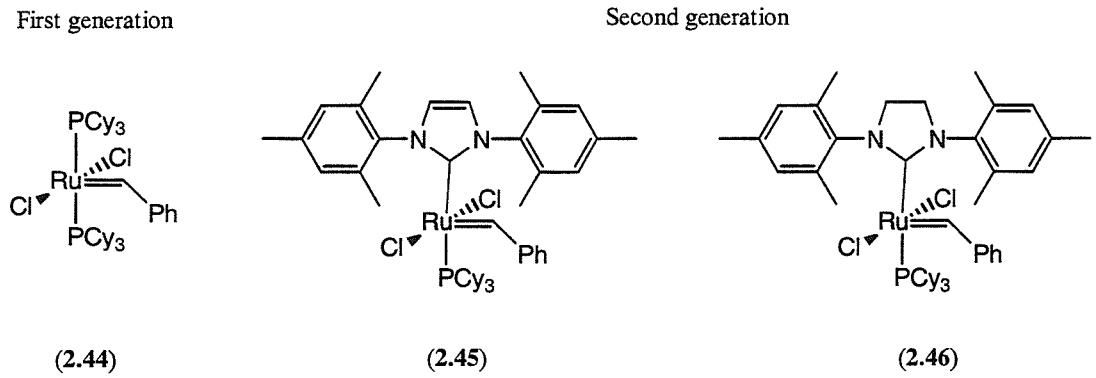
Figure 2.16 Metathesis and metathesis catalysts

Of the several forms of metathesis (Figure 2.16) it has been ring closing metathesis (RCM) that has generated the most interest amongst organic chemists. The two main protagonists in developing this methodology have been Richard Schrock and Robert Grubbs whose prototypical alkylidene catalysts were centered on molybdenum (**2.42**) [51] and ruthenium respectively (**2.43**) [52]. There have been many extensive reviews [4, 53, 54, 55, 56, 57] on this rich area of research and it would be inappropriate to attempt to include another in this thesis. Instead, the following sections will focus on the basics of the Grubbs ruthenium based methodology, its application to RCM and any recent developments pertinent to the application envisaged as a pivotal step during this project.

2.2.1 The Catalyst

The prototype catalyst that involved triphenylphosphine ligands was of only limited utility in metathesis in terms of its reactivity. On exchange to tricyclohexyl phosphines there was a marked increase in reactivity to the extent that acyclic dienes could be induced to undergo RCM. This increase in activity was complimented by the stability of the original catalysts that are uneffected by air and/ or protic solvents, a quality that set them apart from the highly unstable, but extremely reactive, Schrock molybdenum metal alkylidenes.

These first generation catalysts (**2.44**) (Figure 2.17) were subjected to extensive structure activity relationship studies to identify the best combination of phosphine ligand and halogen [58]. In fact, phosphines with larger cone angles benefited activity and the already noted beneficial change of phenyl to cyclohexyl reflected the fact that electron withdrawal disfavoured reaction. The exact converse was noted for halogens. The smaller and more electron withdrawing the halogen the more reactive the catalyst.



(**2.44**) (**2.45**) (**2.46**)

Figure 2.17 First and second generation Grubbs catalysts

More recently a second generation of catalysts [59] have been developed which continues to develop the trends mentioned above. Thus, 1,3-diaryl-4,5-dihydroimidazol-2-ylidene

carbenes were used to replace one of the phosphine ligands (**2.45**). These ligands, which are formal carbenes, are more basic than phosphines in a Lewis sense and are also sterically encumbered. Metatheses using this catalyst were found to be much faster and, more importantly, reactions to form tri- and tetrasubstituted alkenes routinely were feasible with the second generation catalyst [60]. Even more reactive catalysts have been forthcoming using the fully saturated imidazolylidene ligand (**2.46**) whose Lewis basicity was presumed to be enhanced through the absence of the stabilising influence of the π-system [61].

2.2.2 The Mechanism

The Chauvin mechanism [62] has depicted the metathesis process as a series of formal [2 + 2] cycloadditions of an alkene substrate with a metal alkylidene complex followed by cycloreversions to provide a chain carrying metal alkylidene and a new olefin. This mechanism has stood the test of time and extensive study has only been able to add some fine detail to the initial insight of Chauvin and co-workers.

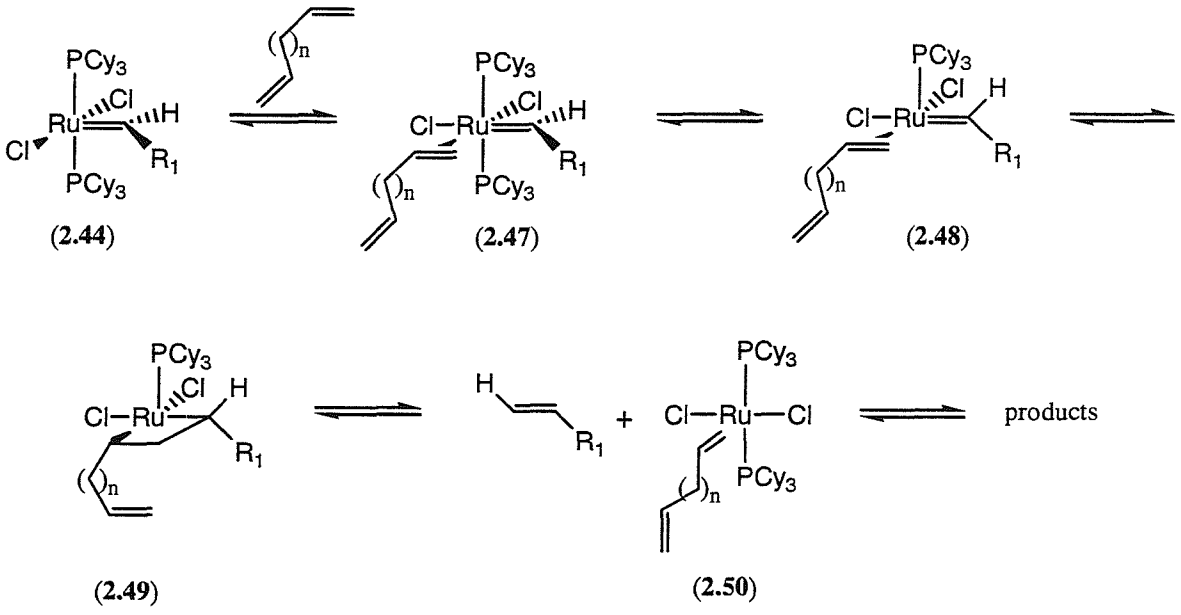


Figure 2.18 The Chauvin mechanism with Grubbs modifications

Grubbs' extensive studies [58] on the mechanism revealed that the reaction was inhibited by addition of phosphines to the reaction mixture. This implied that one of the ligands dissociated during the rate determining step which they correlated with the observation that a larger cone angle of the ligand gives higher reactivity (Figure 2.18).

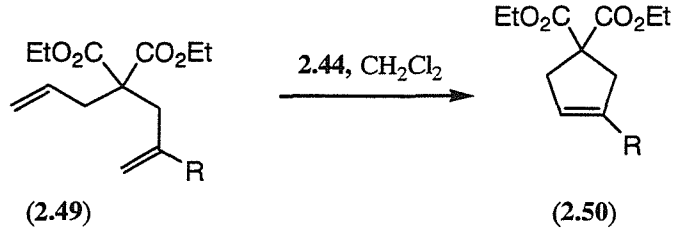
Studies of related metal carbonyl complexes in which the carbon monoxide was used to serve as a model for the carbene have shown that olefins co-ordinate at a site that is *cis*- to

the C≡O. This is presumed to be reflected in the carbene analogues such that alkene association occurs with concomitant migration of Cl to give **2.47**. The halogen co-ordinated *trans-* to the alkene has the capacity to operate a *trans-* destabilising effect on the alkene metal binding. This is minimised with chloride which is consistent with the observation that chloride counterion gives the most effective catalysts.

Phosphine ligand dissociation and a rotation of 90° of the carbene around the axis of the metal carbene bond provide **2.48** in the correct orientation for cycloaddition. The observation that larger phosphines appear to benefit reactivity might be due to the fact that on decomplexation there is a energetically favourable release of steric congestion. More convincing support for this dissociation is that maximising electron donation of the phosphine gives improved reactivity. This is because the *trans-* effect of the remaining ligand would stabilise the developing 16 electron complex (**2.48**) and the critical 14 electron metallocyclobutane (**2.49**).

The ultimate outcome of the reaction will depend on the relative energies of the alkenes that can be produced under thermodynamic conditions as well as being controlled by differentiating factors that might dictate the relative ease of the initial association of an alkene at the metal centre. In general terms RCM reactions are energetically favoured in that the entropy of the system increases on product formation given that ethylene is always a by-product. Also, the loss of ethylene from the reaction system under normal conditions tilts the equilibrium in the desired direction.

In another study on the first generation catalysts Grubbs [63] demonstrated their limitations associated with olefin formation (Figure 2.19). He found that RCM of a terminal olefin with a *gem*-disubstituted olefin could often be affected with maximum efficiency for 5- and 6-membered rings.



(2.49) (2.50)

R	Yield
Et	93%
^{t}Bu	0%
Ph	25%
CH_2OH	98%
CO_2Et	5%

Figure 2.19 The influence of olefin substitution on metathesis catalysed by first generation Grubbs catalyst (2.44)

The influence of the *gem*-substitution is also pronounced with reaction being inhibited by electron withdrawing groups as well sterically challenging ones. It is noteworthy that at

the time of the study the Schrock family of catalysts would affect the cyclisation to sterically demanding alkenes but the Grubbs catalyst was the only one tolerant of free hydroxyl functionality in the substrate.

Analysis of the efficacy of formation of different ring sizes clearly demonstrated that formation of medium rings was not straightforward in the absence of some conformational constraint in the diene. More detail on this subject is described in Section 5.6. Ultimately the initial difficulties in forming medium rings have been overcome with several notable natural products having being prepared using RCM [64].

2.2.3 Metathesis of Enol Ethers

Metathesis to produce cyclic enol ethers from acyclic precursors is a specialist area that has received rather less attention than mainstream cycloalkene formation. Early examples were completed using the active Schrock catalysts but were rarely possible with the first generation Grubbs pre-catalysts.

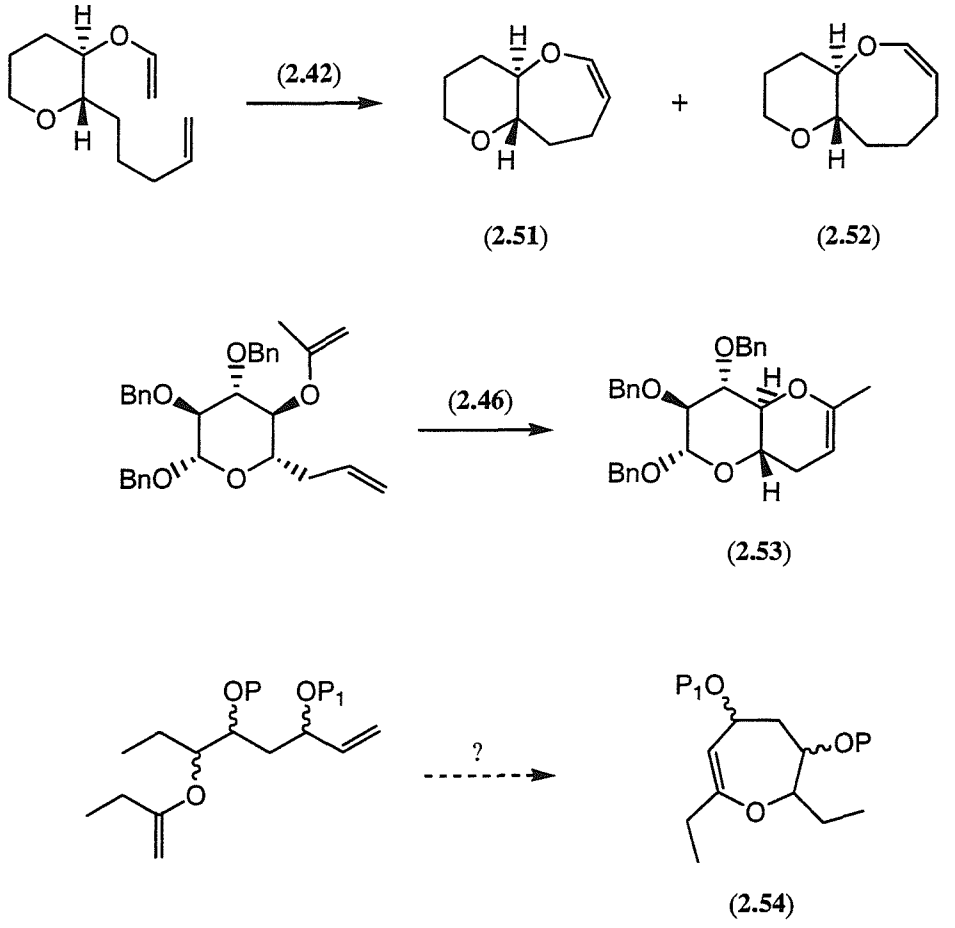


Figure 2.20 Metathesis involving enol ethers

For example, the preparation of medium ring enol ethers (**2.51** and **2.52**) (Figure 2.20) was successful but not always chemoselective. An example of this has been described by Clark

and co-workers [65] wherein **2.51** was produced by isomerisation of the terminal alkene prior to metathesis. Another noteworthy example was the one pot olefination of an ester with Tebbe reagent followed by metathesis brought about by the same reagent in a stoichiometric conversion at elevated temperature [66].

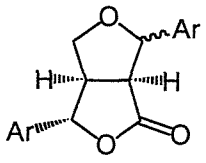
More recently the imidazolylidene ruthenium complexes have been shown to be effective in the transformation in a number of systems although for the most part the target compounds were all 6-membered ring enol ethers, for example **2.53** [67].

The transformation required in our projected synthesis required the preparation of a 7-membered ring enol ether of the general formula **2.54**. Whilst precedented by the prior art this transformation represents a significant challenge. The limited knowledge in this area is such that no rational judgement can be made concerning the likely impact of the functional groups on the ring closure. An obvious problem with the approach is the potential acid instability of both starting and product enol ethers. Additionally, the necessity of hydroxyl functionality will demand careful protecting group selection in the event of resorting to the Schrock methodology. The preference would be for using the second generation Grubbs catalysts although the very high catalyst loading is a general problem that needs to be addressed if this chemistry is to find general application in organic synthesis.

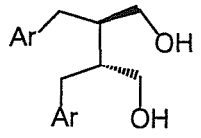
Chapter 3

Furofuran(one) Lignans: Biochemistry, Biological Significance and Chemistry

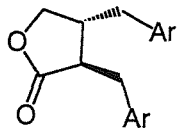
Lignin is a polymeric material found in all fibrous, woody plants throughout the world. It exists in the xylem of the cell walls and in the intracellular spaces with the effect of strengthening the plant's superstructure by binding cellulose fibres together. It is second only to cellulose as the most abundant source of organic matter. All plants that produce lignin also have the capacity to produce lignans (Figure 3.1), a family of compounds whose monomeric origin is shared with lignin.



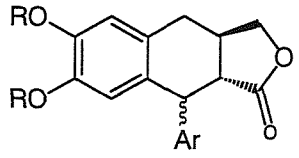
(**3.1**) 2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octane-8-one (furofuranone) *e.g.* styraxin



(**3.2**) Dibenzylbutanediol *e.g.* 3-demethylseco*iso*lariciresinol



(**3.3**) Dibenzylbutyrolactone *e.g.* guamarolin



(**3.4**) Tetrahydronapthalene *e.g.* podophyllin lignans

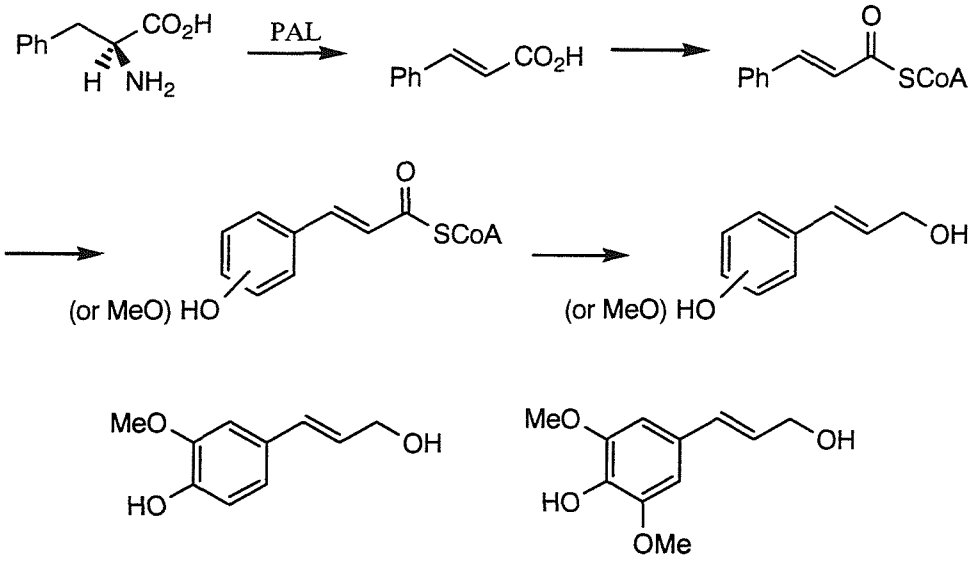
In the generalised structures above Ar represents the variously oxygenated aromatic rings found in lignans and R represents either H- or Me-.

Figure 3.1 Representative structures of lignan natural products

The ready availability of lignans in nature, given their co-production with lignin, has led to a large number of structural types being isolated from various plant families [68, 69, 70] (for example **3.1-3.4**). For instance, the genus *Piperum* alone has been shown to produce around 600 lignan natural products [71]. The relatively recent ability to isolate, identify and biologically evaluate these derivatives has led to a retrospective recognition that lignans often account for the efficacy of traditional medicines. These biological activities, along with their diversity of structure and ready availability from nature, have made them of significant interest to the scientific community.

3.1 Biosynthesis

The evaluation of the biosynthetic pathway followed during the preparation of lignans has always been confused given the commonality with the early stages of lignin biosynthesis. Both derivatives involve the dimerisation of cinnamates that derive, for the most part, from phenylalanine or tyrosine. Stereospecific conversion of L-phenylalanine into an E-cinnamic derivative is accomplished by a phenyl ammonia lyase (PAL) (Figure 3.2). The precise structure and activity of PAL varies between species but they all contain a post translationally produced dehydroalanine residue at the active site. There is some speculation over the existence of the corresponding tyrosine ammonia lyase (TAL). Most research has demonstrated that PAL will utilise both amino acids as a feedstock, but is less efficient with tyrosine. Only in a limited number of cases has a separate TAL activity been identified.



(**3.5**) Coniferyl alcohol (**3.6**) Sinapyl alcohol

Figure 3.2 Biogenesis of cinnamyl alcohol monomers

Oxidases functionalise the aromatic ring with, or without, subsequent specific methylation of the phenolic -OH(s). The coenzyme A esters of the cinnamates are reduced ultimately to the alcohols with $NADP^+$ dependant dehydrogenases [72]. In the case of lignin the two most common cinnamyl alcohol intermediates are coniferyl (**3.5**) and sinapyl (**3.6**) alcohols. At this point lignin biosynthesis proceeds by copolymerisation of the alcohol monomers mediated by cell wall bound peroxidase enzymes. The linkages formed within the polymer are consistent with formation of radicals at all the centres depicted in Figure 3.3. Lignins are believed to be produced in racemic form although there is a body of

opinion that suggests that lignins *are* produced stereospecifically in the first instance. Once polymerised any stereo-integrity is internally compensated and subsequently destroyed during investigative decomposition.

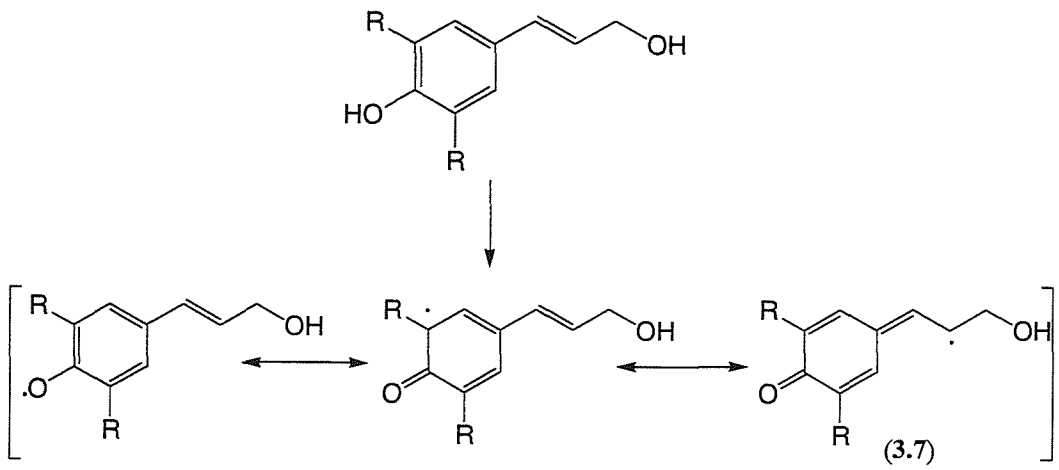


Figure 3.3 Reactive radicals in cinnamate polymerisation

In furofuran(one) (**3.1**) biosynthesis the monomer units suffer a different fate through a related pathway. Radical formation is again initiated by peroxidase enzymes but the first radical dimerisation in lignan formation is regiospecific. The radical **3.7** dimerises to form an intermediate that is further differentiated from its lignin equivalent by virtue of being enantiopure.

These observations were not noted in early studies because the whole cell assays used were complicated by the presence of multiple oxidase enzymes whose collective action often resulted in racemic lignan formation when evaluated *in vitro*. One of the first stereoselective couplings was identified in the dimerisation of coniferyl alcohol to (+)-pinoresinol (**3.8**) [73]. The (+)-antipode was favoured by 2:1 and the process was identified as being mediated by two enzymes, only one of which was acting stereospecifically. Shortly after the action of what was thought to be the stereospecific enzyme was demonstrated by the same workers. They converted coniferyl alcohol into (+)-pinoresinol with a >97 e.e. using a partially purified enzyme preparation from *Forsythia intermedia* [74]. Subsequently, it was identified that the oxidase enzyme has no capacity for stereoselective coupling, its only activity being to form the radical. This would be in accord with the same oxidase initiating both lignan and lignin synthesis. Indeed the former has been detected during *in vitro* lignification studies [75].

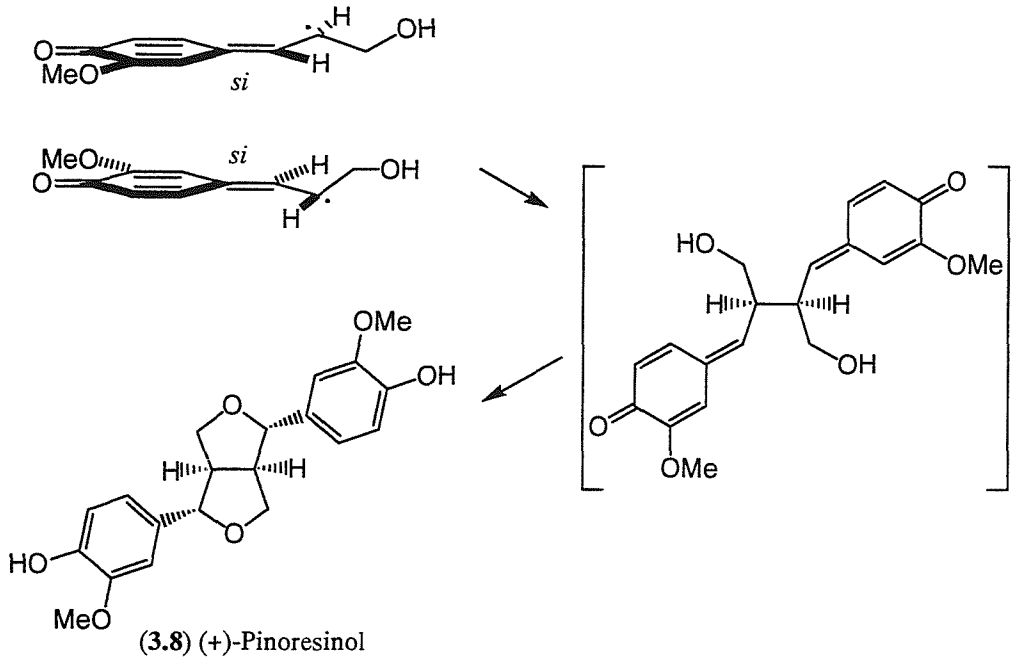


Figure 3.4 Stereospecificity in cinnamyl dimerisation

The auxiliary protein responsible for the enantioselection is proposed to operate by specific recognition of the radicals **3.7**. These are produced in the active site whereupon dimerisation occurs in a *si, si* orientation only. Internal trapping of the quinone methides from the least hindered face provides the final compound furofuran, in the case illustrated pinoresinol (**3.8**) [76].

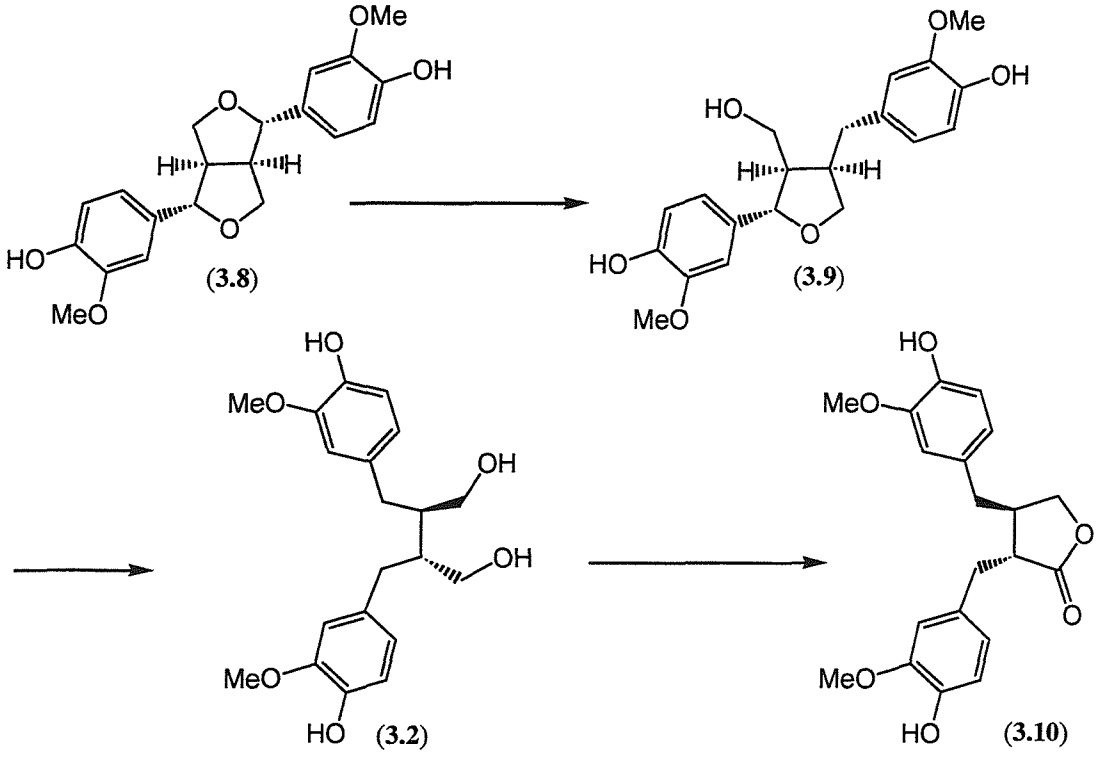


Figure 3.5 Furofurans as biosynthetic intermediates I

The importance of this result is not restricted to the furofuran subclass of lignans. (+)-Pinoresinol is the feedstock for a number of further biosynthetic steps that access other classes of lignans (Figure 3.5). Thus, stereoselective NADPH dependant reductases [77] convert the furofuran into dibenzylbutyrolactones (**3.9**) (*e.g.* lariciresinol) that may be further reduced to the dibenzylbutanediols (**3.2**) (*e.g. seco*lariciresinol). A series of stereospecific oxidations then provides access to podophyllins *via* lactone (**3.10**, matiaresinol) the detail of which is beyond the scope of this document.

(+)-Pinoresinol has also been shown to be an intermediate in the synthesis of other furofurans. *O*-methylation of the phenolic hydroxyl group has been demonstrated as the path to (+)- eudesmin (**3.11**) (Figure 3.6).

It is of note that the post dimerisation methylation process is tolerant of hydroxyl groups *para-* to the point of attachment of the carbon framework. This is in contrast to the selectivity of the methylations on the monomer cinnamyl alcohol derivatives in which selectivity at the *meta-* hydroxyl groups is observed.

Pinoresinol is also converted into sesamolin (**3.12**) by a number of oxidative steps in which the mechanisms are not fully understood (Figure 3.6) [78].

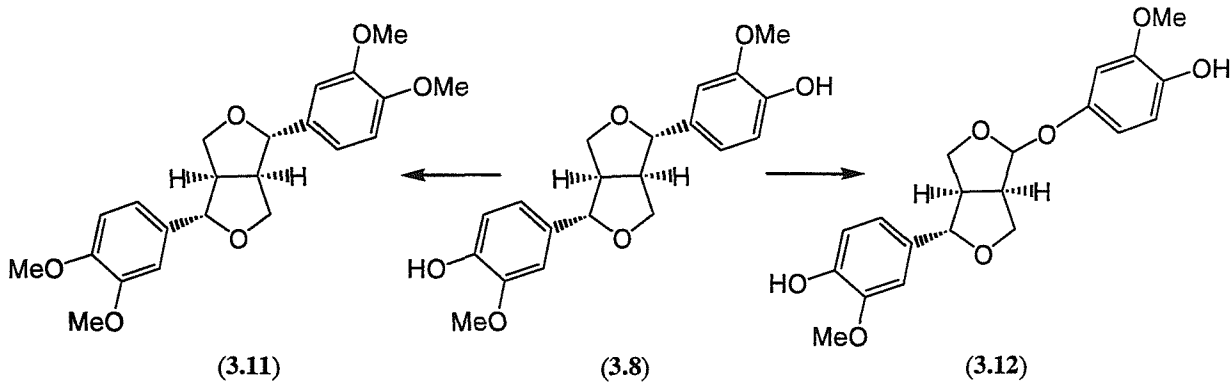


Figure 3.6 Furofurans as biosynthetic intermediates II

The discussion above has focussed on pinoresinol as the initial product of dimerisation of 3-methoxy-4-hydroxycinnamyl alcohol and its subsequent biochemical conversion into other furofurans. Furofurans are also commonly derived from dimerisation of 4-hydroxy-, 2,4-methylenedioxy-, 4-hydroxy-3,5-dimethoxycinnamyl alcohols. Subsequent oxidation, reduction and methylation steps provide access to the hugely diverse pool of lignan natural products.

3.2 Biological Activity of Lignan Natural Products

For centuries traditional medicine depended on an experimental, but pragmatic, approach to effecting a cure to disease. Many plants were identified as having curative properties against a range of diseases but it is only recently that science has advanced enough to identify the active ingredients. In many instances the efficacious effect of tried and tested herbal cures has been attributed to the effect of lignans. Some historical examples are Siberian Ginseng (a general tonic), Cortex Eucommiae (an antihypertensive used in China) and Cortex Fraxini (an anti-inflammatory used in Japan) [79].

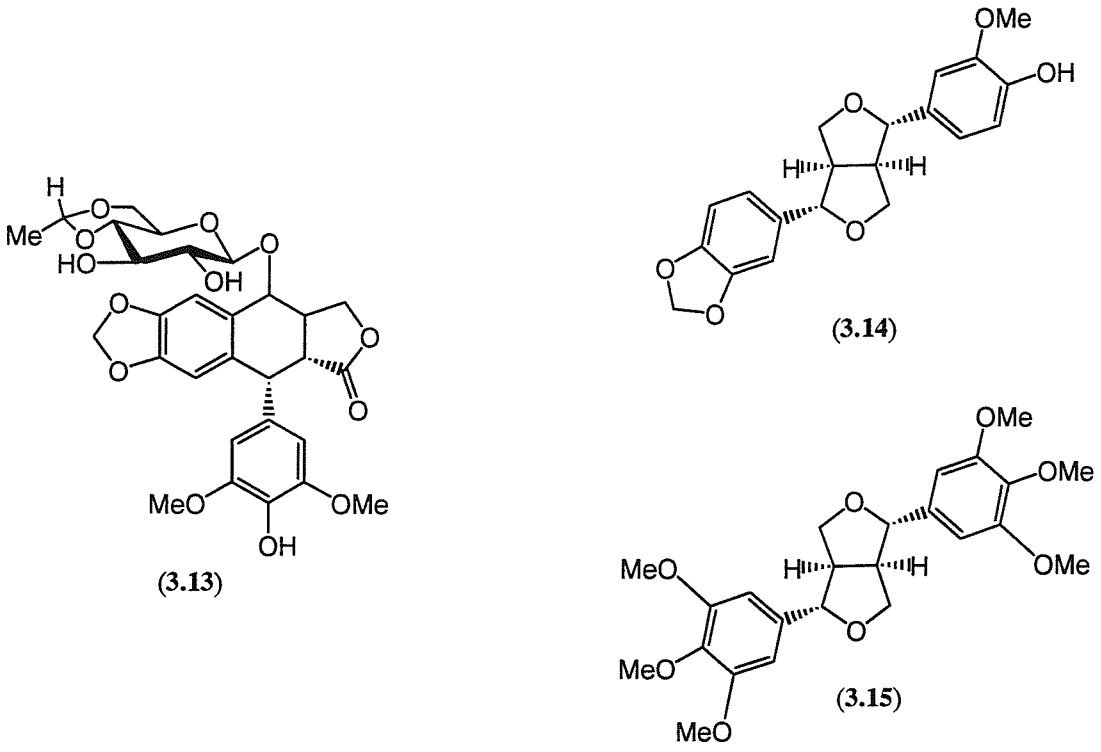


Figure 3.7 Biologically active lignans

Recognition of the significance of lignans in traditional medicines has led to a continuing study of their activities and mode of action. To date the most significant discovery has been the identification of etoposide (**3.13**) (Figure 3.7), an anti-cancer agent used in the clinic. Up to now no furofuran(one) derivative has reached the market as a medicinal agent. Nonetheless, there are many examples of significant activities in these compounds: styraxin (**3.14**) (anti-cancer) [80], yangambin (**3.15**) (antiplatelet aggregation agent) [81], pinoresinol (**3.8**) (phosphodiesterase inhibitory activity) [82].

Recently the benefits of a lignan rich diet in terms of protection against cancer have been described [69]. A number of studies have shown a correlation between a reduction in cancer

incidence with an increase in dietary uptake of lignans. Nonetheless the results are not conclusive as yet.

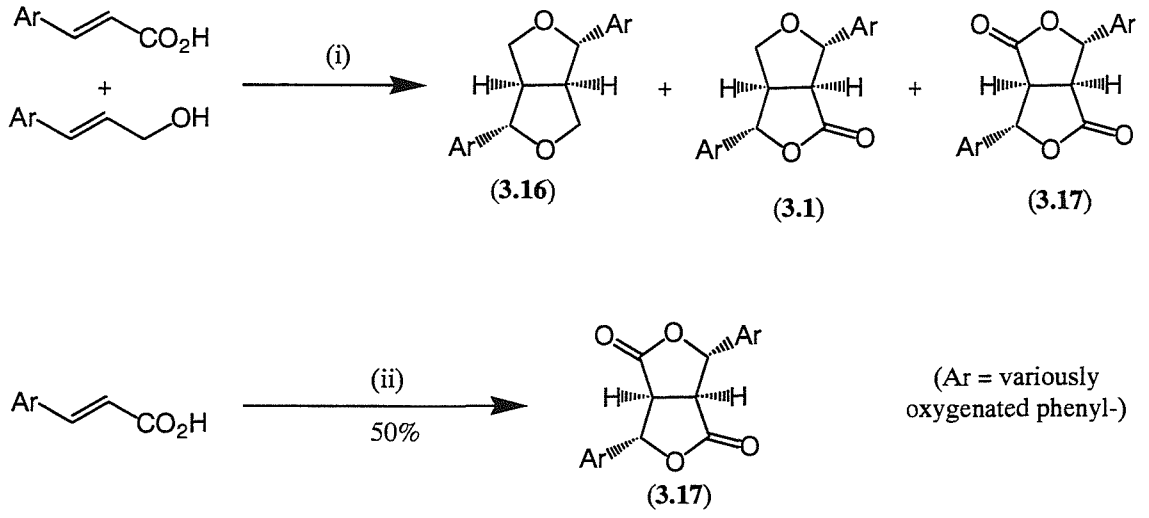
The interesting properties of lignan derivatives make them justifiable targets for synthesis. Although, in the case of furofurans, no highly potent agent has been isolated from nature there is ample justification to believe that structural modification around the bicyclic core could lead to compounds with significantly improved activities. This possibility requires that syntheses be developed that will be conducive to incorporation of diverse functionality so as to truly evaluate the potential of these derivatives.

3.3 Chemistry

The merit of any new synthetic strategy towards furofuranones can only be accurately gauged by comparison with existing methodologies for their preparation. The following section provides details of this prior art, in terms of furofuranones and the closely related furofurans (**3.16**) and *bis*lactone lignans (**3.17**). Detail on syntheses of these latter classes of compound is justified given the close structural relationship between the compounds. Indeed both furofuranones and *bis*lactone lignans have been converted into the naturally most abundant furofurans (*vide supra*).

3.3.1 Synthetic Approaches Involving Oxidation

The first literature method described towards the synthesis of this class of compounds involved an attempt to synthetically mimic the oxidative dimerisation of cinnamyl derivatives that is the biochemical genesis of the lignan natural products. Early efforts using iron(III) chloride as the oxidant in neutral media [83, 84, 85] or silver oxide [75] gave access to a mixture of furofuran (**3.16**), furonfuranone (**3.1**) and *bis*lactone lignans (**3.17**) (Scheme 3.1).

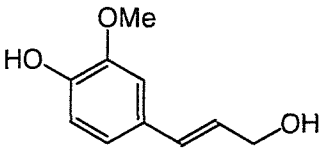


Scheme 3.1

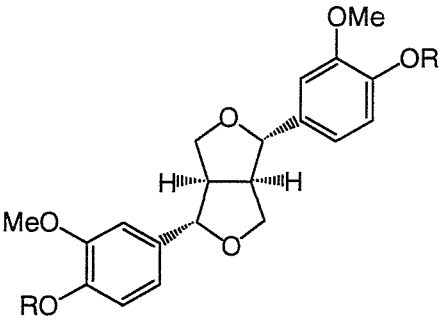
Reagents and conditions: (i) $FeCl_3$, acetone (ii) for example, $Th(O_2CCF_3)_2$, CH_2Cl_2.

Later investigations, deliberately targeted at the *bis*lactones [86] involved using thallium(III) or cobalt(III) salts in the dimerisation of cinnamic acids. The target compounds were isolated in, at best, moderate yields with only the *cis*- ring fused *exo, exo*- isomers being observed (Scheme 3.1). An alternative to the original radical cation coupling mechanism [87] was proposed by the authors on the basis of the product profile that they observed when using thallium(III) trifluoroacetate as the oxidant.

Oxidative strategies using isolated enzymes in cell free systems have been used to prepare racemic furofurans. For instance, Chioccarra *et al.* [88] and Miyachi *et al.* [89] used horse radish peroxidase/ hydrogen peroxide to prepare racemic pinoresinol from coniferyl alcohol (**3.5**). Separation of the enantiomers by chiral HPLC provided the enantiomers in low yield. Under basic conditions these were methylated to provide eudesmin derivatives, also in low yield (Figure 3.8).



(**3.5**)



(**3.8**) R = H Pinoresinol

(**3.11**) R = Me Eudesmin

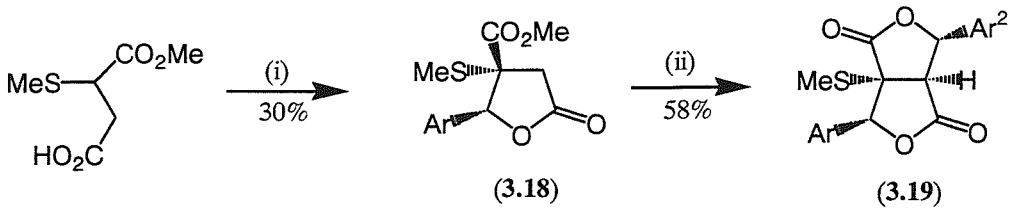
Figure 3.8 Biochemical dimerisation of cinnamyl alcohols

A primary drawback of the oxidative dimerisation is that, even if the yields could be improved, the strategy would be limited to the synthesis of furofurans with symmetrical substituted aromatic rings. The alternative of oxidative cross coupling between differing cinnamic alcohols/ acids has been investigated and some synthetically interesting selectivities were observed. However, there have been no reports that suggest the method would be useful in the formation of bicyclic ethers [90, 91].

3.3.2 Synthetic Approaches using Monolactone Enolates

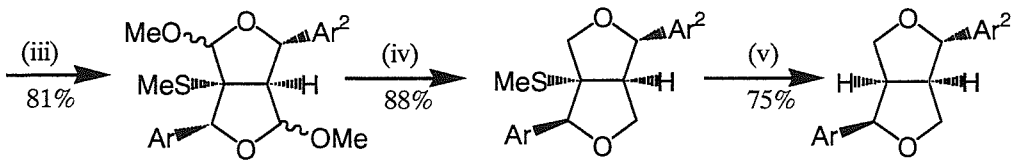
Pelter *et al.* [92] described an improved route in which they used aldol chemistry to prepare lactones (**3.18**) from 2-thiomethyl substituted succinnic half esters and an appropriate aromatic aldehyde (Scheme 3.2). The reactions favoured production of the diastereomer in which the oxygenated aromatic ring was *cis*- to the methylthio- functionality (2:1) but separation of the isomers was 'easy' by chromatography.

The methylthio- group served two purposes. It ensured that deprotonation prior to a second condensation occurred at the 3-position and then that the electrophile was introduced with *trans*- relative stereochemistry. Spontaneous cyclisation provided *bis*lactone (**3.19**) in moderate yield.



(3.18) (3.19)

Other isomer also isolated (ca 15%)



(3.20) (3.21) (3.22)

Scheme 3.2

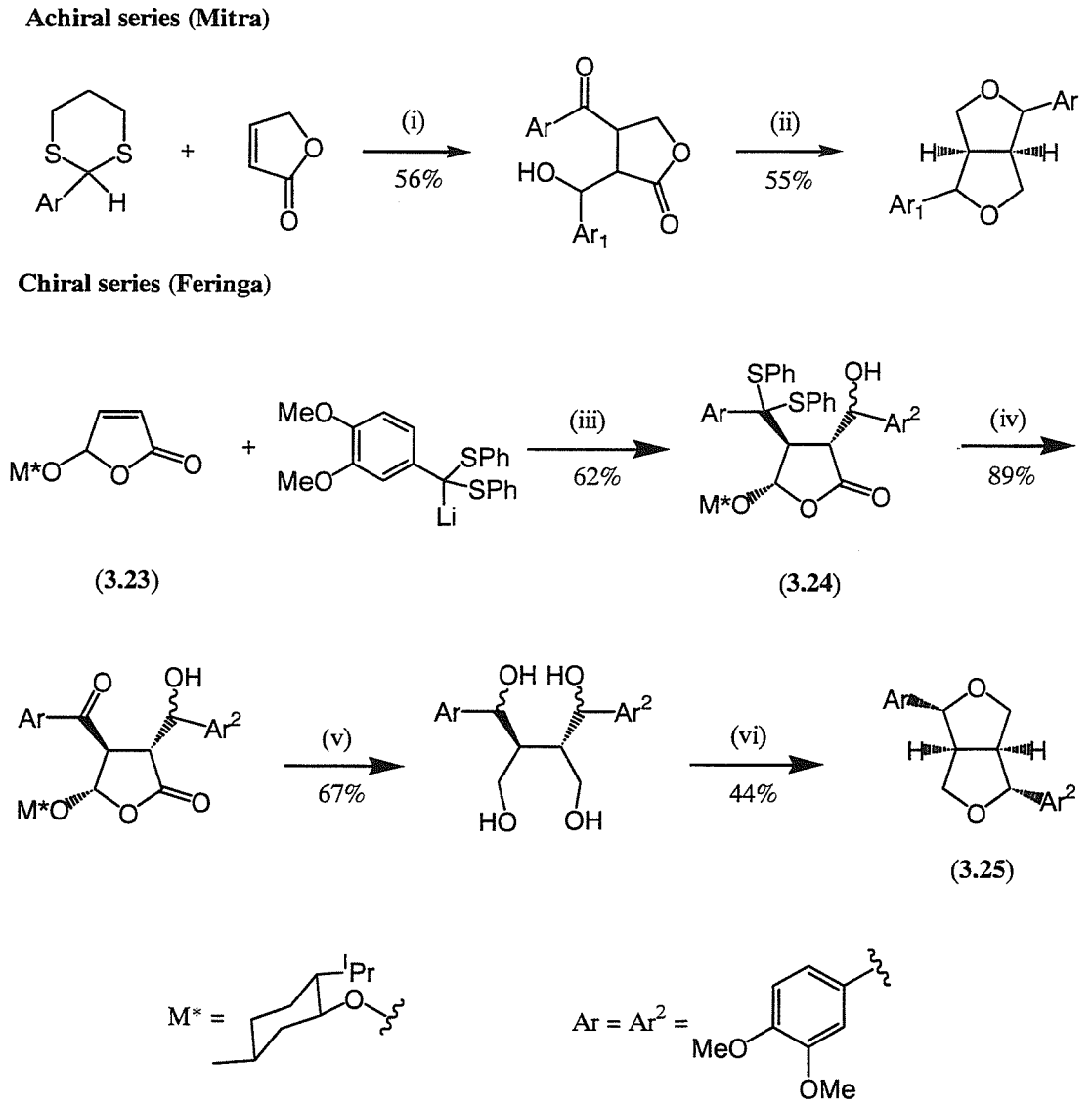
Reagents and conditions: (i) LDA, THF then piperonal (Ar = 3,4-methylenedioxyphenyl-) (ii) LDA, THF then veratraldehyde (Ar^2 = 3,4-dimethoxyphenyl-) (iii) (a) DIBAL, THF (b) MeOH, HCl (iv) Et_3SiH, $BF_3.Et_2O$ (v) Raney nickel, EtOH.

Desulfurisation could not be effected on this compound. Instead it was converted to the *bis*acetal derivative (**3.20**). The acidic conditions favoured formation of the all *exo*-adduct. Raney nickel proved successful at this stage but reduction of a hemiacetal functionality led to a mixture of isomers (not illustrated). Interestingly, the alternative procedure of reducing the hemiacetals first provided a single isomer (**3.21**) which on desulfurisation provided methyl pluviatilol (**3.22**). Thus, the presence of the methylthio-group favours ultimately placed the α-aromatic ring in a *trans*- disposition relative to itself.

Mitra *et al.* [93] were the first to propose the use of conjugate addition to butenolides as the critical step in forming the appropriately substituted intermediates in furofuran synthesis (Scheme 3.3). In general terms their strategy involved conjugate addition of a sulfur stabilised anion to an unsubstituted butenolide. The resulting anion was quenched with an aromatic aldehyde to produce a hydroxymethyl substituted lactone. Exhaustive reduction, which they achieved with sodium borohydride, followed by acid catalysed ring closure provided the target compounds in the racemic series.

This was developed by Feringa *et al.* [94, 95] who adapted the same chemistry to chiral butenolides (**3.23**) either enantiomer of which was readily available. Michael addition using a sulfur stabilised anion provided an ester enolate that was quenched *in situ* with an aromatic aldehyde to provide an all *trans*-lactone (**3.24**). The process exerted stereocontrol

over all carbon centres except for the one bearing the hydroxyl functionality (Scheme 3.3). Both diastereoisomers were converted into (-)-eudesmin (**3.25**) by a desulfurisation, exhaustive reduction and ring closing sequence. Equilibration at the epimeric centres occurs under the thermodynamic conditions of the final step.

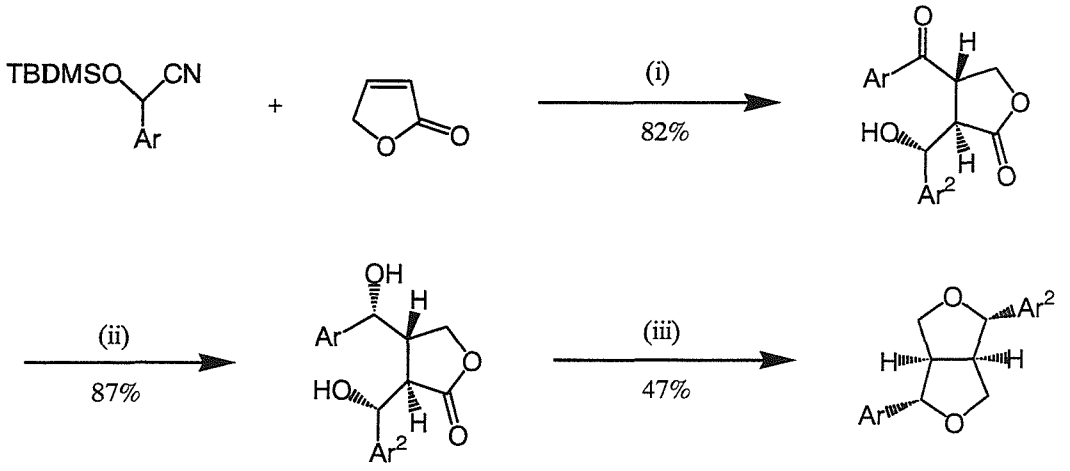


Scheme 3.3

Reagents and conditions (i) (a) *n*BuLi, THF then Ar_1CHO (b) HgO, $BF_3.Et_2O$ (ii) (a) $NaBH_4$, MeOH (b) H_2SO_4, H_2O (iii) THF followed by 3,4-dimethoxybenzaldehyde (iv) HgO, $BF_3.Et_2O$, THF, H_2O (v) $LiAlH_4$, THF (vi) $BF_3.Et_2O$, THF.

This chemistry has subsequently been exploited by Ohmizu *et al.* [96] who demonstrated that a similar tandem addition/ condensation strategy can also be effected using a anion stabilised by an α-siloxy protected cyanohydrin (Scheme 3.4). They were able to obtain

stereoselection to give the *syn*-aldol at the carbinol centre (not achieved in the route outlined by Feringa) by conducting the reaction in the presence of zinc bromide.



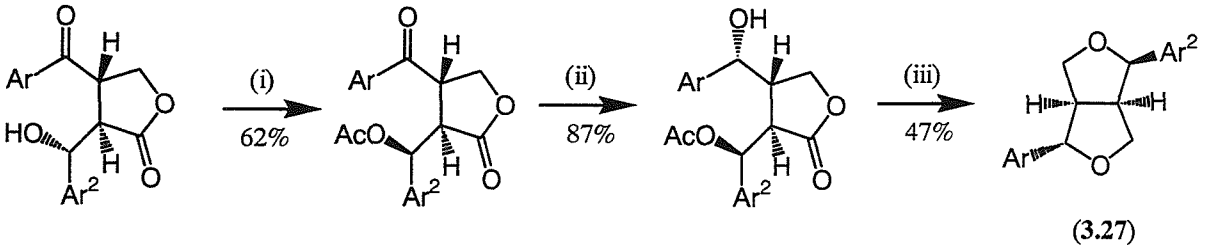
(3.26) **(3.27)**

Ar = 3,4-methylenedioxyphenyl-, Ar^2 = 3,4-dimethoxyphenyl-

Scheme 3.4

Reagents and conditions: (i) LDA, THF followed by 3,4-dimethoxybenzaldehyde, $ZnBr_2$ (ii) L-selectride, THF, -78°C (iii) (a) $LiAlH_4$, THF (b) MsCl, pyridine.

After revealing the ketone functionality, selective reduction with L-selectride gave the product arising from hydride delivery from the least hindered face to give diol (**3.26**). Reduction, followed by mesyl chloride activation and spontaneous cyclisation gave methyl piperitol (**3.27**).



(3.27)

Ar = 3,4-methylenedioxyphenyl-, Ar^2 = 3,4-dimethoxyphenyl-

Scheme 3.5

Reagents and conditions: (i) CH_2Cl_2, AcOH, TFA (1:10:1) (ii) L-selectride, THF, -78°C (iii) (a) $LiAlH_4$, THF (b) MsCl, pyridine

Attempts to isolate the *anti*-aldol product selectively failed but ultimately inversion of the *syn*-alcohol (**3.26**) was effected by treating with TFA in acetic acid which provided the acetate with inversion with reasonable selectivity (7:1) (Scheme 3.5). Subsequent

reduction, activation and cyclisation provided fargesin (**3.27**), and example of an *exo, endo*- furofuran.

Ohmizu subsequently developed the strategy into a stereospecific route by accomplishing the conjugate addition/ aldol reaction on an enantiomerically pure Michael acceptor derived from chiral glyceraldehydes [97, 98] (Figure 3.9).

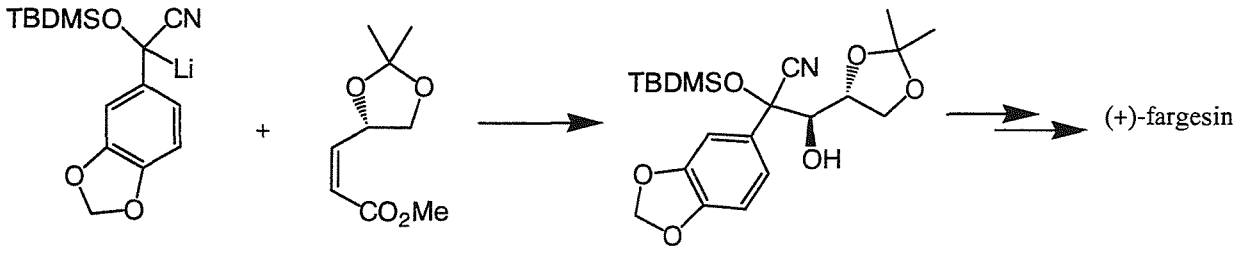
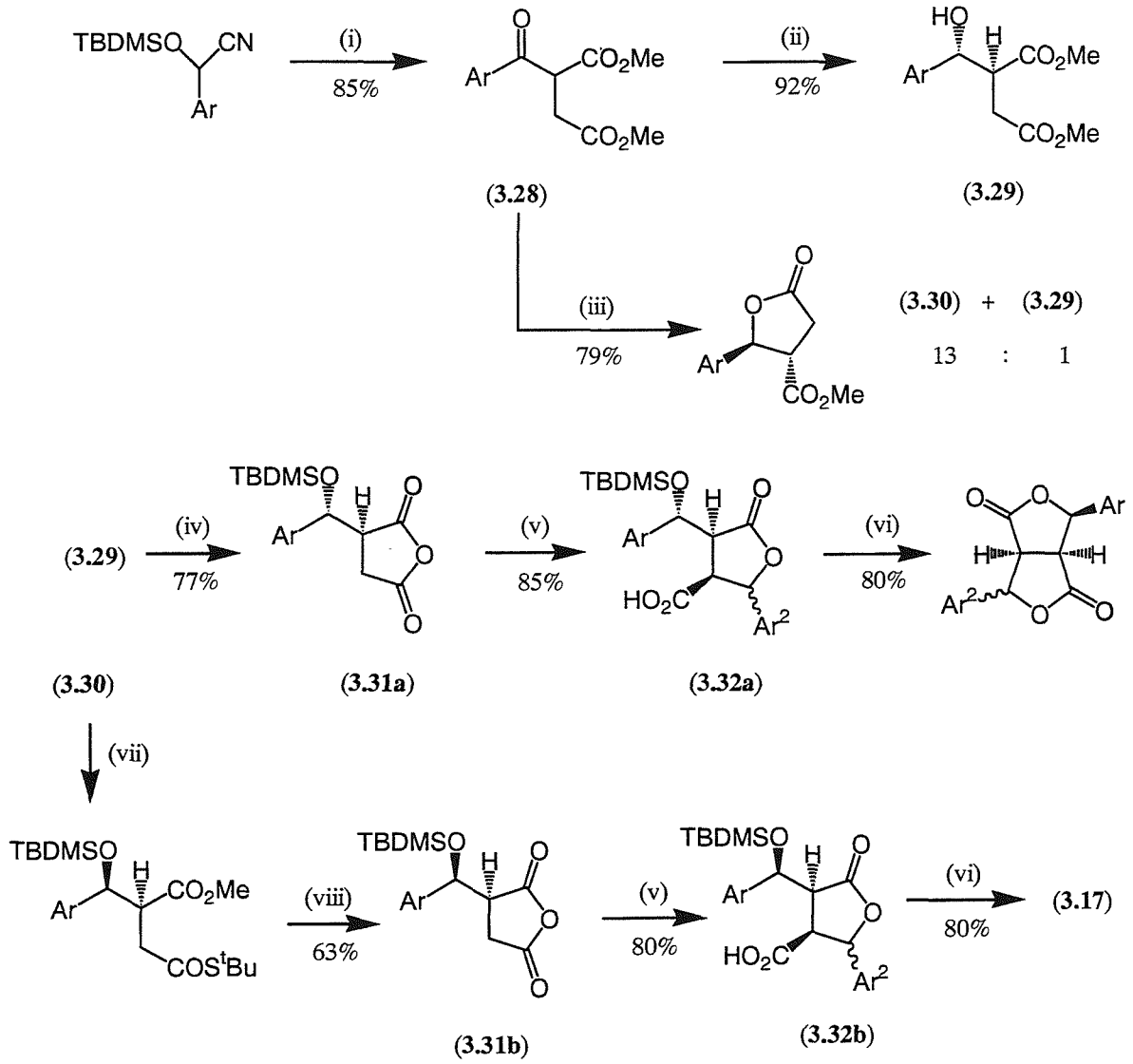


Figure 3.9 Siloxycyanohydrin stabilised anion addition to chiral maleates

The theme was continued in related work towards the synthesis of *bis*lactone lignans [99]. The strategy remained the same but in this instance dimethyl maleate was used as the Michael acceptor (Scheme 3.6).

Action of L-selectride on the ketone (**3.28**) provided alcohol (**3.29**) as a single diastereoisomer, the stereospecificity of the reaction being explained by the Felkin-Anh model.



Scheme 3. 6

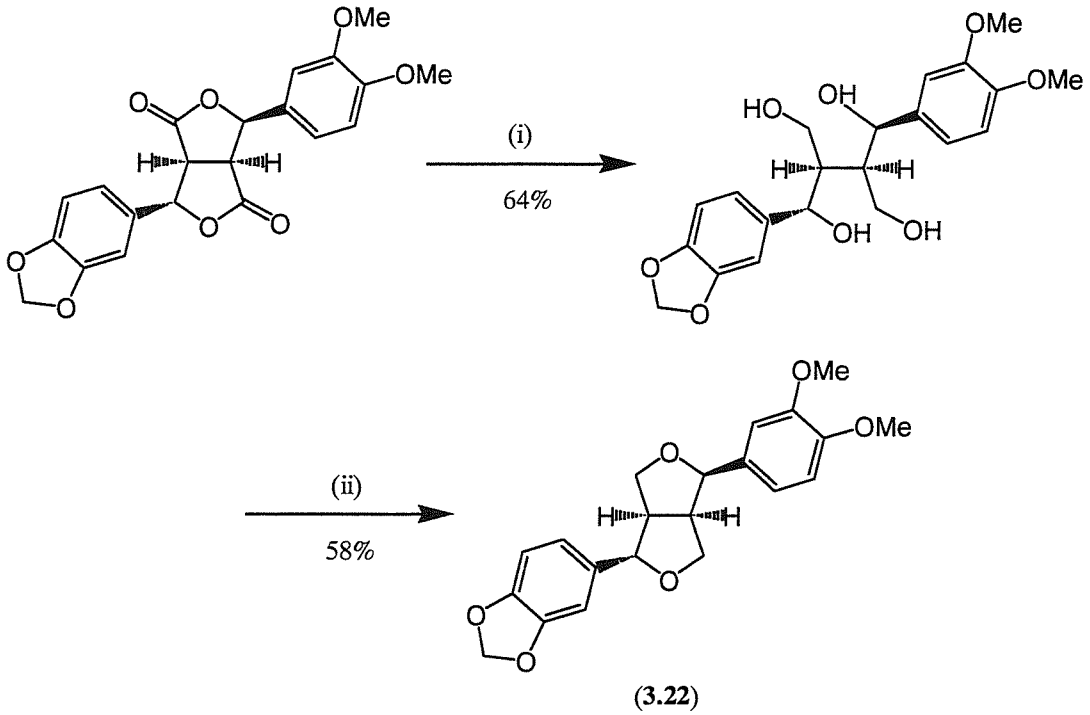
Reagents and conditions: (i) LDA, dimethylmaleate (ii) L-selectride, toluene (iii) $ZnBH_4$, ether
(iv) (a) TBDMS-Cl, imidazole, DMF (b) NaOH (c) Ac_2O (v) LiHMDS, toluene, 2,4-dimethoxybenzaldehyde
(vi) (a) *n*-Bu_4NF, AcOH (b) AcOH or 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide, DMF
(vii) (a) Me_2AlS*t*Bu (b) TBDMS-Cl, imidazole, DMF.

Chelation controlled reduction of (**3.28**) provided the epimeric alcohol that spontaneously lactonised to provide (**3.30**) although the process was rather less diastereoselective than for

the preparation of (**3.29**). Appropriate elaboration of these compounds provided the two stereoisomeric anhydrides (**3.31a** and **3.31b**).

Aldol reaction of these derivatives with the requisite aromatic aldehydes provided lactones (**3.32a** and **3.32b**) with a degree of stereoselectivity that was critically dependent on the solvent and countercation used in the reaction. Toluene and KHMDS provided the best results providing the diastereomer with the 4,5-*trans*- relationship as the major product in both cases (selectivity of greater than 9:1).

The minor diastereomers were separable by careful chromatography and each of the four compounds deprotected and cyclised to give the corresponding *bis*lactones. The utility of these compounds in the preparation of the more common furofurans was demonstrated by their conversion, through exhaustive reduction, primary alcohol mesylation and facile cyclisation, into the target compounds. The procedure is exemplified below in which the methodology was used to prepare methyl pluviatilol (**3.33**), an *exo, endo*- furofuran (Scheme 3.7)



(**3.22**)

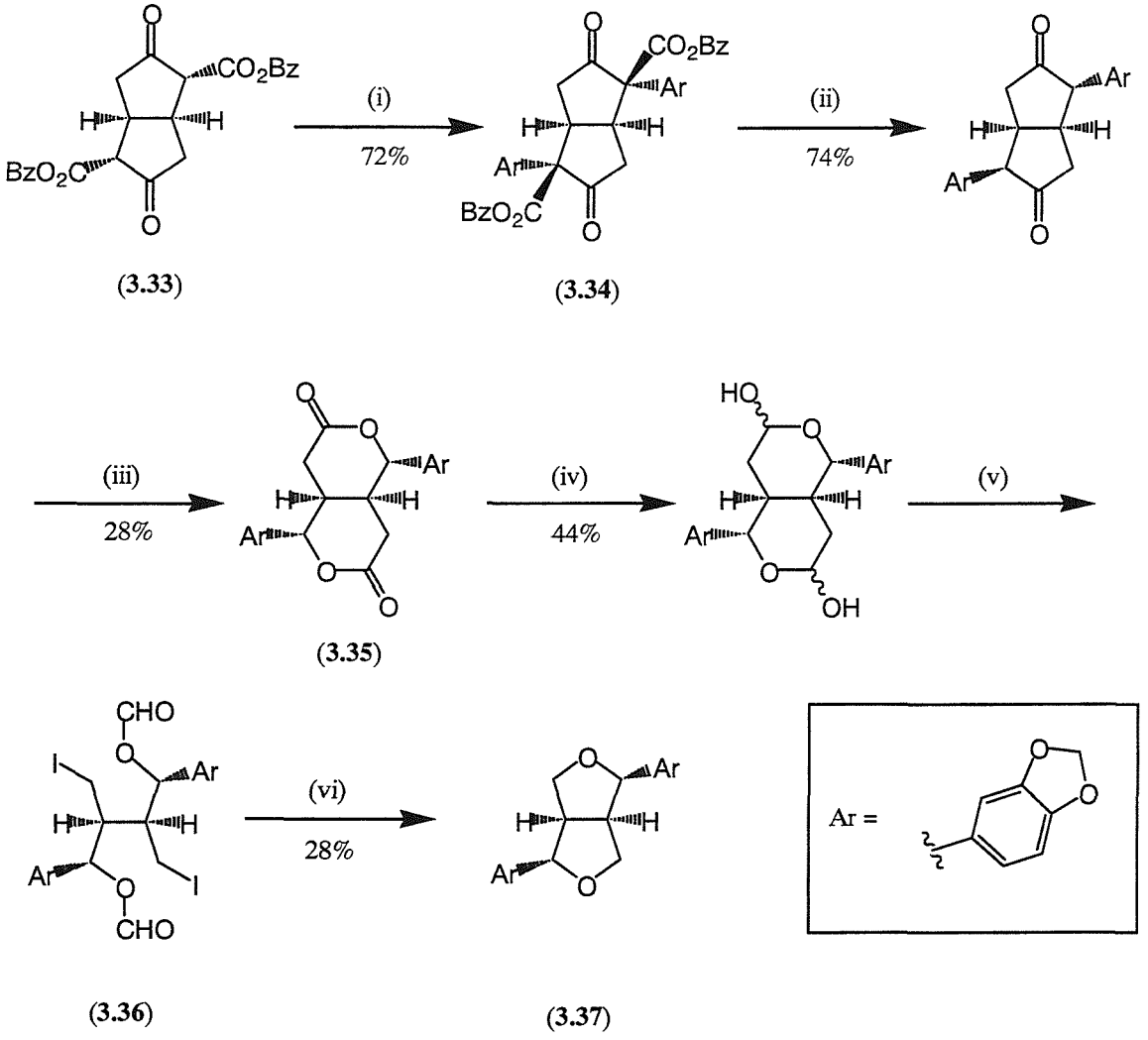
Scheme 3.7

Reagents and conditions: (i) $LiAlH_4$, THF (ii) MsCl, pyridine.

The extensive investigation into Michael additions of cyanohydrin anions to a variety of chiral or achiral acceptors have been reviewed by Ohmizu *et al.* [100]

3.3.3 Synthetic Approaches involving Rearrangements

One of the early syntheses of a furofuran involved an elaboration of a 3,7-dioxo-bicyclo[3.3.0]octane (**3.33**) (Scheme 3.8) [101]. Incorporation of the aromatic substituents was achieved by using their lead derivatives to provide (**3.34**). Hydrolysis and concomitant decarboxylation was followed by a slow and inefficient Baeyer Villiger rearrangement to give the *bis*lactone (**3.35**).



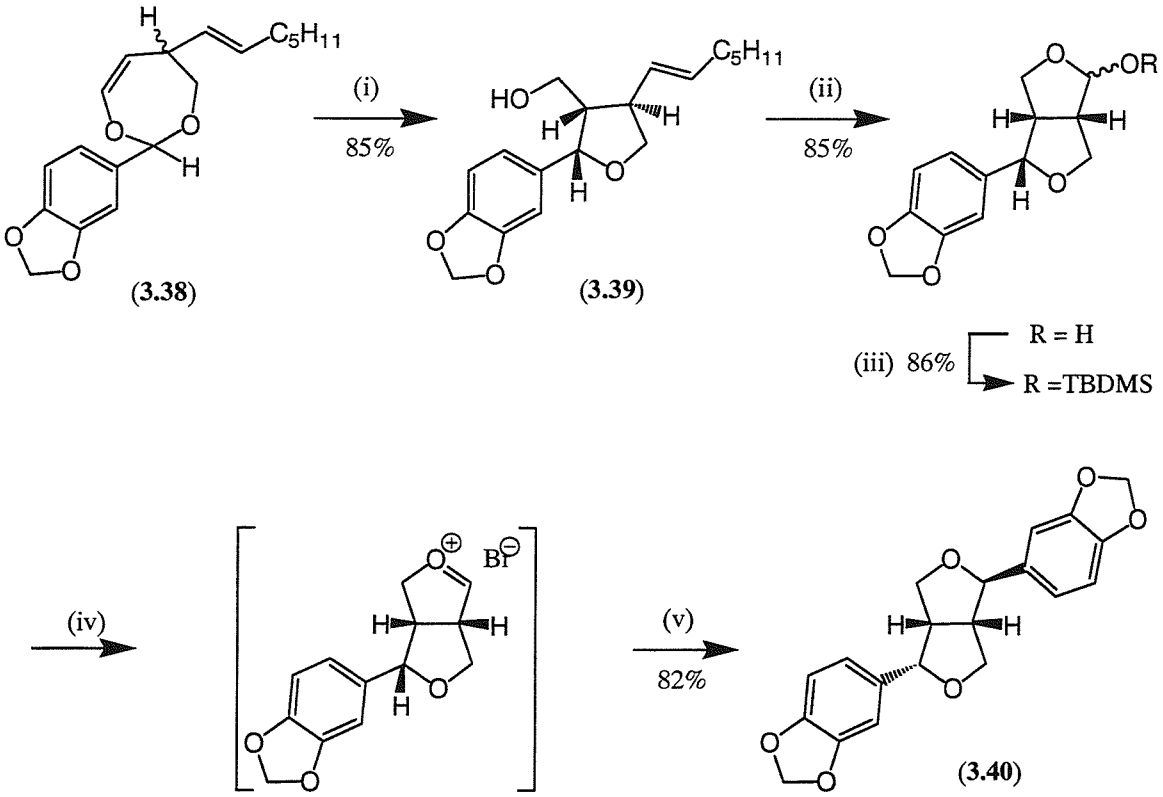
Scheme 3.8

Reagents and conditions: (i) $ArPb(OAc)_3$, pyridine, CH_2Cl_2, Δ (ii) 10% Pd/ C, MeOH (iii) *m*-CPBA, CH_2Cl_2 (iv) DIBAL, CH_2Cl_2 (v) (a) HgO, I_2, PhH (b) hv (300nm) (vi) $NaBH_4$, MeOH.

Reduction, treatment with mercury(II) and iodine followed by irradiation resulted in β-scission of the alkoxy radical generated to give the *bis*formate (**3.36**). Reductive cyclisation provided racemic sesamin (**3.37**) in 6 steps from (**3.36**) in low overall yield.

An unusual, direct approach to furofuranones was described by Takano *et al.* [102] in which a substituted tetrahydrofuran (**3.39**) was the key late stage intermediate (Scheme 3.9). This

was prepared through a Lewis acid catalysed rearrangement of a 1,3-dioxepin derivative (**3.38**), the stereochemical outcome of which could be influenced by the nature of the Lewis acid. Non-chelating conditions provided the intermediate required *via* a final 5-*exo*-trig cyclisation from the sterically most favoured transition state conformation that upon reduction provided the alcohol (**3.39**). Oxidative cleavage of the alkene provided the aldehyde that, under basic conditions, equilibrated to the 3,4-*cis*-derivative of the lactol.

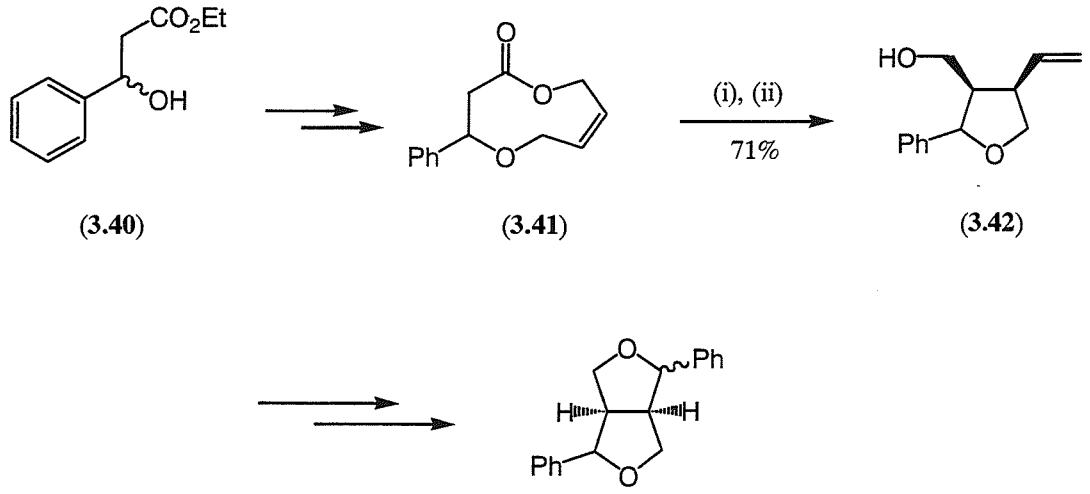


Scheme 3.9

Reagents and conditions: (i) TBDMS-OTf, CH_2Cl_2, $NaBH_4$ (5 eq.), -78°C (ii) (a) OsO_4 (cat.), Me_3NO, THF, H_2O (b) $NaIO_4$, $NaHCO_3$, THF, H_2O (c) NaOMe, MeOH (iii) TBDMSCl, imidazole, DMF (iv) TMS-Br, CH_2Cl_2 (v) (3,4-methylenedioxyphenyl)methylmagnesium bromide, THF, -78°C.

Formation of the haloacetal followed by reaction with the aromatic Grignard reagent provided racemic asarinin (**3.40**), resulting from quenching the intermediate oxonium ion from the least hindered face. The methodology was extended by the use of DIBAL as both Lewis acid and reducing agent to provide racemic samin, an immediate precursor to sesamin (**3.37**) [103]. The same group tried to elaborate the synthesis into a chiral method by preparing analogues of (**3.39**) with chiral centres in the alkene side chain. Carrying out the sequence of reactions described in Scheme 3.9 and separating the isomers as necessary provided either sesamin (**3.37**) or asarinin (**3.40**) in poor conversions and with e.e's of <60% [104].

Knight *et al.* [105,106] employed a strategy based upon the well known Ireland-Claisen rearrangement [107]. The critical reaction involved the rearrangment of the unsaturated macrocyclic lactone (**3.41**) (Scheme 3.10) prepared in four steps from the racemic 3-hydroxy-3-phenyl propionate derivative (**3.40**). Formation of the enolate at reduced temperature and in the presence of trimethylsilyl chloride followed by warming to room temperature gave the 3,4-*cis*-substituted tetrahydrofuran (**3.42**) after an *in situ* reduction. The observed stereochemistry was in accord with that in related 9-11 membered ring systems for which a boat like transition state, imposed by the *cis*- enolate and the olefin provides the 3,4-*cis*-stereochemistry. Elaboration according to methods related to those employed by Takano (*vide infra*) provided the racemic bicyclic tetrahydrofurans.



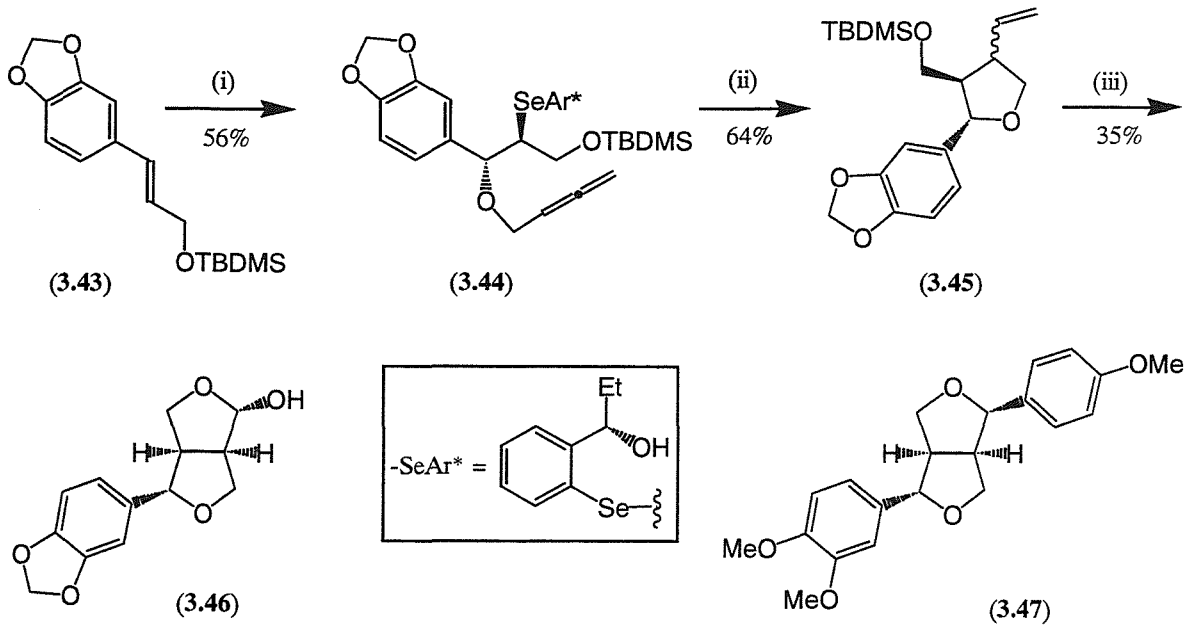
(**3.40**) (**3.41**) (**3.42**)

Scheme 3.10

Reagents and Conditions: (i) LDA, TMS-Cl, -100°C, THF then to RT (ii) $LiAlH_4$.

3.3.4 Synthetic Approaches using Radical Cyclisation

A short stereoselective approach using organoselenium mediated radical chemistry to construct the key tetrahydrofuran has been described by Wirth (Scheme 3.11). Thus, electrophilic addition of a chiral selenium triflate to a cinnamyl alcohol derivative (**3.43**) resulting in formation of a stabilised benzylic cation which was quenched with an allenyl alcohol to provide (**3.44**) as a mixture of diastereomers (*ca.* 9:1). The major diastereomer was subjected to radical cyclisation conditions to provide tetrahydofuran (**3.45**), an intermediate common to the methods of Takano and Knight. Osmylation, periodate cleavage, epimerisation α- to the carbonyl and deprotection furnished (+)-samin (**3.46**) which represents a formal synthesis of a variety of *exo, exo*- furofuranones [108]. Subsequently this methodology was employed in the preparation of (+)-membrine (**3.47**) [109].



Scheme 3.11

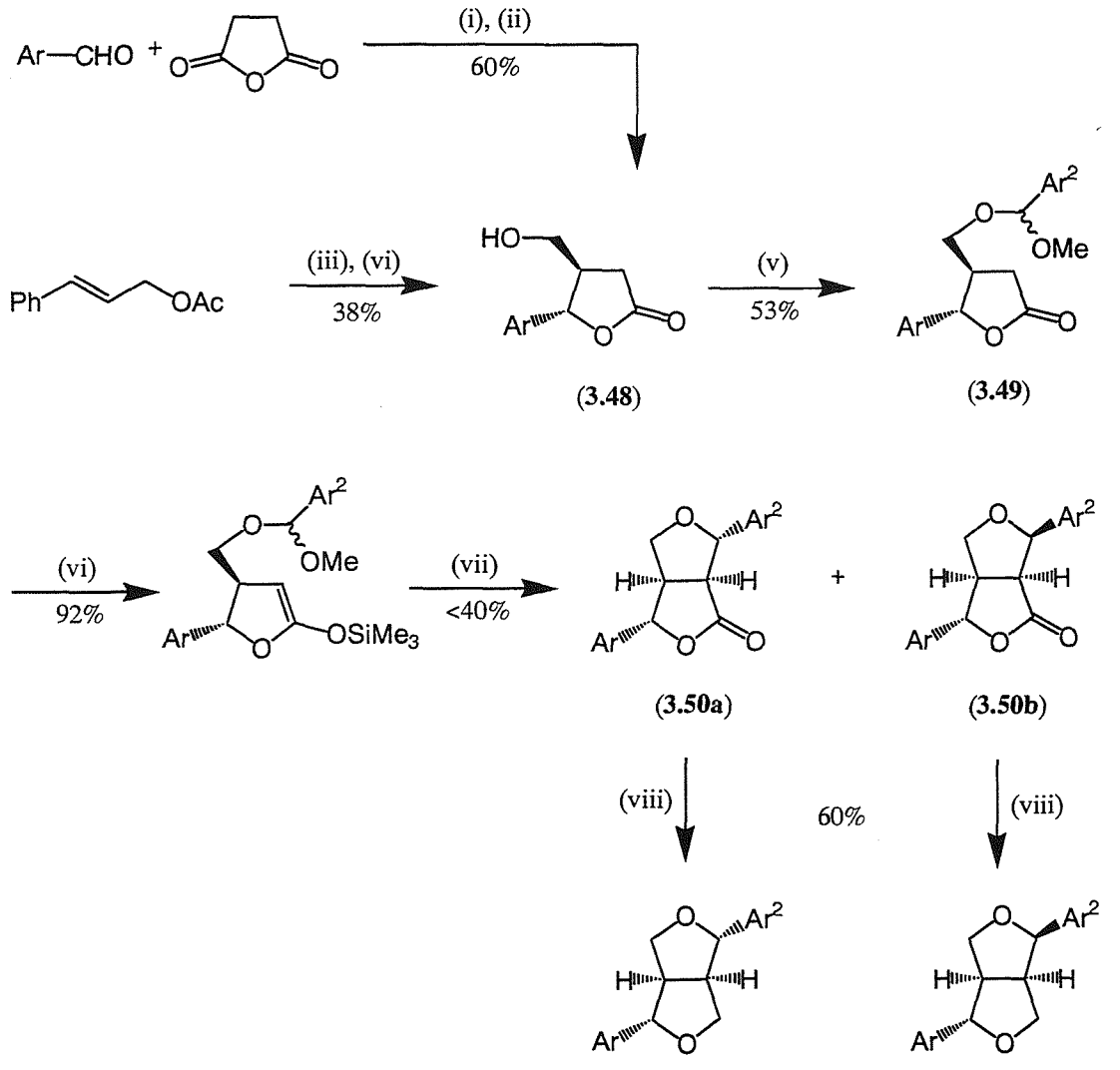
Reagents and conditions: (i) Ar*SeOTf, 2,3-butadiene-1-ol, Et_2O (ii) Ph_3SnH, AIBN, $PhCH_3$, chromatography (iii) TBAF, THF.

3.3.5 Synthetic Approaches using Cationic Cyclisation

The only work to date in which direct synthesis of furofuranones has been the primary objective is that carried out by Whiting *et al.* The crucial intermediates in these studies were the 4,5-*trans*-disubstituted lactones (**3.48**) which were formed by one of two routes (Scheme 3.12).

One approach involved preparation of lactone acid by reaction of an electron rich aromatic aldehyde with succinnic anhydride in the presence of a Lewis acid [110]. Subsequent reduction provided the alcohol that was shown to have the *trans*-relationship between the substituents by nOe interaction between the benzylic methine proton and the methylene group α- to the alcohol. A more commonly employed route involved the oxidative radical addition of acetic acid to an appropriately substituted cinnamyl acetate to prepare the lactone intermediate [111, 112]. Neither of these routes provided the intermediates in high yield. The alcohols were converted to diastereomeric hemiacetals (**3.49**) through reaction with an aromatic α-haloether. No diastereocontrol was exerted at the hemiacetal centre. Formation of the silylketene acetal, followed by treatment with a Lewis acid, brought about a Mukiayama condensation, furnishing the furofuranones in moderate yield (**3.50a, 3.50b**). The diastereomeric ratio was dependent on the nature of the aromatic substitution but in all the cases evaluated mixtures were obtained. Nonetheless, the methodology was used in the preparation of epiaptosimon (**3.50b**, Ar = Ar_2 = methylenedioxyphen-3-yl) and

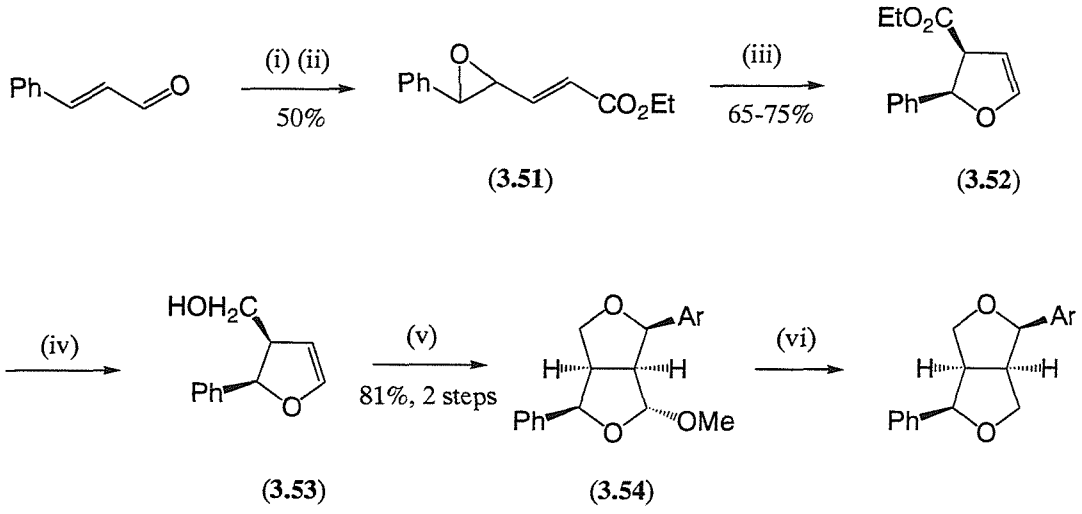
also in the preparation of furofurans (for example, asarinin (**2.40**)) through the reduction/ cyclisation methodology subsequently used by Ohmizu *et al.* (*vide infra*).



Scheme 3.12

Reagents and conditions (i) $ZnCl_2$, CH_2Cl_2, NEt_3 (ii) $BH_3.Me_2S$ (iii) $Mn(OAc)_3$, KOAc, AcOH (iv) HCl, THF (v) α-haloether, CH_2Cl_2, NEt_3 (vi) LDA, THF, TMS-Cl (vii) TMS-OTf, NEt_3, THF (viii) (a) $LiAlH_4$, THF (b) HCl, MeOH.

More recently Aldous *et al.* [113] took a closely related approach in which the acetal formation and the cationic cyclisation occur in one pot (Scheme 3.13). The early stages of the synthesis involve epoxidation of cinnamaldehyde followed by a stereoselective Wadsworth Emmon's reaction to provide vinyl epoxide (**3.51**). The critical reaction was the rearrangement of **3.51** to the dihydrofuran (**3.52**) which occurred with good diastereoselectivity.



Scheme 3.13

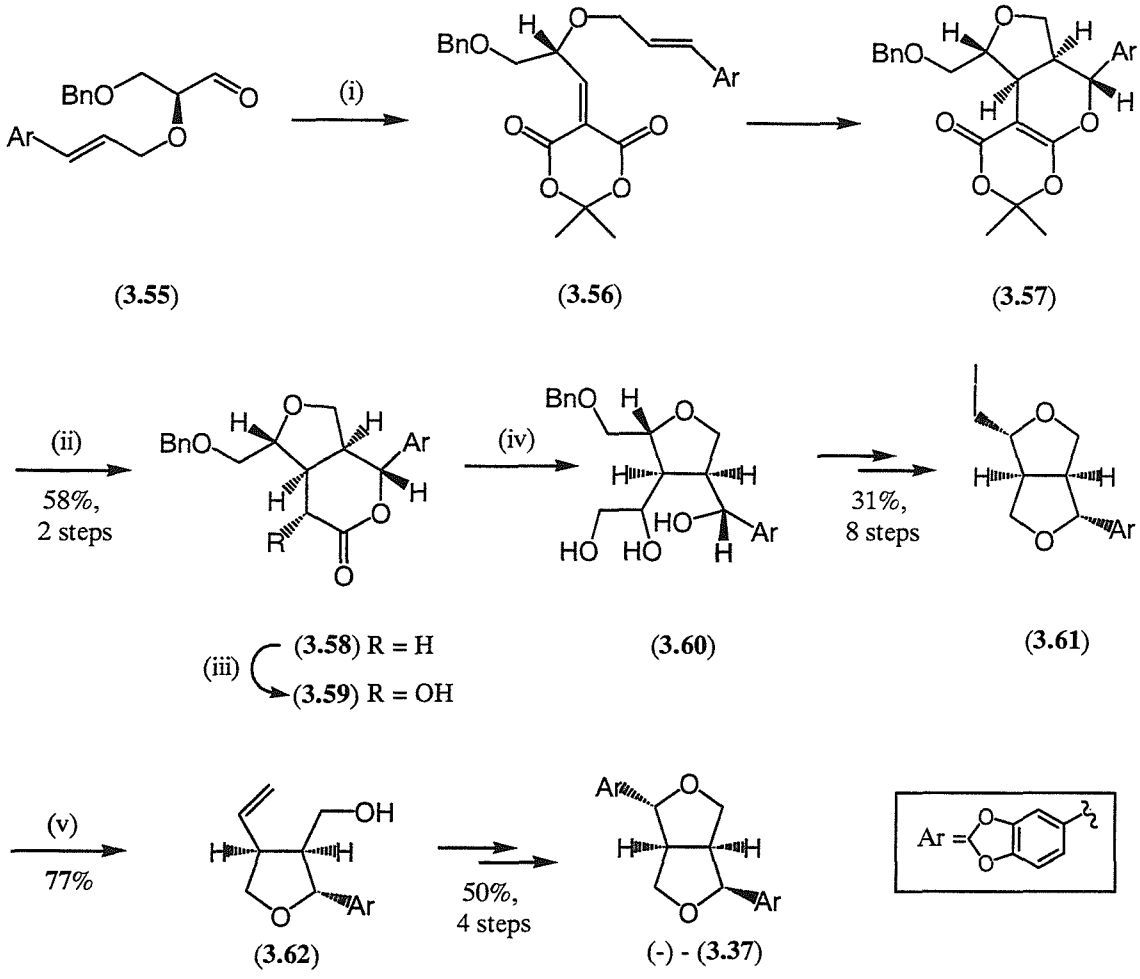
Reagents and conditions: (i) *t*-BuOOH, NaOH (ii) $EtO_2CCH_2P(O)(OEt)_2$, NaH, THF (iii) PhMe, 180°C, 20h (iv) $LiAlH_4$, Et_2O (v) $ArCH(OMe)_2$, TMSOTf, CH_2Cl_2, -20°C (vi) Et_3SiH, BF_3 Et_2O, CH_2Cl_2, 0°C.

The reaction proceeds *via* an ylide like intermediate that undergoes a thermally allowed electrocyclic [2πa+2σs] reaction, thus accounting for the dominance of the *cis* stereochemistry that is observed (*cis/ trans* 10:1). Reduction of the alcohol (**3.53**), followed by reaction with an aromatic aldehyde dimethyl acetal in the presence of a Lewis acid provided the bicyclic core (**3.54**). Complete selectivity for the *endo, endo-* isomer was observed provided the reaction was conducted at low temperature. Allowing the reaction to warm to RT resulted in isolation of a mixture of isomers in a significantly reduced yield.

Reduction using the conditions first described by Pelter [114] provided the furofuran. However, the group has yet to demonstrate the utility of the method in making a natural product in that the model studies entailed use of an unsubstituted aromatic throughout. In addition, the procedure produces the *endo, endo-* relative stereochemistry at the benzylic positions – the least common orientation found in naturally occurring lignans.

3.3.6 Synthetic Approaches using Diels Alder Methodology

The first enantiospecific synthesis of furofuran lignans was reported by Takano as early as 1988 [115]. The route was a convoluted procedure involving 25 steps from the chiral starting material, diethyl–L-tartrate (Scheme 3.14) with a hetero-Diels Alder as the pivotal step.



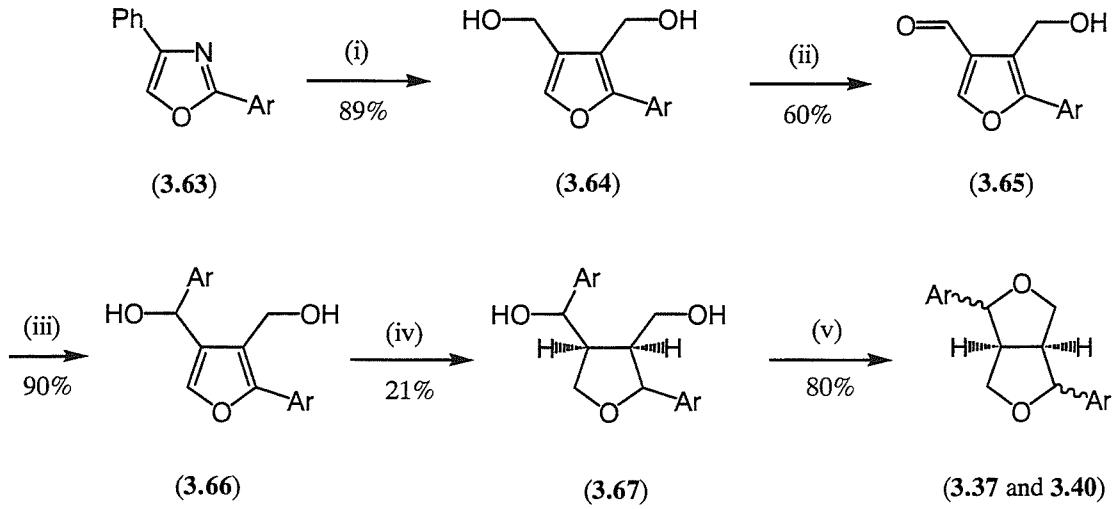
Scheme 3.14

Reagents and conditions: (i) Meldrum's acid, DMAP, CH_2Cl_2 (ii) $MgCl_2$, DMA (iii) LiHMDS, MoOPh (iv) $NaBH_4$ (v) Zn, MeOH.

The chiral ether (7 steps from diethyl-L-tartrate) (**3.55**) was condensed with Meldrum's acid to produce the unstable hetero-Diels Alder substrate (**3.56**). Spontaneous cycloaddition gave **3.57** that was hydrolysed to give the substituted δ-lactone (**3.58**). Formation of the lactone enolate and quenching with an electrophilic source of oxygen provided alcohol (**3.59**) that was subjected to a protracted sequence of functional group interconversions ultimately furnishing bicyclic ether (**3.61**). A reductive ring opening gave the alkene intermediate (**3.62**) which is readily converted into sesamin (**3.37**) in 4 steps that were subsequently used by Knight [106]. The complexity of the route was compensated for

by the production of chiral products and by the fact that four separate natural products are readily available through the common intermediate (**3.62**).

Only one route has been published to date in which aromatic heterocycles were used as intermediates in the formation of furofurans (Scheme 3.15) [116].



Scheme 3.15

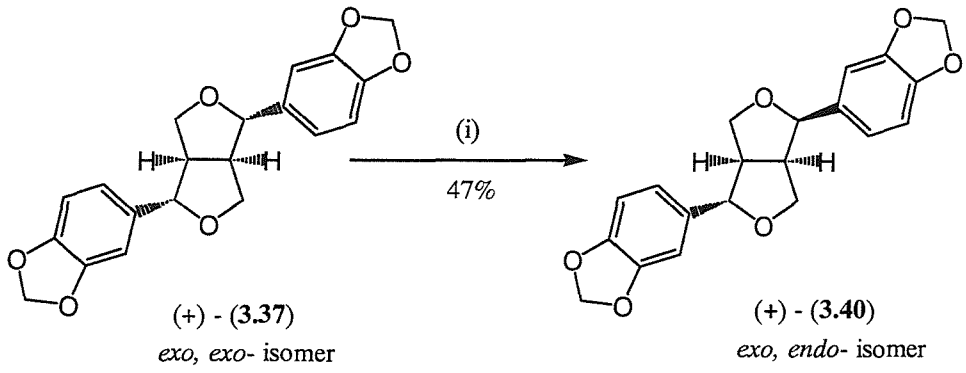
Reagents and conditions: (i) (a) 2-butyn-1,4-diacetate, Na_2CO_3, MeOH (b) KOH, MeOH
(ii) $(HCrO_4)_2(pyr)_4Co(II)$, DMF (iii) ArMgBr, THF (iv) H_2, Pd/ C, EtOH, 80atm (v) MeOH, HCl

Suitably substituted oxazoles (**3.63**) where prepared by the classical condensation reaction of acetamide with benzoylmethyl (3,4-methylenedioxy)benzoate in the presence of a Lewis acid. Hetero-Diels Alder with a suitably substituted alkyne provided (**3.64**) after hydrolysis of the acetate groups. Mono-oxidation to **3.65** was achieved using a bulky Co(II) chromate complex although even with this some dialdehyde (easily separated from the monoaldehyde) resulted. Grignard addition introduced the second aromatic functionality but reduction of the resulting furan (**3.66**) was not chemoselective. Over-reduction of the desired product resulting in loss of the benzylic hydroxyl group provided the main product. The diol (**3.67**) that was isolated was converted to a mixture of isomers of furofurans, sesamin (**2.37**) and asarinin (**2.40**) (the aromatic substituents were both 3,4-methylenedioxyphenyl).

3.3.7 Miscellaneous Approaches to Furofuran(one)s

A number of biotransformations have been used to interconvert furofuran derivatives as described earlier in this chapter. Chemically mediated isomerisation is less commonplace. One useful method recently published allowed for the chemical isomerisation of *exo, exo*-furofurans into their *exo, endo*- isomers [117]. The epimerisations were induced by clay

catalysed microwave irradiation in the presence of a clay catalyst and were found to be more efficient than the acid mediated epimerisations used in earlier work [118]. The method appeared to be chemoselective, producing epimerisation at only one of the benzylic centres.



Scheme 3.16

Reagents and conditions: (i) Montmorillonite KSF, microwave, 2 min.

Whilst it is clear from the preceding discussion that there are many different ways to synthesise this class of natural products it is also clear that there is scope to develop the area further. Many of the current routes suffer from being convoluted and lengthy and do not have the flexibility to allow access to all the substitution patterns or relative and absolute stereochemistries found in nature. Arguably, the most elegant and concise synthesis, the one described by Wirth, had problems associated with the use of stoichiometric selenium, which might well have proven a problem on scale up. Thus, whilst the interest in the biological properties and their wide occurrence in nature suggested an untapped potential it was the belief that there remains a contribution to be made in the synthesis of furofurans that was the impetus behind the project.

Chapter 4

Diazo-transfer/ Insertion Strategies Towards Furofuran(one) Lignans

The aim of this project was to investigate a route for the preparation of furofuranone and furofuran lignans that would accommodate the criteria outlined below.

- to allow for the introduction of the variously substituted aromatic groups common to this class of compounds.
- to give access to derivatives in which the two aromatic groups are different.
- to be amenable to subsequent modification to provide enantiopure products.
- to provide selective access to both the *exo, exo-* and *exo, endo-* series of compounds through a common late stage intermediate.

Whilst many of the previous syntheses of these compounds have satisfied the first three criteria, with varying degrees of success, they have often failed in the fourth.

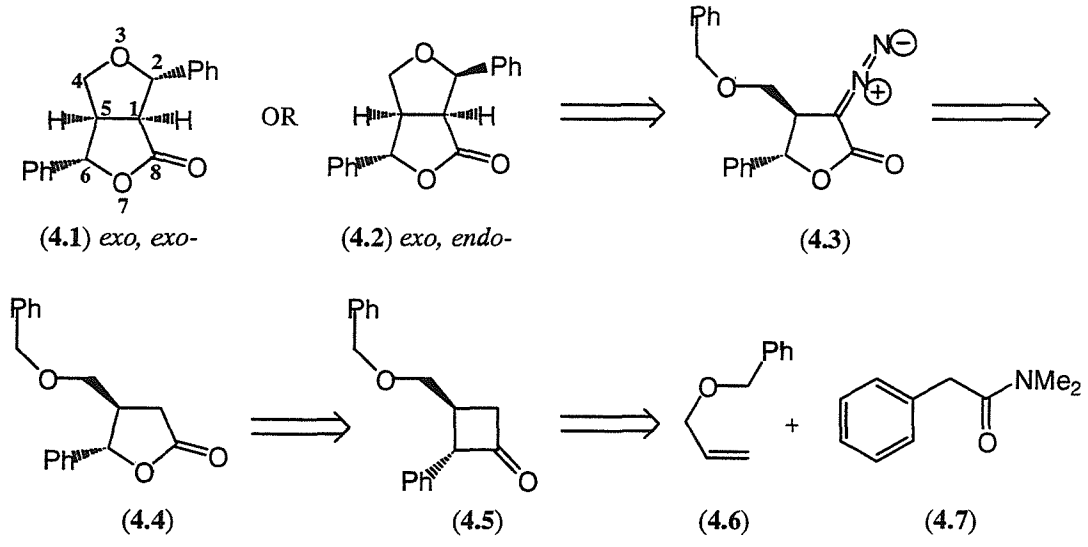


Figure 4.1 The retrosynthetic analysis

We elected to investigate a route in which the furofuranone scaffold (**4.1, 4.2**) would be assembled through a C–C bond forming reaction between the pro C-1 and C-2 carbon atoms (Figure 4.1). Our strategy was to probe the utility of accomplishing this final connection through a carbene or carbenoid insertion into the appropriate C–H bond.

We targeted the diazolactone (**4.3**) as the intermediate from which the carbenoid species would be generated. We felt there were two factors that favoured the desired ring closure of this reactive intermediate over alternative reaction pathways.

- Literature precedent covering diazo insertion chemistry describes the predisposition of C–H insertion reactions to give 5-membered rings over other alternative reaction pathways [28].
- In our system the likelihood of formation of a five membered ring is further enhanced by the presence of an activating sp^3 oxygen α- to the C–H insertion centre [34].

What remained unknown was the nature of the relative stereochemistry at the termini of the newly formed C–C bond. From the outset we hoped that by using the various different techniques for diazoinsertion that we might be able to selectively influence the configuration at this carbon centre and thus satisfy the last of the synthetic criteria described above.

The earlier stages of the synthetic strategy also raised some interesting questions. In particular, the efficient formation of the 4,5-disubstituted diazolactone (**4.3**) is unprecedented. Preparation of such a derivative might well be of some utility beyond being the pivotal intermediate in the synthesis of the target compounds. A general application in the the synthesis of lactone containing natural products with substitution α- to the carbonyl group, would certainly be of value.

Our initial work was directed at the synthesis of a diazolactone using methods that did not require additional activation of the α-carbon of the lactone. We envisaged that the required lactone (**4.4**) would be available through a regiospecific Baeyer Villiger reaction on the corresponding cyclobutanone (**4.5**). A critical step in the early part of the synthesis was the proposed [2 + 2] cycloaddition reaction between an alkene (**4.6**) and a ketiminium salt derived from the substituted *N,N*-dialkylamide (**4.7**). We anticipated that the correct relative stereochemistry of the pro C-5, C-6 positions would be established through this cycloaddition reaction.

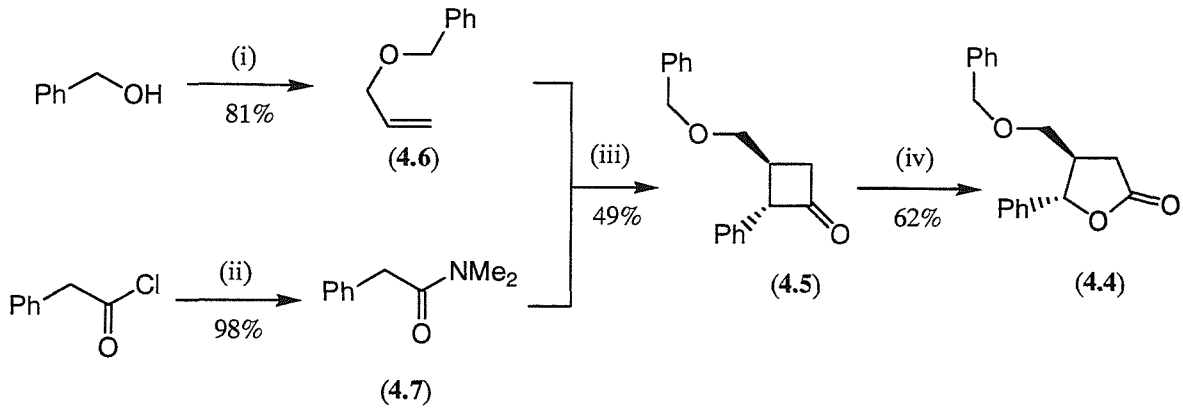
The following sections will describe in detail each of the reactions employed in an attempt to realise the goals outlined above. As is often the case in natural product synthesis the first investigations were conducted on a model series of compounds using monosubstituted aromatic starting materials. Subsequent investigation of the natural products themselves was guided by the results of these model studies. The following discussion reflects this sequence of events in that the bulk of the description of literature precedent, observations, and conclusions will be associated with the model series of compounds. The knowledge accumulated during the model studies will be taken as read in the section describing the natural product synthesis, wherein only the synthetic idiosyncrasies caused by the functionality of the natural system will be discussed.

4.1 Investigations in the Preparation of a Model for the Furofuran(one) Lignans

As a model study we targeted the compound which retained the bicyclic core of the furofuranones, with the correct relative stereochemistry, but with simple phenyl functionality instead of the oxygenated aromatics that typify the natural products.

4.1.1 Preparation of the *trans*-4,5-Disubstituted Lactone (4.4)

The synthetic sequence employed to access lactone (**4.4**) is outlined in Scheme 4.1.



Scheme 4.1

Reagents and Conditions: (i) (a) NaH, DMF (b) allyl bromide, NaI (ii) $NHMe_2$ (aq.), CH_2Cl_2 (iii) (a) Tf_2O, CH_2Cl_2, -25°C (b) 2,6-di*tert*-butylpyridine, allylbenzylether, CH_2Cl_2 (c) $NaHCO_3$, Δ (iv) *m*-CPBA, CH_2Cl_2, or H_2O_2, AcOH.

The critical reaction was the [2 + 2] cycloaddition reaction between benzylallyl ether [119] and *N,N*-dimethylphenylacetamide [120], wherein we anticipated the *trans*- relative stereochemistry of the pendant functionality would be established [121].

Initial treatment of the disubstituted amide with triflic anhydride according to the method of Ghosez *et al.* [122] provided the keteniminium triflate salt (**4.8**). Immediate addition of a mixture of benzylallylether and 2,6-di*tert*-butylpyridine provided the cyclic keteniminium salt (**4.10**). Upon completion of cycloaddition the cyclobutanone (**4.5**) was furnished after mildly basic hydrolysis of (**4.10**). The progress of each step in the reaction was conveniently monitored by IR spectroscopy given the characteristic stretching absorptions of both (**4.10**) (υ_{max} ($C=N^+Me_2$), 1740 cm^{-1}) and (**4.5**) (υ_{max} (C=O), 1780 cm^{-1}).

The necessity of using a highly hindered base was demonstrated through attempting the same conversion using collidine as the pyridine base. Only trace quantities of the desired materials were isolated, with the remainder of the mass balance being accounted for by undefined products.

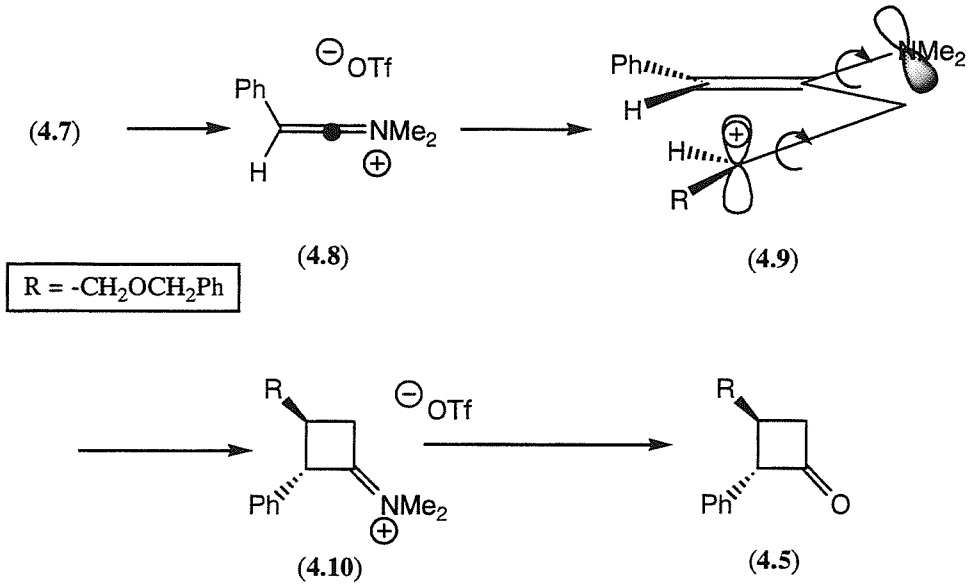


Figure 4.2 Mechanism of keteniminium salt/ alkene cycloaddition

The product, which was unstable to prolonged storage at room temperature, was isolated as a single diastereoisomer and assumed to have the two pendant functional groups in a *trans*-disposition. The mechanistic justification for this provided in Figure 4.2 [123]. Regiospecific electrophilic attack at the terminus of the olefin provides the stabilised carbonium ion (**4.9**). Prior to ring closure the C–N bond must rotate to form an enamine system wherein the nitrogen lone pair is planar with the conjugated π-system. At the same time rotation around the C–C bond would favour placing the large groups remote from each other prior to formation of the cyclic transition state. Provided that the latter rotation is faster than the former then the *trans*- isomer would be expected to predominate at the cyclic ketiminium salt stage. Critically, the work also demonstrated that substantial *cis*- to *trans*-isomerisation occurred during the hydrolysis of the keteniminium salt (**4.10**) to the cyclobutanone (**4.5**).

Regiospecific Baeyer Villiger oxidation furnished the disubstituted lactone (**4.4**) with the desired relative stereochemistry. Either the classical *m*-CPBA or acidic peroxide [124] methodologies were effective in this transformation although the latter generated consistently higher yields.

At this juncture a stereospecific synthesis using this methodology has not been investigated in our laboratories. However, literature precedent does suggest that the cycloaddition reaction outlined above may be accomplished enantioselectively; Ghosez *et al.* [125] have demonstrated that chiral amide derivatives can effect enantioselective cyclobutanone formation under appropriate conditions (Figure 4.3).

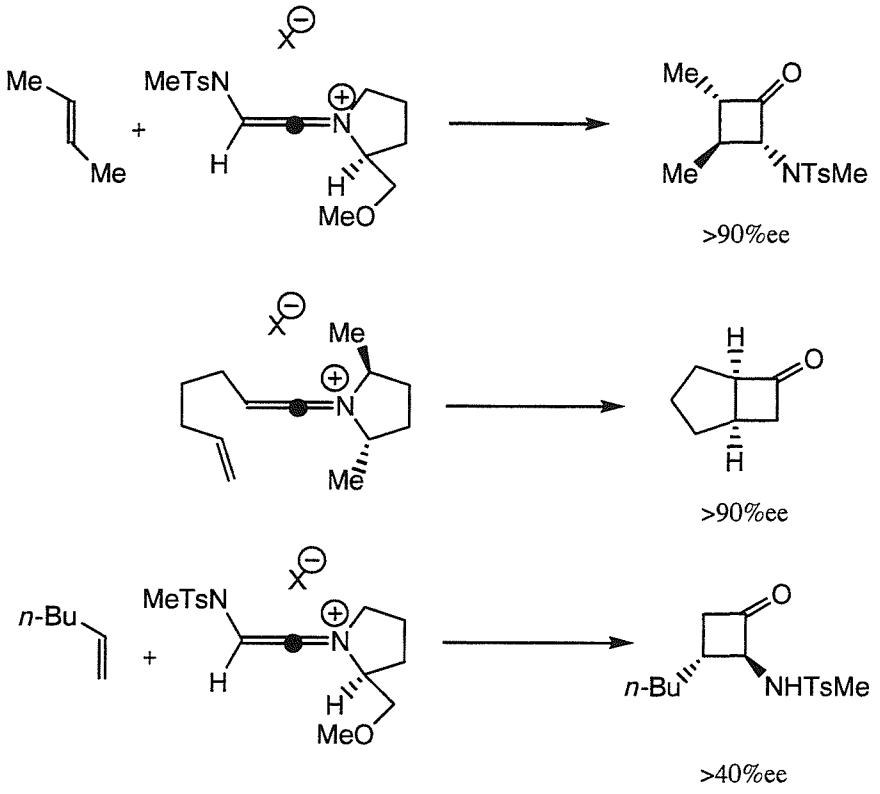


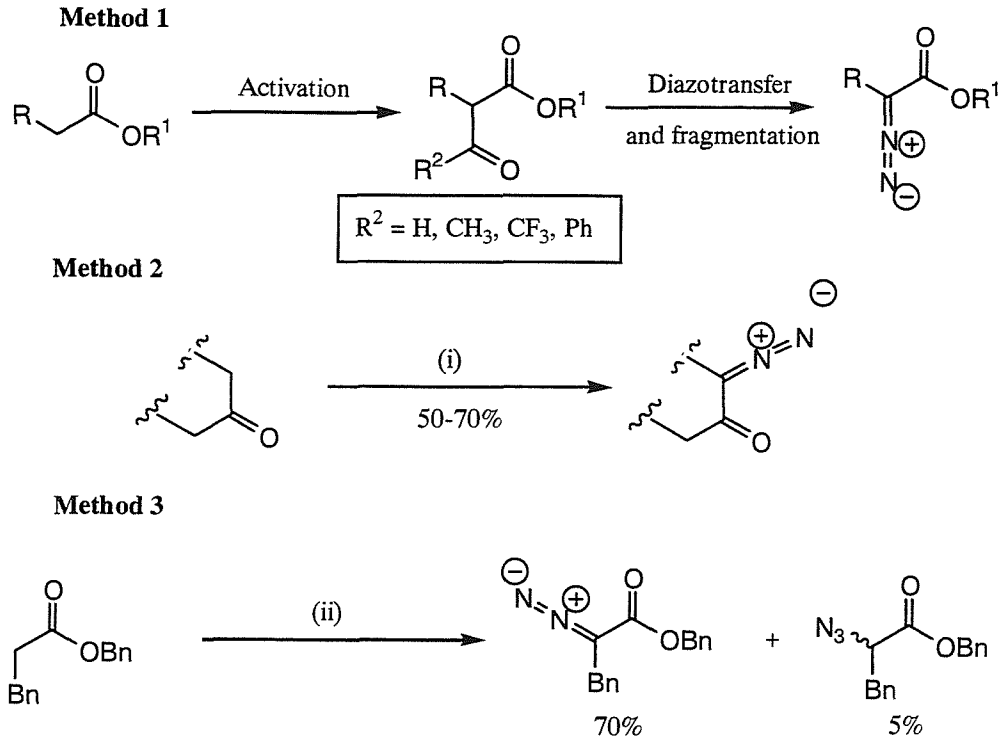
Figure 4.3 Cycloaddition products using chiral keteniminium salts

Initial investigations demonstrated useful enantioselectivities when using amides derived from chiral prolinols. Unfortunately, this level of chiral control was not manifest when using the same auxiliaries in the intramolecular variant of the reaction. In these systems higher enantioselectivities were realised when using C-2 symmetric auxiliaries. Adaption of this methodology to the intermolecular variant worked well for *vic*-disubstituted olefins but was less effective for compounds with terminal double bonds. Nonetheless, there is justifiable hope that investigation of a number of chiral amides might realise the aim of producing *trans*-2,3-disubstituted cyclobutanones in an enantioselective fashion *via* this cycloaddition strategy.

4.1.2 Preparation of 3-Diazo-4,5-*trans* Disubstituted Lactone (4.3)

Of the many methods known for generating diazo compounds it was a diazo transfer to the lactone enolate that occupied our attention in the first instance. There were two main reasons for this that are outlined below.

1. the methodology does not require functional group manipulation on lactone (**4.4**) prior to the diazo-transfer.
2. although there is little literature precedent for diazo-transfer to lactone enolates, there is a wealth of available information about diazo-transfer to esters and, more commonly, β-dicarbonyl derived enolates [126, 127, 128].



Scheme 4.2

Reagents and conditions: (i) $ArSO_2N_3$, *n*-$Bu_4N^+Br^-$, 18-crown-6, benzene, H_2O, KOH (ii) (a) LiHMDS, THF (b) *p*-nitrobenzylsulfonylazide (c) HOAc (N.B. conditions for the activation strategy will be described in another section).

The prior art concerning preparation of α-diazocarbonyl compounds (which have only one diazo stabilising functionality in the final compound) using diazo-transfer is summarised in Scheme 4.2.

Use of a sacrificial activating carbonyl group, as in Method 1, has been demonstrated to be effective in a number of systems. The complexity of the sulfonyl azide's interaction with a doubly stabilised enolate, and its consequent collapse, are exemplified by the fact that the activating group's structure, as well as that of the substrate, is significant in determining the efficiency of the transformation. Formyl- [129,130], acetyl- [131], trifluoroacetyl- [132,133] and benzoyl- [134] groups have all been employed in this capacity. Our efforts in this area are described in Section 4.4.2.

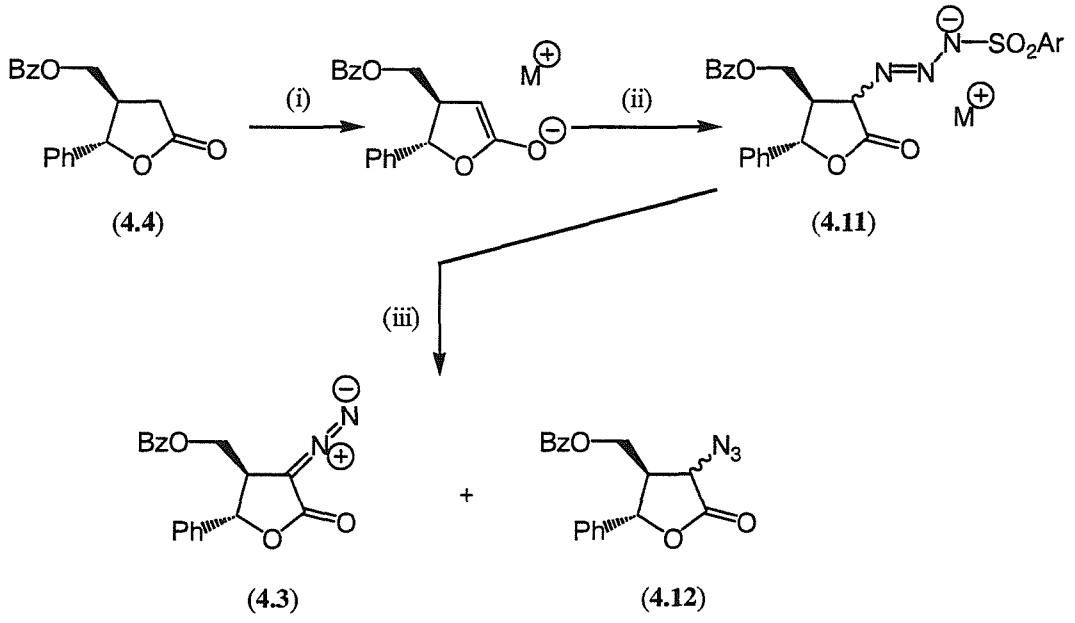
Direct diazo-transfer to singly activated methylene groups is more scarce. The phase transfer methodology (Method 2) has been demonstrated as useful in formation of diazoketones although most of the examples described were benzylic ketones. Lombardo and Mander [135] investigated a number of different sulfonyl azides and found that 2,4,6-tri*iso*propylbenzenesulfonylazide was most effective. They also demonstrated that the reaction could be successfully carried out in the presence of base labile groups (including lactones).

In our hands the conditions did not produce any of the diazo-compound, but azide formation was in evidence. Interestingly, this methodology appeared to produce the epimer at the C-3 position of the lactone when compared to the azide commonly formed under the other conditions investigated (*vide supra*).

A more extensive study of diazoester preparation was carried out by Evans *et al.* [136] They investigated the efficiency of diazo *vs.* azide transfer from aromatic sulfonyl azides to imide or ester enolates in a study for which electrophilic introduction of amines was the main objective.

Whilst the majority of the work was carried out on imide enolates a set of conditions favouring formation of α-diazo esters was described. Our interest in developing a short synthesis of furofuranones led us to investigate the Evans' protocol for diazo-transfer in the first instance. The application of the methodology to the previously described lactone (**4.4**) is outlined in Scheme 4.3. An attempt to form the enolate of the cyclobutanone (4.5) and quench with a sulfonyl azide resulted in decomposition of the starting material.

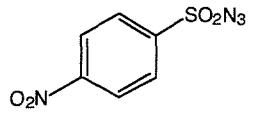
Evans demonstrated that the course of the reaction was dependent on the nature of the counterion of the enolate, the structure of the sulfonyl azide and the nature of the proton source (or electrophile) that was used to quench the reaction. We initially investigated reactions using the optimum conditions described by Evans, and close variants thereof (Table 4.1).



Scheme 4.3

Reagents and conditions: (i) LDA or NaHMDS, THF (ii) $ArSO_2N_3$ (iii) HOAc, pH 7 phosphate buffer.

	Base	Sulfonyl azide	Quench reagent	3-Azido lactone (4.12)	α-Diazo lactone (4.3)
1	LDA	A	pH 7 phosphate	45%	6%
2	LDA	B	pH 7 phosphate	30%	<10%
3	LDA	A	HOAc	58%	-
4	NaHMDS	B	pH 7 phosphate	33%	-

A = 

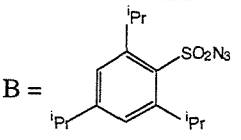
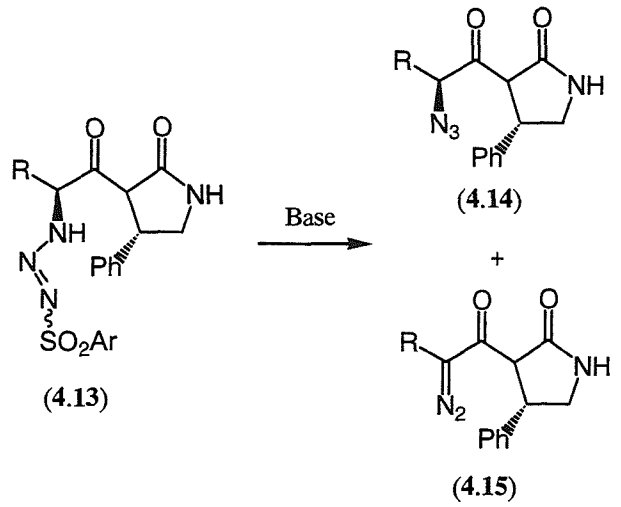
B = 

Table 4.1 Variation of base, sulfonyl azide, and quench reagent in diazo-transfer methodology

It was gratifying that the optimal conditions for diazo-transfer described by Evans did furnish some of our target compound, albeit in very low yield, and as a minor by product relative to the amount of azide isolated. However, it was frustrating that minor modifications made to the reaction conditions had, at best, no impact at all on the ratio of azide/ diazo-transfer. Given the low combined recovery of the products under all the conditions investigated it was easy to speculate that diazo-lactone was being produced, but its instability under the reaction conditions led to its immediate decomposition.



Base	% 4.14	% 4.15
KOAc	84	0
Et_3N	57	38
$KHCO_3$	22	71
pyridine	6	82

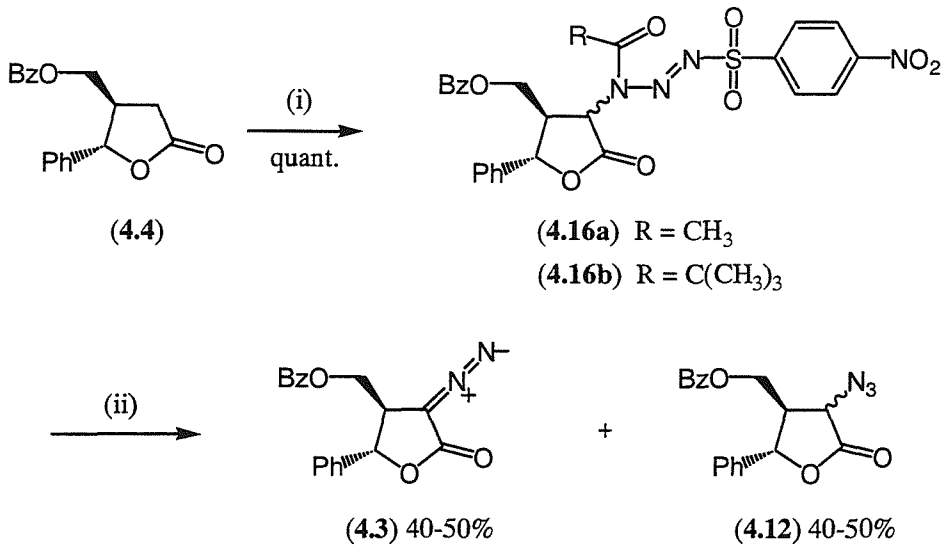
Figure 4.4 The influence of base on triazene decomposition

In their work on diazo-transfer to imide enolates the Evans' group had been able to protonate the triazene anion and isolate the purified product. Subsequently, they treated the triazene (**4.13**) with a variety of bases (a selection of which are shown in Figure 4.4) and found that they could selectively produce either the azide- (**4.14**) or the diazo- transfer

product (**4.15**). They observed no trends in their observations and, as a consequence, were not able to offer a clear rationale explaining the chemoselectivity that they observed.

Thin layer chromatographic analysis of our reaction mixtures did indicate the presence of an intermediate immediately after addition of sulfonyl azide to the lactone enolate. It was quickly consumed, even at -78°C, which precluded a study of the type outlined above. However, we were able to trap the intermediate by quenching the triazene anion with acetyl chloride (Scheme 4.4).

Acylated triazines have been synthesised before: Denmark *et al.* [137] have isolated products from the reaction of phosphorus stabilised anions with sulfonyl azides following trapping with acetic anhydride. However, the resulting acylated triazenes have been treated to reductive conditions to prepare amines. No investigation was described concerning decomposition to give azide or diazo- derivatives.



Reagents and conditions: (i) (a) LiHMDS, THF (b) *p*-nitrobenzenesulfonylazide, THF (c) acetyl chloride (ii) DMAP, THF.

Scheme 4.4

The acylated triazene (**4.16a**) was isolated as a mixture of isomers. The nature of the isomeric population is unclear, but was assumed to arise from epimers at C-3 (although the 2,3-*trans*- derivative would be expected to predominate) as well as *cis/ trans* isomerisation around the N–N double bond. Purification of the isomeric mixture did not prove possible given the compound's instability to protracted chromatography on silica gel. An investigation into the decomposition of **4.16a** was undertaken. Prolonged storage in concentrated solution did lead to slow production of both azide (**4.12**) and diazo- (**4.3**) derivatives. Heating, or the addition of acid, either in the form of acetic acid or silica gel,

failed to accelerate the reaction. Similarly, treatment with zinc chloride failed to bring about any decomposition.

Investigation of basic reaction conditions for the decomposition revealed that pyridine had no effect and *N,N*-di*iso*propylethylamine caused very slow decompostion to both azide and diazo- compounds over the period of a week. However, *N, N*-dimethylaminopyridine (DMAP) caused rapid decomposition to azide and diazo- derivatives within 4 hours at room temperature. Careful purification by chromatography allowed for the isolation of each derivative in 40-50% yield with likely explanation for any loss of material being the repetitive purifications required to separate the two compounds.

Given the utility of the DMAP methodology we decided not to investigate the mechanism of the decomposition reaction further. Literature precedent suggests that such an investigation might provide ambiguous results. From the limited number of reagents investigated it would appear that the decomposition is triggered through interaction of the triazene with a nucleophile, and is not initiated through deprotonation.

We also investigated the use of pivaloyl chloride as the acylating agent in the reaction. Thus, triazene (**4.16b**) was prepared by quenching the reaction with pivaloyl chloride and allowing the reaction to warm until the deep red colour of the anion had dissipated. In this case the reaction had to reach -20°C before this occurred. Isolation of the acylated triazene followed by its subsequent decomposition suggested that >50% of the diazo compound was being formed. However, this result could not be reproduced and the reality appears to be that both the acetyl- and pivaloyl- derivatives are decomposed to produce the same relative quantities of diazo- (**4.3**) and azido- (**4.12**) compounds.

The methodology outlined above represents the first diazo-transfer reaction to a lactone without additional activation of the α-methylene group. Indeed, there has been only one description of diazo-transfer with additional activation at this position, in which the diazo compound was prepared in 14% yield [129]. This work, describing the reaction of sulfonyl azide with an α-formyl lactone, exemplifies the only known α-diazolactone prior to those described herein. Whilst there is ample scope for optimisation of these novel reaction conditions, the compounds prepared in this initial study were immediately used to evaluate the efficiency of the critical diazo-insertion reaction.

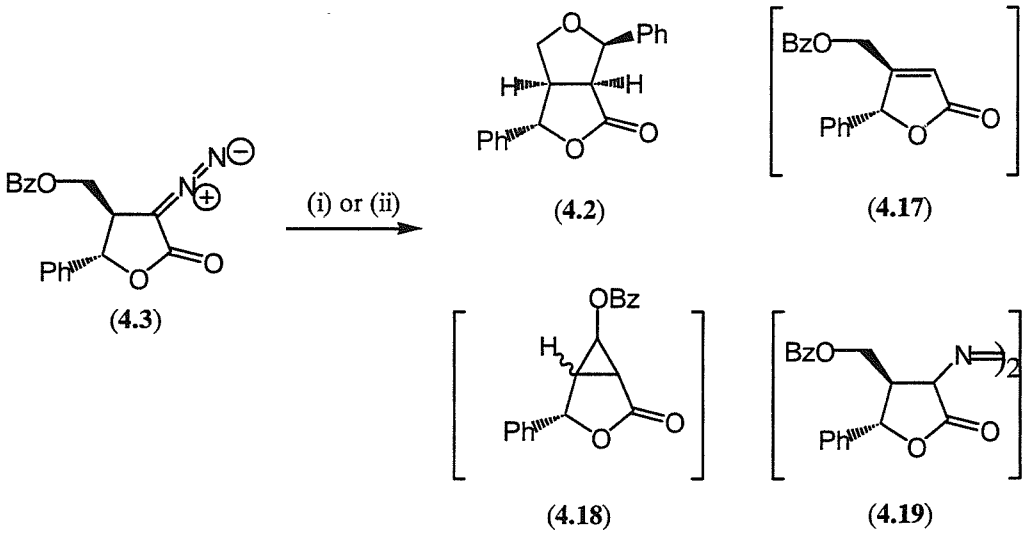
It is noteworthy that the azide product (**4.12**) is isolated as predominantly one diastereoisomer. No effort was made to identify the relative stereochemistry of the azide in this model series. However, by correlation with the results obtained in natural product

series (*vide supra*) **4.12** was assumed to have the *trans*-disposition relative to the functionality at C-4 of the lactone.

Clearly, there is also scope for utilisation of the azide in the production of the diazo-compound (**4.3**) by alternative means. Some attempts were made to improve the overall efficiency of the synthesis in this fashion. These will be described in a later section 4.4.1.

4.1.3 The Diazoinsertion Reaction

Our initial attempt at the diazoinsertion involved generation of a rhodium carbenoid by reaction of our diazo- derivative with dirhodium(II) tetraacetate, the prototypical rhodium based diazo- decomposition catalyst [138]. At the outset we anticipated that that the diazo-derivative (**4.3**) might suffer up to four different fates depending on the chemoselection showed by the catalyst system. Any of 1,2- (to give **4.17**), 1,3- (to give **4.18**), or the desired 1,5-insertion could occur, as could the dimerisation of the carbenoid (**4.19**). When the reaction was conducted at room temperature in dichloromethane it was found to be both chemoselective for 1,5-insertion and also diastereoselective in terms of producing only the *cis*- relative stereochemistry across the newly formed carbon-carbon bond (**4.2**) (Scheme 4.5).



Reagents and conditions: (i) $Rh_2(OAc)_4$, CH_2Cl_2, RT **or** (ii) Δ, $ClCH_2CH_2Cl$.

Scheme 4.5

The absence of products arising from cyclopropanation or dimerisation is amply justified by the chemical literature. Chemoselectivity for 1,3-insertion is normally only noted in compounds in which conformational constraints place the insertion centre close to the metal carbene [139]. Dimerisation occurs with reactive unstabilised carbenes although it has been noted as a by-product of rhodium mediated decomposition of α-diazo carbonyl

compounds in the past [140, 44]. The absence of any alkene (**4.17**) arising from 1,2-insertion was more pleasing given its relatively common identification in diazo decomposition reactions of α-diazo carbonyl compounds [140]. The *cis*- relative stereochemistry around the newly formed carbon-carbon bond was confirmed initially by nOe experiments (Figure 4.5) and translated into the formation of the *exo, endo*- isomer of the furofuranone.

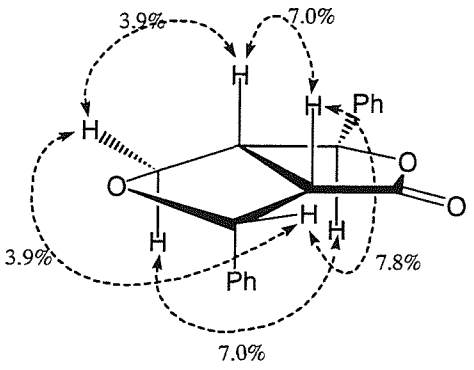
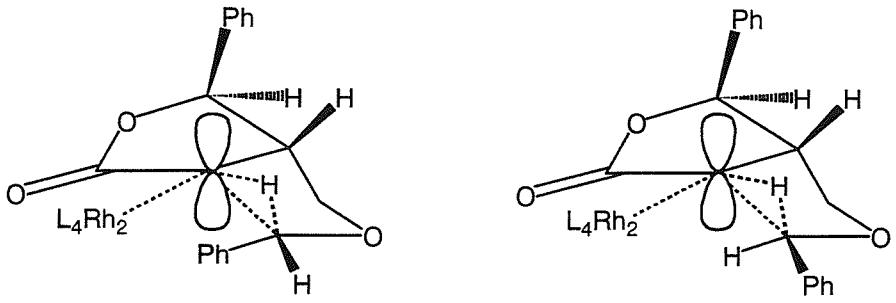


Figure 4.5 nOe Assignment of stereochemistry of furfuranone (4.2)

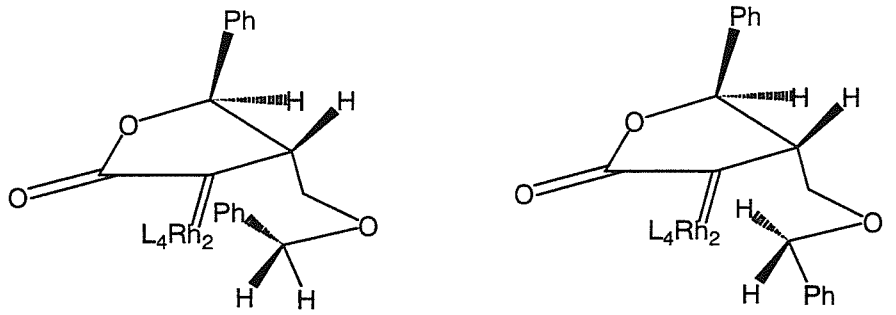
The formation of a C3–C4 *cis*- relative stereochemistry was an anomalous result compared to the prior art. In nearly all the preparations of either cyclopentanones or γ-lactones the substituents across the newly formed bond had a *trans*- relationship. Adopting the mechanism proposed by Doyle *et al.* [141] the structures of the two possible transition states for insertion into the diastereotopic methylene group would look like those depicted in Figure 4.6a. For the sake of completeness a depiction of the transition states according to the later Taber model [43] (see Scheme 4.6b) are also included (see section 2.1.4).

In both scenarios it appears that on steric grounds alone the conformation required to access the transition state for the product that is observed (**4.20a** and **4.21a**) would be disfavoured. The phenyl group is being directed under the pre-existing lactone ring and not into space as in structures **4.20b** and **4.21b**. Although far from clear using the two dimensional models above a possible explanation for the selectivity is a favourable interaction between the electron rich aromatic and the electrophilic carbenoid. The exact nature of this interaction and the reason why it does not lead to insertion into the aromatic C–H are issues that remain unresolved by the current work. Furthermore, the part played by the departing rhodium complex, in terms of both steric and electronic effects, on determining the structure of the reactive conformation is also unclear.



(4.20a) **(4.20b)**

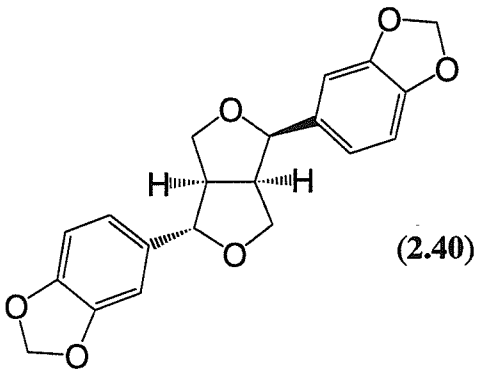
Figure 4.6a Transition states for insertion products – the Doyle model



(4.21a) **(4.21b)**

Figure 4.6b Transition states for insertion products – the Taber model

An initial attempt at performing the insertion in the absence of catalyst by simply heating the reaction appeared to give a quantitative yield of the same product. This result proved not to be reproducible. Larger scale attempts did produce the desired product but in poor yield and in the presence of recovered starting material and trace quantities of a number of other products.



(2.40) Asarinin

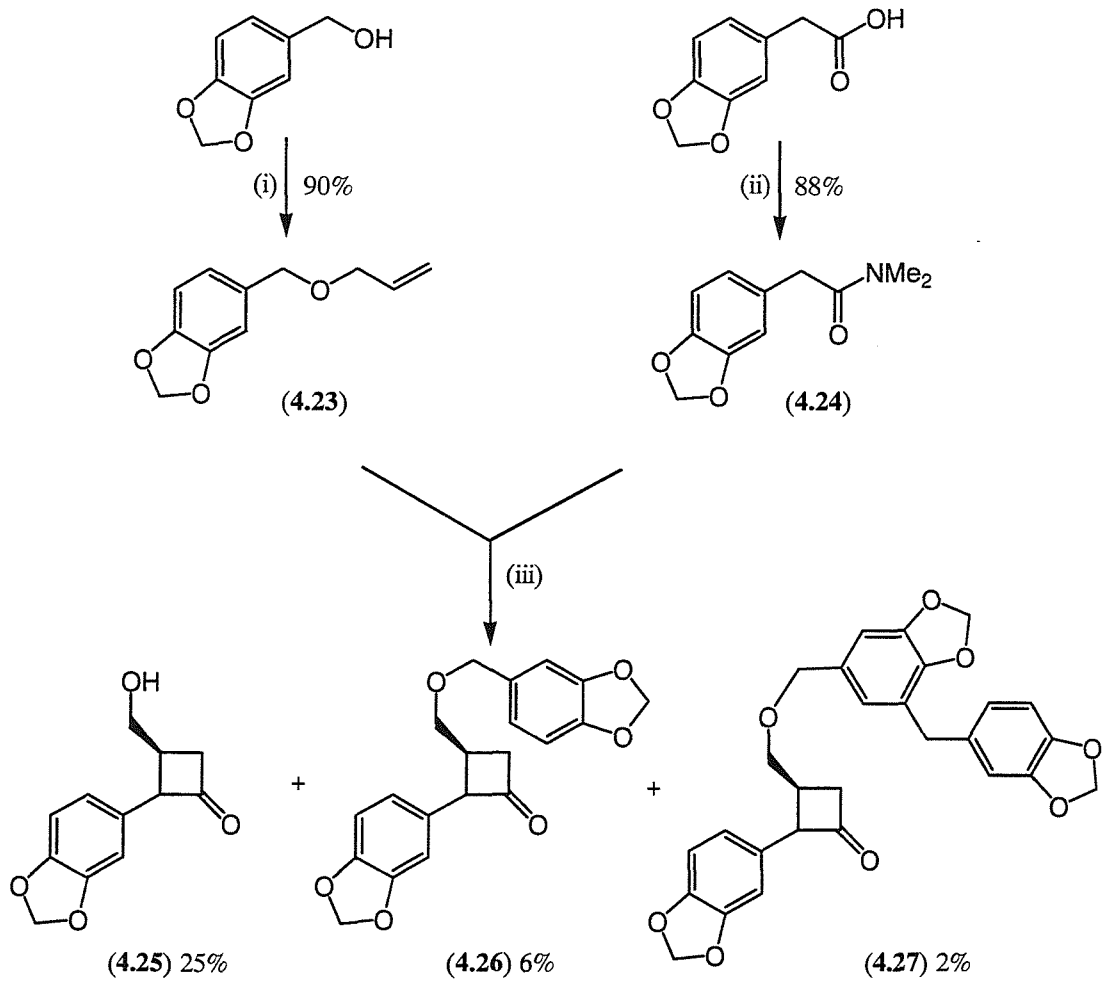
Although the stereochemistry across the newly formed C-C bond remained unexplained we decided to exploit the new methodology in a natural product series (*vide supra*) prior to embarking on an exercise aimed at investigating the diastereoselectivity. It should be

noted that there are no known examples of natural products in the furofuranone series with the *exo, endo-* relative stereochemistry. Nonetheless, bicyclic lactone intermediates (*e.g.* **4.2**) of this type are well documented as being useful intermediates in the preparation of the common furofurans [99]. Our first target in this area was the preparation of the symmetrically substituted derivative asarinin (**2.40**).

4.2 The Synthesis of (±)-Asarinin – A Furofuran Lignan with Symmetrically Substituted Aromatic Groups

4.2.1 Preparation of the Lactone Intermediate

The precursor alkene (**4.23**) and amide (**4.24**) required for the ketenimium cycloaddition strategy were prepared by standard methodology, as outlined in Scheme 4.6. However, cycloaddition under the same conditions as in the model series resulted in the isolation of a complex mixture of products, the majority of which was insoluble matter that precipitated on warming to room temperature.



Reagents and Conditions: (i) (a) NaH, DMF (b) allyl bromide, NaI (ii) (a) $(COCl)_2$, CH_2Cl_2, cat. DMF (b) $NHMe_2$ (aq.), CH_2Cl_2 (iii) (a) Tf_2O, CH_2Cl_2 -25°C (b) 2,6-di*tert*butylpyridine, (**4.23**), CH_2Cl_2 (c) $NaHCO_3$ aq., Δ.

Scheme 4.6

Inspection of the product mixture clearly revealed that some of the desired cyclobutanone (**4.26**) is formed along with byproducts arising from the cleavage of the benzylic ether. It would appear that the mildly acidic reaction conditions result in cleavage of this bond to

give alcohol (**4.25**) and a Friedel Crafts adduct (**4.27**)(Figure 4.7). The acidity of the pyridinium triflate salt (**4.28**), in concert with activation by the electron rich aromatic nucleus, is such that the benzylic ether is cleaved to provide the reactive electrophile (**4.29**). The precipitation of an intractable solid suggests that this electrophile predominantly polymerises, but to a lesser extent it undergoes a Friedel Crafts alkylation to produce (**4.27**). Which of the two aromatic rings underwent the Friedel Crafts reaction is unclear from the analytical data.

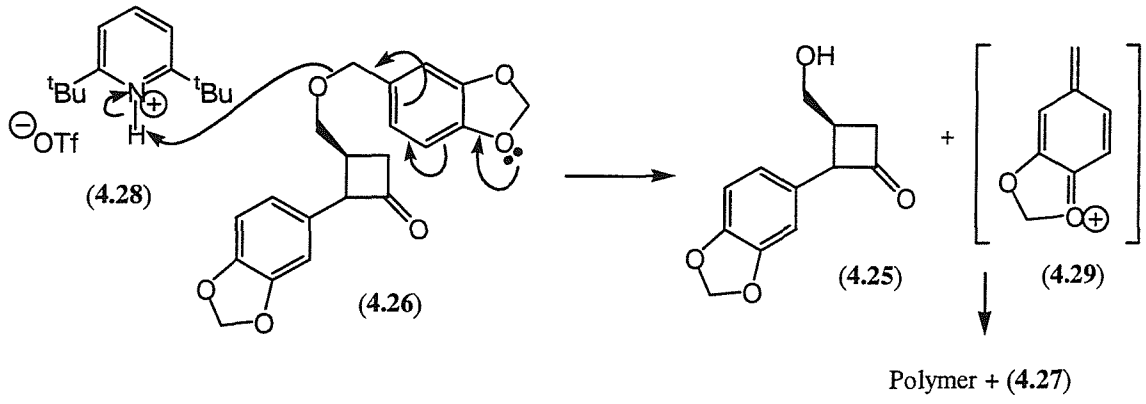
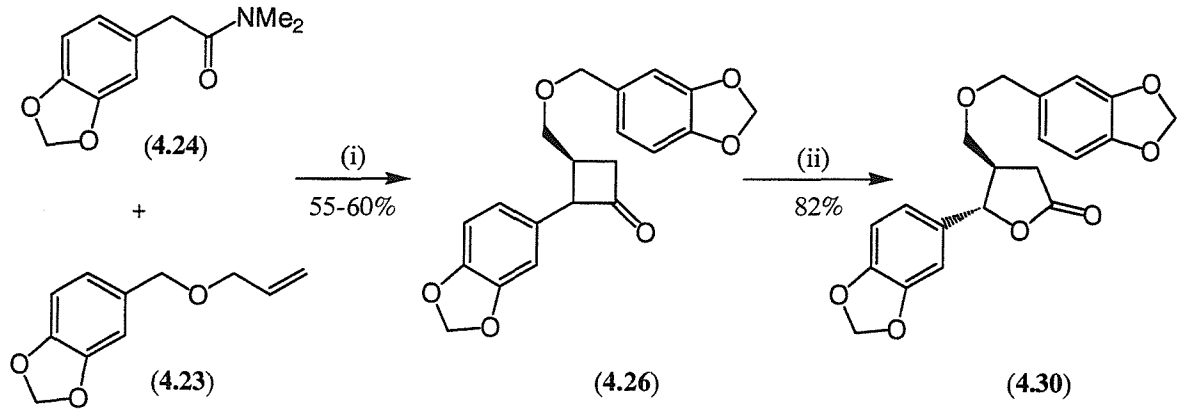


Figure 4.7 Friedel Crafts formation of byproducts in cycloaddition reaction

Our first attempt to overcome this problem was to conduct the reaction at a lower temperature throughout the entire cycloaddition stage, and to ensure that there was a slight excess of the organic base relative to the triflic anhydride. Unfortunately, no cycloaddition products were isolated after prolonged stirring at 0°C. Raising the temperature any higher resulted in the formation of a precipitate indicative of ether cleavage and polymerisation that we had observed previously. TLC analysis of the reaction mixture after hydrolysis revealed the same complex product profile as before.

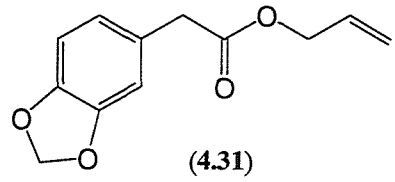
We transferred out attention to trying to buffer the cycloaddition reaction by using an inorganic base. Our first attempt used potassium carbonate for this purpose. It was added after formation of the acyclic iminium salt and immediately prior to the addition of the alcohol/ organic base mixture. In the model system the presence of potassium carbonate had no effect on the yield of the cycloaddition. Gratifyingly, the same reaction in the asarinin system gave the desired compound (**4.26**) in a 55-60% yield, with no evidence for the formation of any products derived from ether cleavage. The compound was a mixture of diastereoisomers isolated in a ratio of 10:1 *trans/ cis* that could only be partially purified by chromatography on silica gel (Scheme 4.7).



Reagents and conditions: (i) (a) Tf_2O, CH_2Cl_2 -25°C (b) K_2CO_3 then 2,6-di*tert*butylpyridine, (**4.23**), CH_2Cl_2 (c) $NaHCO_3$, Δ (ii) H_2O_2, AcOH.

Scheme 4.7

In the light of the expense of the 2,6-di*tert*butylpyridine we conducted the cycloaddition in the presence of potassium carbonate with only 0.5 equivalents of the organic base.

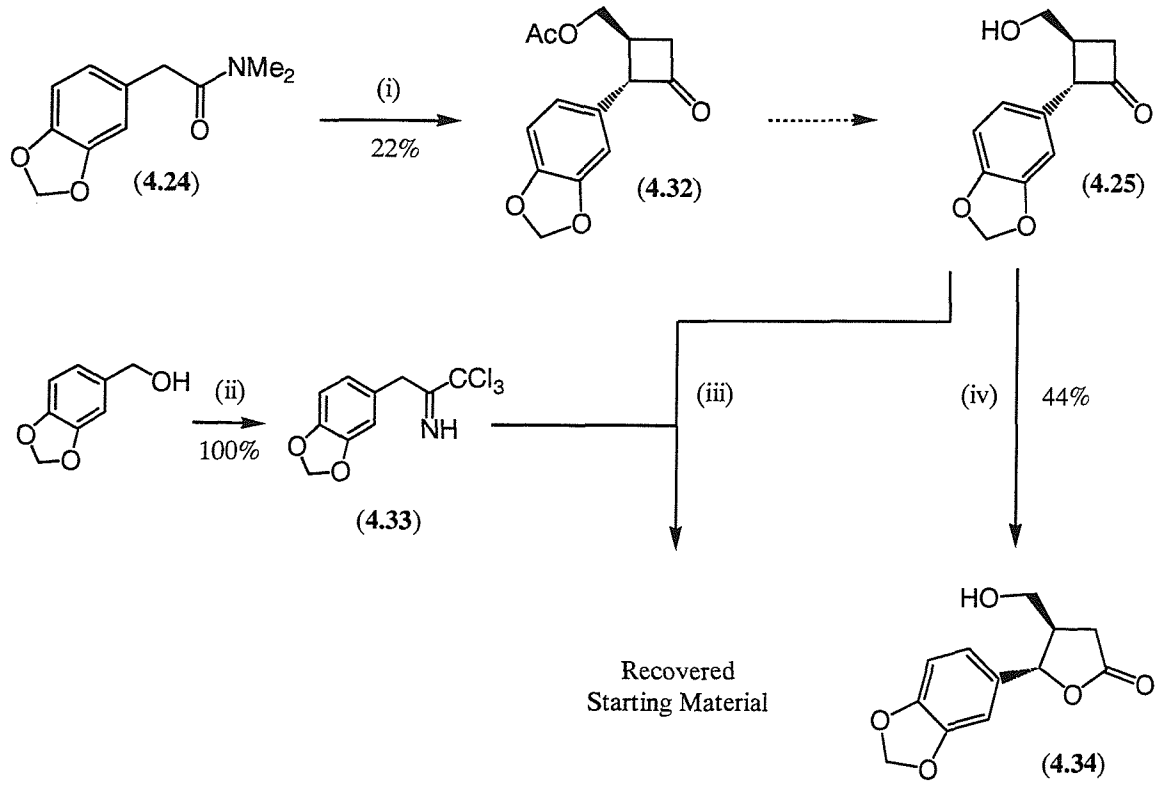


Unfortunately no cyclobutanone derivative was isolated in this case. The main product was ester (**4.31**) (45%) arising from cleavage of the carbon-oxygen bond in ether (**4.23**), followed by nucleophilic attack of the resultant allyl alcohol at the acyclic iminium species before hydrolysis.

Baeyer Villiger oxidation of cyclobutanone (**4.26**) provided the lactone (**4.30**). Fortunately it proved relatively easy to purify the desired *trans*-lactone isomer by column chromatography. The minor, more polar, isomer was only isolated in a pure state from a larger scale reaction and after repeated chromatography.

Overall the sequence of reactions towards **4.30** was more efficient in the asarinin series than with the model compound. We anticipated that the buffering methodology described herein would provide a general method for the preparation of cyclobutanones substituted with acid sensitive functionality. Unfortunately its generality was called into question by later work during this project.

Prior to the successful conclusion to the cycloaddition work outlined above we investigated the possibility of preparing alcohol (**4.25**) and utilising it as an intermediate in the preparation of differentially substituted lignan compounds. Some trial reactions were carried out, the results from which are outlined in Scheme 4.8.



Reagents and Conditions: (i) (a) Tf_2O, CH_2Cl_2 -25°C (b) 2,6-di*tert*butylpyridine, allyl acetate, CH_2Cl_2 (c) $NaHCO_3$ aq., Δ (ii) KOH (50% aq.), $Bu_4N^+HSO_4^-$, Cl_3CCN, CH_2Cl_2 (iii) H_2O_2, AcOH (iv) TfOH, CH_2Cl_2.

Scheme 4.8

Cycloaddition to provide the acetate derivative (**4.32**) occurred to give the desired compound in a relatively poor yield. It should be noted that this was carried out in the absence of K_2CO_3 and use of our modified strategy might prove beneficial to the efficiency of the transformation.

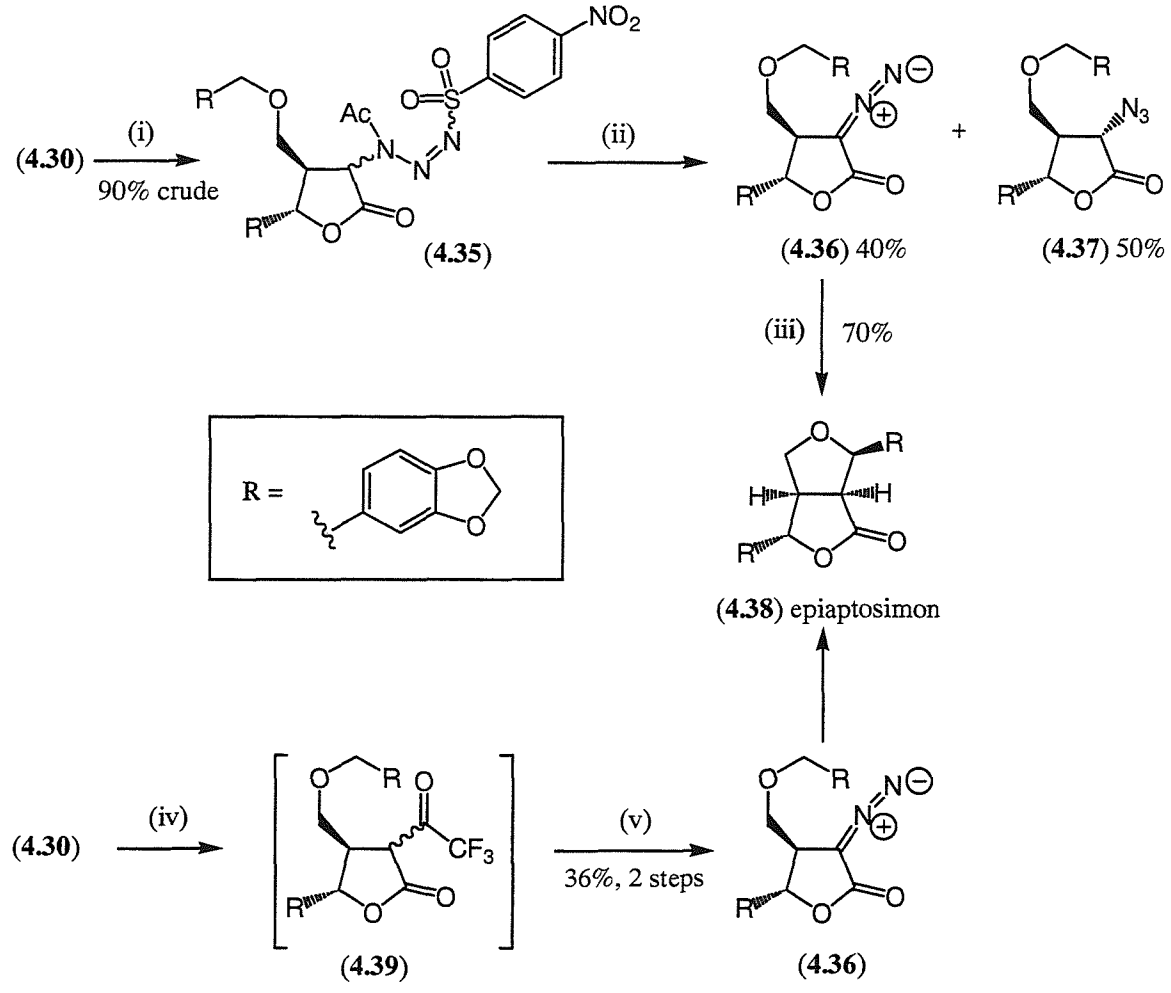
There were several alternatives at this stage; the one followed was indicated by the availability of intermediates from previous reactions. Baeyer Villiger oxidation of the hydroxymethylcyclobutanone (**4.25**) provided the lactone (**4.34**) although in a poorer yield than any of the previous oxidations undertaken. Both of the alcohols (**4.25**) and (**4.34**) represent viable starting materials for reaction with appropriately substituted trichloroacetimidates in the preparation of ethers. The only etherification reaction attempted to date involved attempted alkylation of an alcohol with a trichloroacetimidate (**4.33**), prepared under phase transfer conditions [142], with (**4.25**). Acid catalysed etherification [143] failed to return any of the desired product.

In the light of the ultimate success of the cycloaddition strategy the chemistry outlined above was not pursued any further. However, there remains scope for further investigation

should a differentiating route to furofuranone lignans, in terms of introduction of the second aromatic functionality, become a priority.

4.2.2 Preparation of Epiaptosimon [112]

The diazo-transfer and insertion methodologies were carried out according to the detail in Scheme 4.9. Formation of the lithium enolate of the lactone followed by reaction with the sulfonyl azide and trapping with acetyl chloride provided the acylated azene (**4.35**) which was immediately decomposed to the azide (**4.37**) and diazo- (**4.36**) compounds.



Reagents and conditions: (i) (a) LiHMDS, THF (b) *p*-nitrobenzenesulfonylazide, THF (c) acetyl chloride (ii) DMAP, THF (iii) CH_2Cl_2, $Rh_2(OAc)_4$ (iv) LiHMDS, $CF_3C(O)CH_2CF_3$, THF (v) *p*-nitrobenzene-sulfonylazide, NEt_3, CH_3CN, H_2O.

Scheme 4.9

Similar yields to those experienced in the model system were obtained although purification was complicated by the fact that lactone, acylated triazene, azide and diazo-derivatives were extremely difficult to resolve during purification by chromatography on silica gel. The stereochemistry of the major isomer of the azide was determined from the results of nOe experiments (Figure 4.8).

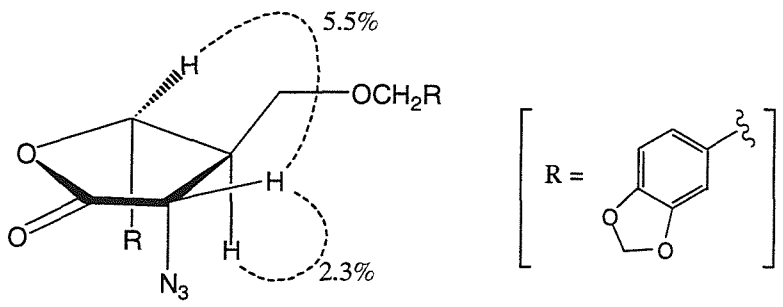


Figure 4.8 nOe Assignment of relative stereochemistry of azide (4.37)

A single reaction was conducted utilising NaHMDS as the base in the formation of the lactone enolate. Treatment of the sodium enolate with the diazo- transfer agent gave a deep purple triazene anion (the lithium enolate gave a distinctly different deep red colouration which persisted until treatment with the acylating agent) which very rapidly decolourised. Treatment of the reaction mixture with acetyl chloride and then warming resulted in the lactone (**4.30**) being the only material recovered in any quantity (45%).

Although our focus remained on attempting to control the Evans' chemistry such that the diazo- derivative (**4.36**) was produced selectivity we did undertake a single investigation of the two step strategy first described by Danheiser *et al.* [133] In our hands conversion to the trifluoroacylated lactone (**4.39**) followed by diazo-transfer provided the target compound in a yield that was lower than the current best method. Nonetheless, it did have the merit of being chemoselective which eased purification and there was ample scope for optimisation. In the first instance the natural product studies continued to be funded through diazo- compound preparation using the azene methodology whilst optimisation studies on the Danheiser route were initiated elsewhere within the Brown group.

The rhodium catalysed diazoinsertion accomplished the relevant C–H bond insertion with only a single diastereomer being produced [144]. Once again the compound was shown to belong to the *endo, exo-* class of compounds (**4.38**) through correlation with data from the model series, through comparison with literature data for epiaptosimon [112] and through the irrefutable results of X-ray crystallographic studies which are represented pictorially below (Figure 4.9). The insertion appeared to be slightly less efficient and no other definable products were isolated. Even more unusual was the fact that the heat mediated diazoinsertion failed to give any product after heating under reflux for 48 hours in dichloroethane. Under these conditions approximately 60% of the diazo compound (**4.36**) was recovered. These results would not appear to be in accord with the fact that the rhodium carbenoid is expected to be electrophilic in the first instance. The electron rich aromatic should further activate the benzylic C–H positions towards reaction with the

carbenoid in comparison with the unsubstituted phenyl ring of the model compound. The most likely explanation at this point is that, in the case of the model series the heat mediated insertion reaction might have been carried out in glassware contaminated with a metal salt capable of mediating the diazo-decomposition.

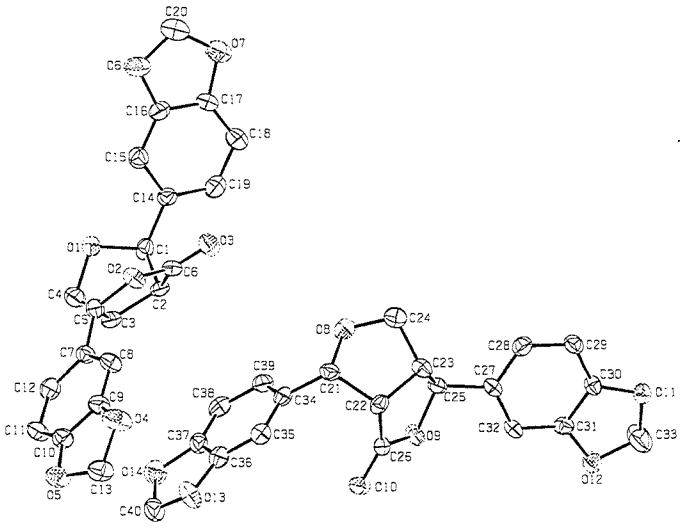
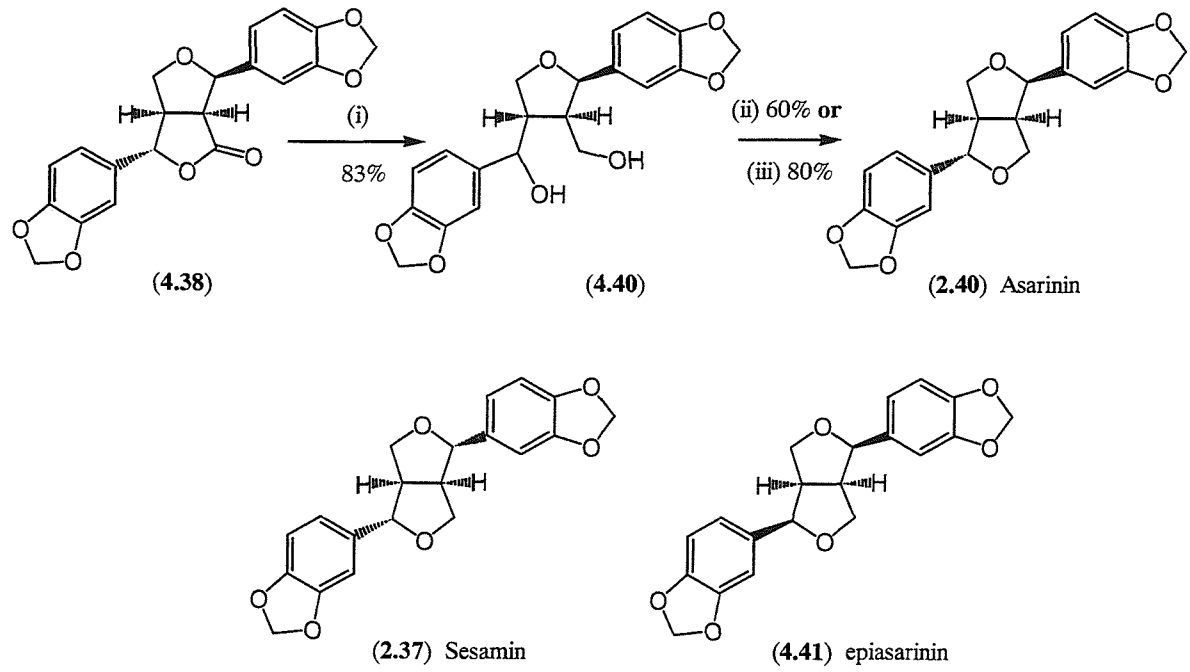


Figure 4.9 Crystal structure of *epi*-aptosimon (4.38) [145]

4.2.3 Conversion of Epiaptosimon to Asarinin

The work outlined thus far constitutes a formal synthesis of asarinin. However, we decided to complete the total synthesis by using the two literature methodologies to confirm that furofuranone derivatives genuinely do represent synthetically useful intermediates in the preparation of furofurans. Thus, the two methods were employed to convert the lactone into a tetrahydrofuran moiety (Scheme 4.10).

Reduction of epiaptosimon to the diol (**4.40**) was accomplished using lithium aluminium hydride. Subsequent ring closure was described as being accomplished on treatment of the diol with aqueous acid as part of the work up of the reduction reaction [112]. In our hands no sign of ring closure was observed during the work up procedure. Indeed, treatment of **4.40** (after isolation and purification) with HCl (aq.) in methanol caused cyclisation to occur over a period of 3 days. Asarinin (**2.40**) was isolated in 60% after this time and 12% of the diol (**4.40**) was recovered from the reaction. In addition, on larger scale reactions it became apparent that another product was also being formed in the reaction which was eventually isolated (in approximately 5% yield).



(**4.38**) (**4.40**) (**2.40**) Asarinin

(**2.37**) Sesamin (**4.41**) epiasarinin

Reagents and conditions: (i) $LiAlH_4$, THF (ii) HCl, MeOH **or** (iii) $MeSO_2Cl$, pyridine.

Scheme 4.10

The ^1H and ^{13}C NMR data of this derivative indicate that the furofuran is symmetrical, but suggest that the byproduct is not the *exo, exo-* isomer sesamin (**2.37**) [114]. Instead it appears to belong to the *endo, endo-* class of compounds, examples of which have been isolated from natural sources [71]. Indeed, epiasarinin (**4.41**) is a known compound, first described by Beroza and co-workers in 1956 [146]. Their study involved taking sesamin (**2.37**) and refluxing in methanolic HCl before isolating from the subsequent equilibium mixture a compound isomeric with sesamin and asarinin that they concluded was the *endo, endo-* structure (**4.41**). Proof that this was the case was taken from the fact that re-isomerisation of (**4.41**) produced a mixture of the thermodynamically more stable isomers sesamin (**2.37**) and asarinin (**2.40**).

Comparison of the NMR data acquired on the byproduct with closely related structures proved inconclusive. No NMR data for (**4.41**) itself is available in the chemical literature and the data for related series of compounds is not necessarily representative. Data on the isolated byproduct, sesamin, and representative pair of *exo, exo-* and *endo, endo-* furofurans are presented on the following page (Table 4.2).

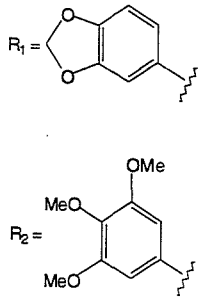
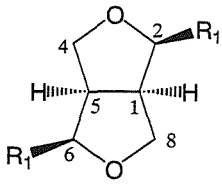
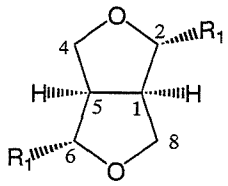
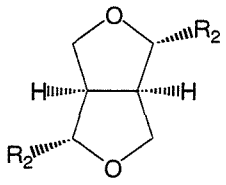
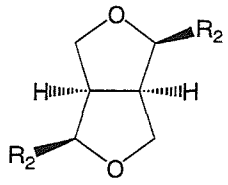
				
	Byproduct (proposed structure)	**Sesamin [114]**	**Yangambin [147]**	**Diayangambin [147]**
1, 5 H	3.14 (m)	3.05 (m)	3.12 (m)	3.22 (m)
4, 8 H	3.53 (dd, *J* 9.9, 6.6Hz)	3.86 (dd, *J* 9.0, 4.0 Hz)	3.95 (dd, *J* 9.5, 3.5 Hz)	3.61 (dd, *J* 9.5, 8.5 Hz)
4, 8 H	3.73 (dd, *J* 9.9, 1.8 Hz)	4.23 (dd, *J* 9.0, 7.0 Hz)	4.32 (dd, *J* 9.0, 7.0 Hz)	3.76 (dd, *J* 9.5, 2.5 Hz)
2, 6 H	4.88 (d, *J* 5.5 Hz)	4.71 (d, *J* 4.5 Hz)	4.76 (d, *J* 4.0 Hz)	4.93 (d, *J* 4.5 Hz)

Table 4.2 ^{1}H NMR data on *exo, exo-* and *endo, endo-* symmetrically substituted furofuranones

The best fit is with the diayangambin family of compounds that contain the *endo, endo-* skeleton supporting the proposal of *endo, endo-* stereochemistry in our by product

The alternative process of forming a mono-mesylate, that spontaneously cyclised under the reaction conditions, proved to be much more effective. After a period of 5 hours all the diol was consumed and asarinin **(2.40)** was the only product isolated. The relative stereochemistry of the two aromatic bearing carbon atoms was established by X-ray crystallographic analysis (Figure 4.10).

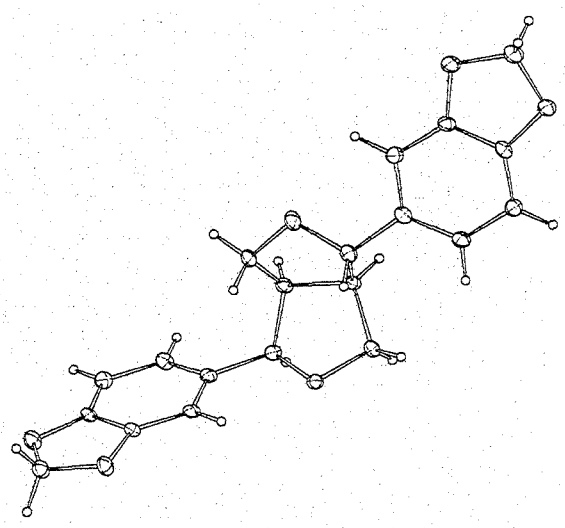
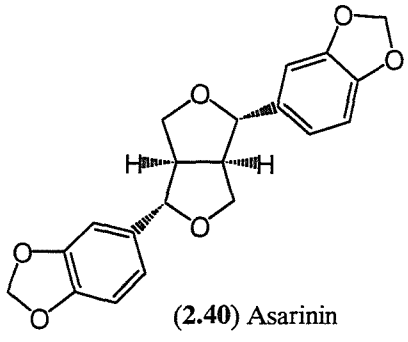


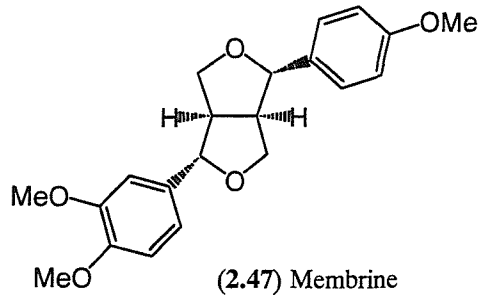
Figure 4.10 Crystal structure of racemic asarinin (2.40) [148]

Thus, the *exo, endo*- substituted furofuran lignan asarinin (**2.40**) was synthesised in 6 steps [149] from readily available starting materials in an overall yield of approximately 9%. Comparison with some of the prior art revealed the methodology employed to be at least comparable and in most cases more efficient than previous work: Ogasawara's racemic synthesis of asarinin [104] was 18% efficient over 8 steps with multiple complex purifications; Whiting's racemic method [112] involved 6 steps in an overall yield of 6%; Wirth's enantioselective methodology [109] yielded membrine (**2.47**) in 5 steps in 4% overall yield.

Clearly the methodology described was yet to meet some of the criteria laid out at the beginning of this section. Nonetheless, its success compared with other methods in the literature suggested that further investigation was justified. The next challenge was to prepare a furofuran lignan in which the aromatic groups were differentially functionalised to confirm its utility with this class of compounds. It was anticipated that a more general demonstration of the method's utility in the synthesis of racemic furofurans would support a more protracted evaluation of the diastereoselection during C–H insertion and the enantioselectivity of the synthesis as a whole.



(**2.40**) Asarinin



(**2.47**) Membrine

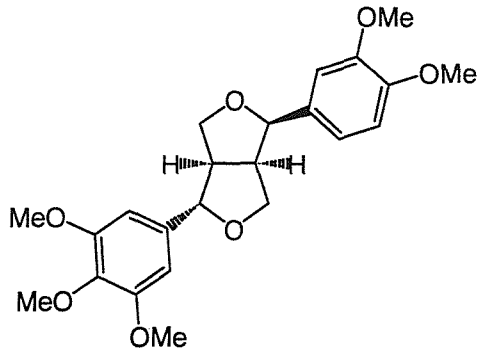
Whiting: 6 step racemic synthesis - overall yield 6%
Ogasawara: 9 step racemic synthesis - overall yield 18%

Wirth: 5 step chiral synthesis - overall yield 4%

Figure 4.11 Comparative efficiency of furofuran syntheses

4.3 The Synthesis of (±)-Epimagnolin A – A Furofuran Lignan with Unsymmetrically Substituted Aromatic Groups

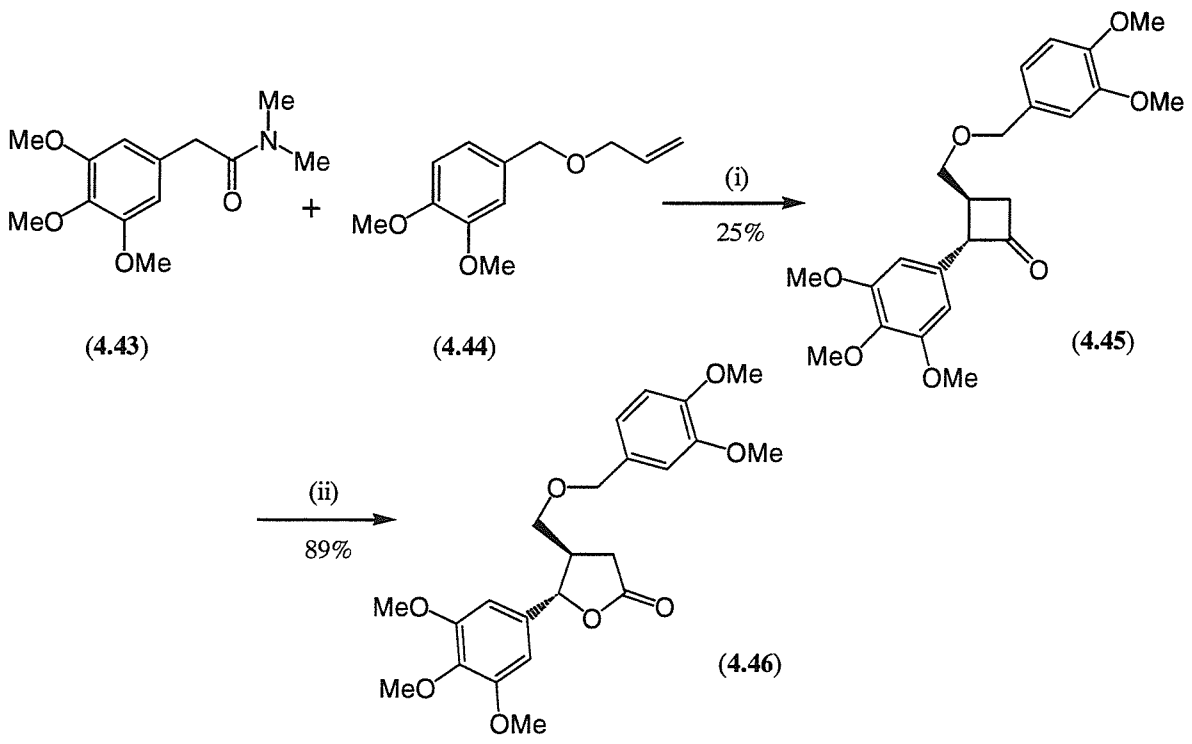
Epimagnolin A (**4.42**) is a furofuran lignan originally isolated from the buds of *Magnolia fargesii* which has been demonstrated to have insecticidal activity in the form of growth inhibition of *Drosophilia melanogaster* [150].



(**4.42**) Epimagnolin A

Since it was first reported in 1994 the compound has been utilised as a starting material in a series of experiments evaluating its microbial oxidation [151]. The feedstock for this study was material isolated from the natural source; the compound itself has never been subjected to total synthesis. This fact along with our interest in preparing a furofuran lignan with differentially substituted aromatic groups led us to select epimagnolin A (**4.42**) as our next target.

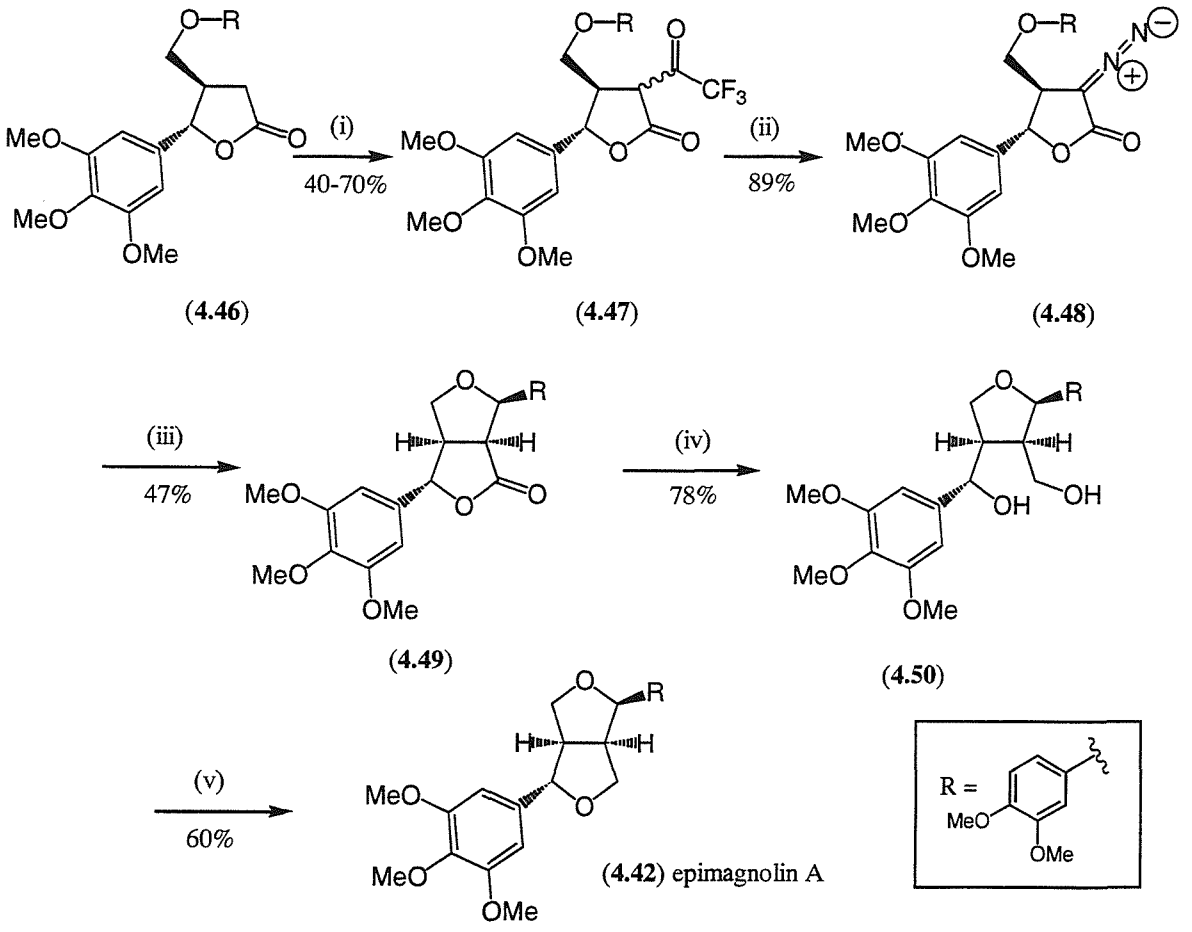
The *N,N*-dimethylphenylacetamide (**4.43**) and benzylallyl ether (**4.44**) derivatives were prepared using the previously described methods in yields of 89% and 70% respectively. Cycloaddition to the cyclobutanone derivative (**4.44**) proved problematical (Scheme 4.11). The compound could be isolated in only 20-25% yield. It would appear that the buffering influence of the potassium carbonate does not have a beneficial effect on this reaction although the control experiment in the absence of inorganic base has not been conducted. Given the diastereoselectivity of the reaction, and our experience with it, we elected to continue to use it to fund our studies although we recognised it as a limiting factor in the applicability of the method. Baeyer Villiger oxidation provided the lactone (**4.46**) in high yield.



Reagents and conditions: (i) (a) Tf_2O, CH_2Cl_2 -25°C (b) K_2CO_3, 2,6-di*tert*butylpyridine, (**4.44**), CH_2Cl_2 (c) $NaHCO_3$ aq., Δ (ii) H_2O_2, AcOH

Scheme 4 .11

At this point our synthesis took a different route (Scheme 4.12). In part this was forced upon us by the fact that the much increased polarity of the compounds in the epimagnolin A series, relative to their asarinin analogues, caused all the purifications to be troublesome. The likely purification difficulties in the non-chemoselective diazo compound preparation might have proved insurmountable. Separately, other work in the Brown group was re-evaluating diazotransfer to lactones substituted with α-trifluoroacetyl functionality, a method that had proved useful but no improvement on the azene methodology on first inspection. However, repeat experiments showed that with careful temperature control, work-up and purification the diazotransfer to trifluoroacetyl derivatives (**4.47**) could be completed effectively. As a consequence the latter route was used during this synthesis (a discussion of other diazotransfers to acyl substituted lactones may be found in section 4.4.2).



(4.46) (4.47) (4.48)

(4.49) (4.50)

(4.42) epimagnolin A

Reagents and conditions: (i) LiHMDS, THF (b) $CF_3C(O)OCH_2CF_3$ (ii) *p*-nitrobenzenesulfonyl azide, NEt_3, CH_3CN, H_2O (iii) CH_2Cl_2, $Rh_2(OAc)_4$ (iv) $LiAlH_4$, THF (v) $MeSO_2Cl$, pyridine.

Scheme 4.12

Thus, diazo-transfer was accomplished over two steps with, at best, 62% efficiency to provide diazolactone (**4.48**). Subsequent insertion produced furofuranone (**4.49**) as the only isolable compound. Reduction followed by cyclisation by previously described methods provided epimagnolin A (**4.42**) [152, 153]. In this instance care had to be taken to avoid over reduction of the benzylic hydroxyl functionality.

The methodology utilised in the previous sections successfully met several of the objectives established at the outset of the project. We have prepared furofurans with differentially substituted aromatic rings in a diastereoselective fashion that favoured the *endo, endo-* relative stereochemistry. Our results compare favourably with alternative preparations described in the literature and add to its substance by providing to methods for the preparation of α-diazolactones. The outstanding work of investigating the impact of ligands on rhodium and the conversion to a stereoselective preparation will the subject matter of later research programmes.

4.4 Alternative Strategies for the Preparation of Diazolactones

4.4.1 Utilisation of the Azide Intermediates

At the outset of the investigation into preferential electrophilic diazo- *vs.* azido-functionalisation we hoped to be able to reproduce Evans' complete selectivity in favour of diazo formation. Our results have shown no evidence to support the notion that this might be achievable. Nonetheless, the relative efficiency of the process, in terms of mass balance was seen as a step forward compared to the prior art. A problem with the lack of chemoselectivity was the increased difficulty of purification given the similar chromatography characteristics of the diazo- and azido- compounds. However, with care separation was possible. Given that azides can themselves be converted into diazo compounds one way of improving the overall efficiency, albeit in a round about fashion, would be to evaluate the feasibility of this conversion. Only two attempts to achieve this goal have been made, both without any success.

Reduction of the azide to the amine, with a view to preparation of the diazo- derivative using $NaNO_2$/ HCl, failed when using ammonium formate in the presence of 5% palladium on carbon [154]. A more speculative strategy, based on some preliminary results described by G. Feigelson [155] involved preparation of an iminophosphorane by treatment of the azide with triphenylphosphine followed by treatment with nitrosonium tetrafluoroborate and *N,N*-di*iso*propylethylamine (Figure 4.12).

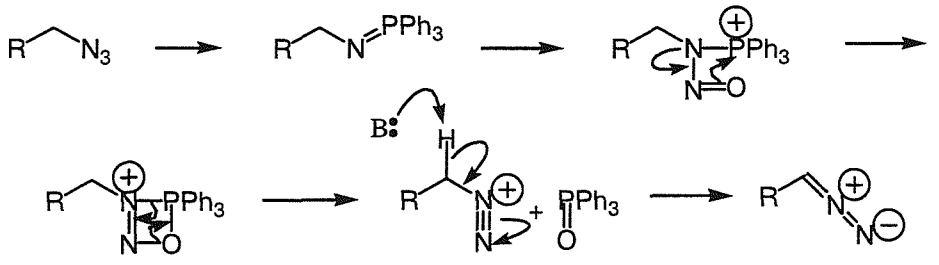


Figure 4.12 Proposed mechanism for the conversion of iminophosphoranes into diazo-derivatives

In our hands the reaction of the azide did produce an intermediate (evidence by TLC) which did not react with the NO^+ in the manner outlined above. The crude product did not contain diazo- or γ-lactone functionality (determined by IR). In view of the poor yield described in the literature, and the observation that the nitrosonium tetrafluoroborate was not fully soluble in the reaction solvent (CH_2Cl_2), the methodology was not investigated any further.

4.4.2 Activation at the C-3 Position of the Lactone

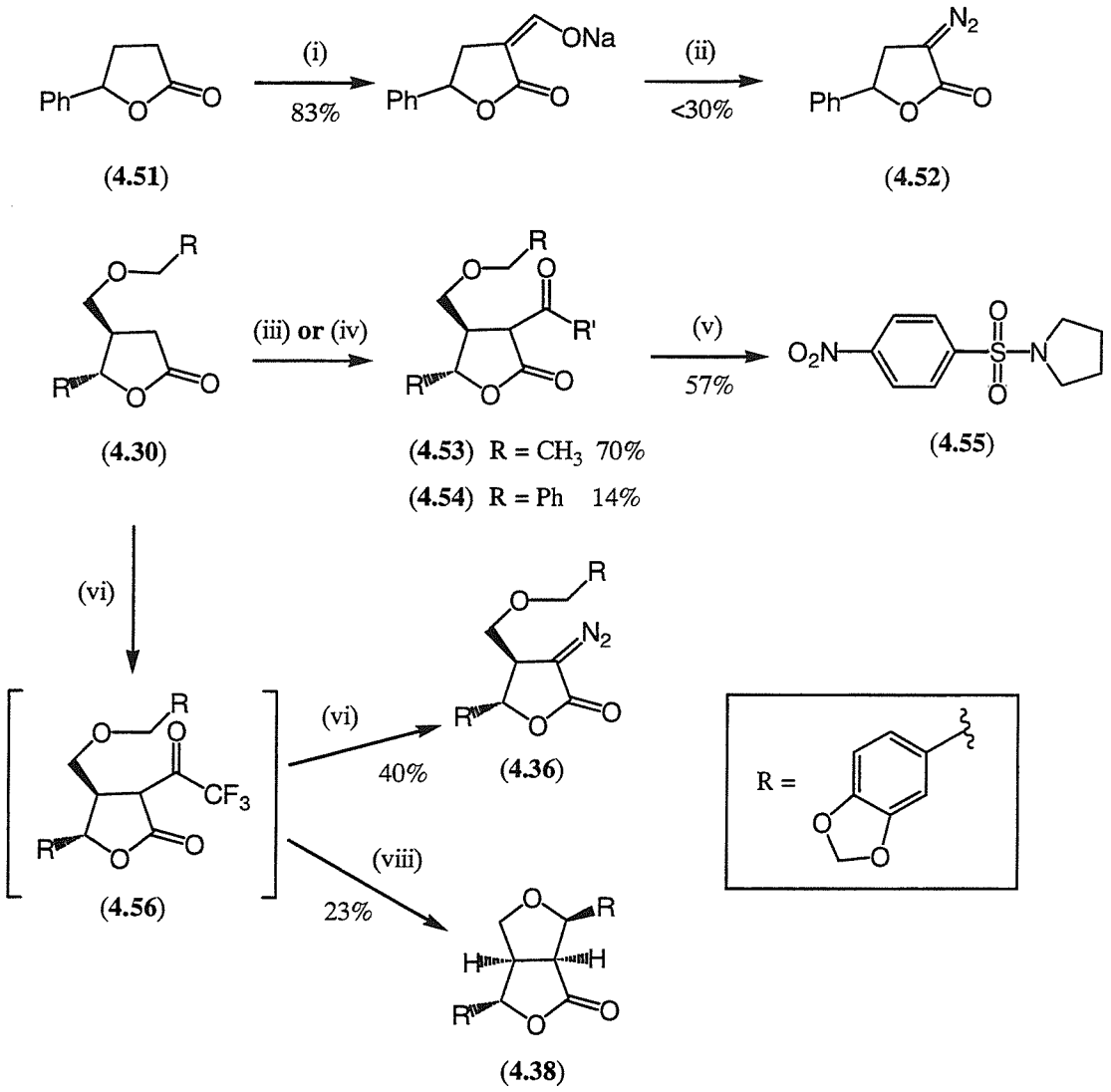
A commonly used approach in the preparation of α-diazocarbonyl compounds is to activate the α-position by transforming the compound into a β-dicarbonyl in which the new carbonyl group is used in a sacrificial sense during the diazo-transfer reaction. Indeed, formylation of γ-butyrolactone followed by diazo-transfer represents the only previously described method for the synthesis of α-diazolactones, in only 14% yield [129]. A single attempt to reproduce these results, on a related model compound (**4.51**), did result in isolation of the diazo- derivative (**4.52**) in an improved yield compared to that described.

More recent work describes the use of acylation as a means of activation of ketones [131]. Thus, acylation with acetyl chloride [156] proceeded as required to provide the acetyl derivative (**4.53**), although precise confirmation of structure was difficult because of a mixture of epimers at C-3 and keto/ enol tautomerism.

However, we were unable to isolate any diazo- derivative after treatment of (**4.53**) according to the literature protocol. Treatment of (**4.53**) with *p*-nitrobenzylsulfonyl azide and DBU, followed by a pyrrolidine resulted in the isolation of sulfonamide (**4.55**) that accounted for 60% of the azide transfer agent employed in the reaction.

Benzoylation, as a means of activation, has also been described by Taber and colleagues [157]. Evaluation of this strategy faltered at the first hurdle in that the target β-dicarbonyl compound (**4.54**) could only be isolated in approximately 14% yield.

The most common means of activation which has been used widely is the trifluoroacetylation method described by Danheiser *et al.* [133] Once again a brief initial investigation was conducted using the asarinin precursor lactone (**4.30**). The activated intermediate (**4.56**) was prepared and immediately treated with a mixture of the water, triethylamine and the diazo-transfer reagent. In the first instance the reaction provided the diazo- derivative (**4.36**) along with a recovered lactone, compounds which could be reasonably easily separated by silica gel chromatography.



Reagents and Conditions (i) ethyl formate, NaH, EtOH, THF (ii) *p*-nitrobenzenesulfonyl azide, DMF (iii) (a) LiHMDS, THF (b) $CH_3C(O)Cl$ (iv) NaH, $PhCO_2Me$, THF (v) (a) *p*-nitrobenzenesulfonyl azide, DBU, CH_2Cl_2 (b) pyrollidine (vi) (a) LiHMDS, THF (b) $CF_3C(O)OCH_2CF_3$ (vii) *p*-nitrobenzenesulfonyl azide, NEt_3, CH_3CN, H_2O. (viii) as for (vii) except part (b) involved addition of reagent at 0°C.

Scheme 4.13

A repeat reaction, intended to confirm the result in terms of the efficiency of preparation of **(4.36)** failed to isolate it in any more than trace quantity. Surprisingly, purification of the crude reaction mixture resulted in the isolation of epiaptosimon **(4.38)** arising from diazoinsertion occurring in the same reaction as the diazotransfer, that is, without recourse to metal catalysis or heating. At this juncture there is no explanation for this observation. It is unlikely that trace acid would be responsible as this would favour formation of diazonium species that, on loss of nitrogen, would form an unstabilised carbocation that would be susceptible to rapid elimination to provide a dihydrofuran product.

The method, even in the face of this anomalous result, represented a viable alternative to the azene decomposition strategy for the preparation of the diazo intermediates. The yields

of the two methods were similar in these early investigations but the trifluoroacylative transfer methodology had the merit of being chemoselective. As a consequence, purification of the diazo- compound was more straightforward. Nonetheless, the azene decomposition method was used for the whole asarinin synthesis part of the programme. The later synthesis of *epi*magnolin A (*vide infra*) demonstrated the superior efficacy of Danheiser's methodology and further work in Brown's group has clearly established it as the method of choice in the synthesis of 4,5-disubstituted-3-diazolactones [153].

4.4.3 The Bamford Stevens Approach

An alternative approach to the work described thus far is to generate a diazo- species by fragmentation of an appropriate functionality already established in a molecule. There are a number of ways of achieving this, one of which is the Bamford Stevens reaction [158]. This reaction has been used in the past as a means of generating alkenes from tosylhydrazones. It is still used in this capacity in more recent syntheses [159, 160] although it has been superceded by the Shapiro reaction which has wider applicability [161]. The reaction involves the decomposition of a tosylhydrazone by base in either protic or aprotic solvents under the influence of either heat or light (Figure 4.13).

Camphor tosylhydrazone (**4.57**) decomposes with heating, in the presence of base, to give diazo- compound (**4.58**). Under protic conditions this is protonated to give a diazonium compound (**4.59**) which collapses to carbocation (**4.60**). A series of carbocation rearrangements provides camphene (**4.61**). Under aprotic conditions the diazo compound undergoes a unimolecular decomposition to a carbene (*e.g.* **4.62**) which, in this case, inserts into a suitably disposed C–H bond to give the tricycle (**4.63**).

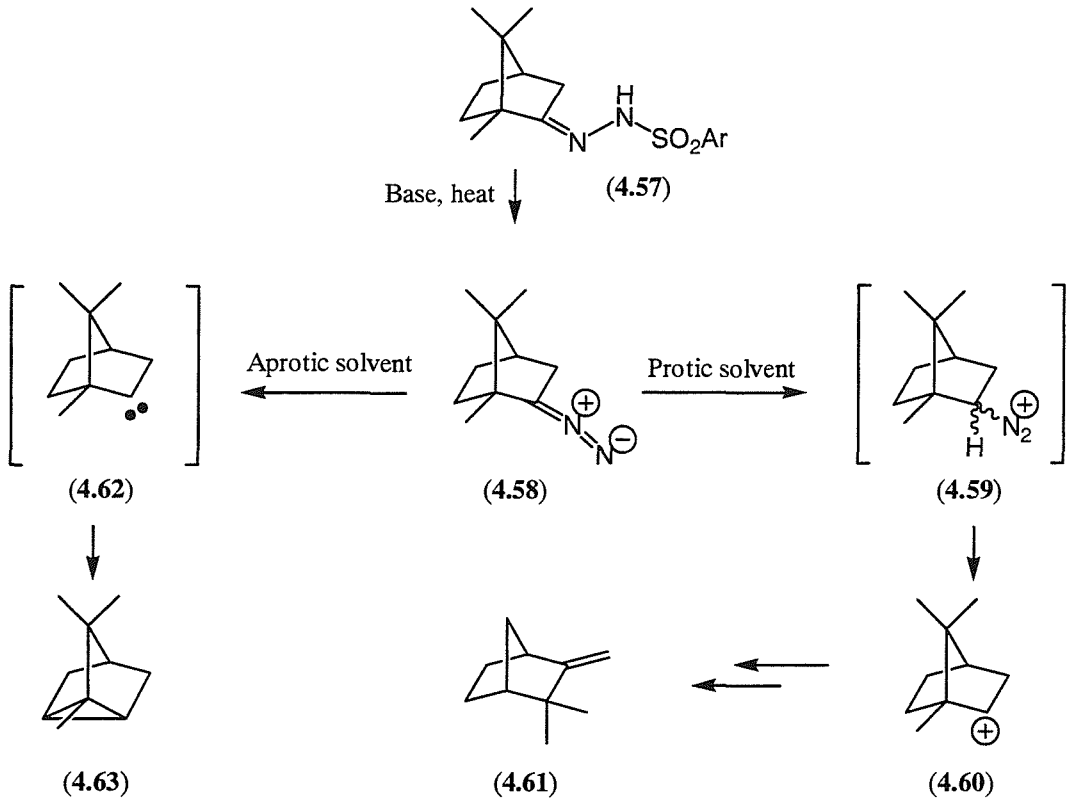


Figure 4.13 The two mechanisms of the thermal Bamford Steven's reaction

In general, protic conditions are not synthetically useful because of the ionic rearrangements that tend to lead to complex mixtures in anything but the most simple substrates. Aprotic conditions give products with greater chemoselectivity but may still operate by an ionic mechanism if the protonation of the diazo compound (*e.g.* **4.58**) to form a poorly solvated carbonium ion is faster than its decomposition to the carbene (*e.g.* **4.62**). This can be controlled in favour of carbene formation by ensuring an excess of base is present [162].

In general, tosylhydrazones of cyclopentanones and cyclohexanones were found to give 1,2-C–H insertion on decomposition under aprotic conditions [163]. Essential to our aims is the statement in the prior art that 1,2-C–H insertion is favoured when no competitive intramolecular option was available.

We hoped that we might be able to take an appropriately substituted tosyl hydrazone (**4.64**) and deprotonate under aprotic conditions in the presence of dirhodium (II) tetraacetate. The question to be answered was would the resultant unstabilised carbenoid (**4.65**) show a similar reactivity to the α-carbonyl stabilised intermediates implicated in our successful preparation of furofurans? In essence would 1,5-C–H insertion occur in preference to 1,2-C–H insertion (Figure 4.14) and, if so, what would be the stereochemistry of the insertion?

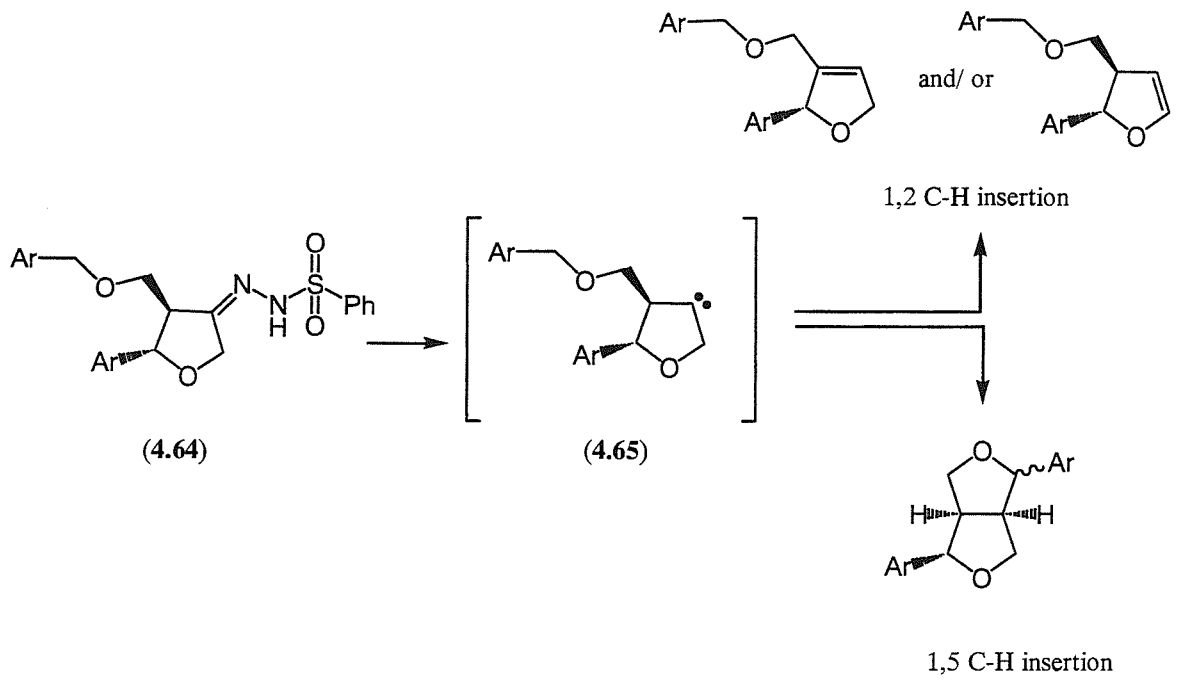


Figure 4.14 Chemoselectivity in the insertion of carbenes generated in a thermal Bamford Stevens reaction

Although this transformation is not widely precedented we took a lead from some work undertaken by Aggarwal and co-workers [164]. They established an effective reaction system involving decomposition of diazocompounds in the presence of Rh(II) during the synthesis of epoxides (Figure 4.15). To date they have used preformed stabilised carbenes in their work but careful control of conditions did prevent inter- and intramolecular side reactions from occurring. Reactions with unstabilised carbenes (for instance, diazomethane) were more difficult to control with appreciable dimerisation occurring [165]. Expansion of their system to include formation of the diazo- compound by decomposition of tosyl hydrazones (as depicted) was underway and was highlighted as having potential application in our work [166].

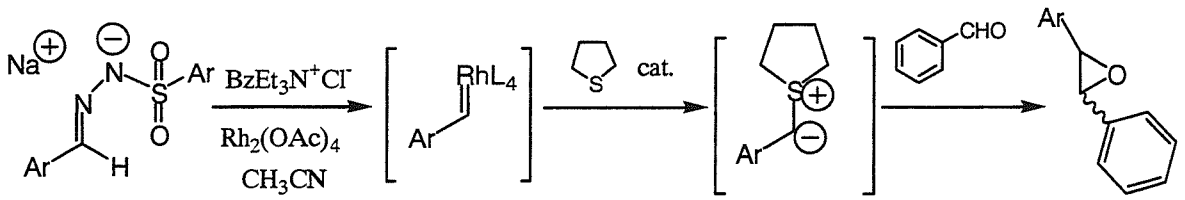
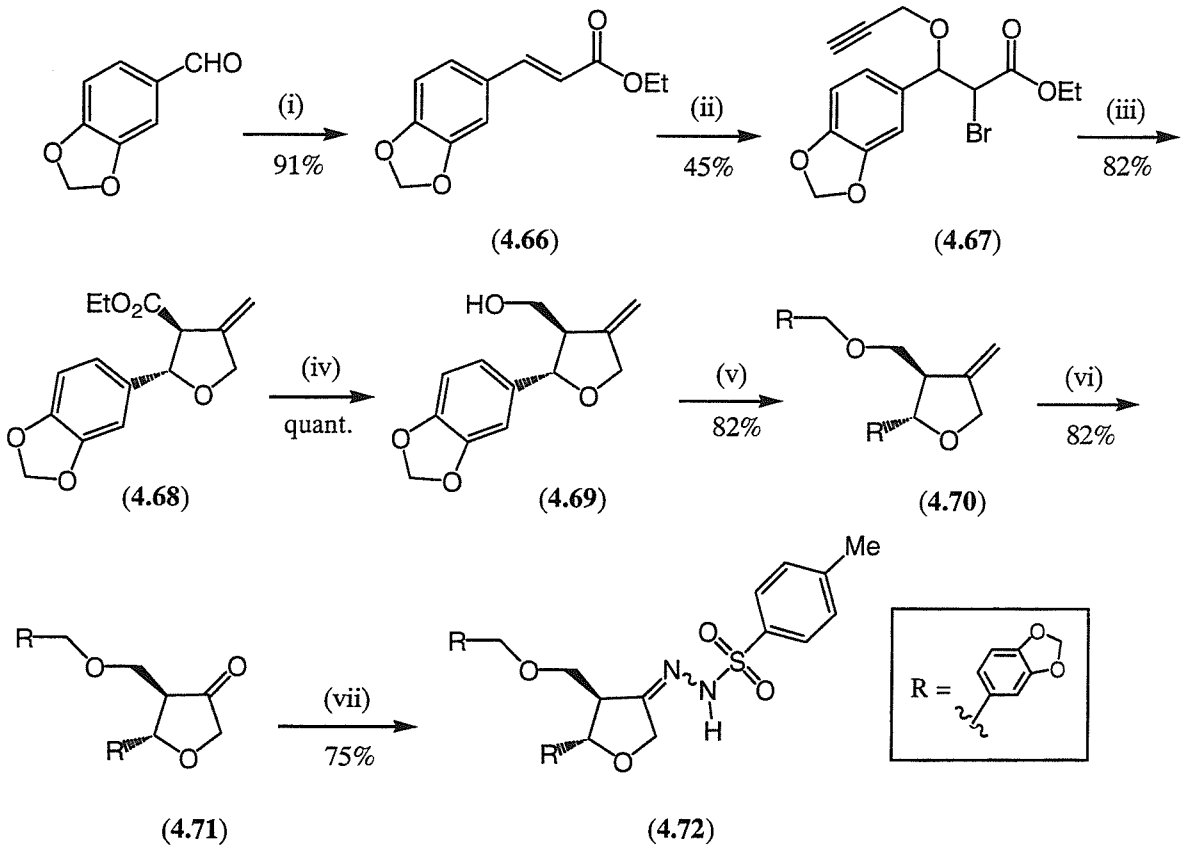


Figure 4.15 A one-pot protocol for metallocarbenoid generation and reaction

Our system would require the generation of an unstabilised metal carbene that would be susceptible to both of the unwanted side reactions, namely carbene dimerisation and 1,2-C–H insertion. However, we felt that the geometry of the system might promote 1,5-C–H

insertion that was demonstrably facile in the stabilised metal carbene analogue used in our earlier syntheses.



Reagents and Conditions: (i) $EtO_2CCH_2CO_2H$, pyridine, piperidine (ii) *N*-bromosuccinimide, propargyl alcohol, CH_2Cl_2 (iii) *n*-Bu_3SnH, AIBN, PhH (iv) $LiAlH_4$, THF (v) NaH, 3,4-methylenedioxybenzyl bromide, THF (vi) OsO_4, $NaIO_4$, 1,4-dioxan, H_2O (vii) *p*-toluenesulfonyl hydrazine, MeOH

Scheme 4.14

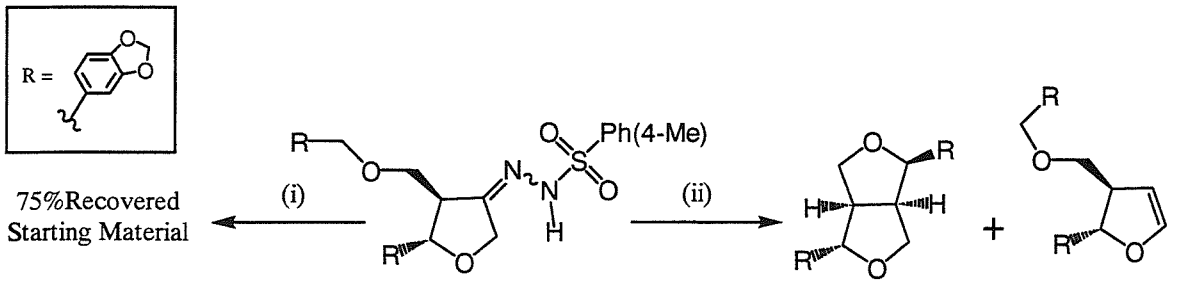
In addition, we were unsure of the effect of having a sp^3 hybridised oxygen atom, β- to the carbene centre, on the overall course of the reaction. We also felt that we might be able to exert some control on the course of the reaction by changing the ligands on Rh (II). This strategy has been employed with some success by Taber during the synthesis of cyclopentanones [140]. These unknowns, along with the relative ease of preparing the necessary substrate (**4.72**), suggested that a brief study of this reaction would be worthwhile.

The preparation of the requisite hydrazone is outlined in Scheme 4.14. The *exo*methylene derivative (**4.70**) was prepared according to the method of Chandra Roy *et al.* [167] who required the intermediate in their synthesis of a 2-hydroxy-6-aryl furofuran derivative, samin.

Knoevenagel condensation of piperonal with the half ester of diethyl malonate [168] provided the cinnamate derivative (**4.66**) [169] in good yield. Electrophilic attack of NBS at the electron rich olefin, followed by trapping of the resulting benzylic carbonium ion, provided the bromoether derivative (**4.67**) as a single isomer after purification (other isomers were most likely formed in the reaction but decomposed on storage before an opportunity arose to complete characterisation). Homolytic cleavage of the C–Br bond generated a radical α- to the ester that underwent a 5-*exo*-dig cyclisation, furnishing the *exo*-methylene tetrahydrofuran derivative (**4.68**) after reduction of the olefinic radical by tri-*n*-butyltin hydride. Reduction with lithium aluminium hydride provided the known alcohol (**4.69**) which was alkylated with 3,4-methylenedioxybenzyl bromide to provide cyclic ether (**4.70**).

Oxidative cleavage was attempted using catalytic osmium tetroxide in the presence of an excess of sodium periodate. The choice of the organic co-solvent proved critical in this reaction. Diethyl ether provided the desired ketone (**4.71**) in poor yield (mainly starting material recovered) even after stirring at room temperature for 36 hours and activating by ultrasound. The same reaction with dioxan as co-solvent went to completion within 3 hours [170]. Finally, the required hydrazone (**4.72**) was prepared, as a 9:1 mixture of isomers, by condensation of *p*-toluenesulfonyl hydrazine [171] with the ketone (**4.71**).

The preparation of the anion of the hydrazone and its subsequent decomposition were investigated under a number of conditions which are summarised in Scheme 4.15.



Reagents and Conditions: (i) (a) LiHMDS, THF (b) $Rh_2(OAc)_4$, $BzN^+Et_3Cl^-$, CH_3CN (ii) (a) NaH, DME (b) $Rh_2(OAc)_4$, $BzN^+Et_3Cl^-$, DME, Δ **or** $BzN^+Et_3Cl^-$, DME, Δ **or** $Rh_2(OAc)_4$, $BzN^+Et_3Cl^-$, CH_3CN, Δ.

Scheme 4.15

Under the conditions examined the predominant product arose from 1,2-C–H insertion (**4.73**). Insertion always occurred into the C–H α- to the sp^3 oxygen, an observation that is consistent with the fact that the carbenoid will insert into the most electron rich C–H bond.

In addition, traces of asarinin (**2.40**) were noted in all the reactions by TLC and were isolated from the reaction in which the rhodium catalyst was omitted.

With the benefit of hindsight it was, perhaps, optimistic to hope that this methodology would provide access directly to furofuran lignans. Indeed, subsequent to the investigation being carried out it was discovered that a related strategy has been used as a two carbon homologation of acid chlorides; The critical step of the method involved the 1,2-insertion of a carbene species into a C–H bond α- to a sp^3 oxygen[172] (Figure 4.16).

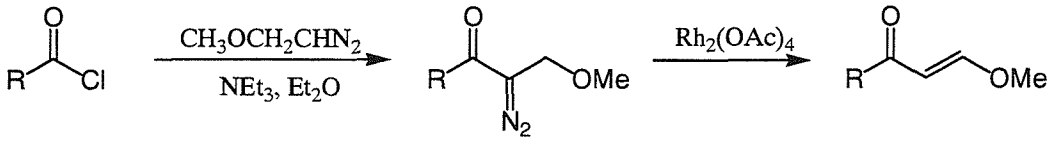
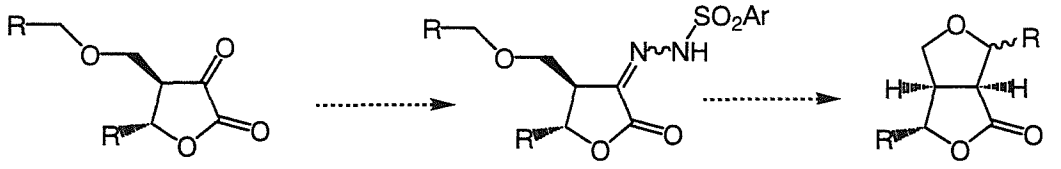


Figure 4.16 A literature strategy for acid homologation using metallocarbenoid 1, 2-insertion

Future investigations in this area would be warranted if it proved possible to prepare the α-ketolactone (**4.74**) as a precursor to the hydrazone (**4.75**) (Figure 4.17). Upon decomposition this would yield a stabilised carbenoid species that might react in the manner required.



(**4.74**) (**4.75**)

Figure 4.17 A future strategy for lignan synthesis

4.5 Concluding Comments

The preparation of a series of model compounds and of two natural products, one of them being prepared for the first time, is testament to the overall success of this research programme. The synthesis of both asarinin and epimagnolin A stands up to comparison with many of the previous syntheses of this class of compounds. In addition, two different approaches to the preparation of α-diazolactones, potentially usefully intermediates in the synthesis of lactone (and subsequently cyclic ether) containing natural products, have been developed.

A more detailed inspection of the aims of the programme reveals that there still remains a significant amount of work to complete in this area before the strategy could be described as mature. One aspect not investigated is the impact of changing the ligand attached to rhodium on the selectivity of the insertion reaction. With the benefit of a closer inspection of the literature it is clear that it is unlikely that changing to a less electron withdrawing ligand would switch the diastereoselectivity of the insertion reaction. Likewise, changing to a more electron withdrawing ligand is likely to decrease both the chemo- and diastereoselectivity of the insertion. A more fruitful approach might be to check the selectivity of the insertion using different metal catalysts, for instance copper and palladium. Likewise, use of the Bamford Stevens reaction to produce a α-carbonyl stabilised carbenoid (from **4.75**) and its subsequent insertion, as well as the investigation of carbenoids derived from hypervalent iodine complexes [173] might prove productive.

More particularly the route has not been adapted to provide enantiomerically pure furofurans. In principle there is scope for the preparation of chiral cyclobutanones using the cycloaddition strategy. However, there is sufficient literature precedent against this being a productive exercise that, coupled with the moderate yields of the reaction, an alternative route to either chiral cyclobutanones or γ-lactones would be desirable. Some feasible strategies include the asymmetric Baeyer Villiger reaction [174] on achiral cyclobutanones; preparation of chiral cyclobutanones from electron rich alkenes and chromium alkoxycarbene complexes [175] (reaction 1, Figure 4.18); the preparation of chiral cyclobutanones by ring expansion of 1,1-disubstituted alkoxycyclopropanes [176] (reaction 2, Figure 4.18); the preparation of appropriately 5-substituted butenolides [177] in enantiomerically pure form [178] followed by stereospecific introduction of the required C-4 functionality. Of the above alternatives the last is likely to be the most profitable area for future investigation.

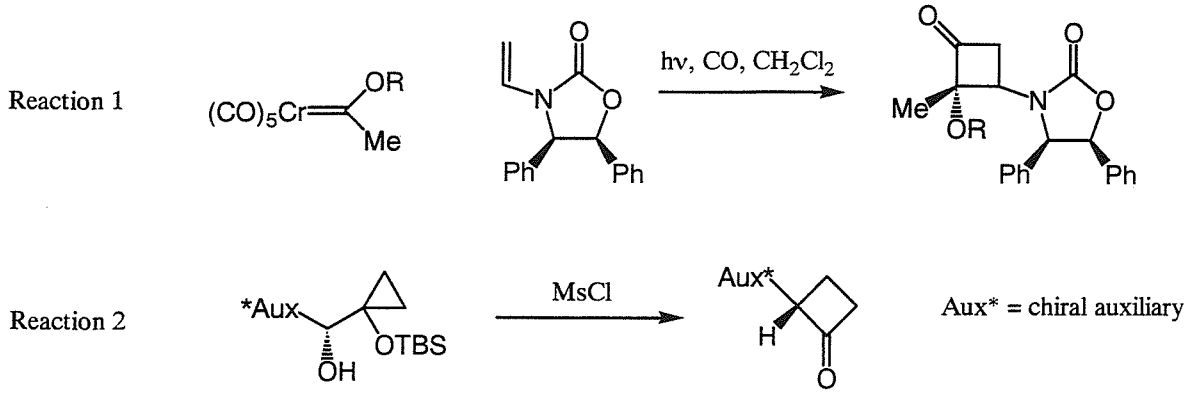


Figure 4.18 Alternative chiral cyclobutanone syntheses

The methodologies applied to the preparation of diazolactones both represent improvements over the prior art. As the programme progressed, and based on the more comprehensive results from a parallel research programme, it appears that the most general routes is diazo-transfer to lactones activated with a α-trifluoroacetyl group. The ability to access these intermediates is something that might well prove useful in the preparation of other natural products. In general, these would be most favourable when the known preferences for C-H insertion are accommodated by the chosen substrate. One class of lignan natural products that might be prepared by this strategy is the podophyllins structural type to be constructed by a 6-membered ring forming insertion provided 1,2-insertion is not a competing process (Figure 4.19).

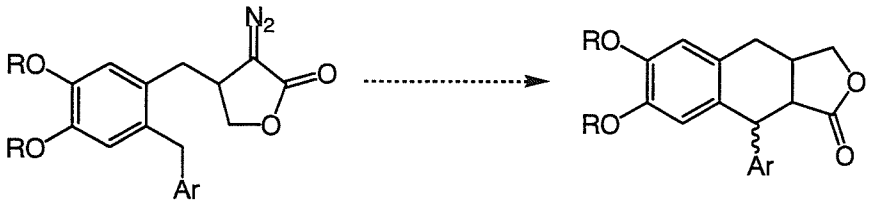


Figure 4.19 A route to podophyllins

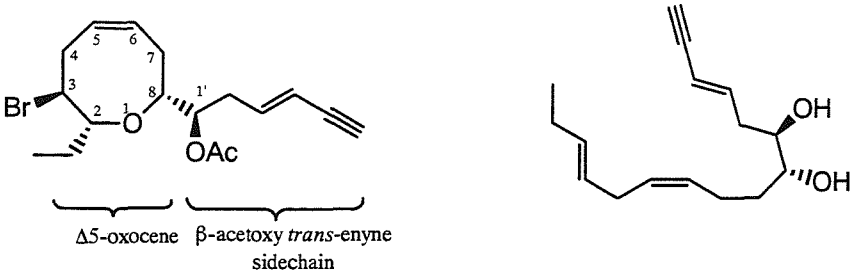
As with all successful research the reward for success is the achievement of the original aim. As always the provision of one or two answers raises many more questions. The provision of answers to some of these is the aim of work currently being conducted within the Brown group.

Chapter 5

The Development of Total Syntheses of the Marine Natural Product Laurencin.

Laurencin (**5.1**) was first isolated from *Laurencia glandulifera* in 1968 [179]. It is a metabolite of red algal [180-182] which, along with most of the members of its family, show little or no interesting biological activity. Nonetheless, its structure has excited interest as an appropriate challenge to new synthetic methodology, in particular, for new methods allowing preparation of medium ring ethers with defined stereochemistry.

There have been several syntheses of laurencin described in the last three decades that are reviewed in the following chapter. As implied above it is the approaches to the preparation of the oxocene ring, with appropriate stereochemistry and correct positioning of the endocyclic double bond, that define each of the differing methods. As a consequence the review of the literature to date will concentrate on this aspect of the syntheses. The chapter is arranged according to the retrosynthetic disconnection made in the ring forming step of the reaction sequence. In addition, the first sections deal with the biomimetic and ring expansion/ fragmentation methodologies that were the focus of the early research in this area.



(**5.1**) (+)-Laurencin (**5.2**) Laurediol

Figure 5.1 Laurencin marine natural products

5.1 Biomimetic Routes

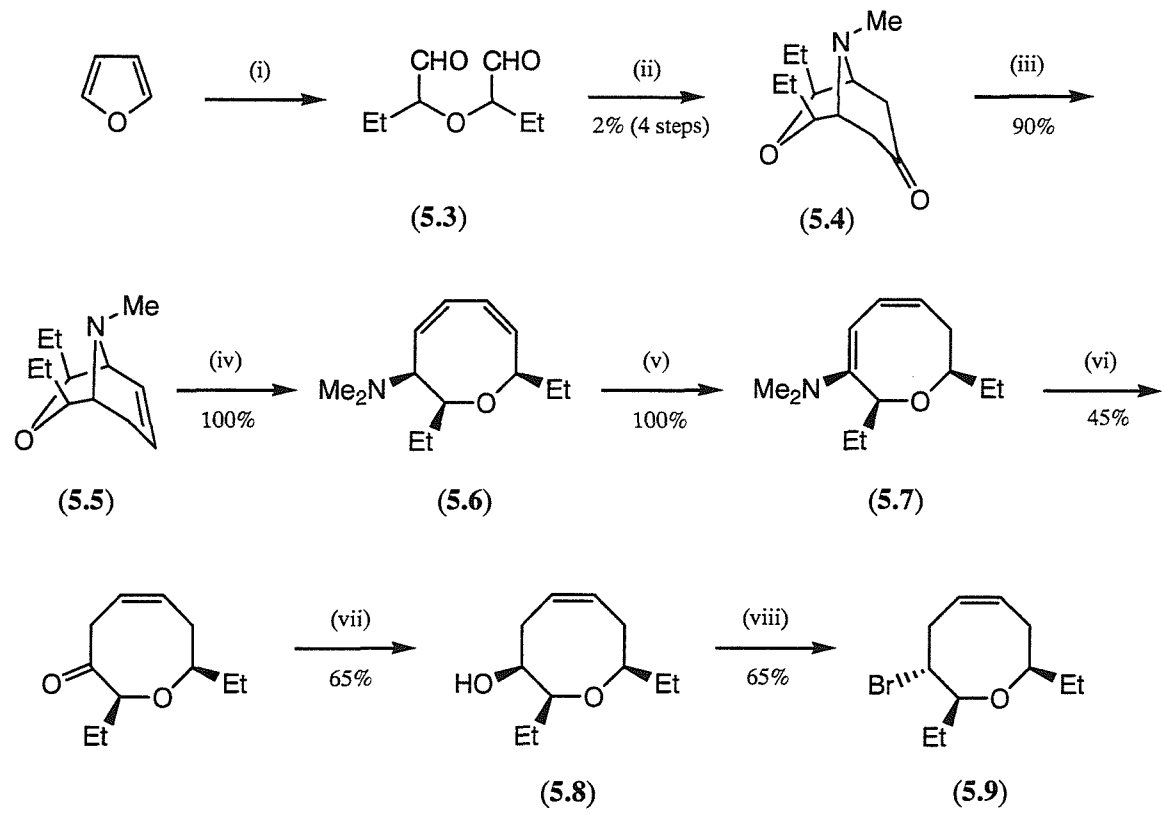
After the original discovery of laurencin Masamune and co-workers [179] embarked on a study of its total synthesis. Their experiments were described in a series of papers spanning the period from 1975 to 1980. Initial work began with an attempt to develop a biomimetic route to laurencin (**5.1**) from the naturally occurring laurediols (**5.2**) (Figure 5.1) whose structure strongly implicates them as being likely bio-precursors for laurencin itself. Preparation of a range of simplified diols (with the enyne moiety replaced by an alkyl group) proved to be resistant to all attempts at cyclisation either by direct

intramolecular hydration of the *trans*-alkene or by nucleophilic ring opening of the epoxide derived from it.

The poor results led to them abandoning this until Murai, one of Masamune's original co-workers, revisited the area [183]. He was successful in transforming laurediol (**5.2**) into laurencin (**5.1**) using a lactoperoxidase in the presence of hydrogen peroxide and bromide ion. The yield of 1% with only 50% consumption of starting diol was taken to prove the intermediacy of laurediol (**5.2**) in laurencin biosynthesis but was not revisited as a viable means for its synthesis.

5.2 Ring Expansion/ Fragmentation Methodologies

A more fruitful area of study was the use of a classical Robinson tropinone annulation as a means of ultimately accessing the required 8-membered ring. Initial studies were completed on a model series of compounds wherein both the 2- and 8-positions were functionalised with ethyl groups [184] (Scheme 5.1).



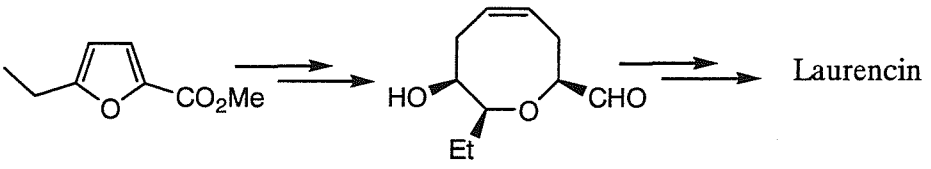
Reagents and conditions: (i) (a) Br_2 (b) EtMgBr (c) O_3, EtOAc (ii) acetone dicarboxylic acid, $MeNH_2$, pH 5.0 (iii) (a) $LiAlH_4$ (b) H_2SO_4, AcOH, Δ (iv) MeI, Δ (v) Δ (vi) HBF_4 (aq.) (vii) $LiAlH_4$ (viii) CBr_4, PPh_3.

Scheme 5.1

The required oxaglutaraldehyde (**5.3**) was prepared from furan in three steps. Treatment with acetone dicarboxylic acid and methylamine provided the tropinone ring system as a

mixture of isomers. The *cis*- disubstituted product (**5.4**), the minor isomer, was isolated from the *trans*- by reduction to the alcohol at which point the two isomers were separable. Re-oxidation gave pure material that which was identified as being the *cis*- relative stereochemistry by the simplicity of the NMR spectrum caused by the plane of symmetry. NMR analysis also implied that the ethyl groups occupied the axial positions that, in turn, suggests a β-configuration of the functionalities flanking the oxygen in the ring. The ketone was reduced to give predominantly the α-hydroxy derivative that was eliminated to give alkene (**5.5**).

Quaternisation and Hoffman elimination gave the cyclic diene (**5.6**) that was induced to undergo an efficient 1,5-sigmatropic rearrangement by the action of heat to give enamine (**5.7**). Hydrolysis followed by carbonyl reduction gave an epimeric mixture of alcohols (**5.8**). They were separated and the portion of the NMR spectrum containing resonances from the protons at the pro-C3 and pro-C4 positions of each epimer compared with the data for laurencin itself. It was determined that the major isomer had the incorrect relative stereochemistry at pro-C4. In fact, this was the desired result as bromination resulted with inversion at this carbon to give a model for the laurencin system (**5.9**).



(5.10)

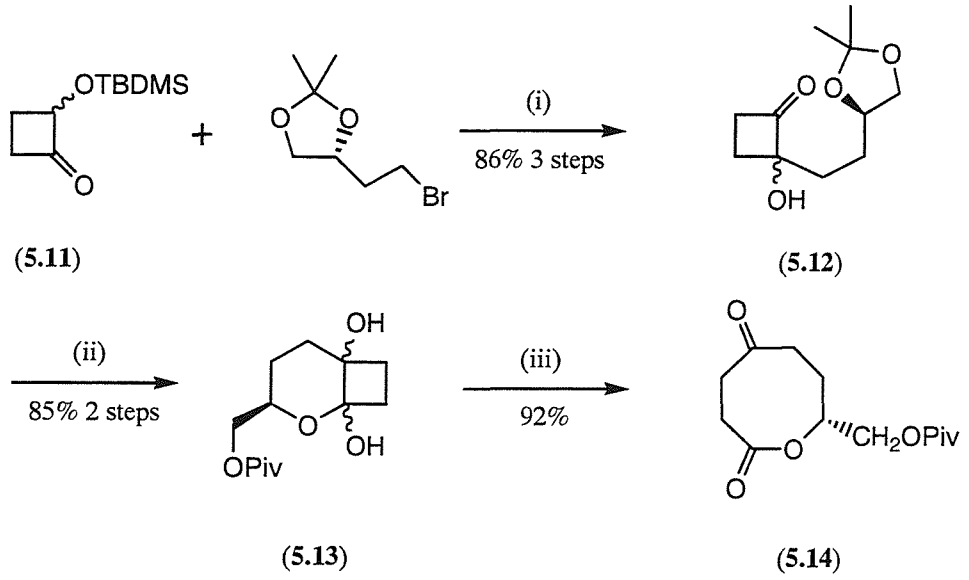
Figure 5.2 The first synthesis of (±)-Laurencin

Later work by the same group [185, 186] using the same methodology but starting from 5-ethyl-2-furoic acid provided an intermediate (**5.10**) that was ultimately converted into racemic laurencin (**5.1**) [187] (Figure 5.2).

The involvement of over 30 steps, multiple isomer separations and an overall yield of a fraction of a percent clearly did not support this chemistry being adapted any further. Nonetheless, the preparation of this class of compounds using a classical condensation/ elimination sequence as the key step was a significant achievement.

Murai also developed a ring fragmentation method that involved the formation of the oxocene ring by oxidative cleavage of a 2-oxabicyclo[4.2.0]octane derivative (**5.12**) at the core of the process [188]. Murai's route targeted the enantiopure (+)-laurencin by

establishing the stereocentre at the pro C2 centre from the chiral pool and hoping that this would control the stereochemistry at the other asymmetric carbon atoms.

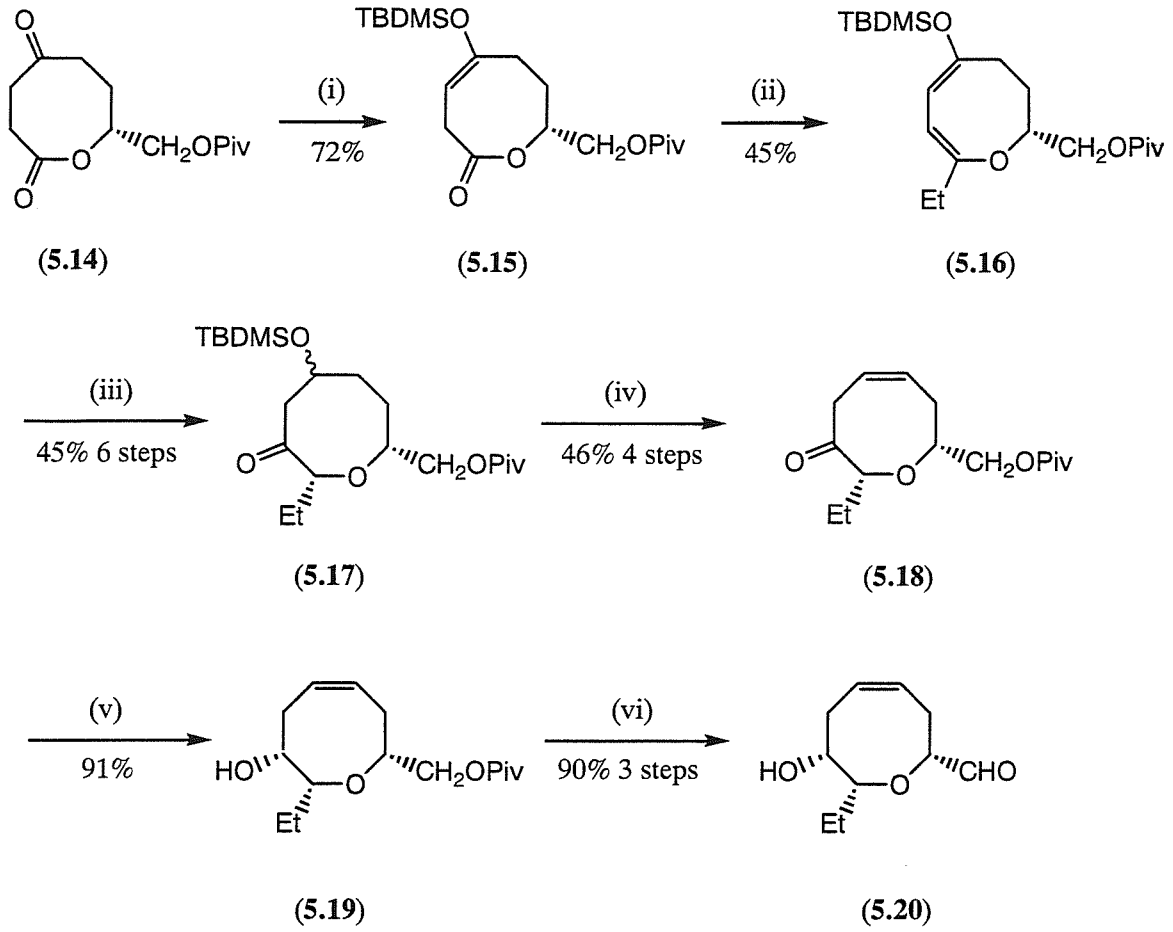


Reagents and conditions: (i) (a)Li, THF (b) TBAF (c) $Pyr.SO_3$, NEt_3, DMSO, CH_2Cl_2 (ii) (a) PTSA, THF, H_2O (b) PvCl, pyridine (iii) $Pb(OAc)_4$, $PhCH_3$.

Scheme 5.2

Addition of the organolithium derivative of the optically pure bromide [189] to 2-silyloxycyclo-butanone (**5.11**) provided cyclobutanone (**5.12**), after deprotection and oxidation. Treatment with acid provided the bicyclic hemiacetal which was selectively protected at the primary alcohol as the pivalate (**5.13**). Oxidative ring expansion provided a 2,5-dioxaoxocane (**5.14**) with the 8-position functionalised with the appropriate (R)-configuration.

A somewhat protracted series of reactions was used to establish the oxocene central core (Figure 5.3). Conversion of **5.14** into silyl enol ether (**5.15**) resulted in the isolation of a mixture of Δ^3 and Δ^4double bond isomers (12:1). These were separable and the major Δ^3 isomer, was converted to the enol triflate and treated with diethylcuprate to provide **5.16**. The ketone at pro-C5, revealed upon desilylation, was reduced and re-protected before introducing the ketone at the pro-C3 carbon *via* an oxidative hydroboration method. Final Swern oxidation of the alcohol resulting from this sequence of reactions caused epimerisation at the ethyl substituted carbon to give exclusively the 2,8-*cis*-isomer (**5.17**)



Reagents and conditions: (i) TBDMS-OTf, SiO_2, CH_2Cl_2, separate isomers (ii) (a) LiHMDS, $PhNTf_2$ (b) Et_2CuLi (iii) (a) TBAF, THF (b) $NaBH_4$ (c) TBDMS-OTf, NEt_3 (d) BH_3, THF (e) H_2O_2, NaOH (f) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2 (iv) (a) HF, CH_3CN (b) CCl_4, $P(Oct)_3$ (c) DBU, $PhCH_3$ (x2) (v) L-selectride (vi) (a) TBDMS-OTf, NEt_3 (b) DIBAL (c) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2.

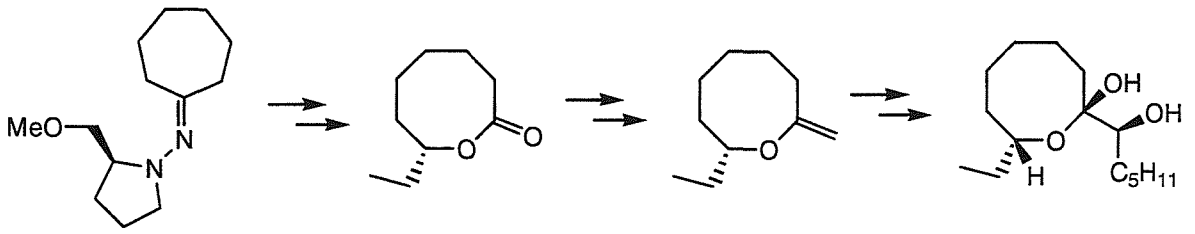
Scheme 5.3

Deprotection, conversion to the chloride and elimination gave another mixture of double bond isomers favouring the undesired α-isomer. Fortunately, this could be isomerised to the β-isomer by the action of DBU to provide alkene **5.18**. Reduction to the alcohol, arising from delivery of hydride from the least hindered face, gave **5.19**. Conversion of this to the 8-formyl compound (**5.20**) with all the ring stereo- and regiochemistry established was completed in 3 steps. This compound was converted into laurencin over 5 further reactions.

The overall efficiency of the first enantiospecific preparation of laurencin was 2.5% in a process involving 27 steps. The ring expansion process itself is efficient but does not allow for the necessary functionality to be incorporated prior to preparation of **5.14**. The obvious consequence of this is that protracted functional group interconversions are

required to install the alkene and the 3-hydroxyl group. Even so, Murai's synthesis remained the benchmark in the area for several years to come.

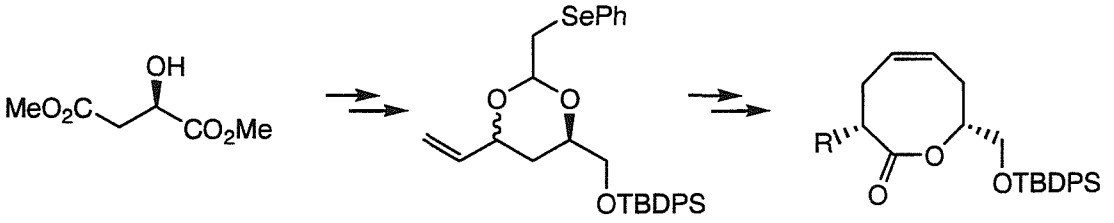
Holmes *et al.* investigated a number of different approaches to 2,8-*cis*-disubstituted oxocanes, not all of which proved to be adaptable to the target compound.



(5.21) (5.22) (5.23) (5.24)

Figure 5.3 SAMP hydrazone methodology in the preparation of 2,8-*cis*-oxocanes

One model series of studies utilised the asymmetric alkylation of SAMP hydrazones introduced by Enders [190]. Thus, cycloheptanone was converted to the chiral hydrazone (**5.21**) which was deprotonated prior to alkylation from least hindered face of the resulting anion (Figure 5.3). Regioselective Baeyer Villiger oxidation gave lactone (**5.22**) in high enantiomeric excess. This was transformed into the enol ether (**5.23**) that was stable enough for purification by chromatography on silica in the presence of triethylamine. A series of functional group interconversions provided the 2,8-*cis*-disubstituted oxocane (**5.24**), a known degradation product of laurencin [191].



(5.25) (5.26) (5.27) R = H

(5.28) R = OH

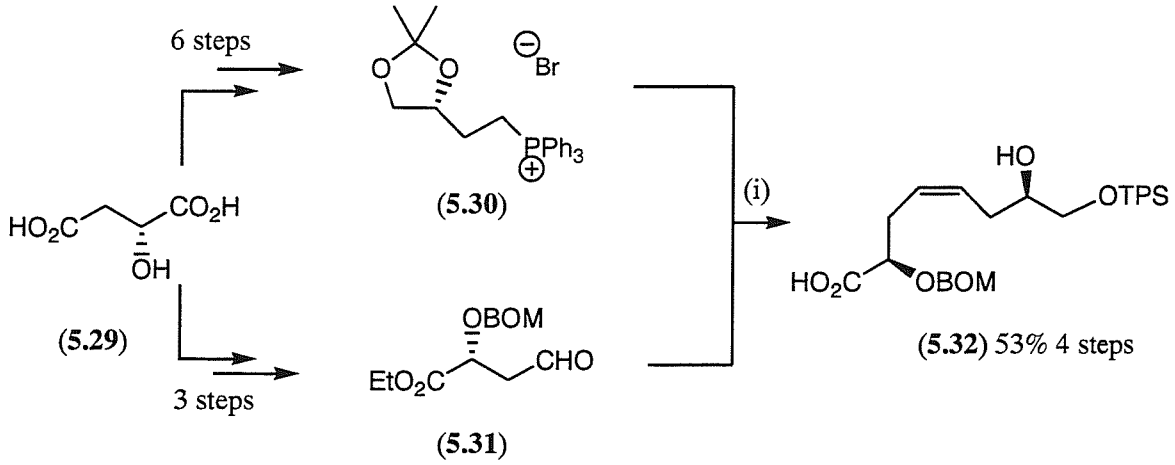
Figure 5.4 Claisen rearrangement in preparing oxocenes

A second strategy utilised a Claisen rearrangement in directly setting up the oxacene system [192] using dimethyl malate (**5.25**) as the chiral precursor (Figure 5.4). An *O*-allyl-*O*-vinyl system was set up from the appropriate alkyl selenide (**5.26**) that was oxidised to the selenoxide that was induced to eliminate, and cyclise, by the action of heat to give lactone (**5.27**). Davis's chiral oxaziridine [193] was used to hydroxylate α- to the carbonyl group to provide the alcohol (**5.28**). Unfortunately this conversion was inefficient (20%) and also presented some difficulties in the assignment of stereochemistry that ultimately led to a

retraction of the claims for a new total synthesis. Although a revised synthesis did make the natural product the route was not optimised (26 steps, <0.2% overall yield) [194].

5.3 1,2-Disconnection of the Oxocene

Holmes' third approach [195] entailed a macrocyclisation protocol from a chiral alicyclic material (**5.32**) in which the pro-C3, pro-C8 and alkene structural elements were in place prior to cyclisation.



Reagents and conditions: (i) (a) BuLi, THF, -78°C (b) AcOH, H_2O (c) TPSCl, imidazole, DMF (d) LiOH, THF, H_2O.

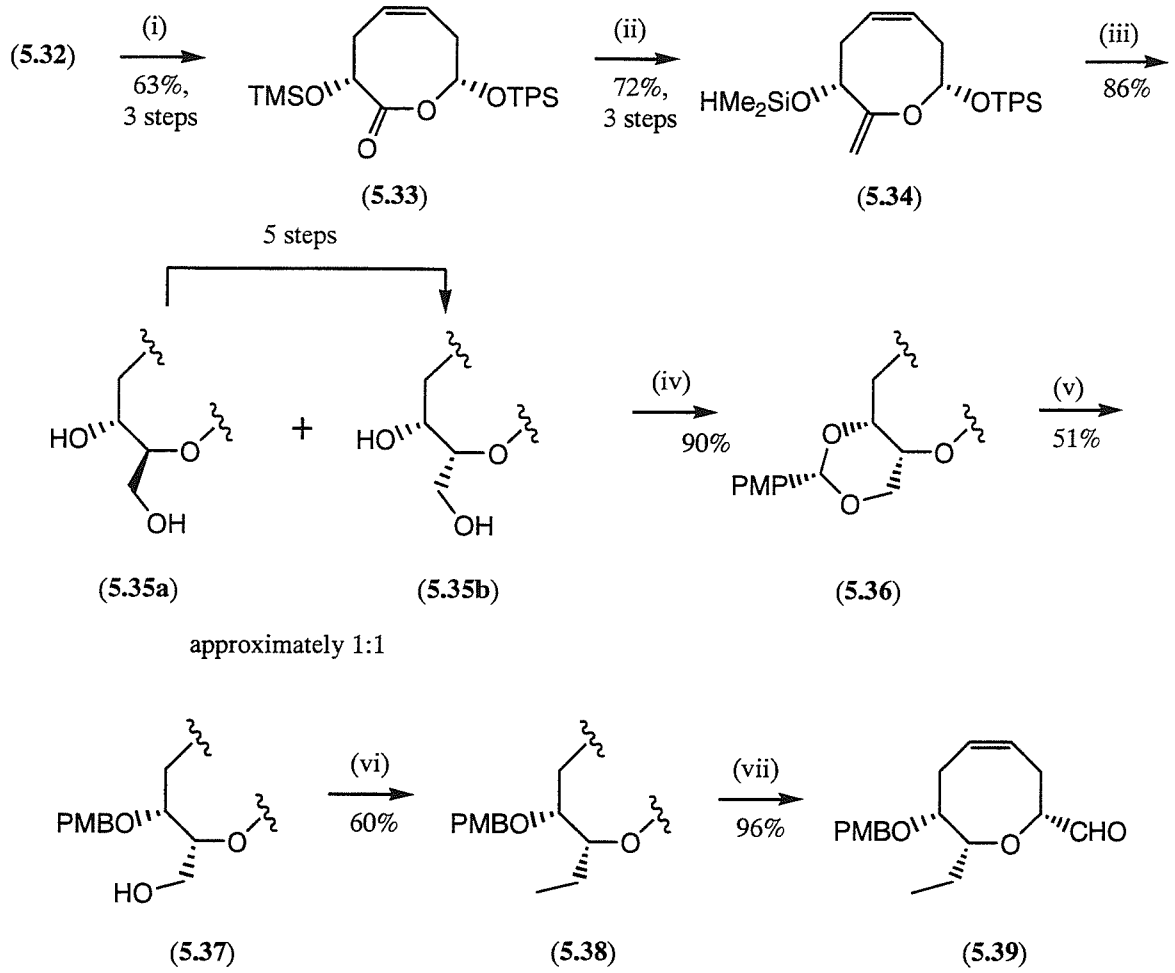
Scheme 5.4

Once again, (R)-malic acid (**5.29**) provided the chiral centres at C-3 and C-8 (through the intermediacy of phosponium salt (**5.30**) and aldehyde (**5.31**)) of laurencin and also induced the necessary relative stereochemistry at C-2 (Scheme 5.4).

Subjecting **5.32** to Yamaguchi macrolactonisation [196] conditions provided the 8-membered ring lactone in high yield. The only complication was the formation of some nine membered ring lactone arising from some primary to secondary hydroxyl silyl migration prior to lactonisation. Although only formed in low yield the removal of this byproduct was a problem. It required removal of the BOM group and trimethylsilylation of the resulting alcohol before it was separable from the desired 8-membered ring lactone (**5.33**) by chromatography (Scheme 5.5).

The major flaw in this route proved to be the complexity of transforming the lactone carbonyl into an ethyl group with the correct *cis*- stereochemistry relative to both of the other chiral centres. Olefination using Petasis' reagent [197], transformation to the hydrosilane (**5.34**) and a non-selective internal hydrosilation reaction provided a mixture of

isomers (**5.35a, 5.35b**) which, in general, favoured the undesired 2,3-*trans*- relative stereochemistry. It proved possible to convert the **5.35a** into **5.35b** over a 5 step process.



Reagents and conditions: (i) 2,4,6-trichlorobenzyl chloride, Et_3N, THF followed by DMAP, $PhCH_3$, Δ (b) $BCl_3.SMe_2$, CH_2Cl_2 (c) TMSCl, NEt_3, THF (ii) (a) Cp_2TiMe_2, $PhCH_3$ (b) K_2CO_3, MeOH (c) $(Me_2SiH)_2NH$, NH_4Cl (iii) (a) $Pt(DVS)_2$ (b) KOH, H_2O_2, MeOH, THF (iv) *p*-$MeO(C_6H_4)CHO$, PPTS, PhH, $MgSO_4$ (v) DIBAL, CH_2Cl_2 (vi) (a) Tf_2O, CH_2Cl_2, pyridine (b) Me_2CuLi, Et_2O, PhH (vii) (a) TBAF, THF (b) TPAP, NMO, CH_2Cl_2.

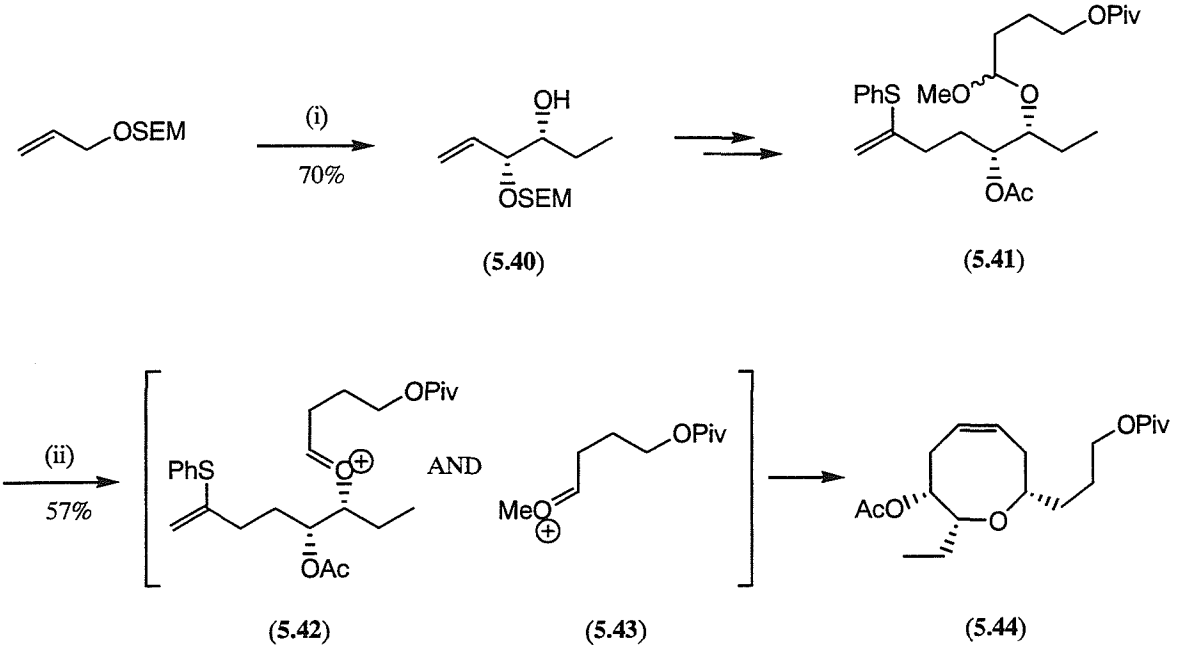
Scheme 5.5

Incorporation of the ethyl group required activation of the primary alcohol and displacement with a source of methyl anion. When this sequence was pursued on the diol, by activating the primary hydroxyl as a tosylate and treatment with a higher order methyl cuprate, it afforded only the oxetane that proved stable in the presence of MeLi (not illustrated). To overcome this problem the diol was protected as acetal (**5.36**) that, on reductive ring opening selectively gave the secondary PMB ether (**5.37**). Tosylation and displacement with a cuprate proved inefficient, a problem which was partly overcome by activation of the alcohol as the triflate. Displacement with methyl cuprate gave **5.38** that

was desilylated at the 8-silylether and oxidised to provide the core nucleus of laurencin (**5.39**). With an overall yield of less than 1% over 30 steps this work does not challenge that of Mori in terms of efficiency. The difficulties associated with the transformation of the lactone carbonyl into the ethyl group would suggest that cyclisation at this oxidation level is not a viable route to this class of compounds.

5.4 1,8-Disconnection of the Oxocene

Overman *et al.* [198] investigated an approach that accessed the cyclic ether directly *via* a Prins cyclisation of a vinyl sulfide onto an appropriate oxocarbenium ion. The requisite alicyclic substrate (**5.41**) was prepared in a series of high yielding reactions. Pivotal amongst these was the stereoselective allylation of propionaldehyde mediated by a chiral boron reagent [199]. The resulting protected diol (**5.40**) was subjected to Suzuki coupling [200], mixed acetal formation and protecting group switch from silyl ether to acetate to provide **5.41** (Scheme 5.6). After a protracted series of model experiments the appropriate cyclisation conditions were identified.



Reagents and conditions: (i) Methoxydi*iso*campheylborane, *s*-BuLi, EtCHO (ii) (a) $BF_3.Et_2O$, *t*-BuOMe, 0.05M (b) Raney Ni.

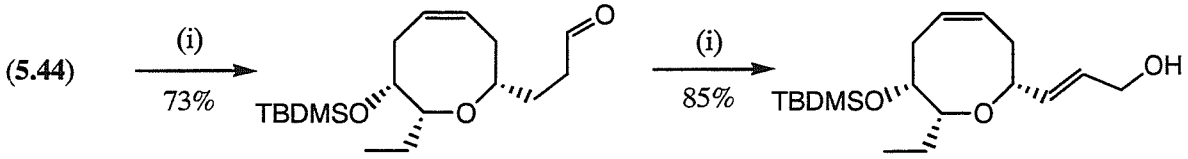
Scheme 5.6

Two problems had to be addressed in particular. Firstly, the reaction conditions had to avoid protic acid to prevent the extremely facile isomerisation of the vinyl sulfide (**5.41**) from the *exo*- to the *endo*- alkene. Secondly, the choice of the protecting group at the secondary alcohol proved to be particularly critical. With silyl ether protection the

exclusive product arose from the quench of the desired oxocarbenium ion (**5.42**) by the sp^3 oxygen of the silyl ether to give a dioxolane ring containing product (not shown). Attenuation of the nucleophilic activity of this oxygen was accomplished by protecting it with an acetate group. Electron withdrawal completely prevents participation of the acetyl's sp^3 oxygen in the reaction pathway that produces the dioxolane.

A less desirable influence of the same acetate protection is that this same electron withdrawal appears to destabilise fragmentation to the desired carbenium intermediate (**5.42**). As a consequence the alternative oxocarbenium ion (**5.43**), and products derived from it, account for a more significant proportion of the product mixture. Even so, the desired cyclisation occurred in good yield to produce a single diastereoisomer of the desired oxocene product (**5.44**) (after desulfurisation with Raney Ni) along with other products that were easy to remove during purification. The only consequence of this reactivity on the synthesis as a whole was that it necessitated some protecting group switches that lengthened an otherwise concise synthesis.

Conversion of the alkyl ether side chain into a functional group appropriate for elaboration into laurencin was accomplished by a switch of protecting groups followed by reductive removal of the pivalate ester and oxidation to the aldehyde (**5.45**). α,β-Unsaturation was introduced by oxidation under Saegusa-Ito conditions [201] to give a conjugated aldehyde exclusively as the *E*-isomer. Reduction to give the allylic alcohol (**5.46**) provided an intermediate that was converted into laurencin in a further 8 reactions (a total of 24 steps with an overall yield of 2%).



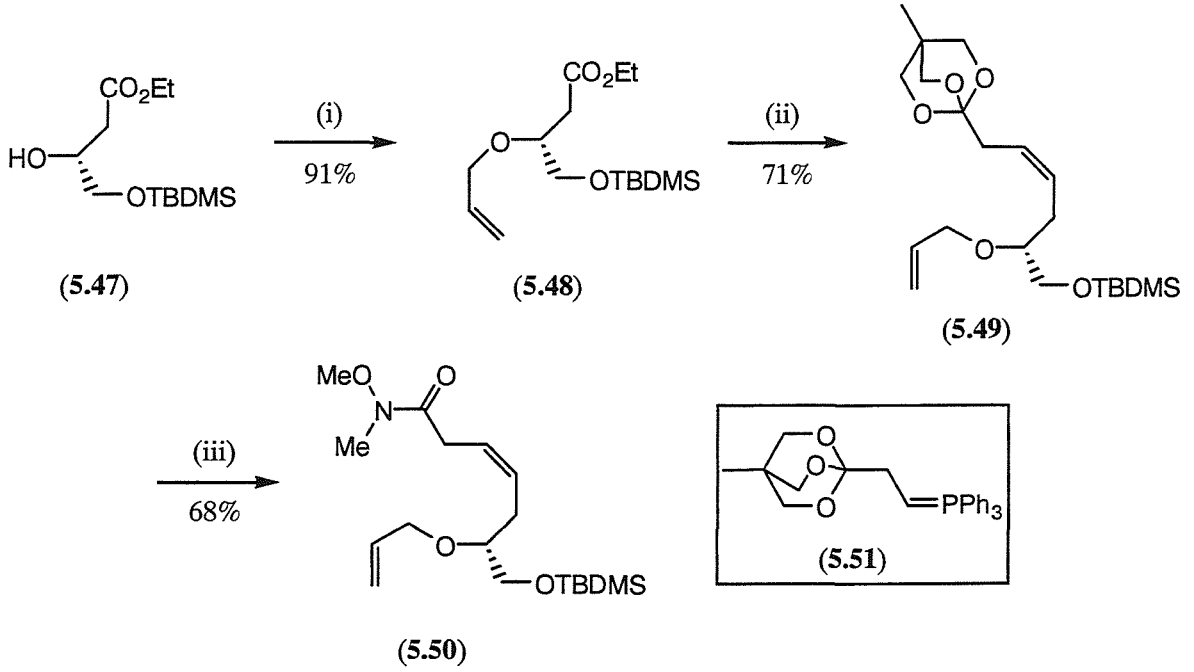
(5.45) **(5.46)**

Reagents and conditions: (i) (a) LiOH (b) TBDMS-OTf (c) DIBAL (d) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2 (ii) (a) TMS-OTf, *i*-Pr_2NEt, $Pd(OAc)_2$, Na_2CO_3 (b) DIBAL.

Scheme 5.7

5.5 2,3-Disconnection of the Oxocene

The asymmetric allylation of aldehydes, used so effectively early in Overman's synthesis, was investigated as the means of cyclisation by Hoffman *et al.* [202] Like Holmes he chose (R)-malic acid as the source of chirality in the generation allyl boron compounds with an appropriately disposed aldehyde functionality.



(5.47) (5.48) (5.49) (5.50) (5.51)

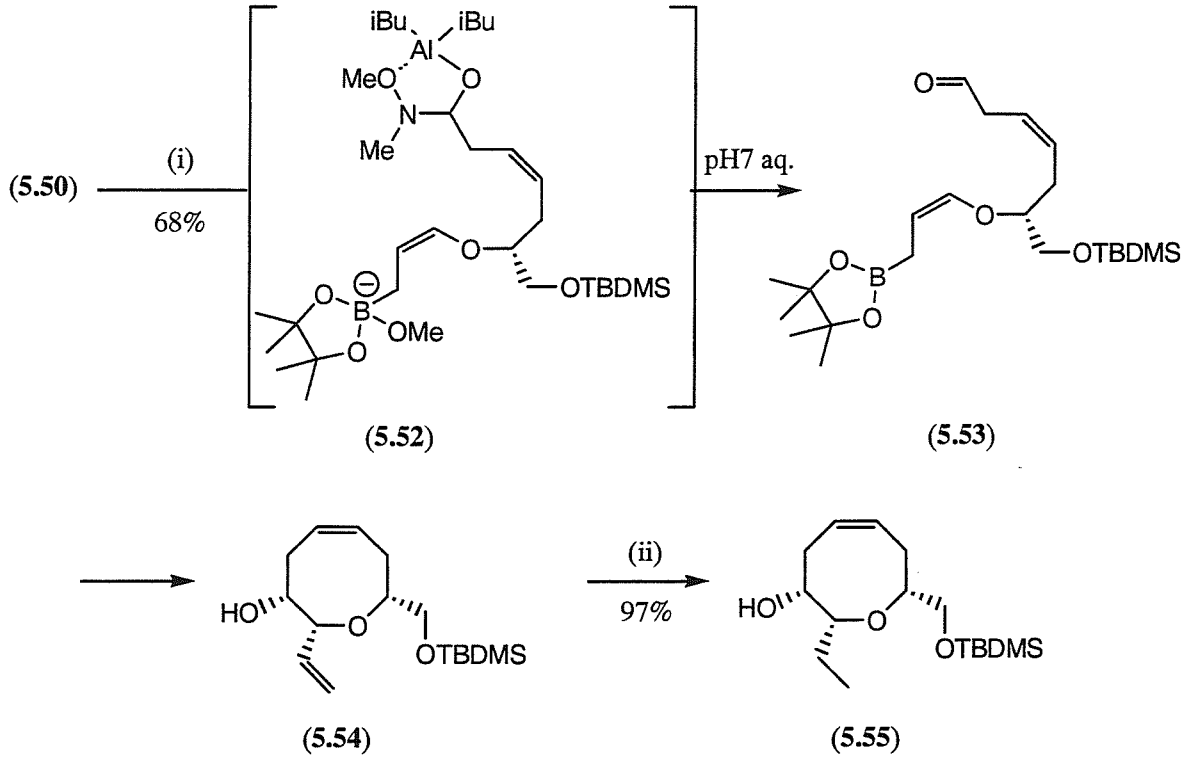
Reagents and conditions: (i) allyl trichloroacetimidate, Tf_2O (ii) (a) $LiAlH_4$ (b) Dess-Martin periodinane (c) **5.51** (iii) $NaHSO_4$ (b) LiOH (c) DCC, DMAP, MeNHOMe.

Scheme 5.8

Thus, the alcohol (**5.47**) was alkylated using a trichloroacetimidate protocol to provide ether (**5.48**) without competing silyl migration that had occurred under more basic conditions (Scheme 5.8). Transformation to the aldehyde and reaction with a Wittig reagent containing a latent carboxylic acid [203] produced alkene (**5.49**) as the *cis*- isomer exclusively. Conversion to the Weinreb amide (**5.50**) [204], in this instance being used as a latent aldehyde, was effected over three steps.

The difficulty associated with this type of ring closure is the controlled release of an aldehyde in the presence of an acid sensitive allyl metal complex. Hoffman's strategy neatly dealt with this in that reduction of a Weinreb amide with DIBAL produces the stable aluminate complex (**5.52**) that is central to the reactivity of these derivatives. In the same pot an allyl boronate complex is generated by treatment of the allyloxy functionality with *s*-BuLi, also in a stable form as the ate complex. It is not until work up that the aldehyde

and the allylboron moiety are released together (**5.53**) at which point they may either cyclise or react intermolecularly. Model studies confirmed the substrates with a *Z*-double bond were predisposed to cyclise as the favoured conformation brings the reacting centres close together (it is worth noting that in completely saturated substrates no cyclisation occurs presumably because of too great a conformational flexibility).



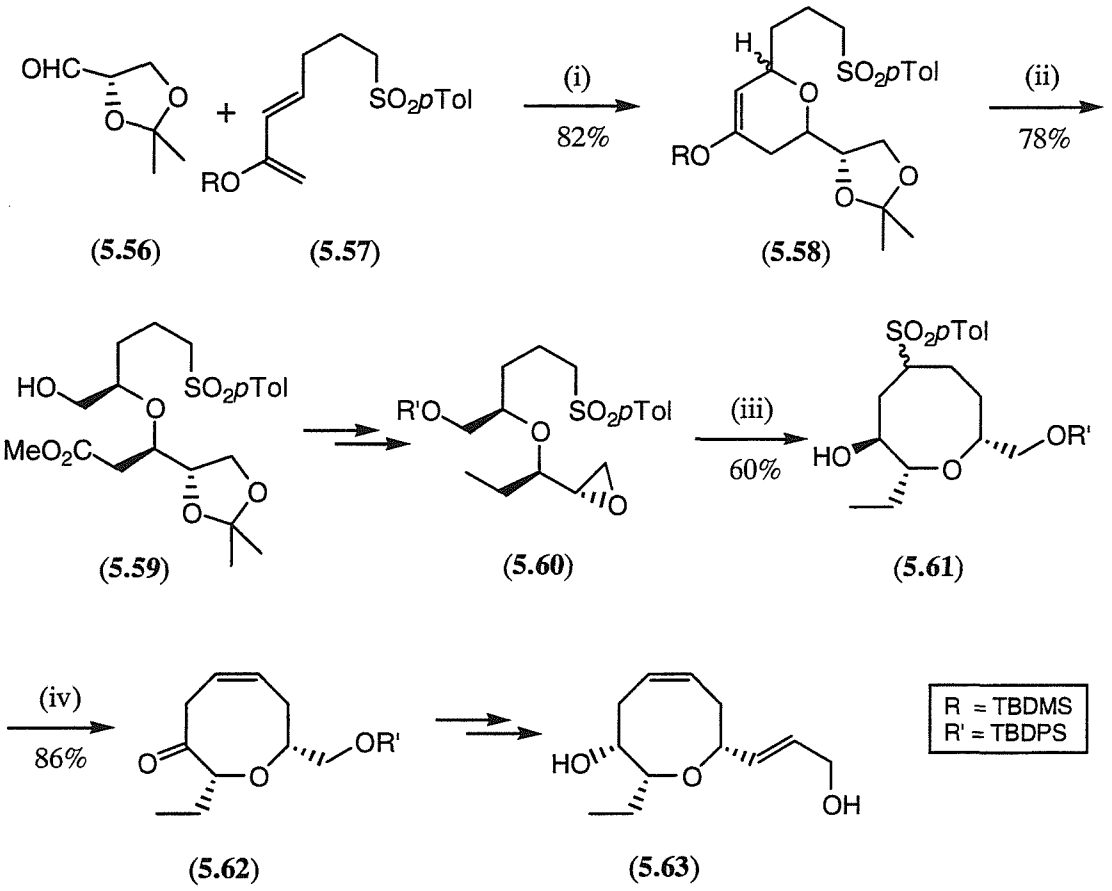
Reagents and conditions: (i) (a) DIBAL (b) *s*-BuLi (c) boronic ester (ii) H_2, Pd/ C.

Scheme 5.9

Not only did **5.53** cyclise to give the desired product (**5.54**) but did so in such a fashion that the chiral centre in the substrate induced the desired all *cis*- relative stereochemistry at the 3 stereogenic centres (a scenario that had been predicted by molecular modelling). Selective hydrogenation of the exocyclic double bond was accomplished in high yield to give (**5.55**), an intermediate already converted to laurencin by Holmes *et al.* [202]

5.6 4,5-Disconnection

Palenzuela's group [205, 206] adopted a strategy wherein nucleophilic ring opening of an epoxide featured as the critical ring closing step. The substrate was assembled *via* a hetero-Diels Alder involving a chiral dienophile (**5.56**) and an electron rich diene (**5.57**) (Figure 5.10). The cycloadduct (**5.58**) was isolated as a mixture of isomers, the most abundant one being derived from *endo*- Cram approach of the reactants during the cycloaddition.



Reagents and conditions: (i) (a) $BF_3.Et_2O$, Et_2O (ii) (a) O_3, CH_2Cl_2, MeOH, $NaBH_4$ (b) CH_2N_2, Et_2O (iii) LDA, THF (iv) (a) $(COCl)_2$, NEt_3, DMSO, CH_2Cl_2 (b) DBU, $PhCH_3$.

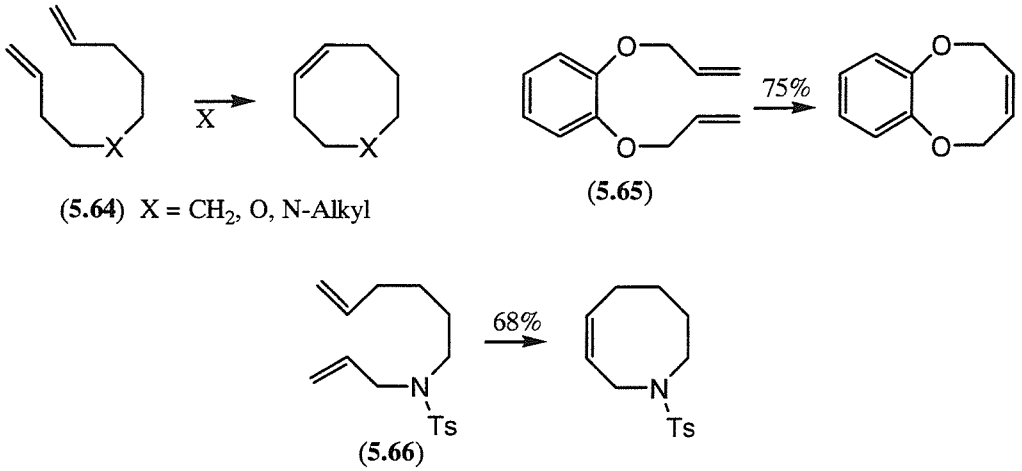
Scheme 5.10

The mixture was carried through an ozonolysis (with reductive work up) and esterification before separating the isomers. The major (required) isomer (**5.59**) was converted to epoxide (**5.60**) over several steps. Generation of the sulfonyl stabilised anion resulted in cyclisation to the oxocane (**5.61**). Elimination of the sulfonate gave the oxocene (**5.62**) that was converted to **5.63** using standard methodology. A critical requirement of these latter transformations was to invert the stereochemistry at C-3 (achieved *via* an oxidation and subsequent face selective reduction protocol).

5.7 5,6-Disconnection of the Oxocene

More recently two groups have focussed their efforts on utilising ring closing metathesis (RCM) as a means of forming the oxocene ring. Original studies in the area by Grubbs [207, 208] had identified problems with the cyclisation of dienes to give cyclooctanes with, or without, heteroatoms in the ring. His studies showed that whilst the preparation of 5- to 7-membered rings could be accomplished with ease by RCM the substrates for 8-membered ring formation simply formed dimers on exposure to the same conditions.

His interpretation of these results was that cyclisation to an 8-membered ring from a sterically unconstrained diene incurred too great an entropic penalty to be an energetically viable process. This point was proven by subsequent experimentation that demonstrated that metathesis substrates that did contain some form of steric constraint (for instance, **5.65**) provided 8-membered rings under the same conditions (Figure 5.5).



(**5.64**) X = CH_2, O, N-Alkyl

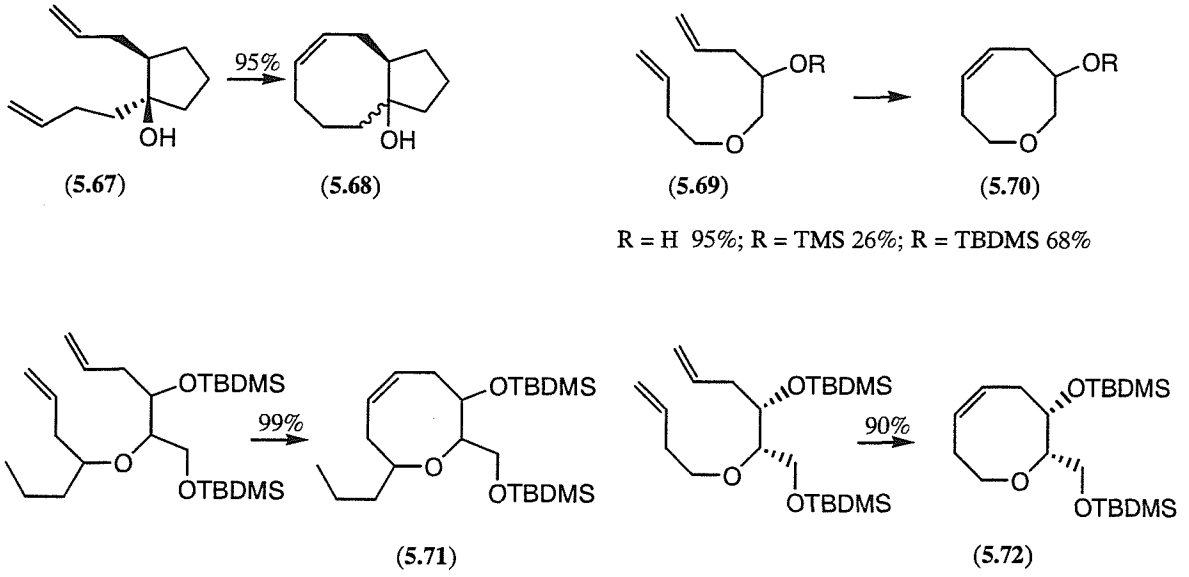
(**5.65**)

(**5.66**)

Figure 5.5 Conformational restraint in RCM to give 8 membered rings

More pertinent, but not encouraging, results came from Hoveyda's group [209]. He found that the diene (**5.64**) would not cyclise which was consistent with Grubbs' earlier results. However, a diene with an integral sulfonamide moiety (**5.66**), did undergo RCM under the same conditions. This result was the first example of RCM providing an 8-membered monocyclic product. It demonstrated that the level of conformational constraint required to effect cyclisation was not as extreme as had been implied in earlier experiments. Even so, it did not provide any support for the belief that an sp^3 hybridised oxygen, in the form of an ether, might facilitate metathesis.

In the light of these results it seemed that the synthesis of laurencin by metathesis might not be possible. However, Taylor and colleagues [210] made experimental observations that went some way to disproving the notion that formation of 8-membered oxygen containing rings by RCM, from conformationally unrestricted dienes, was a synthetically inefficient process.



(5.67) (5.68) (5.69) (5.70)

R = H 95%; R = TMS 26%; R = TBDMS 68%

(5.71) (5.72)

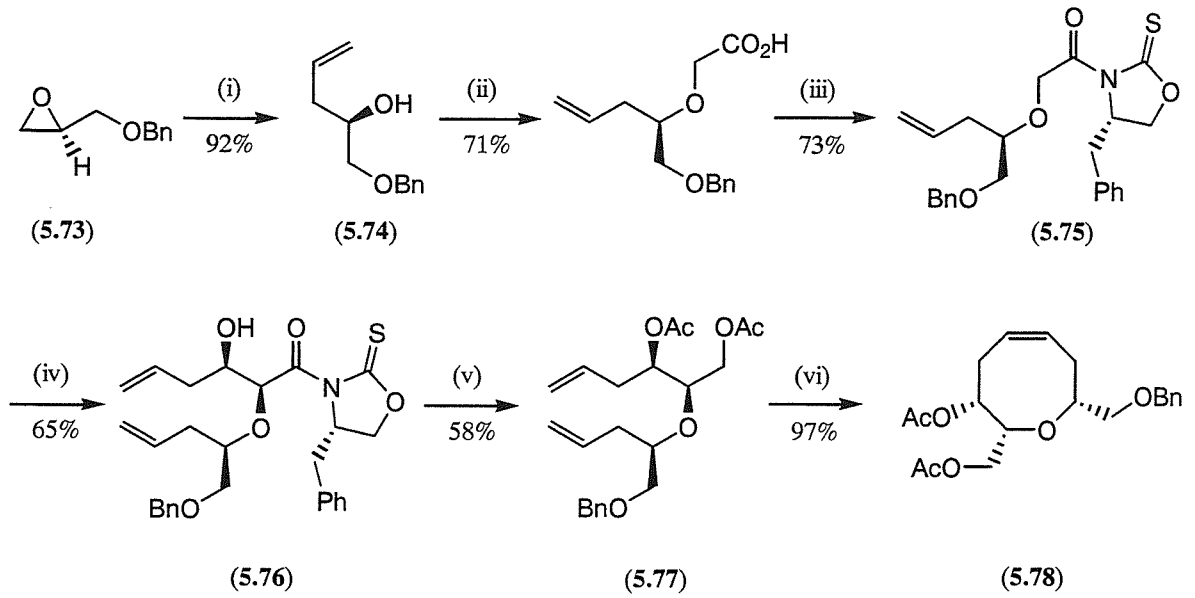
All reactions carried out in CH_2Cl_2 at reflux with 10 mol% of $Cl_2(Cy_3P)_2Ru{=}CHPh$.

Figure 5.6 Initial studies into the formation of oxocenes by RCM

In a series of model studies they demonstrated that metathesis was effective in dienes that contained pre-existing rings to provide entropic assistance in the cyclisation process. For example diene (**5.67**) gave a mixture of isomers (**5.68**) in which the *trans*- fused ring predominated. More importantly, they demonstrated that a non-cyclic diene (**5.69**) could be induced to undergo the same reaction to give oxocene (**5.70**) although the fickle nature of the reaction was indicated by the variance in the yield with the change in silyl protection of the alcohol.

The method was adapted to an achiral model for laurencin (**5.71**) as well as a stereospecific synthesis of a prelaurentin compound (**5.72**) which lacked substitution at C-8. Another group, led by Crimmins, supplied a viable explanation of these, on first inspection, rather surprising results (*vide supra*).

Crimmins *et al.* [211-213] developed a enantiospecific route to laurencin derivatives that also had the capacity to generate 1,8-*cis*- and 1,8-*trans*- stereochemistry [214] common to some halogenated natural products isolated from marine organisms.



Reagents and conditions: (i) vinyl MgBr, CuI, THF (ii) bromoacetic acid, NaH, THF (iii) (a) $(COCl)_2$, CH_2Cl_2 (b) 4 (S)-benzyl oxazolidinethione, NEt_3 (iv) (a) $TiCl_4$, (-)-sparteine, but-3-enal, CH_2Cl_2 (v) (a) $LiBH_4$, Et_2O, MeOH (b) Ac_2O, NEt_3, DMAP, CH_2Cl_2 (vi) $(CyP)_2Cl_2Ru$=CHPh, CH_2Cl_2, 0.003M.

Scheme 5.11

The stereochemistry at the carbon atoms that would eventually be part of the oxocene was established prior to cyclisation. (R)-Benzyl glycidyl ether (**5.73**) provided the necessary pro-C8 stereochemistry. This was ring opened by vinyl magnesium bromide in the presence of copper (I) to provide homoallyl ether (**5.74**). Alkylation, acid activation and acylation of the oxazolidinethione chiral auxiliary gave **5.75**. Asymmetric aldol reaction [215] with butenal in the presence of a Lewis acid (-)-sparteine gave exclusively the *syn*- aldol product (**5.76**). Reductive removal of the auxiliary followed by acylation gave diacetate (**5.77**).

Ring closing metathesis to provide oxocene (**5.78**) was completed in almost quantitative yield provided the reaction was carried out at high dilution. Functional group interconversion provided an intermediate isolated by Holmes some years earlier during his total synthesis of laurencin.

Crimmins provided some justification for the success both he and Taylor experienced with their chemistry when compared to earlier observations made by both Grubbs [207] and Hoveyda [209].

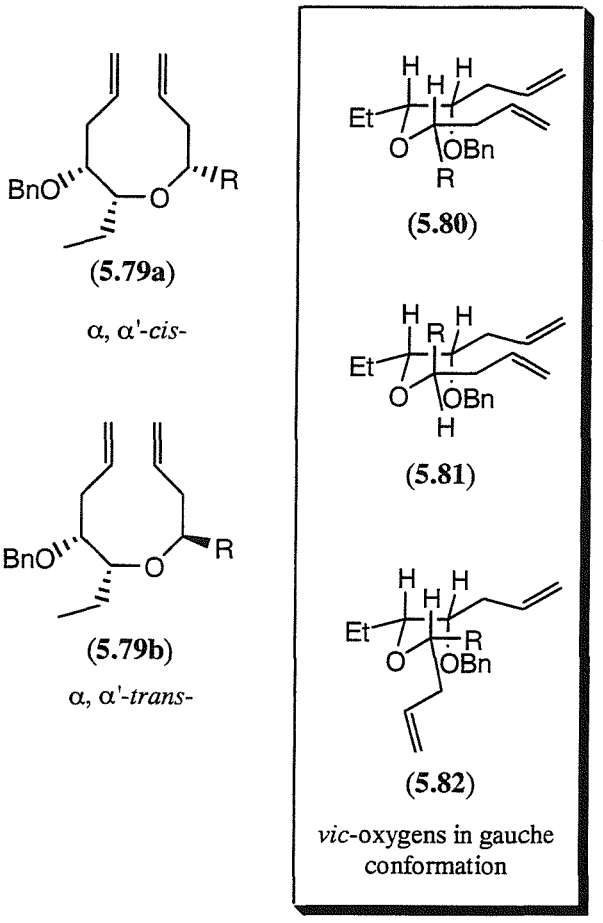


Figure 5.7 The gauche effect in RCM to alkoxy substituted 8 membered ring ethers

The substrates involved in the RCM towards laurencin type natural products all contained a vicinal dioxygenated moiety. Crimmins proposed that the conformation of these substrates would be profoundly influenced by the gauche effect of these two oxygen atoms. Conformational analysis of the two isomers (**5.79a** and **5.79b**) showed that *cis-* isomer (**5.79a**) with the two oxygen atoms in the gauche conformation had all the substituents in the pseudoequatorial positions and the two alkene groups proximate to each other (**5.80**). The observation of a rapid and high yielding cyclisation is consistent with this being of significance in the formation of the transition state. Isomer **5.79b** however has a predicted lowest energy conformation that places the alkenes remote from one another (**5.82**). In this instance the activation energy needed to access the higher energy conformation (**5.81**) could at best slow the reaction or, at worst, alter its pathway altogether. Experimental observation supported these proposals in that whilst the cyclisation of **5.79b** was effective it was much slower than a directly analogous **5.79a**.

The stabilisation energy gained from the stereoelectronic interaction of the the best donor orbital (C–H or C–C σ) into the best acceptor orbital (C–O σ*) that is the consequence of the gauche effect is not so significant as to be ajudged as the only influence that drives

these metathesis in the desired direction. Nonetheless, the essentiality of having a vicinal ether motif in the substrate for the success of the reaction does strongly support that the gauche effect plays a significant role.

Furthermore, whilst targeting the laurencin natural products Crimmins also made some Δ^3-oxocenes by metathesis. He found that these compounds cyclised rather less efficiently than their Δ^4 analogues and the reaction also gave rise to a significant quantity of acyclic dimer. Molecular modelling studies on Δ^3 and Δ^4 oxocenes revealed that the latter had an appreciably lower energy. This was considered to be in accord with the experimental observations assuming that the entropy change in both instances was the same in going from starting material to products. Both of the observations above infer that the efficacy of RCM in reactions starting with sterically unconstrained olefins may be predicted by a careful inspection of the stereoelectronic influences on conformation as well as considering the energies of the products from the reaction.

Whilst all of the syntheses of laurencin described in this section have their merits overall there is still scope for improvement. The compound itself if not of significant interest but its use to evaluate chemistry targeted at the preparation of medium ring ethers remains a interesting area for research.

Chapter 6

Progress towards the Synthesis Models for the Laurencin Class of Marine Natural Products

We chose to evaluate a ring expansion route to Laurencin that in some regard involves a return to the strategy of the earliest syntheses of the compound. There were several reasons why the chemistry implied in our retrosynthesis (Figure 6.1) was perceived to be attractive. Firstly, the ring opening of fused cyclopropyl carbinols (*e.g.* **6.2**) in the presence of Lewis acids is a strategy that has been extensively evaluated by Hoberg *et al.* [216] in their work on cyclopropanated glycals. It was also chemistry that was of current interest within the Brown group.

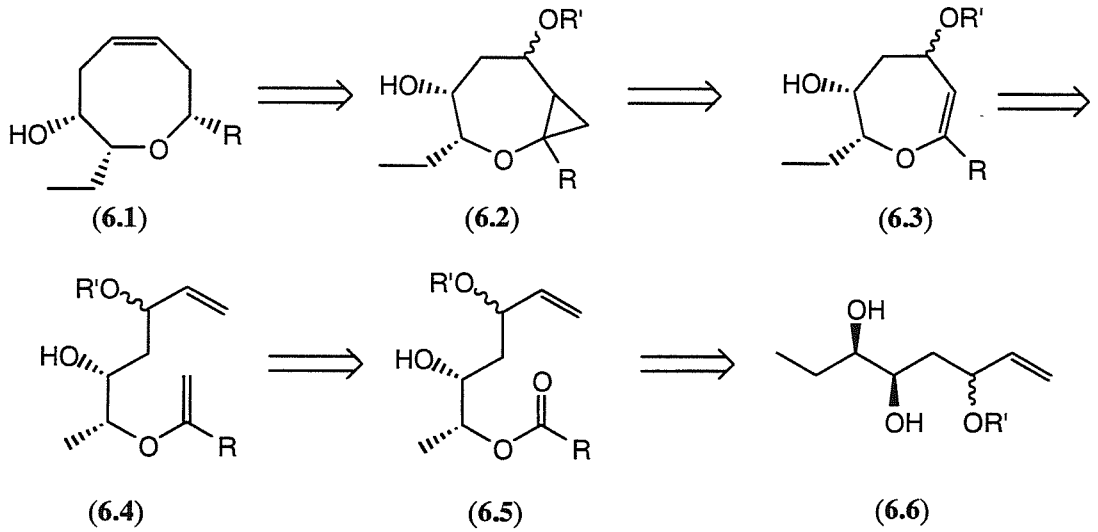


Figure 6.1 Retrosynthesis of laurencin

Secondly, the method involved ring closing metathesis (RCM) to give a 7-membered ring (*e.g.* **6.3**) from acyclic precursors that, at the outset of the programme, was believed to be much more efficient than 8-membered ring formation by same method. Thirdly, the challenge of undertaking metatheses with electron rich olefins (*e.g.* **6.4**) was one that was being met by a new generation of catalysts. Finally, there were several different enantiospecific routes to the early stage intermediates (*e.g.* **6.5** and **6.6**) that would have facilitated a chiral synthesis of model laurencin compound (**6.1**).

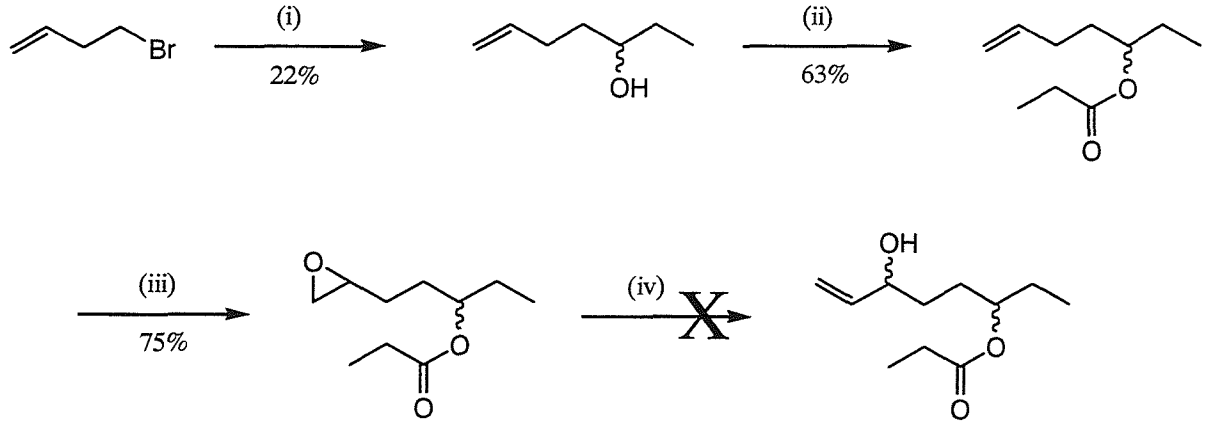
For all the potential benefits mentioned above the reaction scheme is one that contains many challenges. To try and facilitate a rapid access to compounds that would answer some questions about the later stage of the synthesis we decided to simplify the structure of our substrates as much as possible. We modelled the side chain at C-8 of laurencin as an

ethyl group and undertook the preparation of either suitably substituted 1,2,4-triols or 1,4-diols as precursors to our cyclisation substrates.

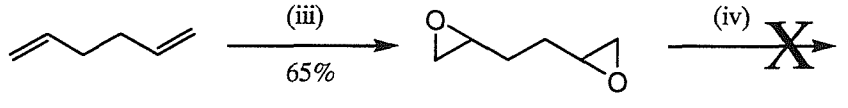
6.1 Preparation of substituted 1,4-diol precursors

The first approach sought to make use of the conversion of epoxides into the corresponding allylic alcohols. The method, described by Alcaraz and co-workers [217] utilises ylides formed on deprotonation of either trimethylsulfoxonium or trimethylsulfonium iodide in a substitution/ elimination approach.

The requisite epoxide (**6.7**) was prepared by standard methodology. Thus, the Grignard reagent derived from 4-bromobutene was reacted with propionaldehyde in a poor but manageable yield. Acylation of the free hydroxyl and treatment with *m*-CPBA provided an epoxide (**6.7**) that proved to be inert to either of the sulfur ylides. We envisaged that deprotonation at the ester would not be a problem given that the pKa of the conjugate acid of the trimethylsulfoxonium stabilised intermediate is estimated to be 18. In addition, the argument that the ester functionality was responsible for the difficulties appeared to be refuted by the fact that a significant proportion of the starting material (**6.7**) was recovered in each case.



(**6.7**)



(**6.8**)

Reagents and conditions: (i) Mg, Et_2O, CH_3CH_2CHO (ii) AcCl, NEt_3, CH_2Cl_2 (iii) *m*-CPBA, $CHCl_3$ (iv) $Me_3S^+I^-$, *n*-BuLi, THF **or** $Me_3S^+(O)I^-$, *n*-BuLi, THF.

Scheme 6.1

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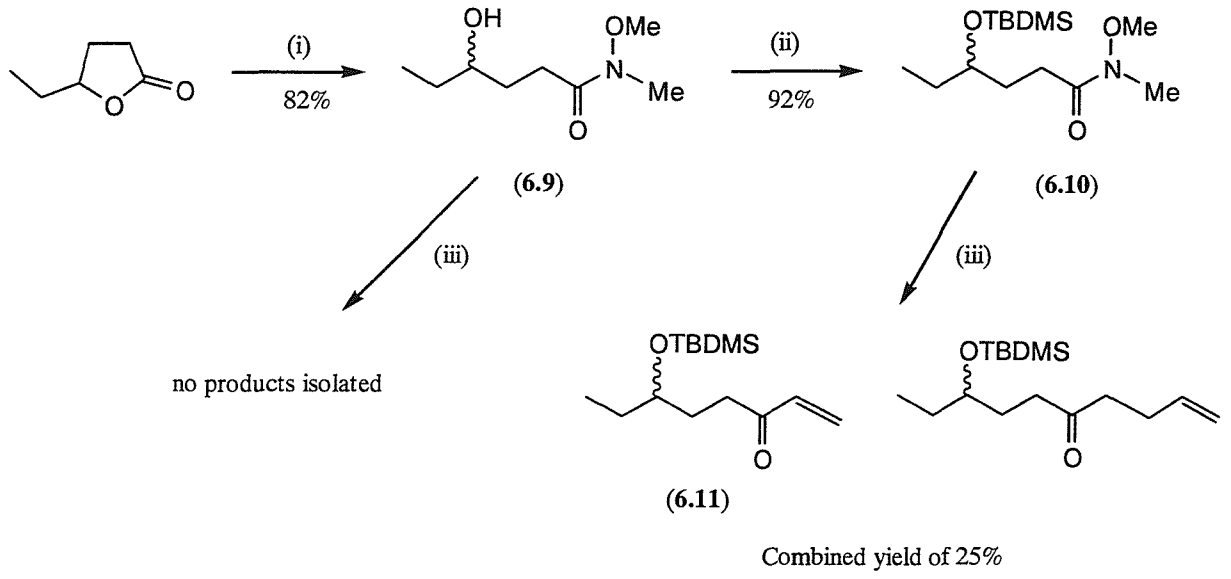
Even more optimistic was the investigation of the *bis*epoxide (**6.8**) [218] either with a view to effecting desymmetrisation during the addition/ elimination protocol or by undergoing double epoxide ring opening. Once again the substrate proved inert to the reaction conditions.



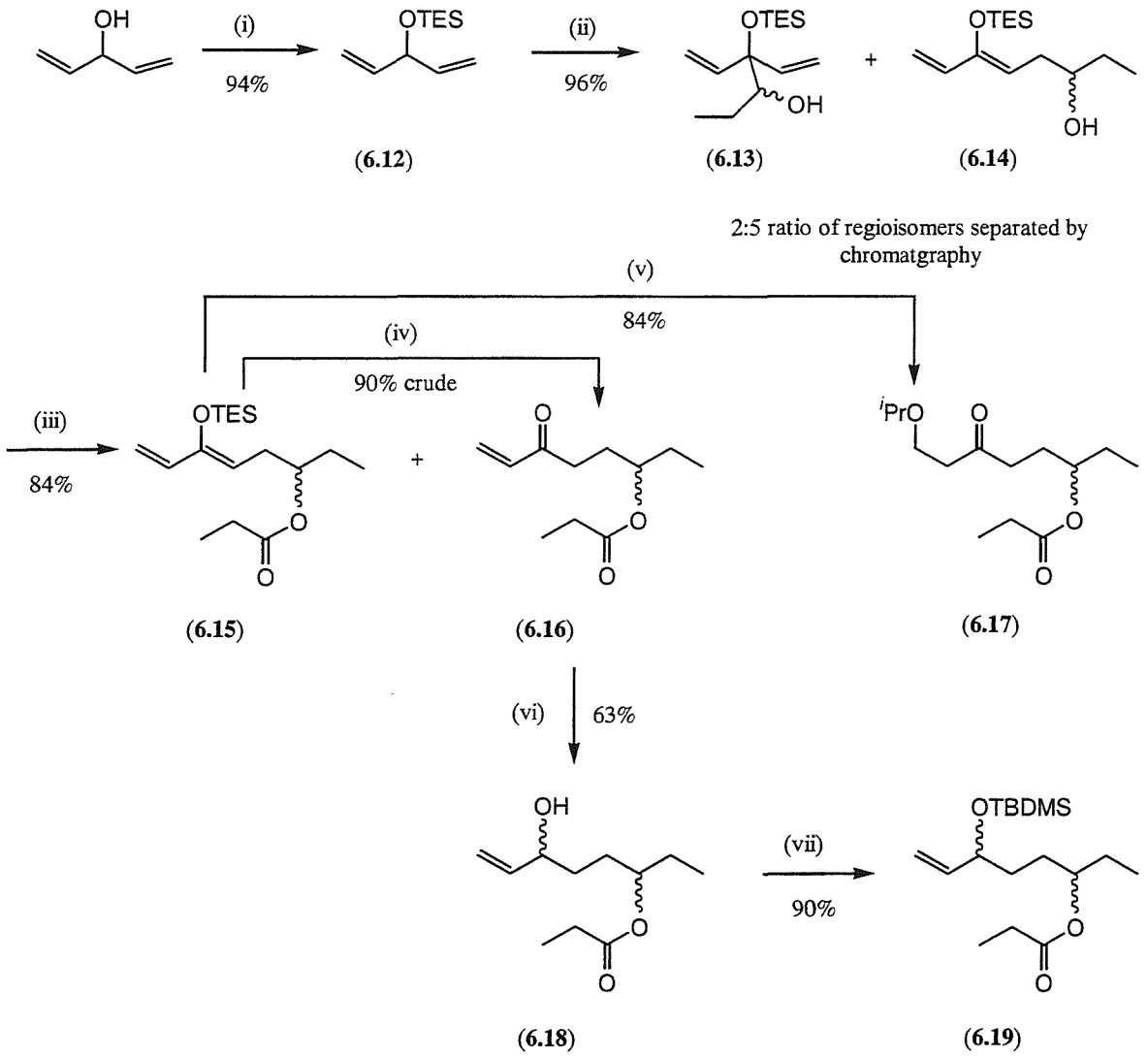
Reagents and conditions: (i) Me_3Al, MeONHMe.HCl, PhH (ii) TBDMSCl, imidazole, DMF (iii) $CH_2CHMgBr$, THF.

Scheme 6.2

An alternative procedure used the commercially available γ-caprolactone in the well-tested methodology of mono-addition of nucleophiles to the Weinreb amides [219]. Reaction of the lactone with trimethylaluminium in the presence of *N,O*-dimethyl hydroxylamine [220] gave the Weinreb amide (**6.9**) along with some recovered starting lactone. It was assumed that this arose from incomplete conversion but later results (*vide supra*) demonstrated that γ-hydroxy Weinreb amides are susceptible to lactonisation. Reaction of the free hydroxy compound with 2 equivalents of vinyl Grignard reagent resulted in no identifiable products being isolated, probably because of the capacity to polymerise through Michael addition. Protection of the hydroxyl group as the silyl ether (**6.10**) followed by treatment with vinyl magnesium bromide produced the desired compound (**6.11**) contaminated with the Michael addition product in a low yield.

A final investigation did provide the desired diol but was fraught with purification problems associated with the triethylsilyl protecting group used during the synthesis. The method used reaction of the anion derived from deprotonation of a silyl protected 1,4-pentadien-3-ol (**6.12**) with propionaldehyde. It was based upon work described by

Oppolzer [221] in which the critical feature is the preparation of protected vinyl ketones, in the presence of a γ-hydroxyl group. Thus, provided a method for acylation of the free hydroxy (in the presence of the silyl enol ether) could be identified it would be possible to avoid the unstable intermediate (**6.11**) identified as a problem in previous work.



Reagents and conditions: (i) TES-Cl, imidazole, DMF (ii) (a) *s*-BuLi, THF (b) CH_3CH_2CHO (iii) $(CH_3CH_2C(O))_2O$, pyridine (iv) PTSA, CH_2Cl_2 (v) KF, *i*-PrOH (vi) $NaBH_4$, $CeCl_3$, MeOH (vii) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2.

Scheme 6.3

A problem with the route is that the anion derived from **6.12** is not regioselective in its reaction with electrophiles. Products from reaction through either the α- or the γ- positions are isolated with the ratio of the two depending on the reactivity of the electrophile. The reaction with propionaldehyde provided alcohols **6.13** and **6.14** in a ratio of 1: 2. They proved to be separable on silica gel.

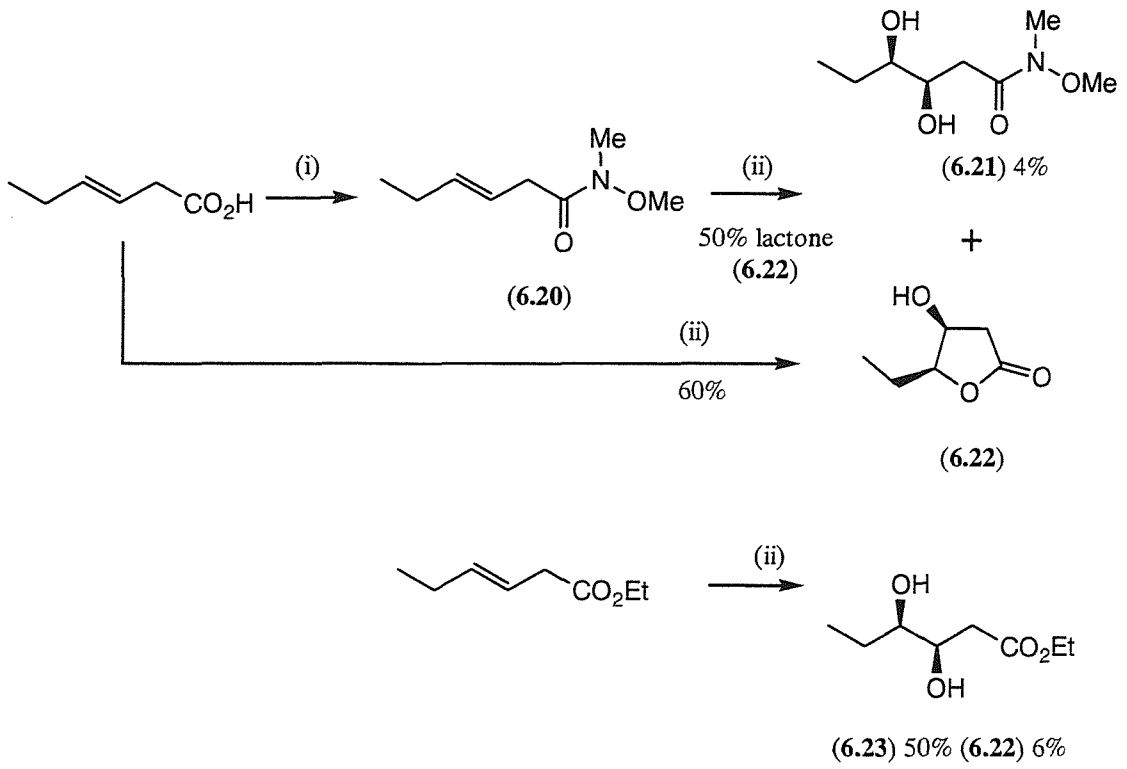
Acylation of alcohol **6.14** was undertaken by a number of methods. Carbodiimide mediated ester formation failed to give the desired compound and treatment with propionyl chloride in the presence of triethylamine gave the desired product (**6.15**) in only 30% yield. Most effective was treatment of the alcohol with propionic anhydride in pyridine with DMAP catalyst although which provided **6.15** in 68% yield along with the product arising from concomitant cleavage of the silyl enol ether to give **6.16**.

The literature method for deprotection of the silyl enol ethers [221] prescribed the use of KF in a hydroxylic solvent. Methanol was often used at reduced temperature but on occasions resulted in the Michael addition of the solvent with the conjugated ketone formed in the reaction. This problem was routinely overcome by using the more sterically challenging *iso*propyl alcohol at room temperature. In our hands even the latter conditions resulted in Michael addition to produce **6.17**. A number of alternatives were investigated the most efficient of which was the use of *p*-toluenesulfonic acid in dichloromethane. The conversion could only be estimated as being quantitative because it proved impossible to remove the residual triethylsilanol from **6.16** on anything but the smallest scale.

Nonetheless, the material was progressed through Luche reduction [222] to give the allylic alcohol (**6.18**). Efficient protection of this allylic alcohol proved not to be a trivial matter with introduction of triethylsilyl or benzyl protecting groups proceeding in very low yields. Eventually the use of TBDMS-triflate in the presence of 2,6-lutidine provided the protected material (**6.19**) that still could not be separated easily from the triethylsilanol byproduct produced in a previous reaction. Bulb-to-bulb distillation (under high vacuum at 200°C) of the crude mixture did remove a substantial proportion of the more volatile silanol but at the same time caused partial cleavage of the TBDMS ether! After several attempts a sample of **6.19** was produced that was deemed to be of sufficient purity to act as a substrate for the subsequent enol ether preparations.

6.2 Access to 1,2,4-trihydroxy derivatives

Two further strategies were investigated, both of which incorporated the masked bromo-functionality required in the final compound. This series of model compounds were not pursued in the first instance because of the assumed ease of synthesis of the 1,4-diols. Given that this proved not to be the case the apparently more complex, but arguably more relevant models, were targeted. They have the additional advantage that the methodology employed should be adaptable to the enantiomerically pure series.



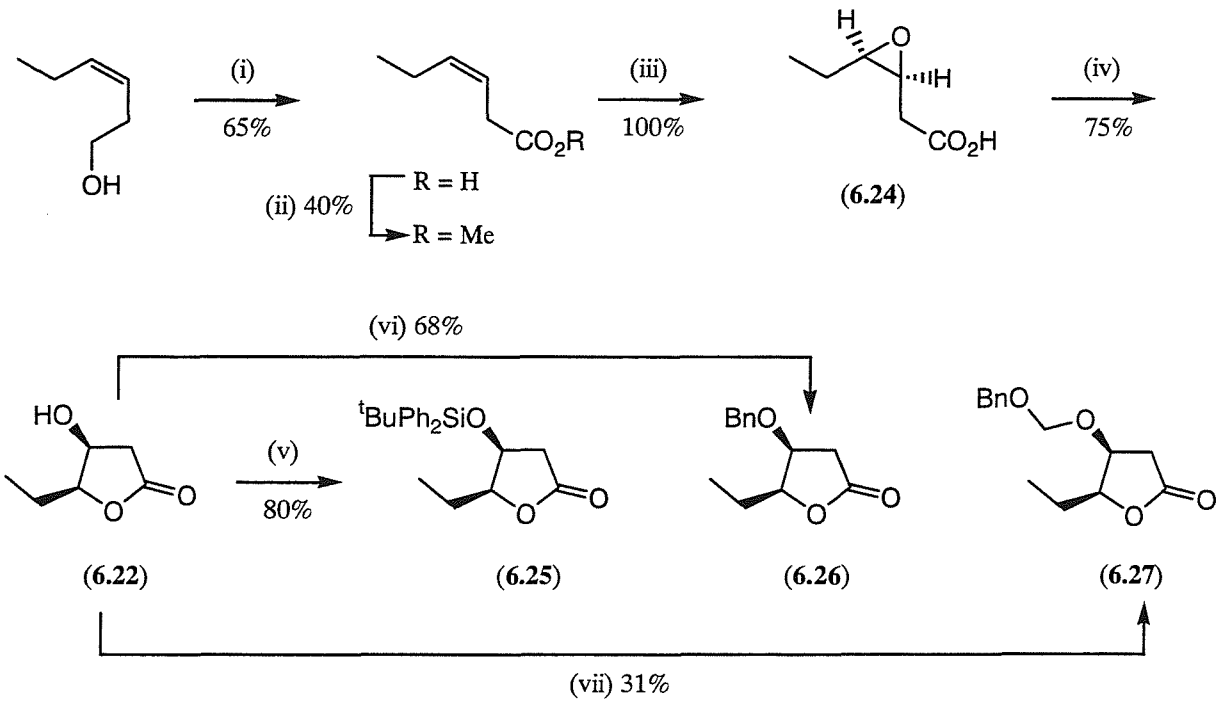
Reagents and conditions: (i) (a) $(COCl)_2$, CH_2Cl_2, DMF (b) MeO(Me)NH.HCl, NEt_3 (ii) OsO_4, *N*-methylmorpholine-*N*-oxide, acetone, water.

Scheme 6.4

Firstly the utility of the diastereoselective dihydroxylation of *trans*-hex-3-enoic acid derivatives was investigated. Conversion of the acid to the Weinreb amide (**6.20**) proceeded *via* the acid chloride. Attempted dihydroxylation provided a poor recovery of the desired diol (**6.21**) with the major product being the lactone (**6.22**). This result throws a different light on the observation that the formation of a Weinreb amide from a γ-lactone might not have gone to completion. Instead the *N*-methoxy-*N*-methylamine appears to be a better leaving group than expected.

Treatment of the ethyl ester was more successful in that the dihydroxylation product (**6.23**) was favoured over the lactone by a factor of 10 to 1. Similar treatment of the free acid resulted in formation of the lactone in moderate yield. In this case the difficulty of extracting the product from the aqueous phase was particularly manifest although it almost certainly had a part to play in lowering the recoveries from the other reactions. Prolonged continuous extraction with ether was effective to some extent in solving the problem.

The relatively disappointing yields of all the conversions outlined above led us to look at the possibility of using an alternative stereochemically defined approach to the same produts. Thus, formation and ring opening of an epoxide as an appropriate route to the requisite lactone was undertaken in parallel to the work outlined above.

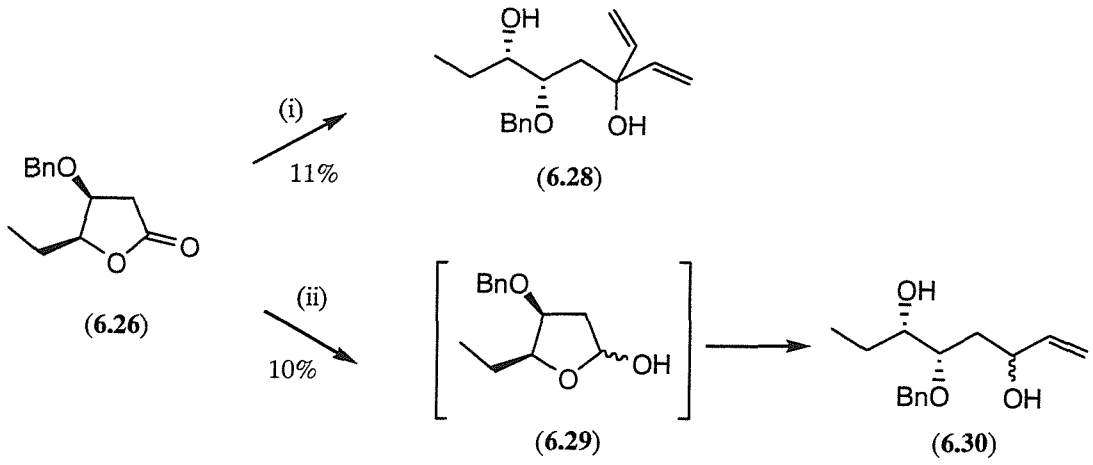


Reagents and conditions: (i) Jones' reagent, acetone (ii) MeOH, H_2SO_4 (iii) *m*-CPBA, NaOAc, CH_2Cl_2 (iv) THF, H_2SO_4 (v) *t*-$BuPh_2SiCl$, imidazole, DMF (vi) benzyltrichloroacetimidate, TfOH, $PhCH_3$, cyclohexane (vii) $PhCH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2.

Scheme 6.5

Precedent for the approach was provided by the work of Holmes *et al.* [223] who used *trans*-hex-3-enoic acid to produce (4R*, 5S*) 5-ethyl-4-hydroxy-γ-butyrolactone. Our work required the diastereisomeric lactone suggesting the same strategy starting with *cis*-hex-3-enoic acid should bear fruit. The feasibility of the method was evaluated using commercially available *cis*-hex-3-enoic acid that is available as a 9:1 mixture of stereoisomers. Esterification, epoxidation and lactone formation under acidic conditions did indeed form the desired material but it proved impossible to separate the minor diastereoisomer from the desired product at any stage. Stereochemically pure acid [224] was prepared by Jones oxidation of the commercially available homoallylic alcohol and the sequence of reactions to prepare **6.22** repeated.

A variety of different protecting groups were investigated. BOM protection (to give (**6.27**)) proved to be inefficient whilst formation of the *tert*-butyldiphenylsilyl- (**6.25**) or benzyl- (**6.26**) protected alcohols proceeded in moderate to good yields.

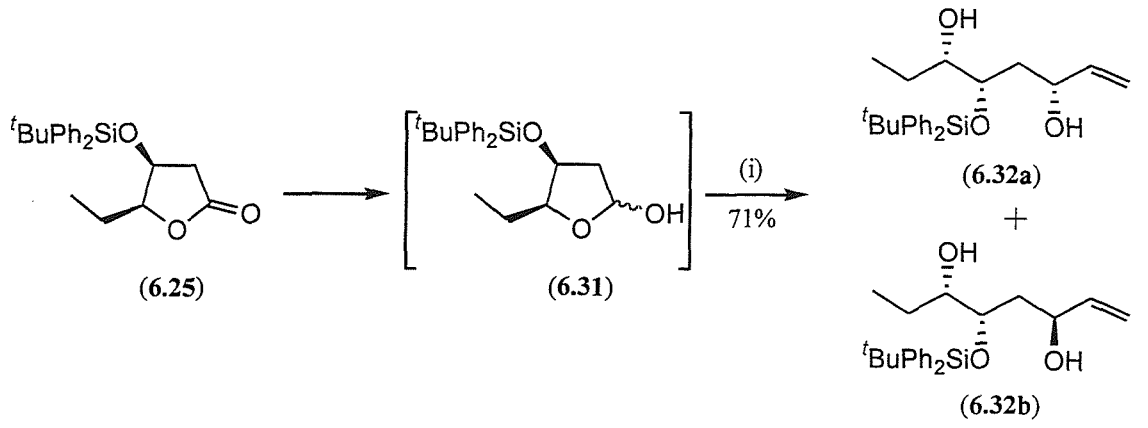


Reagents and conditions: (i) $CH_2CHMgBr$, THF (ii) (a) DIBAL, CH_2Cl_2 (b) $CH_2CHMgBr$.

Scheme 6.6

Several attempts were made to effect mono-addition of vinyl magnesium bromide to benzyloxy- substituted lactone (**6.26**) even in the face of the likely problems from di-addition of the organometallic, or reaction of the Michael acceptor resulting from mono-addition with the organometallic reagent. Chemoselective mono-addition of organometallic derivatives is not a commonly reported procedure but there was precedent to suggest that a brief investigation was merited [225]. For the most part these reactions were only effective with 3-alkoxy substituted lactones wherein the metal alkoxide produced on mono-addition is additionally stabilised by the extra oxygen atom [226]. In our system reaction showed no evidence of mono-addition producing only a mixture of the di-addition product (**6.28**) and recovered starting material. Carrying out the addition in the presence of TMS-Cl, in the hope of trapping the alkoxide arising from mono-addition as the transiently stable silylenol ether, also proved to be a fruitless exercise. In our hands the starting material was recovered (30%) along with benzyl alcohol that accounted for a further 35% of the starting material. The latter presumably arose from the Grignard reagent acting as a base on lactone (**6.26**) and elimination of benzyl alcohol from the resultant lactone enolate. The possibility of employing metallo acetylides in a mono-addition reaction was not investigated although there have been examples of high yields in the addition of the dichlorocerium acetylide to 3 unsubstituted lactones [227].

The more likely two step route involving reduction of the lactone to the lactol followed by Grignard addition also proved problematical. In part the difficulty was the monitoring of the reduction in which the lactol (**6.29**) proved to have very similar polarity to the lactone. Even in reductions where TLC and υ_{max} suggested conversion was complete the subsequent addition resulted in isolation of only the di-addition product (**6.28**).



Reagents and conditions: (i) (a) DIBAL, CH_2Cl_2 (b) $CH_2CHMgBr$.

Scheme 6.7

The efficiency of the reduction was improved with a switch of solvent from THF to dichloromethane. Even so the highest yield of the partially protected triol (**6.30**) arising from mono-addition to the lactol (**6.29**) that was achieved was a lowly 10%.

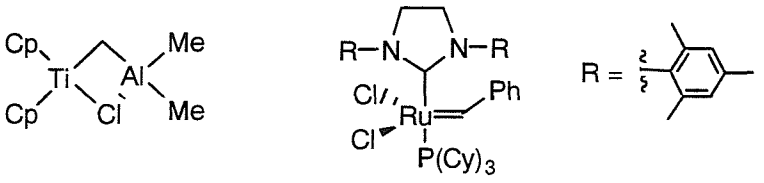
Application of the two-step procedure to the silyloxy lactone (**6.25**) was rather more productive. Thus, reduction of the lactone to the lactol (**6.31**) followed by addition of vinyl magnesium bromide produced the desired compound as a 3:2 mixture of diastereoisomers (**6.32a, 6.32b**) that were separable by a combination of chromatography on silica gel and crystallisation. To date acylation reactions on either of these diastereoisomers has failed to show any selectivity between the allyl and the secondary hydroxyl centres.

6.3 Enol ether formation and ring closing metathesis

Enol ether formation on ester (**6.19**) was undertaken using the well-documented Tebbe titanium alkylidene carbene mediated methodology [228]. A particular attraction of this route was the potential of effecting the olefination reaction and subsequent metathesis in one pot using the same reagent. This approach has been demonstrated by Nicolaou in the synthesis of brevetoxin analogues [66] wherein the only problem was the use of stoichiometric Tebbe reagent (**6.33**). This difficulty was academic given that the reaction using **6.19** failed to produce any enol ether whether carried out with or without catalytic pyridine [229]. The possibility that the commercial reagent used in the reaction might have been inactive was refuted by the success in olefination of the ethylene ketal of ethyl acetoacetate; this literature procedure was accomplished in a 92% yield.

The alternative Takai olefination strategy was also investigated [230]. This methodology, in which the critical intermediate is also believed to be a titanium alkylidene carbene, has become more useful since the observation that catalytic lead(II) salts [231] increase the

efficiency of the reaction. Although not fully understood these salts are believed to favour the formation of the dialkyl zinc intermediates over the monoalkylzinc halides. Efficient generation of the former is to be essential prior to a series of transmetallations leading to formation of the titanium alkylidene carbene.

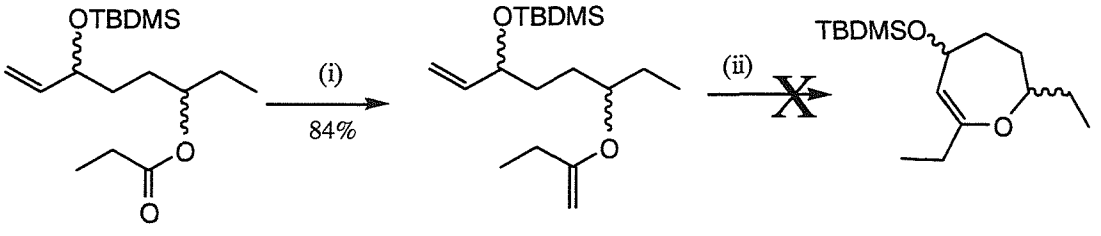


(6.33) (6.35)

Figure 6.2 The metathesis catalysts

The reaction using ester **6.19** proved to be effective although somewhat capricious. Use of dibromomethane as the carbene precursor, instead of diiodomethane, appeared to be necessary, as did the need for care in avoiding acidic conditions during work-up and purification. The enol ether product **(6.34)** appeared to have a lifetime of several days if stored at 0°C.

The enol ether **(6.34)** was challenged to RCM conditions employing the new generation Grubb's catalyst **(6.35)** which has shown utility in the metathesis of alkenes resistant to both first generation ruthenium catalysts [232] as well as the more reactive but harder to handle molybdenum catalysts used by Schrock [51]. In particular, the new catalyst has been shown to be effective in producing sterically crowded alkenes [60] as well as being effective in metathesis of enol ethers [67].



(6.19) (6.34) (6.36)

Reagents and conditions: (i) $TiCl_4$, TMEDA, $PbCl_2$, Zn, CH_2Br_2, THF (ii) **6.35**, PhH **or** CH_2Cl_2.

Scheme 6.8

Enol ether **(6.34)** appeared resistant to the catalyst and resulted in only the recovery of starting material under a variety of different conditions. Use of 5 mol% of catalyst, a higher loading being recommended for the reaction with electron rich alkenes, in

dichloromethane or in benzene resulted in no reaction whether at room temperature or at elevated temperature.

Clearly, this extremely limited survey does not justify the conclusion that formation of the required oxocycloheptene (**6.36**) is unfeasible using this methodology. However, at the conclusion of this project it is clear that much work is still necessary to prove its utility one way or the other.

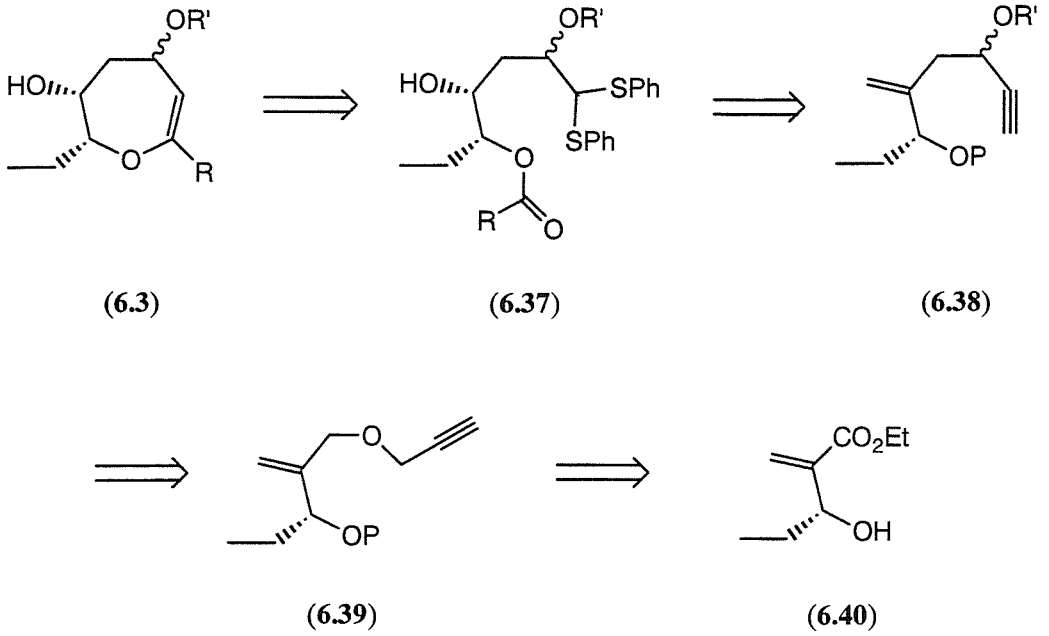
6.4 Concluding Comments

At the outset of this programme of work the application of metathesis to the preparation of 8-membered oxygen containing rings was not a well-known process. As a consequence the proposal of using the much more commonplace reaction to form a 7-membered ring by alkene metathesis was well founded and the subsequent ring expansion was of interest in its own right. However, since late 1999 the application of metathesis to the production of 8-membered rings in general, and laurencin in particular, has been well documented by Crimmins and co-workers [213].

The work undertaken towards the preparation of substrates to evaluate the feasibility of the ring closing metathesis has also proved somewhat difficult. In part this was due to some inappropriate target selection of model compounds where selection of substrates more closely related to the natural product system might well have been no more problematic than those actually undertaken.

Finally, although not tested the metatheses of enol ethers remains a difficult process entailing the use of either capricious molybdenum catalysts or very high loadings (20 mol%) of expensive, but effective, ruthenium catalysts.

Whilst none of the observations above would be reason for abandoning an area of research if taken in isolation their combination does present a strong argument against the continuation of this strategy as a means of preparing laurencin. Nonetheless, a number of alternatives that make use of metal carbene intermediates do suggest themselves.

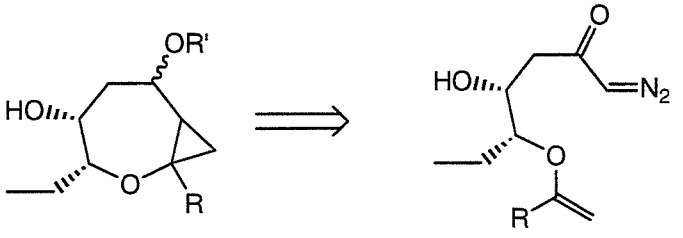


(6.3) (6.37) (6.38)

(6.39) (6.40)

Figure 6.3 An alternative strategy using Takeda olefination methodology

Firstly, Takeda and co-workers have developed a olefination reaction involving titanium alkylidine carbenes derived from dithioacetals and their subsequent reaction with carbonyl compounds. The metal carbene forming reagent, $Cp_2Ti(P(OEt)_3)_2$, was originally found to be useful in the intermolecular olefination of ketones and aldehydes [233] and has subsequently been developed into an intramolecular strategy for the preparation of cyclic olefins [234] or enol ethers [235]. Disconnection of the late stage intermediate (**6.3**) in our initial laurencin retrosynthesis (Figure 6.1) reveals dithioacetal that might be susceptible to ring closure using Takeda's conditions. Dithioacetal (**6.37**) itself may be disconnected to eneyne (**6.38**) that could also serve as an intermediate for formation a diene suitable for ring closure using Grubbs metathesis conditions (Figure 6.3). The precedented stereospecific [2,3]-Wittig rearrangement [236] could serve as a means of transforming **6.39** to **6.38** whilst the former can be disconnected back to the Bayliss Hillman [237] adduct (**6.40**). The potential for stereospecific formation [238] of **6.40** would allow for an enantiospecific preparation of laurencin.



(6.2) (6.41)

Figure 6.4 An alternative strategy using diazoinsertion into an alkene

A completely different approach using diazo- insertion into an alkene to form a cyclopropane in the ring-forming step could serve as a means of accessing late stage intermediate (**6.2**) whilst avoiding preparation of a cyclic enol ether. Thus, disconnection of **6.2** back to a stabilised diazoketone (**6.41**) (Figure 6.4) provides an intermediate that could suffer a number of fates. As well as the desired cyclopropanation into the electron rich alkene a competing C–H insertion into the activated position next to the oxygen to form a cyclopentane might prove an insurmountable problem.

Both alternatives outlined above are fraught with difficulties associated with chemo- and/ or stereoselectivity. Nonetheless, the fact that these metal carbene centred strategies are viable synthetic alternatives is illustrative of the speed of development in this area as well as the diversity of its application.

Chapter 7

Experimental Details

7.1 General Experimental

All reactions that required exclusion of moisture and/ or oxygen were conducted under a flow of either nitrogen or argon. Dichloromethane and 1,2-dichloroethane were dried by distillation from CaH_2; DMF was distilled from CaH_2 under reduced pressure; THF was dried by distillation from the sodium ketyl of benzophenone. Other solvents were purified as conditions demanded according to standard methods [239]. Reagents were purchased from all the major commercial suppliers and purified if their analyses implied it was necessary.

Reactions were monitored by TLC using either aluminium or glass backed plates coated with silica gel 60 containing a fluorescence indicator active at 254nm. The TLC plates were developed using combinations of diethyl ether, ethyl acetate or dichloromethane in hexane. Visualisation was accomplished with UV light at 254nm followed by staining with, most commonly, 10% aqueous $KMnO_4$ or 20% phosphomolybdic acid in ethanol.

Chromatographic purification of mixtures was accomplished on silica gel (Merck, mesh size 40-63μm). The quantity of separation media is described by the dimensions of the column (height x diameter in cm) or by the weight of the separation medium (g).

Melting points were collected in open capilliary tubes and are uncorrected.

IR spectra were collected on (i) Perkin Elmer 1600 FT-IR either as neat films or solutions in dichloromethane (ii) Nicolet Impact 400 fitted with a Thunderdome ATR sampling platform as solids or neat liquids (iii) Mattson Satellite fitted with a Specac Golden Gate ATR sampling platform as solids or neat liquids.

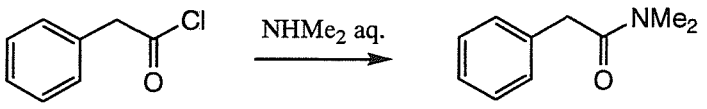
^1H and ^{13}C NMR spectra were collected on Bruker AC300, Bruker AM300 or Bruker DPX400 using appropriate deuterated solvents. Most commonly deuteriochloroform was used with chloroform as an internal standard (δ 7.26 ppm ^1H, δ 77.5 ppm ^{13}C).

Low resolution mass spectra were obtained on a Fisons VG platform single quadropole mass spectrometer in either electrospray, chemical ionisation or electron impact ionisation mode or a Micromass platform mass analyser with an electrospray ion source.

* Spectroscopic details that are highlighted with an asterisk have been acquired during a parallel programme of research conducted within the Brown group.

7.2 Experimental Details of Lignan Preparations

N,N-Dimethyl-2-phenylacetamide (4.7)

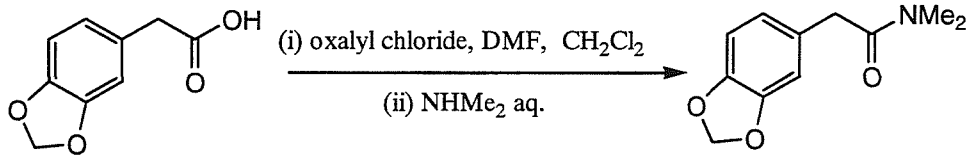


(4.7)

A solution of phenylacetyl chloride (3.86 g, 3.30 mL, 25 mmol) in dichloromethane (30 mL) was cooled on ice and treated with dimethylamine (25% aqueous solution, 10.8g, 11.5 mL, 60 mmol) by dropwise addition. After the evolution of HCl (g) was complete the reaction mixture was allowed to warm to room temperature and stirred overnight. After dilution with dichloromethane (30 mL) the reaction mixture was sequentially washed with 2.0M hydrochloric acid, saturated sodium bicarbonate (aq.), water and brine (30 mL each). After drying ($MgSO_4$) and removal of solvent the crude product was purified by bulb-to-bulb distillation (0.2 mm Hg, oven temperature 170°C) which provided the title compound (**4.7**) as a viscous oil which crystallised on standing (4.03g, 98%). Spectroscopic data were consistent with those described in the literature [120].

MP	40.5-41.5°C (lit. 41°C) [120].
FT-IR (CH_2Cl_2)	3029, 1642, 1495, and 1397 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	2.97 (s, 3H), 3.00 (s, 3H), 3.74 (s, 2H) and 7.20-7.40 (m, 5H) ppm.

N,N-Dimethyl-2-(3,4-methylenedioxyphenyl)acetamide (4.24)



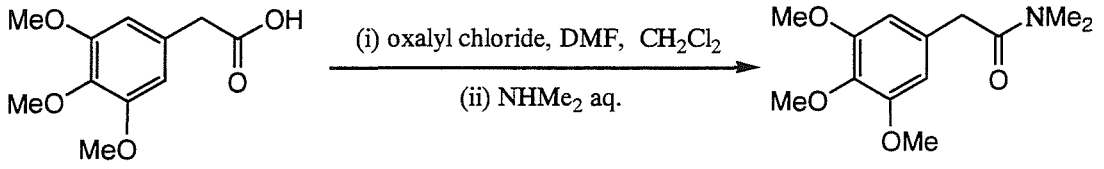
(4.24)

3,4-Methylenedioxyphenylacetic acid (4.83 g, 26.7 mmol) was suspended in dry dichloromethane (25 mL) and treated with a oxalyl chloride (3.72 g, 2.57 mL, 29.4 mmol) followed by dimethylformamide (1 drop). The reaction was stirred until gaseous evolution ceased and the starting acid was fully dissolved. The crude acid chloride (ν_{max} (CH_2Cl_2) 1790 cm^{-1}) was immediately converted to the title compound according to the method outlined for **4.7**. The crude product was purified by bulb-to-bulb distillation (2 mm Hg,

oven temperature >250°C) to give the title compound [240] (**4.24**) as a viscous oil (4.42g, 23.6 mmol, 88%). Crystallisation occurred on standing.

MP	49 – 52 °C.
FT-IR (CH_2Cl_2)	3021, 2934, 1641, 1489, 1443, 1397, 1246, and 1040 cm^{-1}.
^1H NMR (300MHz, $CDCl_3$)	2.97 (s, 3H), 3.01 (s, 3H), 3.62 (s, 2H), 5.94 (s, 2H), 6.68 (dd, J = 7.7, 1.0 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.77 (bs, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	35.8 (CH_3), 37.8 (CH_3), 40.7 (CH_2), 101.1 (CH_2), 108.5 (CH), 109.4 (CH), 121.9 (CH), 128.8 (C), 146.5 (C), 147.9 (C), 171.3 (C) ppm.
LRMS	(ES +ve) *m/z* (relative intensity) 208 (100) $[M+H]^+$, 415 (20) $[2M+H]^+$.

***N,N*-Dimethyl-2-(3,4,5-trimethoxyphenyl)acetamide (4.43)**



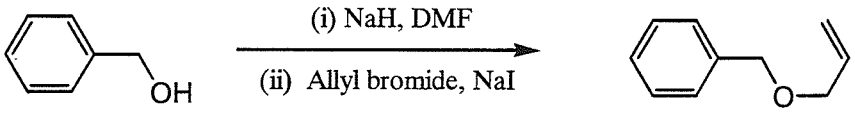
(4.43)

To a suspension of 3,4,5-trimethoxyphenyl acetic acid (7.92 g, 35 mmol) in CH_2Cl_2 (35 mL), at RT, was added oxalyl chloride (3.4 mL, 38.5 mmol) followed by 2 drops of DMF. The reaction was stirred for 6 h whereupon gaseous evolution had ceased and full conversion of acid was observed (monitoring by IR -$C{=}O_{(COOH)}$ 1699 cm^{-1} and –$C{=}O_{(COCl)}$ 1793 cm^{-1}). The crude acid chloride was immediately converted to the amide according to the method outlined for **4.7**. Purification was accomplished by distillation under reduced pressure (bp 136 –139 °C (0.5 mbar)) to give the title compound (**4.43**) (8.45 g, 33 mmol, 95 %) as a viscous, colourless oil that solidified on standing to provide a white solid.

MP	53 – 55 °C (lit. 50-51°C [241]).
CHN	Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.58; H, 7.65; N, 5.45.
FT-IR (neat)	1652 cm^{-1}.
^1H NMR	3.01 (s, 3H), 3.05 (s, 3H), 3.68 (s, 2H), 3.85 (s, 3H),

(400MHz, $CDCl_3$)	3.87 (s, 6H), 6.51 (s, 2H) ppm.
^{13}C NMR	36.1 (CH_3), 38.1 (CH_3), 41.5 (CH_2), 56.5 (CH_3), 61.2 (CH_3),
(100 MHz, $CDCl_3$)	106.3 (CH), 131.1 (C), 137.3 (C), 153.7(C), 171.3 (C) ppm.
LRMS	(ES +ve) *m/z* (relative intensity) 254 (28) $[M+H]^+$, 529 (100) $[2M+Na]^+$.

Allyl benzyl ether (4.6)

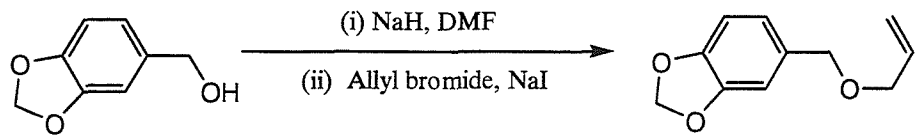


(4.6)

The title compound was prepared according to the method of Arndt *et al.* [119] Sodium hydride (60% dispersion in mineral oil, 2.20 g, 55 mmol) was washed with dry pentane in oven dried apparatus whilst under nitrogen. Dry dimethylformamide (50 mL) was added to the resulting solid. To this suspension was added benzyl alcohol (5.94 g, 5.68 mL, 44 mmol) by dropwise addition and the mixture stirred at room temperature for 45 minutes. Potassium iodide (1.66 g, 20 mmol) was added prior to the addition of a solution of allyl bromide (6.05g, 4.32 mL, 50 mmol) in DMF (5 mL), which was added over a period of 10 minutes. The resulting mixture was left to stir for 16 hours at room temperature before pouring into water (250 mL) (partially saturated with sodium chloride (20 g)) and extracting with diethyl ether (3 x 100 mL). The combined extracts were washed with water and brine (100 mL each) and dried ($MgSO_4$). Purification was effected by vacuum distillation (94-6°C, 12 mm Hg) followed by rapid chromatography on silica gel (70g, using 10% ether in petroleum ether 40/60) to remove trace quantities of unreacted alcohol. The title compound (**4.6**) was isolated as a colourless oil (5.25 g, 36 mmol, 81%). Spectroscopic data were consistent with those described in the literature [119].

FT-IR (CH_2Cl_2)	3063, 3028, 2858, 1646, 1495, 1453, and 1091 cm^{-1}.
^1H NMR	4.05 (dt, J = 5.9, 1.5 Hz, 2H), 4.55 (s, 2H), 5.24 (app. dq, J = 10.3,
(300MHz, $CDCl_3$)	1.5 Hz, 1H), 5.35 (app. dq, J = 17.3, 1.5 Hz, 1H),
	5.98 (ddt, J = 17.3, 10.5, 5.5 Hz, 1H), 7.30-7.50 (m, 5H) ppm.
^{13}C NMR	71.1 (CH_2), 72.3 (CH_2), 117.3 (CH_2), 127.8 (CH), 128.5 (CH),
(75 MHz, $CDCl_3$)	128.6 (CH), 134.9 (CH), 138.4 (C) ppm.

Allyl 3,4-methylenedioxybenzyl ether (4.23)

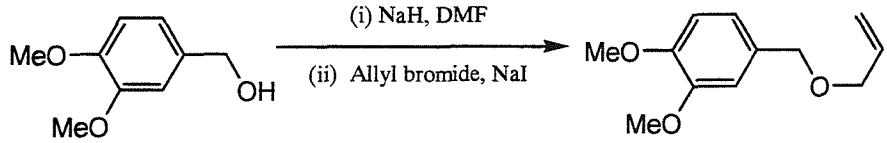


(**4.23**)

The title compound was prepared from 3,4-methylenedioxybenzyl alcohol (10.65 g, 70 mmol) according to the method outlined for **4.6**. The title compound (**4.23**) was purified by distillation (84-88°C, 0.4 mm Hg) to give a colourless oil (12.1g, 63 mmol, 90%). Spectroscopic data were consistent with those described in the literature [119].

FT-IR (CH_2Cl_2)	2891, 1503, 1490, 1252, and 1040 cm^{-1}.
^1H NMR	4.01 (dt, J = 5.9, 1.1 Hz, 2H), 4.43 (s, 2H), 5.22 (app. dq,
(300MHz, $CDCl_3$)	J = 10.3, 1.1 Hz, 1H), 5.31 (app. dq, J = 16.9, 1.5 Hz, 1H), 5.96 (s, 2H) superimposed on 5.89-6.02 (m, 1H), 6.77-6.83 (m, 2H), 6.87 (bs, 1H) ppm.
^{13}C NMR	71.0 (CH_2), 72.1 (CH_2), 101.1 (CH_2), 108.2 (CH), 108.7 (CH),
(75 MHz, $CDCl_3$)	117.3 (CH_2), 121.5 (CH), 132.3 (C), 134.9 (CH), 147.2 (C), 147.9 (C) ppm.

Allyl 3,4-dimethoxybenzyl ether (4.44)



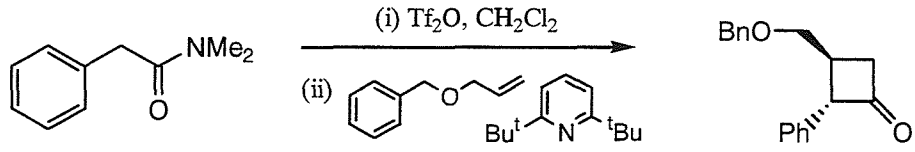
(**4.44**)

The title compound was prepared from 3,4-dimethoxybenzyl alcohol (8.0 g, 48mmol) according to the method outlined for **4.6**. The title compound (**4.44**) was purified by chromatorgraphy on silica gel (32g) eluting with 10% ethyl acetate in hexane to provide the product as a colourless oil (6.98g, 33.6 mmol, 70%).

FT-IR (ATR)	2935, 1592, 1515, 1464, 1138 cm^{-1}
^1H NMR	3.85 (s, 3H), 3.87 (s, 3H), 4.05 (d, J = 5.2Hz, 2H), 4.50 (s, 2H),
(300MHz, $CDCl_3$)	5.20 (d, J = 10.3Hz, 1H), 5.33 (d, J = 16.1Hz, 1H), 5.90 (ddd, J = 16.7, 11.0, 5.2Hz, 1H), 6.80-7.00 (m, 3H) ppm.

^{13}C NMR	55.94 (CH_3), 56.03 (CH_3), 71.07 (CH_2), 72.17 (CH_2), 111.00
(75 MHz, $CDCl_3$)	(CH), 111.20 (CH), 117.27 (CH_2), 120.45 (CH), 130.96 (CH), 134.96 (CH), 148.71 (C), 149.14 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 151 (100) $[M\text{-}CH_2CHCH_2O]^{\bullet+}$, 208 (30) $[M]^{\bullet+}$.

(2S*, 3S*)-3-[(Benzyloxy)methyl]-2-phenylcyclobutanone (4.5)



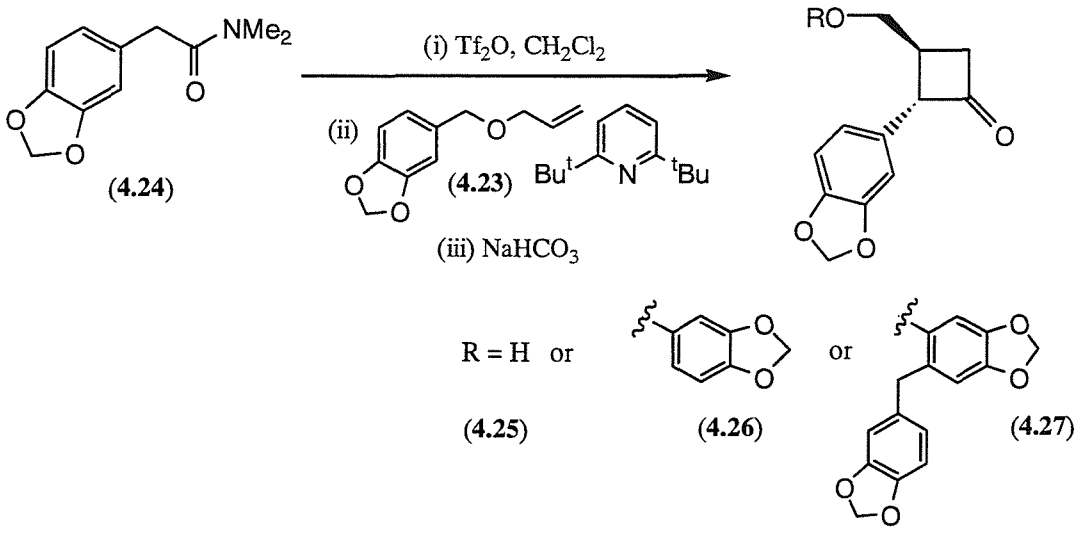
(4.7) (iii) $NaHCO_3$ (4.5)

The title compound was prepared according to the general method described by Ghosez *et al.* [122] *N,N*-Dimethylphenylacetamide (**4.7**) (815 mg, 0.5 mmol) was dissolved in dichloromethane (10 mL) under nitrogen. The solution was cooled to -20°C (internal) and treated with trifluoromethanesulfonic anhydride (1.01 mL, 6 mmol) at such a rate that the temperature did not rise above -15°C. The yellow homogeneous reaction mixture was stirred at -20°C for 10 minutes before adding of a mixture of 2,6-di-*tert*-butylpyridine (1.35 mL, 6 mmol) and allylbenzylether (**4.6**) (1.48 g, 10 mmol) in dichloromethane (10 mL) over a period of 10 minutes. The reaction was stirred at -20°C for 10 minutes and allowed to warm to room temperature. The reaction was monitored by IR (cyclic iminium salt species; υ_{max} 1731cm^{-1}). After 2 hours at room temperature the solution was treated with saturated aqueous sodium bicarbonate solution (20 mL) and warmed to reflux for 20 minutes. After cooling the reaction was diluted with dichloromethane (20 mL) and sequentially washed with water and brine (30 mL each) before drying ($MgSO_4$). After removal of solvent the crude product was purified by chromatography on silica gel (35 g) loading and eluting with 10% ether in pentane followed by 20% ether in pentane. The title compound (**4.5**) was a coloured oil (640 mg, 2.4 mmol, 48%).

FT-IR (CH_2Cl_2)	3029 (w), 2860 (w), 1779 (s), 1496 (m), and 1452 (m) cm^{-1}.
^{1}H NMR	2.32-2.44 (m, 1H), 2.51-2.66 (m, 2H), 3.15 (dd, J = 9.6, 5.9
(300MHz, C_6D_6)	Hz, 1H), 3.21 (dd, J = 9.9, 5.5 Hz, 1H), 4.07 (d, J = 7.7 Hz, 1H), 4.23 (s, 2H), 7.00-7.31 (m, 10H) ppm.

^{13}C NMR	32.6 (CH), 47.2 (CH_2), 67.0 (CH), 72.3 (CH_2), 73.2 (CH_2),
(75 MHz, C_6D_6)	127.2 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 137.1 (C), 138.9 (C), 204.0 (C) ppm.
LRMS	(CI, ammonia) *m/z* (relative intensity) 284 (10) $[M+NH_4]^+$, 91 (100) $[PhCH_2]^+$, 175 (15) $[M-PhCH_2]^+$.
HRMS	(EI) Calcd for $C_{18}H_{18}O_2$: 266.1307. Found 266.1303.

(2S*, 3S*)-2-(3,4-Methylenedioxy)phenyl-3-{[(3,4-methylenedioxybenzyl)oxy] methyl}cyclobutanone (4.26): Method A



The title compound was prepared from (**4.23**) and (**4.24**) using the method outlined for the preparation of (**4.5**) except that an excess of 2,6-di-*tert*-butylpyridine (1.2 equiv.) relative to the trifluoromethanesulfonic anhydride was used in this instance. The reaction produced a solid that was removed by filtration and subsequently shown to be a complex mixture of polymeric materials. The filtrate was subjected to the same extractive work-up procedure outlined above for (**4.5**) and purification accomplished by chromatography on silica gel. Gradient elution beginning with 30% ethyl acetate in hexane and rising to 60% ethyl acetate in hexane provided three separate compounds; the title compound (**4.26**) in 6% yield as a mixture of isomers in a ratio of 9:1, as an oil; (2S*, 3R*) 3-hydroxymethyl-2-(3,4-methylenedioxy)phenyl cyclobutanone (**4.25**) as an oil (25%); a single isomer of a compound resulting from Friedel Crafts alkylation of (**4.27**) (approx. 3%).

Data for cyclobutanone (desired compound) (4.26)

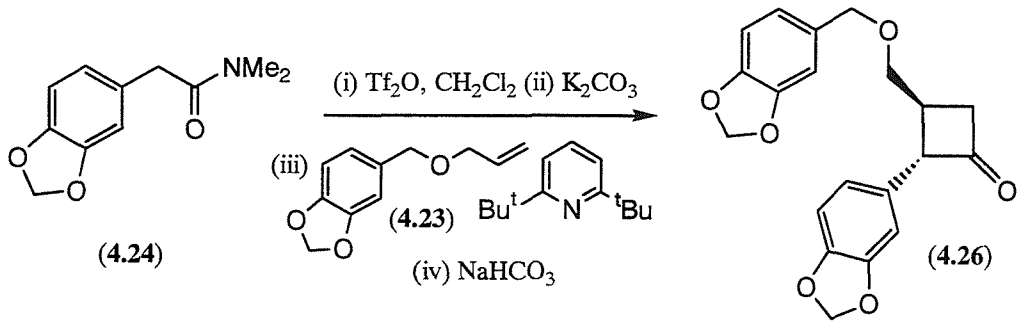
FT-IR (CH_2Cl_2)	2891, 1779, 1503, 1488, 1443, 1239, and 1041 cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$)	2.70-2.82 (m, 1H), 3.04 (d, *J* = 8.5 Hz, 2H), 3.73 (d, *J* = 5.5 Hz, 2H), 4.26 (d, *J* = 7.7 Hz, 1H), 4.50 (s, 2H), 5.93 (s, 2H), 5.96 (s, 2H), 6.70-6.79 (m, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	32.9 (CH), 42.7 (CH), 66.4 (CH), 71.7 (CH_2), 73.2 (CH_2), 101.1 (CH_2), 101.2 (CH_2), 107.9 (CH), 108.3 (CH), 109.1 (CH), 120.4 (CH), 121.4 (CH), 129.8 (C), 132.0 (C), 146.7 (C), 147.4 (C), 148.4 (C), 206.2 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 354 (<5) $[M]^{\bullet+}$, 219 (15) $[M\text{-}C_8H_7O_2]^{\bullet+}$.

Data for cyclobutanone (4.25)

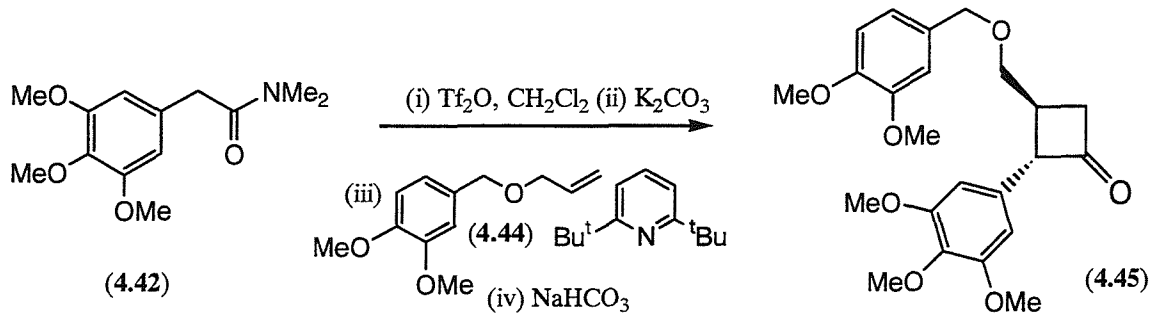
FT-IR (CH_2Cl_2)	3614, 2890, 1779, 1504, 1490, 1235 and 1040 cm^{-1}.
^{1}H NMR (300MHz, C_6D_6)	1.02 (bs, 1H), 2.11 (qt, *J* = 8.1, 5.5 Hz, 1H), 2.49 (d *J* = 8.5 Hz, 2H), 3.19 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.30 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.86 (d, *J* = 8.1 Hz, 1H), 5.30 (s, 2H), 6.64 (s, 2H), 6.84 (s, 1H) ppm.
^{13}C NMR (75 MHz, C_6D_6)	34.7 (CH), 46.3 (CH_2), 64.6 (CH_2), 66.0 (CH), 101.1 (CH_2), 108.4 (C), 108.6 (CH), 120.8 (CH), 130.8 (CH), 147.2 (C), 148.5 (C), 204.1 (C) ppm.

(2S*, 3S*)-2-(3,4-Methylenedioxy)phenyl-3-{[(3,4-methylenedioxybenzyl)oxy] methyl}cyclobutanone (4.26): Method B



The title compound was prepared from (**4.23**) and (**4.24**) using the method outlined for the preparation of (**4.6**) except that dry potassium carbonate (1.0 equiv. relative to trifluoromethanesulfonic anhydride) was added to the mixture immediately prior to the addition of (**4.23**) and 2,6-di-*tert*-butylpyridine. Additionally, the sodium bicarbonate hydrolysis was accomplished at room temperature over a period of 1 hour. The title compound (**4.26**) was isolated as the only product of the reaction, as a coloured oil, in a yield of 60%.

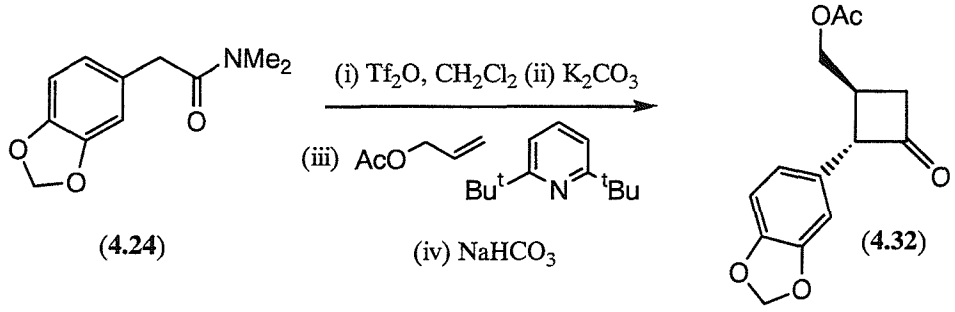
(2S*, 3S*)-3-{[3,4-Dimethoxybenzyl)oxy]methyl}-2-(3,4,5-trimethoxyphenyl) cyclobutanone (4.45)



The title compound was prepared according to the method outlined for **4.6**, whereby *N,N*-dimethyl(3,4,5-trimethoxy)phenylacetamide (**4.43**) (2.78 g, 11.0 mmol) and 4-[(allyloxy)methyl]-1,2-dimethoxybenzene (**4.44**) (3.44 g, 16.5 mmol) were reacted under the conditions described (except reaction quenched at +5 °C after 150 min). Purification was accomplished by flash chromatography on silica gel (5 x 10 cm) eluting with EtOAc/hexane (1:9) followed by EtOAc/hexane (1:1) to yield the title compound (**4.45**) as a 12:1 mixture of diastereoisomers (720 mg, 1.73 mmol, 16 %) as a very pale yellow oil. NMR data is reported for the major diastereoisomer.

FT-IR (neat)	1777 cm^{-1}.
^{1}H NMR	2.77 – 2.86 (m, 1H), 3.04 (dd, *J* = 4.5, 1.5 Hz, 1H),
(400MHz, $CDCl_3$)	3.05 (dd, *J* = 5.5, 1.5 Hz, 1H), 3.71 – 3.78 (m, 2H), 3.79 (s, 6H), 3.80 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.28 (d, *J* = 8.0 Hz, 1H), 4.54 (s, 2H), 6.52 (s, 2H), 6.81 – 6.85 (m, 1H), 6.84 – 6.89 (m, 2H) ppm.
^{13}C NMR	33.0 (CH_3), 47.4 (CH_2), 56.3 (CH_3), 56.4 (CH_3), 56.5 (CH_3),
(100 MHz, $CDCl_3$)	61.2 (CH), 67.3 (CH), 72.5 (CH_2), 73.6 (CH_2), 104.6 (CH), 111.4 (CH), 111.6 (CH), 120.8 (CH), 131.0 (C), 132.0 (C), 137.5 (C), 149.2 (C), 149.3 (C), 153.7 (C), 206.2 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 416 (20) $[M]^{\bullet+}$, 265 (15) $[M\text{-}ArCH_2]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{23}H_{28}O_7$: 416.1835. Found 416.1837.

(2S*, 3S*)-3-Acetoxymethyl-2-(3,4-methylenedioxy)phenylcyclobutanone (4.32)



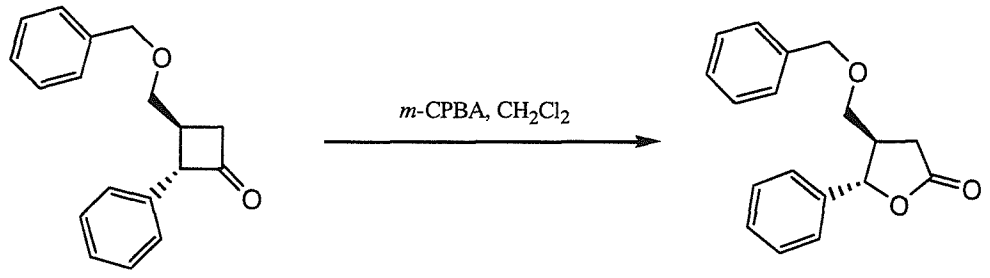
(4.24) (4.32)

The title compound was prepared according to the method outlined for **4.6**, whereby *N,N*-dimethyl (3,4-methylenedioxy)phenylacetamide (**4.24**) (0.57 g, 2.5 mmol) and allyl acetate (0.50 g, 0.54 mL, 5.0 mmol) were reacted under the conditions described. Purification was accomplished by flash chromatography on silica gel (7 x 3 cm) eluting with 20% ethyl acetate in hexane followed by 35% ethyl acetate in hexane. The title compound (**4.32**) was isolated as a oil (143 mg, 0.55 mmol, 22 %).

FT-IR (neat)	3062, 2951, 1783, 1740, 1610, 1241 cm^{-1}.
^{1}H NMR	2.00 (s, 3H), 2.79-2.93 (m, 1H), 3.01 (ddd, *J* = 17.7, 7.7,
(300MHz, $CDCl_3$)	2.2 Hz,1H), 3.13 (ddd, *J* = 17.3, 8.8, 1.8 Hz,1H), 4.22 (d, *J* = 8.1 Hz, 1H), 4.41 (d, *J* = 5.9 Hz, 2H), 5.95 (s, 2H), 6.68-6.79 (m, 3H) ppm.

^{13}C NMR	20.98 (CH), 31.87 (CH_3), 47.29 (CH), 66.47 (CH_2), 66.89
(75 MHz, $CDCl_3$)	(CH_2), 101.22 (CH_2), 107.74 (CH), 108.58 (CH), 120.35 (CH), 129.19 (C), 146.92 (C), 148.09 (C), 171 (C), 204.91 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 262 (20) $[M]^{\bullet+}$, 220 (100) $[M\text{-}C(O)CH_3 + H]^{\bullet+}$.

(4R*, 5S*)-5-Phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (4.4): Method A



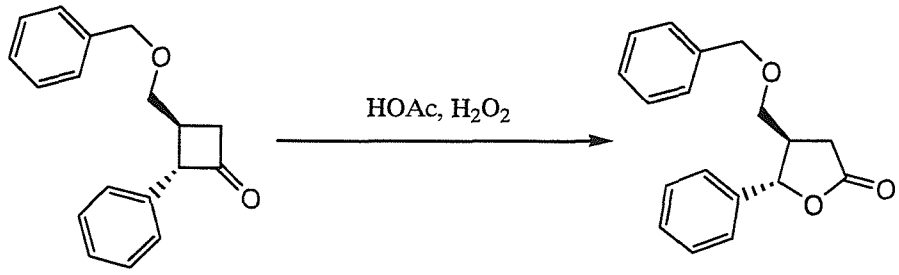
(4.5) **(4.4)**

Cyclobutanone (**4.5**) (1.55 g, 5.84 mmol) was dissolved in dichloromethane (20 mL) and the resulting solution treated with *m*-chloroperoxybenzoic acid (1.11g, 6.43 mmol) which had been purified according to the method described by Perrin *et al.* [239]. The reaction was stirred at room temperature for 24 hours. After dilution with dichloromethane (20 mL) the organic phase was washed with 2% sodium metabisulfite (aq.) solution, sat. sodium bicarbonate (aq.) solution, water and brine (50 mL each) before drying ($MgSO_4$). Purification was accomplished by chromatography on silica gel (40 g) loading in dichloromethane and eluting with 20% diethyl ether in pentane. The title compound (**4.4**) was isolated as a colourless oil (1.03g, 3.65 mmol, 62%).

FT-IR (CH_2Cl_2)	3032, 2863, 1779, 1737, 1496, 1454, 1200, and 1010 cm^{-1}.
^{1}H NMR	2.63-2.77 (m, 3H), 3.54 (dd, J = 9.9, 4.0 Hz, 1H), 3.58 (dd, J =
(300MHz, $CDCl_3$)	9.6, 4.4 Hz, 1H), 4.55 (d, J = 12.1 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 5.39 (, d, J = 5.9 Hz, 1H), 7.10-7.50 (m, 10H) ppm.
^{13}C NMR	31.7 (CH_2), 44.7 (CH), 68.3 (CH_2), 73.3 (CH_2), 82.9 (CH),
(75 MHz, $CDCl_3$)	125.8 (CH), 127.9 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 137.8 (C), 138.9 (C), 176.4 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 282 (<1), $[M]^{\bullet+}$; 191 (100), $M\text{-}C_7H_7]^{\bullet+}$.

HRMS (EI) Calcd for $C_{18}H_{18}O_3$: 282.1256. Found 282.1259.

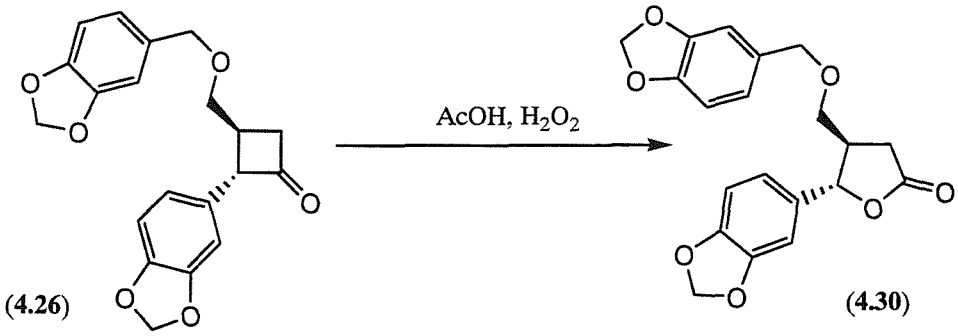
(4R*, 5S*)-5-Phenyl-4-[(benzyloxy)methyl]tetrahydro-2-furanone (4.4): Method B



(4.5) (4.4)

Lactone (**4.4**) was prepared by the general method described by Corey *et al.* [124] Thus, cyclobutanone (**4.5**) (853 mg, 3.2 mmol) was dissolved in glacial acetic acid (10 mL) and the solution cooled to 0°C. 30% Hydrogen peroxide solution (1.08 mL, 9.6 mmol) was added and the reaction maintained at 4°C overnight. Dilution with diethyl ether (40 mL) was followed by sequential washing with sodium bicarbonate (aq.), water and brine (40 mL each), prior to drying ($MgSO_4$). Purification was accomplished according to the protocol described in Method A to give the title compound (**4.4**) as an oil (570 mg, 2.0 mmol, 63%).

(4R*, 5S*) 5-(3,4-Methylenedioxy)phenyl-4-{[(3,4-methylenedioxy)benzyl)oxy] methyl}tetrahydro-2-furanone (4.30)



(4.26) (4.30)

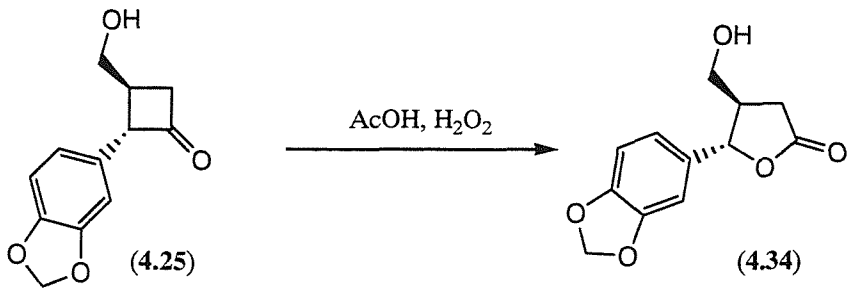
Cyclobutanone (**4.26**) (2.06g, 5.81 mmol) was reacted according to the protocol described for lactone (**4.4**): method B. The title compound (**4.30**), a mixture of diastereoisomers in a ratio of 10:1, was isolated as an colourless oil (1.76 g, 4.8 mmol, 82%). Data is reported for the major isomer.

CHN analysis	Calcd for $C_{20}H_{18}O_7$: C, 64.87; H, 4.89. Found: C, 64.73; H, 4.84.
FT-IR (CH_2Cl_2)	2891, 1778, 1732, 1610, 1503, 1490, 1445, 1250, and 1040 cm^{-1}
^1H NMR (300MHz, $CDCl_3$)	2.56-2.76 (m, 3H), 3.45 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.51 (dd, *J* = 9.6, 4.4 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 5.23 (d, *J* = 6.3 Hz, 1H), 5.95 (s, 4H), 6.70-6.82 (m, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	32.0 (CH_2), 44.8 (CH), 68.0 (CH_2), 73.3 (CH_2), 83.2 (CH), 101.3 (CH_2), 101.5 (CH_2), 106.4 (CH), 108.3 (CH), 108.4 (CH), 108.6 (CH), 119.8 (CH), 121.6 (CH), 131.6 (C), 132.5 (C), 147.5 (C), 148.0 (C), 148.1 (C), 148.3 (C), 176.1 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 370 (40) $[M]^{\bullet+}$, 235 (75) M-$C_8H_7O_2]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{20}H_{18}O_7$: 370.1053. Found $M^{+\cdot}$ 370.1035.

When the reaction was conducted on a larger scale repeated chromatography isolated some of the more polar diastereoisomer (4S*, 5S*) 5-(3,4-methylenedioxy)phenyl-4-{[(3,4-methylenedioxy)benzyl)oxy]methyl}tetrahydro-2-furanone.

FT-IR (CH_2Cl_2)	2984, 1778, 1503, 1490, 1445, 1168, and 1040 cm^{-1}
^1H NMR (300MHz, $CDCl_3$)	2.59 (dd, *J* = 17.3, 5.5 Hz, 1H), 2.73 (dd, *J* = 17.3, 8.1 Hz, 1H), 2.94-3.01 (m, 1H), 3.06 (dd, *J* = 9.2, 5.5 Hz, 1H), 3.12 (dd, *J* = 9.2, 6.3 Hz, 1H), 4.18 (s, 2H), 5.59 (d, *J* = 6.6 Hz, 1H), 5.95 (s, 2H), 6.00 (s, 2H), 6.65-6.82 (m, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	32.5 (CH_2), 40.67 (CH), 68.58 (CH_2), 73.38 (CH_2), 82.77 (CH), 101.18 (CH_2), 101.44 (CH_2), 106.48 (CH), 108.19 (CH), 108.35 (CH), 108.52 (CH), 119.26 (CH), 121.51 (CH), 121.49 (C), 131.47 (C), 147.36 (C), 147.64 (C), 147.88 (C), 148.02 (C), 176.41 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 370 (30) $[M]^{\bullet+}$, 135 (100).
HRMS	(EI) Calcd for $C_{20}H_{18}O_7$: 370.1053. Found $M^{+\cdot}$ 370.1054.

(4R*, 5S*) 4-Hydroxymethyl-5-(3,4-methylenedioxy)phenyltetrahydro-2-furanone (4.34)

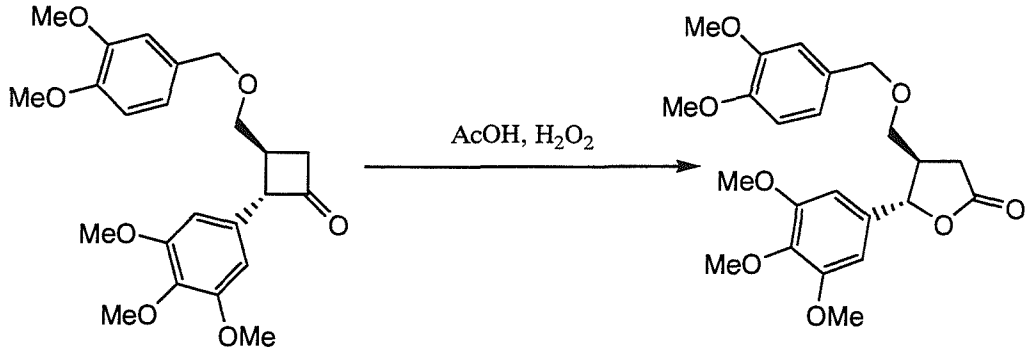


(4.25) (4.34)

Cyclobutanone (**4.25**) (0.17 g, 0.73 mmol) was reacted according to the protocol described for lactone (**4.4**): method B. The title compound (**4.34**) was isolated as a colourless oil (0.08 g, 0.32 mmol, 44%).

FT-IR (CH_2Cl_2)	3616, 3499, 3059, 2888, 1778, 1611, 1505, 1251 cm^{-1}.
^1H NMR (300MHz, $CDCl_3$)	2.45 (m, 4H), 3.71 (br. s, 2H), 5.28 (d, J = 7.0 Hz, 1H), 5.97 (s, 2H), 6.79 (s, 2H), 6.81 (s, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	31.58 (CH_2), 46.29 (CH), 61.15 (CH_2), 83.10 (CH), 101.51 (CH_2), 106.22 (CH), 108.32 (CH), 119.84 (CH), 132.47 (C), 148.06 (C), 148.31 (C), 176.81 (C) ppm.

(4R*, 5S*)-5-(3,4-Methylenedioxy)phenyl-4-{[(3,4-dimethoxybenzyl)oxy]methyl} tetrahydro-2-furanone (4.46)

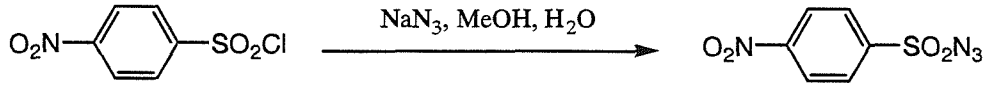


(4.44) (4.46)

Cyclobutanone (**4.45**) (1.50g, 4.05 mmol) was reacted according to the protocol described for lactone (**4.4**): method B. The crude product was isolated as a yellow oil from which the major isomer was purified by chromatography on silica gel (7 x 5 cm) eluting with 40% ethyl acetate in hexane. The title compound (**4.46**) was isolated as an colourless oil (1.11g, 2.87 mmol, 71%).

FT-IR (CH_2Cl_2)	1777 cm^{-1}.
^1H NMR	2.57 – 2.75 (m, 3H), 3.45 – 3.53 (m, 2H), 3.88 (s, 6H), 4.44 (d,
(400 MHz, $CDCl_3$)	J = 11.5 Hz, 1H), 4.49 (d, J = 11.5 Hz, 1H), 5.23 (d, J = 6.5 Hz, 1H), 5.95 (s, 2H), 6.69 – 6.77 (m, 3H), 6.84 (s, 3H) ppm.
^{13}C NMR	32.2 (CH_3), 45.0 (CH_3), 56.3 (CH_3), 56.4 (CH_3), 61.2 (CH),
(100 MHz, $CDCl_3$)	68.6 (CH_2), 73.6 (CH_2), 83.4 (CH), 102.8 (CH), 111.2 (CH), 111.4 (CH), 120.7 (CH), 130.4 (C), 134.8 (C), 138.3 (C), 149.2 (C), 149.4 (C), 153.8 (C), 176.3 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 386 (30) $[M]^{\bullet+}$, 235 (70) $[M-ArCH_2]^{\bullet+}$, 151 (100) $[ArCH_2]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{21}H_{22}O_7$: 386.1366. Found 386.1372.

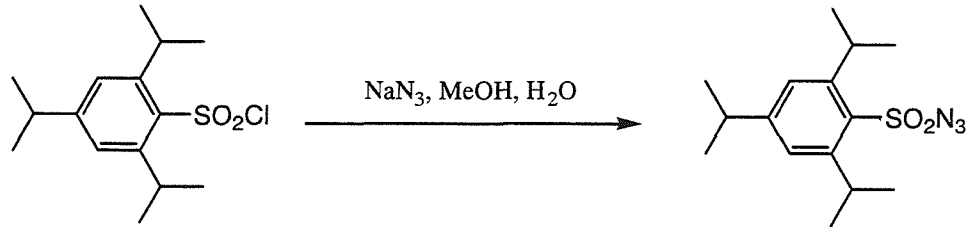
_p_-Nitrobenzenesulfonyl azide



The title compound was prepared according to the method described by Reagan *et al.* [242] Thus, *p*-nitrobenzenesulfonyl chloride (2.5 g, 11.3 mmol) was suspended in methanol (15 mL) and treated with a solution of sodium azide (0.92 g, 14.1 mmol) in water (4 mL). The reaction was stirred at RT for 16 hours whereupon it was diluted with dichloromethane (80 mL). The organic solution was washed with water (60 mL) followed by brine (50 mL) before drying ($MgSO_4$). The solvent was removed by evaporation in vacuo and the resultant oil left to crystallise on standing. The crude material was recrystalllised from dichloromethane and hexane. The title compound was isolated as pale yellow needles (1.99 g, 8.70 mmol, 77%). Analytical data corresponded well with literature data [242].

MP	99-100°C (dichloromethane/ hexane) (lit. 101.5-102°C) [242].
FT-IR (CH_2Cl_2)	3104, 2135, 1608, 1537, 1178 cm^{-1}
^1H NMR	8.19 (d, J = 8.8 Hz, 2H), 8.48 (d, J = 9.2 Hz, 2H), 5.23 ppm.
(300 MHz, $CDCl_3$)	

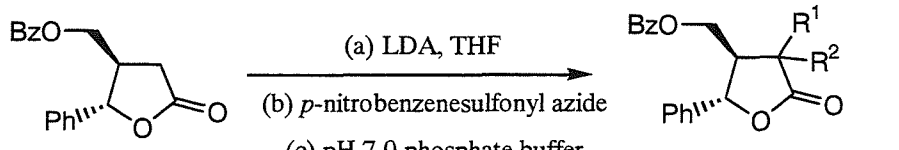
2,4,6-Tri*iso*propylbenzenesulfonyl azide



The title compound was prepared according to the method described by Tsuno et *al.* [243] Thus, *p*-tri*iso*propylsulfonyl chloride (2.5 g, 8.25 mmol) was suspended in ethanol (20 mL) and treated with a solution of sodium azide (0.67 g, 10.3 mmol) in ethanol/ water (1:1, 30 mL). The reaction was stirred at RT for 72 hours whereupon the solid produced in the reaction was collected by filtration. After dissolving in dichloromethane (30 mL) and drying ($MgSO_4$) the solvent was removed to give an oil that crystallised on standing. The title compound was isolated as a white crystalline solid (1.91 g, 6.2 mmol, 75%). Analytical data corresponded well with literature data [244].

MP	41-42 °C (lit. 41-43°C) [244].
FT-IR (CH_2Cl_2)	2963, 2122, 1598 cm^{-1}.
^{1}H NMR	1.27 (d, J = 6.3 Hz, 6H), 1.30 (d, J = 6.6 Hz, 12H), 2.94 (sept.,
(300 MHz, $CDCl_3$)	J = 6.9 Hz, 1H), 4.06 (sept., J = 6.6 Hz, 2H), 7.15 (s, 2H) ppm.

(4R*, 5S*) 3-Diazo-5-phenyl-4-(benzyloxymethyltetrahydro-2-furanone (4.3): Method A



(**4.4**)

(**4.3**) $R^1 = R^2 = N_2^+$

(**4.12**) R^1 = H R^2 = $-N_3$

Diazo derivative (**4.3**) was prepared according to the general procedure described by Evans *et al.* [136] Thus, freshly distilled *N,N*-di*iso*propylamine (110 mg, 110 μL, 1.1mmol) was dissolved in dry THF (3 mL) under an atmosphere of nitrogen and the solution cooled to -78°C. A solution of *n*-BuLi (785 μL of a 1.4M solution in hexanes, 1.1 mmol) was added and the reaction allowed to warm to -20°C for 10 minutes before recooling to -78°C. A solution of lactone (**4.4**) (280 mg, 1 mmol) in THF (4 mL) was added and the resulting

yellow solution stirred at -78°C for 30 minutes. A solution of *p*-nitrobenzenesulfonyl azide (250 mg, 1.1 mmol) in THF (3 mL) was added causing an immediate deep red colouration. After 20 minutes the reaction was treated with 0.1M pH 7 phosphate buffer (5 mL) and immediately allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (30 mL) and brine (50% saturated aq., 30 mL). After separation the aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined extracts washed with brine and dried ($MgSO_4$). Purification by chromatography on silica gel (20 g) eluting with 40% diethyl ether in pentane produced the title compound (**4.3**) as the minor product (18 mg, 0.06 mmol, 6%). The product was crystallised from ether/ hexane.

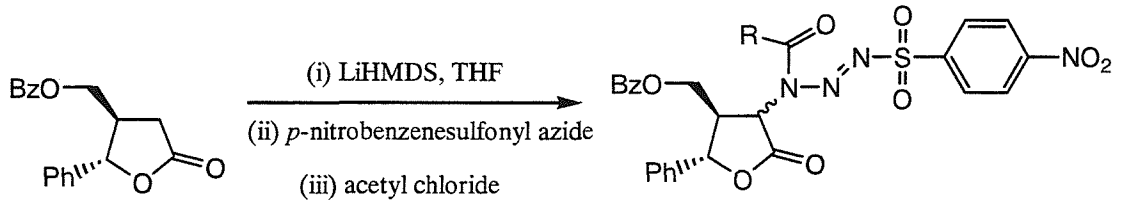
MP*	57 – 59 °C (Et_2O/hexane).
CHN analysis*	Calcd for $C_{18}H_{16}N_2O_3$: C, 70.09; H, 5.23. Found: C, 70.01; H, 5.36.
FT-IR (CH_2Cl_2)	2102 (s) and 1738 (s) cm^{-1}.
UV	(EtOH) λ_{max} 261nm (ε 6628), λ_{max} 320nm (ε 308).
^{1}H NMR (300MHz, $CDCl_3$)	3.72-3.82 (m, 3H), 4.61 (s, 2H), 5.18 (d, J = 4.0 Hz, 1H), 7.20-7.50 (m, 10H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	29.8 (C), 45.5 (CH), 70.8 (CH_2), 73.8 (CH_2), 80.5 (CH), 125.6 (CH), 127.9 (CH), 128.3 (CH), 128.8 (CH), 129.1 (CH), 137.3 (C), 139.0 (C), 169.4 (C) ppm.
LRMS	(LREI) *m/z* (relative intensity) 280 (75) $[M\text{-}N_2]^{\bullet+}$.

The major product isolated under these reaction conditions was azide (**4.12**), as a mixture of isomers (ratio 4:1) isolated as an oil (160 mg, 0.49 mmol, 49%).

FT-IR (CH_2Cl_2)	2116 (s) and 1788 (s) cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	2.36 (ddt, J = 11.2, 10.3, 2.6 Hz, 1H), 3.48 (dd, J = 10.3, 2.6 Hz, 1H), 3.63 (dd, J = 10.3, 2.9 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.64 (d, J = 12.1 Hz, 1H) superimposed on (d, J = 11.0 Hz. 1H), 5.34 (d, J = 11.9 Hz, 1H), 7.15-7.55 (m, 10H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	51.8 (CH), 58.8 (CH), 63.0 (CH_2), 73.4 (CH_2), 79.6 (CH), 126.3 (CH), 128.1 (CH), 128.7 (CH) 128.9 (CH), 129.2 (CH) 136.5 (C), 137.4 (C), 172.6 (C) ppm.

LRMS (EI) *m/z* (relative intensity) 323 (10) $[M]^{\bullet+}$, 91 (100) $[PhCH_2]^{\bullet+}$.

(4R*, 5S*) 3-{(E)-3-Acetyl-3-[(4-nitrophenyl)sulfonyl]-1-triazenyl}-5-phenyl-4-(benzyloxymethyl) tetrahydro-2-furanone (4.16a, R= -CH_3)



(**4.4**) (**4.16a** R = CH_3)

Lithium hexamethylsilylamide (400 μL of a 0.93M solution in tetrahydrofuran, 0.37 mmol) was dissolved in dry tetrahydrofuran (2 mL) and cooled to -78°C under nitrogen. A precooled solution of lactone (**4.4**) (100 mg, 0.35 mmol) in THF (2 mL) was added *via* a cannula and the reaction mixture stirred at -78°C. After 45 minutes a pre-cooled solution of the *p*-nitrobenzenesulfonyl azide (84 mg, 0.37 mmol) in THF (2 mL) was added *via* a cannula and the resulting deep red solution stirred for 10 minutes. Acetyl chloride (110 mg, 100 μL, 1.4 mmol) was added and the reaction allowed to warm slowly to room temperature during which time the red colour dissipated. The reaction mixture was diluted with diethyl ether (30 mL) and washed with water and brine (30 ml) each before drying ($MgSO_4$). The crude title compound (**4.16a**), apparently unstable on silica gel, was isolated as a foam (200 mg, quant.). A small quantity of this material was subjected to radial chromatography on silica gel and spectroscopic data obtained on the purified material. The pure material was shown to be a mixture of isomers.

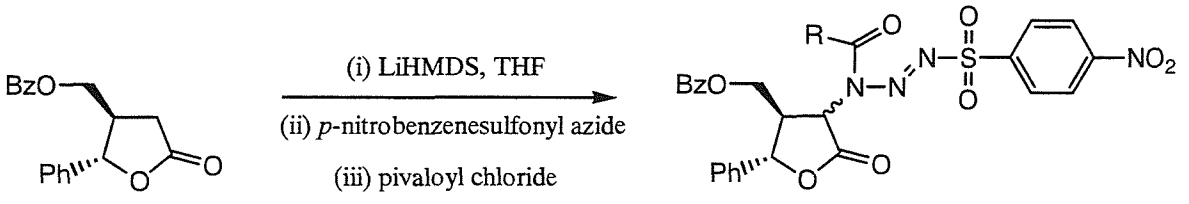
FT-IR (CH_2Cl_2) 1787, 1735, 1537, 1372, and 1162 cm^{-1}.

^{1}H NMR (270MHz, $CDCl_3$) 2.30 and 2.42 (s+s, 3H), 2.95-3.20 (m, 1H), 3.35-3.50 (m, 2H), 4.40-4.60 (m, 2H), 5.30 and 5.33 (d+d, *J* = 9.5 Hz, 1H), 6.16 and 6.17 (d+d, *J* = 10.4 Hz, 1H), 7.10-7.50 (m, 10H), 8.05 and 8.15 (d+d, *J* = ca. 8.0 Hz, 2H), 8.35 and 8.45 (d+d, *J* = ca. 8.0 Hz, 2H) ppm.

13 NMR (75 MHz, $CDCl_3$) 21.5 (CH_3), 21.6 (CH_3), 44.9 (CH), 49.2 (CH), 53.4 (CH), 54.4 (CH), 65.1 (CH_2), 65.4 (CH_2), 73.6 (CH_2), 73.9 (CH_2), 80.7 (CH), 81.0 (CH), 124.5 (CH), 124.6 (CH), 126.6 (CH), 126.7 (CH),

127.6 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.3 (CH), 129.4 (CH), 129.5 (CH), 130.3 (CH), 130.9 (CH), 137.0 (C), 137.2 (C), 137.5 (C), 141.7 (C), 151.4 (C), 168.7 (C), 169.0 (C), 171.1 (C) ppm.

(4R*, 5S*) 3-{(E)-3-Trimethylacetyl-3-[(4-nitrophenyl)sulfonyl]-1-triazenyl}-5-phenyl-4-{[(phenylmethyl)oxy]methyl}tetrahydro-2-furanone (4.16b) (R = -C(CH$_3$)$_3$)



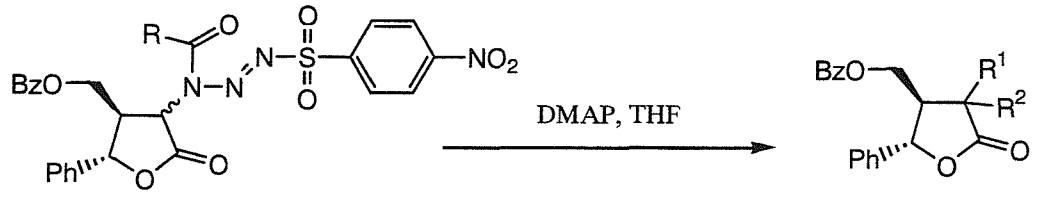
(4.4) **(4.16b)**

Lithium hexamethylsilylamide (527 μL of a 0.74M solution in tetrahydrofuran, 0.38 mmol) was dissolved in dry tetrahydrofuran (2 mL) and cooled to -78°C under nitrogen. A precooled solution of lactone (**4.4**) (100 mg, 0.35 mmol) in THF (2 mL) was added *via* a cannula and the reaction mixture stirred at -78°C. After 45 minutes a pre-cooled solution of the *p*-nitrobenzylsulfonyl azide (84 mg, 0.37 mmol) in THF (2 mL) was added *via* a cannula and the resulting deep red solution stirred for 10 minutes. Pivaloyl chloride (170 mg, 174 μL, 1.4 mmol) was added and the reaction allowed to warm slowly to room temperature. The red colouration eventually dispersed when the reaction temperature was approximately -40°C. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with water and brine (30 ml each) before drying ($MgSO_4$). The crude compound was purified by rapid chromatography on silica gel (6 x 3cm) loading in dichloromethane and eluting with 20% ethyl acetate in hexane. Although resolution of components was incomplete no further purification was attempted given the suspected instability of the acylated triazine. The fraction substantially enriched in the title compound (**4.16b**) product was isolated as a foam (157 mg, 75%).

FT-IR (CH_2Cl_2) 1787, 1735, 1537, 1372, and 1162 cm^{-1}.

LRMS (APCI) (+ve ion) *m/z* (relative intensity) 595 (10%) $[M+H]^+$, 382 (100%).

(4R*, 5S*) 3-Diazo-5-phenyl-4-{[(phenylmethyl)oxy]methyl}tetrahydro-2-furanone Method B (4.3).

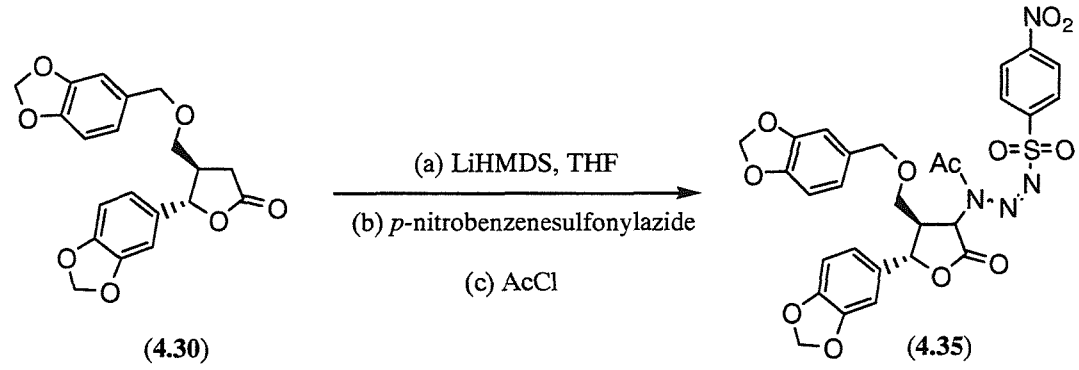


(**4.16a**, R = -CH_3) (**4.3**) $R^1 = R^2 = N_2^+$

(**4.12**) R^1 = H R^2 = $-N_3$

Triazene (**4.16a**, R = -CH_3) (25 mg, 0.05 mmol) was dissolved in THF (2 mL) and treated with *N,N*-dimethylaminopyridine (7 mg, 0.06 mmol) and the reaction maintained at 4°C overnight. The solvent was removed and and the crude material purified by radial chromatography on silica gel using 20% ethyl acetate in hexane as eluent. The title compound (**4.3**) was isolated as an oil (8 mg, 50%) along with azide (**4.12**) (8 mg, 50%).

(4R*, 5S*) 3-{(E)-3-Acetyl-3-[(4-nitrophenyl)sulfonyl]-1-triazenyl}-5-(3,4-methylenedioxy)phenyl-4-{[(3,4-methylenedioxybenzyl)oxy]methyl}tetrahydro-2-furanone (4.35)



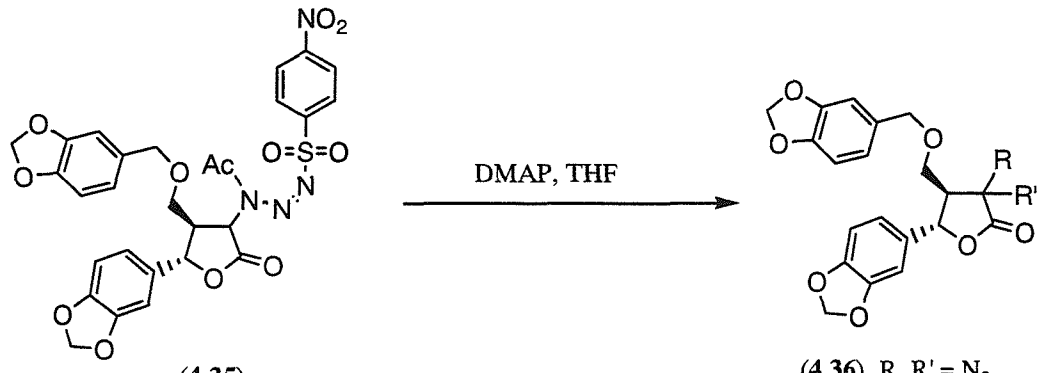
(**4.30**) (**4.35**)

The title compound (**4.35**) was prepared from lactone (**4.30**) (200 mg, 0.54 mmol) according to the method outlined for preparation of (**4.16a**, R = -CH_3). The crude product was isolated according to the aqueous work up procedure previously described. The crude material was subjected to rapid chromatography on silica gel (15 g) eluting in 50% ethyl acetate in hexane, a protocol that removed only very polar impurities. The crude title compound (**4.35**) was isolated as a yellow foam (303 mg, approximately 87%).

FT-IR (CH_2Cl_2) 1783, 1733, 1609, 1536, 1503, 1491, 1446, and 1372 cm^{-1}.

LRMS (ES +ve) *m/z* (relative intensity) 658 (100), $[M+NH_4]^+$.

(4R*, 5S*)-5-(3,4-Methylenedioxy)phenyl-3-diazo-4-{[(3,4-methylenedioxybenzyl)oxy] methyl} tetrahydro-2-furanone (Method A)



(**4.35**)

(**4.36**) R, R' = N_2

(**4.37**) R = H, R' = N_3

The partially purified azene (**4.35**) (251 mg, 0.39 mmol) was dissolved in THF (5 mL) and treated with DMAP (53 mg, 0.43 mmol) and the reaction stirred at rt for 16 h. The solvent was removed and the crude material was purified by chromatography on silica gel (4.5 x 3 cm) eluting with 20% EtOAc in hexane (1:4) providing the title diazo compound (**4.36**) as a coloured oil (71 mg, 0.179 mmol, 46 % from the triazine) along with the azide (**4.37**) (50 mg, 0.122 mmol, 31 % from the triazine) which was isolated from the reaction mixture as a 5:1 mixture of diastereoisomers.

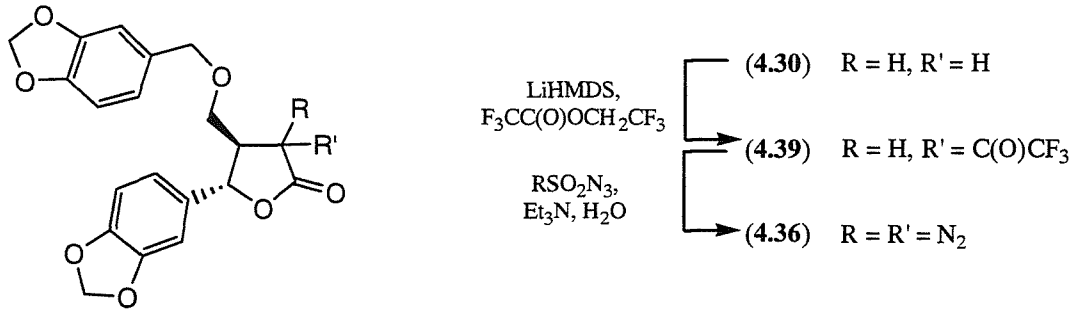
Data for (4R*, 5S*)-5-(3,4-methylenedioxy)phenyl-3-diazo-4-{[(3,4-methylenedioxy benzyl)oxy]methyl}tetrahydro-2-furanone (**4.36**).

FT-IR (CH_2Cl_2)	2102, 1736 cm^{-1}.
^{1}H NMR	3.62 - 3.73 (m, 3H), 4.47 (s, 2H), 5.03 - 5.07 (m, 1H), 5.98
(300MHz, $CDCl_3$)	(s, 2H), 5.99 (s, 2H), 6.60 - 6.80 (m, 6H) ppm.
^{13}C NMR	45.4 (CH), 53.0 (C), 70.3 (CH_2), 73.6 (CH_2), 80.6 (CH), 101.3
(75 MHz, $CDCl_3$)	(CH_2), 101.6 (CH_2), 106.1 (CH), 108.4 (CH), 108.5 (CH), 119.6 (CH), 121.7 (CH), 131.1 (C), 132.6 (C), 147.7 (C), 148.1 (C), 148.3 (C), 148.5 (C), 169.2 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 368 (40) $[M-N_2]^{\bullet+}$.
	(ES +ve) *m/z* (relative intensity) 414 (80) $[M+NH_4]^+$; 810 (100), $[2M+NH_4]^+$.

Data for (4R*, 5S*)-5-(3,4-Methylenedioxy)phenyl-3-azido-4-{[(3,4-methylenedioxy benzyl)oxy]methyl} tetrahydro-2-furanone (**4.37**)

FT-IR (CH_2Cl_2)	2113, 1784 cm^{-1}.
^1H NMR	2.31 (dt, *J* = 10.7, 2.9 Hz, 1H), 3.41 (dd, *J* = 10.3, 2.6 Hz, 1H),
(300MHz, $CDCl_3$)	3.57 (dd, *J* = 10.3, 2.9 Hz, 1H), 4.41 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 5.19 (d, *J* = 9.9 Hz, 1H), 5.95 (s, 4H), 6.65 - 6.85 (m, 6H) ppm.
^{13}C NMR	51.6 (CH), 59.0 (CH), 62.9 (CH_2), 73.4 (CH_2), 79.8 (CH),
(75 MHz, $CDCl_3$)	101.4 (CH_2), 101.6 (CH_2), 106.7 (CH), 108.4 (CH), 108.8 (CH), 120.8 (CH), 122.0 (CH), 130.0 (C), 131.1 (C), 147.8 (C), 148.2 (C), 148.4 (C), 148.6 (C), 172.4 (C) ppm.
LRMS	(ES +ve) *m/z* (relative intensity) 429 (100) $[M+NH_4]^+$, 840 (95) $[2M+NH_4]^+$.

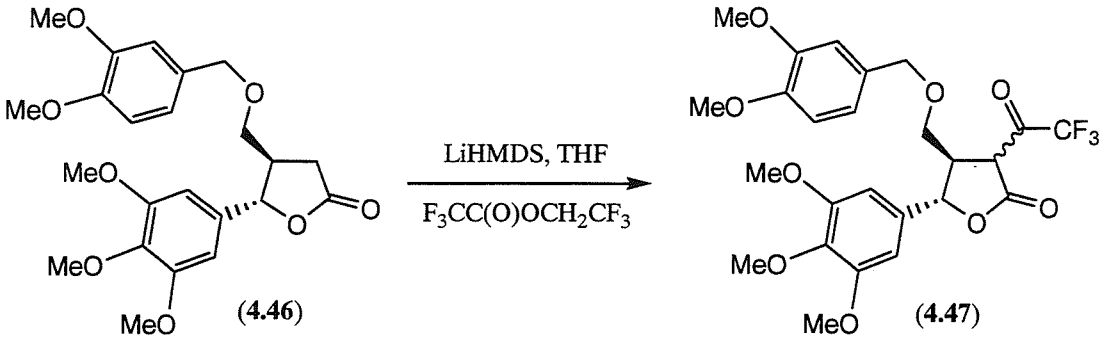
(4R*, 5S*)-5-(3,4-Methylenedioxy)phenyl-3-diazo-4-{[(3,4-methylenedioxybenzyl)oxy] methyl} tetrahydro-2-furanone (4.36) (Method B)



Hexamethyldisilazane (0.6 mL, 0.436g, 2.7 mmol) was diluted with dry THF (5 mL) and cooled on ice whilst stirring for 10 minutes whilst under an atmosphere of nitrogen. The solution was then cooled to -78°C and then added to a solution of lactone (**4.30**) (473 mg, 1.28 mmol) which had been pre-cooled to -78°C. After 30 minutes at this temperature 2,2,2-trifluoroethyl trifluoroacetate was added by dropwise addition. The solution was stirred for a further 30 minutes and then diluted with ethyl acetate (40 mL) and HCl (2.0M, 40 mL). The phases were separated and the aqueous phase was re-extracted with ethyl acetate (30 mL). The combined organic phases were where washed with saturated sodium chloride (20 mL) and then dried ($MgSO_4$). The crude trifluoroacylated material (**4.39**), identified as predominantly one component by TLC, was used immediately in the next reaction. Thus, after dilution with dry acetonitrile (5 mL) the reaction was treated with dry

triethylamine (0.28 mL, 2.02 mmol) and *p*-nitrobenzyl-sulfonyl azide (330 mg, 1.45 mmol). The solution was stirred at rt overnight before diluting with dichloromethane (25 mL) and washed with sodium hydrogen bicarbonate, water and brine (20 mL of each) and then dried ($MgSO_4$). The crude product (880 mg) was purified by chromatography on silica gel (38 g) eluting with a gradient of 15% ethyl acetate in hexane rising to 25% ethyl acetate in hexane. The title compound (**4.36**) was isolated as a coloured foam (190 mg, 75 mmol, 38%).

(4R*, 5S*)-4-{[(3,4-Dimethoxybenzyl)oxy]methyl}-3-(trifluoroacetyl)-5-(3,4,5-trimethoxyphenyl)-tetrahydro-2-furanone (4.47)



The title compound was prepared according to the method outlined for **4.36** (method B). Reaction of lactone (**4.46**) (347 mg, 0.8 mmol) with lithium hexamethyldisilylazide (1.6 mmol) and 2,2,2-trifluoroethyltrifluoroacetate (0.14 mL, 0.179g, 0.90 mmol) under the conditions described gave crude product. This compound was purified by chromatography on silica gel (22 g) eluting with 25% ethyl acetate in hexane. The title compound (**4.47**) was isolated as a yellow oil (0.291 g, 0.55 mmol, 69%).

FT-IR (CH_2Cl_2) 1777, 1592, 1514, 1463, 1261 and 1140 cm^{-1}.

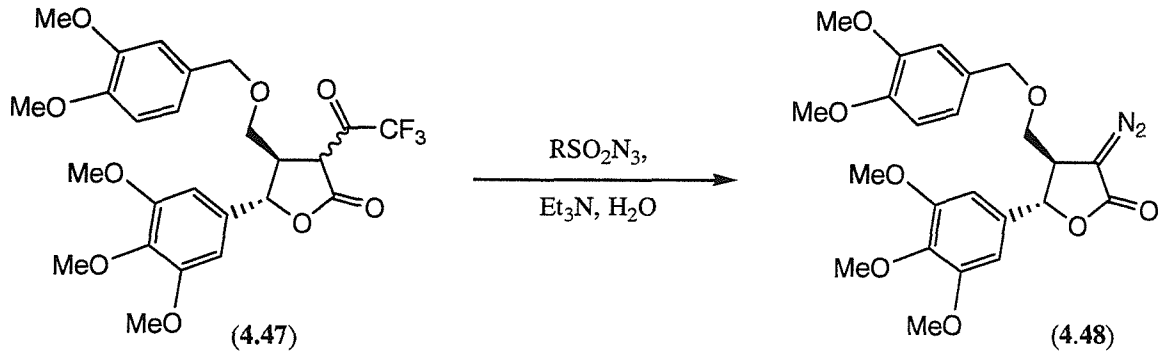
^{1}H NMR (300 MHz, $CDCl_3$) 2.85 (m, 1H), 3.30 (d, J = 8.0 Hz, 1H), 3.51 (m, 1H), 3.71 (s, 6H), 3.75 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 4.35 (d, J = 11.5 Hz, 1H), 4.50 (2H, m), 5.16 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 9.5 Hz, 2H), 6.77 (3H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 44.3 (CH), 44.8 (CH), 52.4 (CH_2), 55.1 (CH_3), 59.8 (CH), 72.2 (CH_2), 82.4 (CH), 83.1 (CH), 100.8 (CH), 102.5 (CH), 109.8 (CH), 110.0 (CH), 119.3 (CH), 119.9 (CH), 128.8 (C), 132.6 (C), 137.4 (C), 147.9 (C), 148.0 (C), 176.2 (C) ppm.

LRMS (EI) *m/z* (relative intensity) 528 (17) $[M]^{\bullet+}$, 377 (7) $[M\text{-}C_9H_{11}O_2]^{\bullet+}$.

HRMS (EI) Calcd for $C_{21}H_{22}O_7$: 528.16072. Found 528.15973.

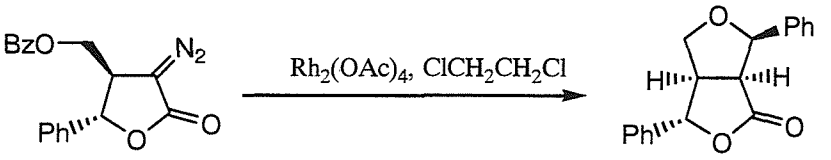
(4R*, 5S*)-3-Diazo-4-{[(3,4-dimethoxybenzyl)oxy]methyl}-5-(3,4,5-trimethoxyphenyl)- tetrahydro-2-furanone (4.48).



Compound **4.37** (235 mg, 0.5 mmol) was treated with *p*-nitrobenzensulfonyl azide (230 mg, 1.00 mmol) in acetonitrile (15 mL) in the presence of triethylamine (0.14 mL, 1.0mmol) and the reaction conducted as described for the preparation of **4.36** (method B). The crude material was purified by chromatography on silica gel (23 g), eluting with 25% ethyl acetate in hexane). The title compound (**4.48**) was isolated as an orange foam which could subsequently be converted into a pale yellow solid by trituration in ethyl acetate and diethyl ether (158 mg, 0.35 mmol, 75%).

MP*	131 – 132°C.
CHN analysis*	Calcd for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11. Found: C, 60.21; H, 5.78; N, 6.21.
FT-IR (CH_2Cl_2)	2110, 1730 cm^{-1}.
^{1}H NMR (300 MHz, $CDCl_3$)	3.71 – 3.81 (m, 3H), 3.82 (s, 6H), 3.83 (s, 3H), 3.88 (s, 3H), 3.88 (s, 3H), 4.51 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 11.5 Hz, 1H), 5.09 (d, J = 4.0 Hz, 1H), 6.49 (s, 2H), 6.84 (s, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	45.7 (CH), 53.2 (C), 56.31 (CH_3), 56.35 (CH_3), 56.65 (CH_3), 61.26 (CH_3), 70.72 (CH_2), 74 .01 (CH_2), 80.98 (CH), 102.8 (CH), 111.41 (CH), 111.46 (CH), 120.89 (CH), 130.05 (C), 134.79 (C), 138.77 (C), 149.46 (C), 149.67 (C), 154.11 (C), 169.47 (C) ppm.

(1S*, 2R*, 5R*, 6S*) 2,6-Diphenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (4.2) Method A.

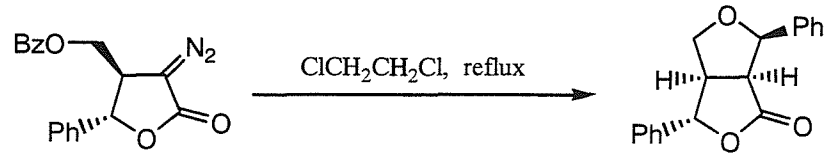


(4.3) (4.2)

The diazo compound (**4.3**) was dissolved in dichloroethane (1 mL) and treated with dirhodium (II) tetraacetate. The reaction was monitored by TLC until no starting material remained. The crude reaction mixture was purified by chromatography on silica gel (2 g) eluting with 20% diethyl ether in pentane. The title compound (**4.2**) was isolated as an oil (18 mg, quant). Larger scale repeat reactions allowed for further purification of the title compound by crystallisation from diethyl ether/ hexane mixtures.

MP	121 – 123°C (Et_2O/hexane).
CHN analysis	Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.27; H, 5.79.
FT-IR (CH_2Cl_2)	3053, 2871, 1773, 1604, 1465,1456, 1173, and 1063 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	3.27 (ddd, J = 9.4, 6.5, 5.5 Hz, 1H), 3.61 (t, J = 8.9 Hz, 1H), 3.96 (dd, J = 9.9, 5.0 Hz, 1H), 4.38 (d, J = 9.4 Hz, 1H), 5.12 (d, J = 8.9 Hz, 1H), 5.33 (d, J = 6.5 Hz, 1H), 7.32 – 7.45 (m, 10H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	51.4 (CH), 51.7 (CH), 72.1 (CH_2), 84.1 (CH), 85.6 (CH), 125.6 (CH), 126.4 (CH), 128.7 (CH), 128.9 (CH), 129.1 (CH), 136.2 (C), 139.7 (C), 175.0 (C) ppm.
LRMS	(EI) 280 (25), $[M]^{\bullet+}$, 262 (5) $[M\text{-}H_2O]^{\bullet+}$, 234 (7%, $[M\text{-}CO_2]^{\bullet+}$; (CI, ammonia) 281 (65) $[M+H]^+$, 298 (100) $[M+NH_4]^+$, 263 (20) $[M\text{-}H_2O+H]^+$.
HRMS	Calcd for $C_{18}H_{16}O_3$: 280.1099. Found 280.1094.

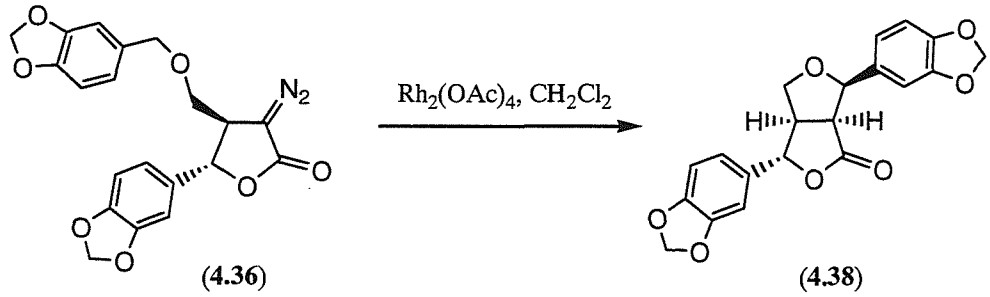
(1S*, 2R*, 5R*, 6S*) 2,6-Diphenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (4.2): Method B.



(4.3) (4.2)

Diazo compound (**2**) was dissolved in dichloroethane and the reaction warmed to reflux. The reaction was monitored by TLC until all the starting material had been consumed (within 4 hours). After cooling the reaction mixture was subjected to column chromatography and the product finally isolated as an oil.

(1S*, 2R*, 5R*, 6S*) 2-(3,4-Methylenedioxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (4.38)



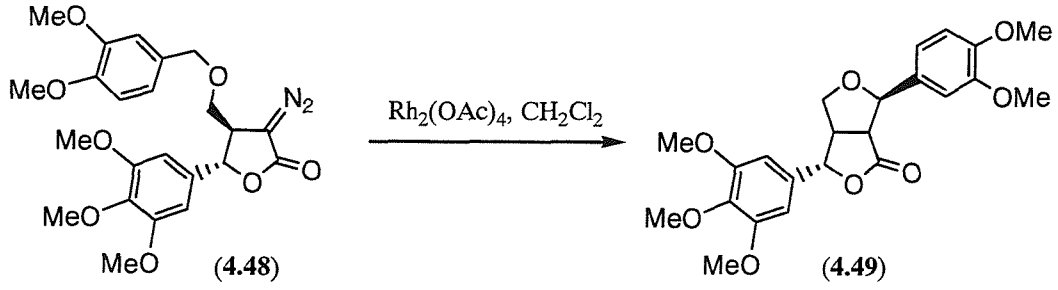
(4.36) (4.38)

The title compound [112]was prepared from the diazo derivative (**4.36**) (160 mg, 0.4 mmol) according to the method described for the preparation of (**4.2**) method A. The title compound (**4.38**) was isolated as a white crystalline solid (91 mg, 62%). Spectroscopic data were consistent with those described in the literature [112]

MP	142-3°C (ethyl acetate/ hexane) (Lit. 158 – 159 °C, ethyl acetate /hexane) [112].
FT-IR (CH_2Cl_2)	2889, 1774, 1733, 1612, 1504, 1492, 1447, 1173 and 1040 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	3.21 (ddd, *J* = 9.0, 6.7, 4.5 Hz, 1H), 3.54 (app. t, *J* = 6.9 Hz, 1H), 3.90 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.28 (d, *J* = 9.7 Hz, 1H), 5.02 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 6.6 Hz, 1H), 5.99 (s, 4H), 6.81-6.88 (m, 6H) ppm.
^{13}C NMR	51.3 (CH), 51.7 (CH), 71.8 (CH_2), 83.9 (CH), 85.7 (CH), 101.3 (CH_2), 101.5 (CH_2), 106.1 (CH), 106.8 (CH),

(75 MHz, $CDCl_3$)	108.4 (CH), 108.6 (CH), 119.6 (CH), 120.0 (CH), 130.0 (C), 133.3 (C), 147.8 (C), 148.0 (C), 148.2 (C), 148.5 (C), 174.4 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 368 (100) $[M]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{20}H_{16}O_7$: 368.0896. Found 368.0886.

(1S*, 2R*, 5R*, 6S*) 2-(3,4-Dimethoxy)phenyl-6-(3,4-methylenedioxy)phenyl-3,7-dioxabicyclo[3.3.0]octan-8-one (4.49)



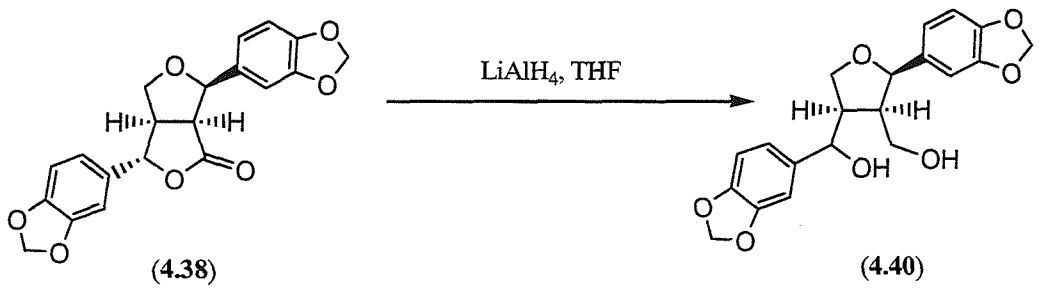
(4.48) (4.49)

The title compound was prepared according to the method outlined for (**4.2**), whereby reaction of diazo-lactone (**4.48**) (0.072 g, 0.15 mmol) with dirhodium (II) tetraacetate (5 mg, 0.01 mmol) and work-up under the conditions described gave the crude product. Purification was accomplished on silica gel (12 g) eluting with 50% ethyl acetate in hexane to yield the title compound (**4.49**) as a crystalline solid (0.035 g, 0.09 mmol, 66 %).

MP*	175 – 176°C.
CHN analysis*	Calcd for $C_{23}H_{26}O_8$: C, 64.18; H, 6.09. Found: C, 63.87; H, 5.89.
FT-IR (neat)	1763 cm^{-1}.
^{1}H NMR **(400MHz, $CDCl_3$)**	3.24 (ddd, *J* = 9.0, 6.5, 4.5 Hz, 1H), 3.55 (t, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.88 (s, 9H), 3.90 (s, 3H), 3.94 (dd, *J* = 9.5, 4.5 Hz, 1H), 4.34 (d, *J* = 9.5 Hz, 1H), 5.05 (d, *J* = 8.5 Hz, 1H), 5.24 (d, *J* = 6.5 Hz, 1H), 6.54 (s, 2H), 6.87 – 7.00 (m, 3H) ppm.
^{13}C NMR **(100 MHz, $CDCl_3$)**	51.77 (CH), 51.89 (CH), 56.23 (CH_3), 56.33 (CH_3), 56.62 (CH_3), 56.74 (CH_3), 61.29 (CH_3), 72.15 (CH_2), 84.30 (CH), 85.89 (CH), 100.96 (CH), 108.53 (CH), 110.56 (CH), 117.89 (CH), 127.38 (C), 134.08 (C), 137.32 (C), 148.02 (C), 148.14 (C), 152.76 (C), 173.38 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 430 (100), $[M]^{\bullet+}$.

HRMS (EI) Calcd for $C_{23}H_{26}O_8$: 430.1654. Found 430.1637.

(2R*, 3R*, 4S*) 2[(3,4-Methylenedioxy)phenyl]-3-hydroxymethyl-4-{[(3,4-methylenedioxy) phenyl]hydroxy}methyltetrahydrofuran (4.40)



(4.38) (4.40)

Lithium aluminium hydride (57 mg, 1.5 mmol) was suspended in THF (2 mL) under nitrogen. A solution of the furofuranone derivative (**4.38**) (56 mg, 0.15 mmol) in dry THF (3 mL) was added and the reaction warmed to reflux for 1 hour. After allowing to cool the reaction mixture was treated with wet THF/ MeOH followed by 2.0M HCl (30 mL) before extracting with ethyl acetate (2 x 30 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The crude material was prefiltered through silica before purification by radial chromatography eluting with 40% ethyl acetate in hexane. The title compound (**4.40**)was isolated as a white solid which was crystallised from ethyl acetate and hexane (47 mg, 0.13 mmol, 83%).

MP 153-155°C (ethyl acetate/ hexane).

FT-IR (CH_2Cl_2) 3604, 3459, 2888, 1504, 1490, and 1040 cm^{-1}.

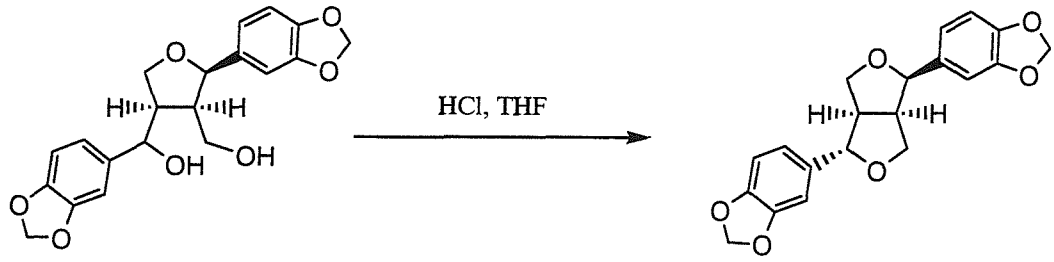
^{1}H NMR (300MHz, $CDCl_3$) 2.65 (approx. tt, J = 5.9, 2.9 Hz, 1H), 2.97 (qd, J = 9.6, 6.2 Hz, 1H), 3.29 (dd, J = 11.1, 2.9 Hz, 1H), 3.50-3.65 (m, 3H), 4.68 (d, J = 10.3 Hz, 1H), 5.01 (d, J = 5.5 Hz, 1H), 5.96 and 5.97 (s+s, 4H), 6.70-6.89 (m, 6H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 47.4 (CH), 51.5 (CH), 59.4 (CH_2), 68.9 (CH_2), 73.5 (CH), 83.5 (CH), 101.0 (CH_2), 101.1 (CH_2), 106.2 (CH), 106.6 (CH), 108.2 (CH), 118.7 (CH), 120.0 (CH), 132.8 (C), 136.6 (C), 146.8 (C), 147.5 (C), 147.9 (C), 148.1 (C) ppm.

LRMS (EI) *m/z* (relative intensity). 372 (40) $[M]^{\bullet+}$, 354 (40) $[M\text{-}H_2O]^{\bullet+}$.

HRMS (EI) Calcd for $C_{20}H_{20}O_7$: 372.1209. Found 372.1203.

(1R*, 2R*, 5R*, 6S*) 2,6-Di[(3,4-methylenedioxy)phenyl]-3,7-dioxabicyclo[3.3.0]-octane – (±) Asarinin (2.40) (Method A)

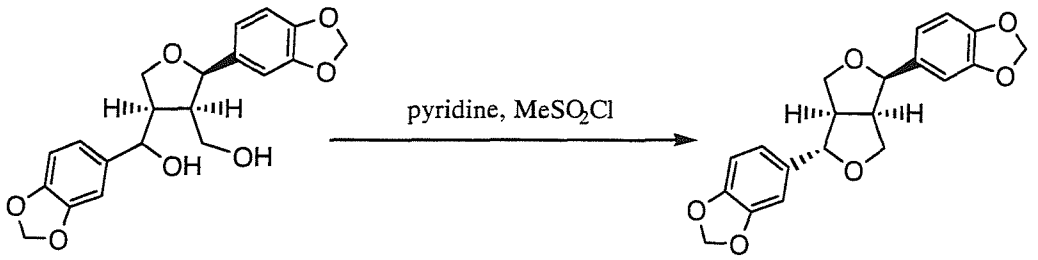


(4.40) **(2.40)**

Diol (**4.40**) (42 mg, 0.11 mmol) was dissolved in THF (5 mL) and treated with 2.0M HCl (5 mL). The reaction was stirred at room temperature for 3 days. Although still not complete the reaction was diluted with diethyl ether (10 mL) and washed with sat. sodium bicarbonate (aq.), water and brine (10 mL of each) before drying ($MgSO_4$). The crude material was subjected to radial chromatography eluting with 20% ethyl acetate in hexane. The title compound (**2.40**) was isolated as a crystalline solid (27 mg, 65%) along with recovered starting material (8 mg, 20%). The data corresponded with those described in the literature [245].

MP	130-131°C (dichloromethane/ hexane) (lit. 132-133°C [246]).
FT-IR (CH_2Cl_2)	2964, 2866, 1609, 1504, 1490, 1442, 1040 and 936 cm^{-1}.
^1H NMR (360MHz, $CDCl_3$)	2.85 (q with fine coupling, J = 7.3, 0.9 Hz, 1H), 3.27-3.33 (m, 2H), 3.83 (dd, J = 9.4, 6.2 Hz, 1H) superimposed on 3.83-3.87 (m, 1H), 4.10 (d, J = 9.2 Hz, 1H), 4.39 (d, J = 7.2 Hz, 1H), 4.83 (d, J = 5.4 Hz, 1H), 5.95 and 5.97 (s+s, 4H), 6.77-6.87 (m, 6H) ppm.
^{13}C NMR (90 MHz, $CDCl_3$)	50.3 (CH), 54.8 (CH), 69.8 (CH_2), 71.0 (CH_2), 82.1 (CH), 87.8 (CH), 101.1 (CH_2), 101.2 (CH_2), 106.5 (CH), 106.6 (CH), 108.2 (CH), 118.8 (CH), 119.7 (CH), 132.3 (C), 135.2 (C), 146.7 (C), 147.3 (C), 147.8 (C), 148.1 (C) ppm.

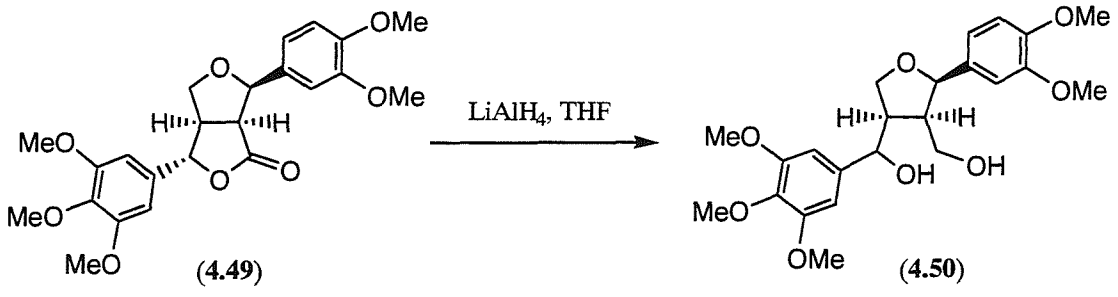
(1R*, 2R*, 5R*, 6S*) 2,6-Di[(3,4-methylenedioxy)phenyl]-3,7-dioxabicyclo[3.3.0]-octane – (±) Asarinin (2.40) (Method B)



(4.40) (2.40)

The diol (**4.40**) (80 mg, 0.22 mmol) was dissolved in dry dichloromethane and the solution cooled on ice. Pyridine (0.18 mL, 2.2 mmol) was added rapidly followed by methanesulfonyl chloride (0.025 mL, 0.33 mmol) and allowing the reaction to warm to room temperature. After stirring for 5 hours a further aliquot of methanesulfonyl chloride (0.005 mL, 0.06 mmol) was added and the reaction stirred for an additional 12 hours. The solution was diluted with dichloromethane (30 mL) and washed sequentially with 1.0 M HCl (aq.), sat. sodium hydrogen carbonate (aq.), water and brine (20 mL of each). After drying ($MgSO_4$) and removal of solvent the crude product was purified by chromatography on silica gel (3 x 3 cm) eluting with 50% ethyl acetate in hexane. The title compound (**2.40**) was isolated as a white solid (60 mg, 0.17 mmol, 77%).

(2R*, 3R*, 4S*) 2[(3,4-Dimethoxy)phenyl]-3-hydroxymethyl-4-{[(3,4,5-trimethoxy) phenyl]hydroxy}methyltetrahydrofuran.

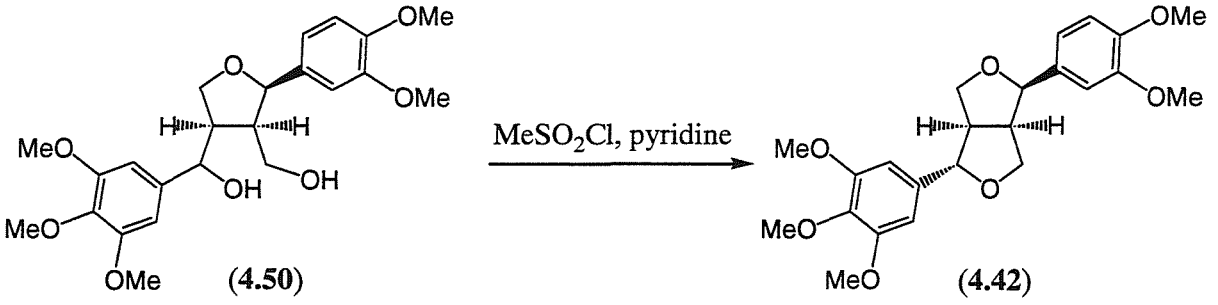


(4.49) (4.50)

The title compound was prepared according to the method outlined for **4.40**. Reaction of furofuranone (**4.49**) (165 mg, 0.38 mmol) with $LiAlH_4$ (43 mg, 1.14 mmol) and work-up under the conditions described gave crude diol as a white solid (166 mg). Purification was accomplished by chromatography on silica gel (10 x 2.3 cm) eluting with 70% ethyl acetate in hexane to yield the title compound (**4.50**)(149 mg, 0.34 mmol, 90 %) as a powdery white solid.

MP*	141 – 143°C.
CHN analysis*	Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: C, 63.31; H, 6.99.
FT-IR (neat)	1241 cm^{-1}.
^{1}H NMR* **(400MHz, $CDCl_3$)**	2.55 (br s, 1H), 2.69 – 2.76 (m, 1H), 3.05 (dq, J = 6.5, 9.5 Hz, 1H), 3.39 (d, J = 11.0 Hz, 1H), 3.61 – 3.69 (m, 2H), 3.72 (q, J = 9.0 Hz, 1H), 3.84 (s, 3H), 3.87 (s, 6H), 3.87 (s, 6H), 4.76 (d, J = 10.5 Hz, 1H), 5.08 (d, J = 5.0 Hz, 1H), 6.61 (s, 2H), 6.79 – 6.86 (m, 3H) ppm.
^{13}C NMR **(100 MHz, $CDCl_3$)**	47.78 (CH), 51.89 (CH), 56.33 (CH_3), 56.35 (CH_3), 56.57 (CH_3), 60.10 (CH_2), 61.24 (CH_3), 69.16 (CH_2), 74.34 (CH), 83.72 (CH), 103.59 (CH), 109.21 (CH), 111.63 (CH), 118.17 (CH), 125.91 (CH), 131.97 (CH), 138.13 (CH), 138.71 (CH), 148.63 (CH), 149.42 (C), 153.83 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 434 (100) $[M]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{23}H_{30}O_8$: 434.1491. Found 434.1973.

(1R*, 2R*, 5R*, 6S*) 2-(3,4-Dimethoxy)phenyl-6-(3,4,5-trimethoxy)phenyl-3,7-dioxabicyclo[3.3.0]octane – (±) Epimagnolin A (4.42)



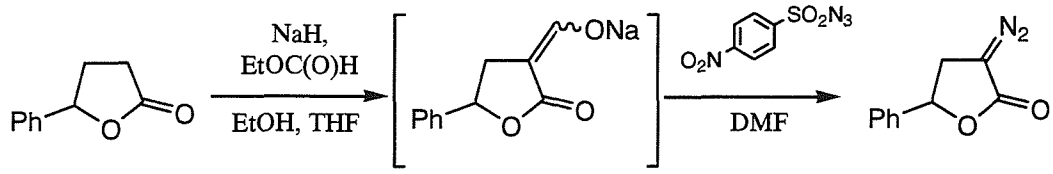
(4.50) (4.42)

To a solution of diol (**4.50**) (40 mg, 0.092 mmol) in CH_2Cl_2 (1 mL) at 0 °C (ice/salt) was added Et_3N (38 μL, 0.276 mmol) and DMAP (1 mg, cat.) followed by MsCl (9 μL, 0.11 mmol). The reaction mixture was allowed to warm to rt and stirred for 6 h before additional MsCl (4 μL, 0.046 mmol) was added and the reaction stirred for a further 12 h. TLC analysis still showed starting diol (**4.50**) so NEt_3 (38 μL, 0.276 mmol) and MsCl (18 μL, 0.221 mmol) were again added and the reaction stirred for 15 min before pipetting

onto water (5 mL) and diluting with CH_2Cl_2 (8 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1N HCl (aq) (15 mL) and brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo* to yield an orange oil (58 mg). Purification was accomplished on silica gel (2.3 x 2 cm) eluting with 60 % ethyl acetate in hexane to yield epimagnolin A (**4.42**) (29 mg, 0.070 mmol, 76 %) as a glassy solid/viscous oil. Spectroscopic data were consistent with those reported previously [150].

FT-IR (neat)	1234, 1127 cm^{-1}.
^{1}H NMR	2.90 – 2.97 (m, 1H), 3.31 – 3.39 (m, 2H), 3.84 (s, 3H), 3.86 –
(400MHz, $CDCl_3$)	3.91 (m, 2H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 3H),
	4.17 (d, J = 9.0 Hz, 1H), 4.45 (d, J = 7.0 Hz, 1H),
	4.89 (d, J = 5.5 Hz, 1H), 6.60 (s, 2H), 6.87 (s, 2H),
	6.95 (s, 1H) ppm.
^{13}C NMR	52.57 (CH), 57.07 (CH), 58.38 (CH_3), 58.41 (CH_3),
(100 MHz, $CDCl_3$)	58.63 (CH_3), 63.29 (CH_3), 72.29 (CH_2), 72.55 (CH_2),
	84.50 (CH), 90.28 (CH), 105.45 (CH), 111.49 (CH),
	113.57 (CH), 120.19 (CH), 133.37 (C), 139.33 (C),
	140.07 (C), 150.54 (CH), 151.36 (C), 155.89 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 416 (100) $[M]^{\bullet+}$.
HRMS	(EI) Calcd for $C_{23}H_{28}O_7$: 416.1835. Found 416.1821.

α-Diazo-5-phenyl-γ-butyrolactone (4.52)



(4.52)

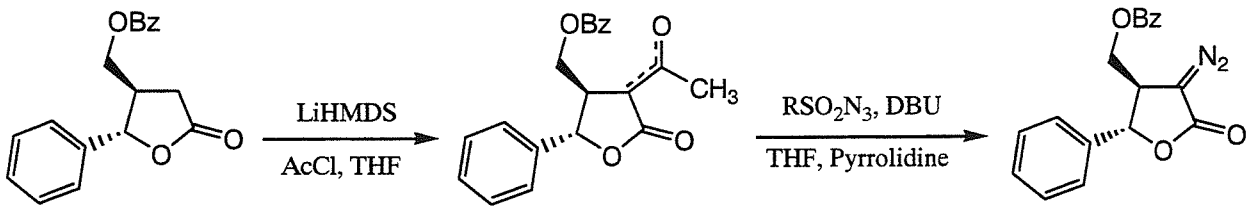
A 55% dispersion of sodium hydride (152 mg, 3.2 mmol) was washed with pentane prior to suspending in dry THF. A mixture of 5-phenyl-γ-butyrolactone (500 mg, 3.1 mmol) and ethyl formate (250μL, 3.1 mmol) in THF (3 mL) were added according to the method of Murray *et al.* [247] Ethanol (100μl) was then added resulting in immediate evolution of hydrogen and precipitation of a buff solid. After 30 minutes the reaction was diluted with sodium dried ether (10 mL) and the solid collected by filtration which was washed with an

additional portion of dried ether. The crude sodium salt of α-formyl lactone was isolated as a buff solid (544 mg, 83%). Spectroscopic data were acquired on the formyl lactone produced on acidification of a portion of the sodium salt (ν_{max} 1774, 1749, 1729, 1698, 1188 cm^{-1}; δ_c 32.1, 77.7, 100.5, 125.1, 127.8, 128.3, 140.8, 152.8, 172.9 ppm)

The sodium salt of the formyl derivative (50 mg, 0.24 mmol) was dissolved in dimethylformamide (1 mL) at RT and treated with *p*-nitrobenzenesulfonyl azide (54 mg, 0.24 mmol) according to the method described by Schmitz *et al* [129]. An immediate red colouration occurred. After 5 minutes a further portion of *p*-nitro-benzylsulfonyl azide was added (15 mg) and stirred at RT for a further 20 minutes. The reaction was partitioned between diethyl ether (10 mL) and hydrochloric acid (10 mL, 0.5M). The aqueous phase was re-extracted with diethyl ether (10 mL) before washing the combined organic phases with brine (10 mL) and drying ($MgSO_4$). The crude material was purified by chromatography on silica gel (6 x 1 cm) loading in dichloromethane and eluting with 50% diethyl ether in pentane. A quantity of sulfonyl azide transfer agent (8 mg, 12% of reagent) and *p*-nitrobenzylsulfonamide (28 mg, 62%) were isolated along with the title compound (17 mg, <37%) albeit contaminated with undefined impurities. Selected data on the title compound is described below.

FT-IR (CH_2Cl_2)	2945, 2871, 2098, 1782, 1737 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	3.29 (dd, *J* = 12.9, 6.6 Hz, 1H), 3.76 (dd, *J* = 12.9, 8.8 Hz, 1H), 5.57 (dd, *J* = 8.8, 6.6 Hz, 1H), 7.20-7.50 (5H, m) ppm.

Attempted preparation of 3-Acetyl-4-benzyloxymethyl-5-phenyl-γ-butyrolactone and subsequent diazotransfer.



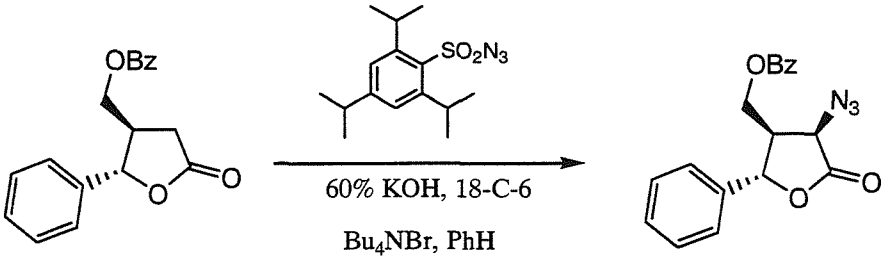
(**4.4**)

The lactone (**4.4**) (100mg, 0.354 mmol) was dissolved in dry THF (3 mL), under an atmosphere of nitrogen, and cooled to -78°C according to the method described by Jedlinski *et al.*[156]. The solution was treated with LiHMDS (0.74M solution in THF, 0.57 mL, 0.42 mmol) and stirred at -78°C for 30 minutes before adding acetyl chloride

(41 mg, 36 μL, 0.53 mmol) was added and the reaction stirred for 5 minutes. The reaction was treated with 0.5M HCl (2 mL) and allowed to warm to RT. The mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The organic phase was separated before re-extracting the aqueous phase with ethyl acetate (10 mL) and washing the combined organic phase with water (10 mL) and brine (10 mL) before drying ($MgSO_4$). After removal of solvent the crude oil (110 mg) was purified by chromatography on silica gel (4 x 3 cm) loading in dichloromethane (5 mL) and eluting with 30% ethyl acetate in hexane. The title compound, a mixture of keto (x2) and enol tautomers, was isolated as an oil (84 mg, 73%). Attempts to purify the compound further by radial chromatography failed.

The crude material (0.07 mg, 0.22 mmol) was dissolved in dry dichloromethane and treated with *p*-nitrobenzenesulfonyl azide (0.055g, 0.24 mmol) and DBU (0.065 mL, 0.44 mmol) according to the method described by Padwa *et al.* [131] The reaction was stirred at 0°C for 20 mins before passing through a pad of silica gel eluting with dichloromethane. After reducing the volume to approx. 5 mL the solution was treated with pyrrolidine (0.46 mmol) and the reaction stirred for 3 hours. The mixture was partitioned between ethyl acetate and water and the organic phase washed sequentially with water and brine before drying ($MgSO_4$). The crude mixture was subjected to purification by chromatography on silica gel (5 x 1 cm) eluting with 20% ethyl acetate in hexane. None of the desired product was isolated. Instead, *N*-(4-nitrobenzenesulfonyl)pyrrolidine accounting for 60% of the sulfonyl azide starting material was isolated.

Attempted phase transfer mediated diazoinsertion to lactone (4.4)



(**4.4**)

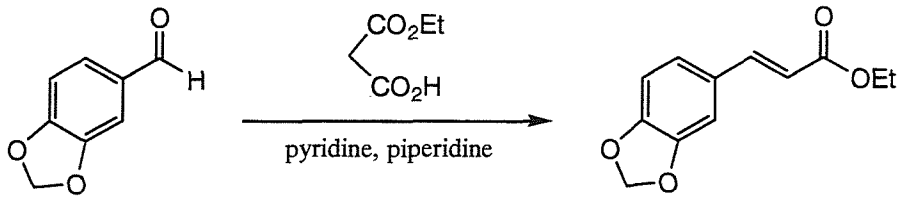
The reaction was carried out as according to the method of Lombardo and Mander [135]. Thus, a solution of tetra-*n*-butylammonium bromide (10 mg), 18-crown-6 (5 mg), and tris-2,4,6-tri*iso*propylbenzenesulfonyl azide (25 mg, 0.09 mmol) and the lactone (**4.4**) (20 mg, 0.08 mmol) in benzene (2 mL) was treated with KOH (60% aq., 2 mL) and the biphasic mixture stirred vigorously at RT. After 30 minutes the reaction was diluted with diethyl ether and water (10 mL each). The organic phase was separated and washed with water and brine and dried ($MgSO_4$). The crude material was purified by chromatography on

silica gel (1g) loading and eluting with 20% diethyl ether in pentane. Two compounds were isolated; tris-2,4,6-tri*iso*propylbenzene sulfonamide (6 mg, 29%), and an azide substituted lactone (12 mg, <<50%). Selected data indicated that the favoured isomer produced under these conditions was the different from the one isolated on azide transfer to the lithium lactone enolate.

FT-IR (CH_2Cl_2) 2112, 1789 cm^{-1}.

^1H NMR (300MHz, $CDCl_3$) 2.82 (ddd, J = 9.2, 7.7, 4.8 Hz, 1H), 3.52 (dd, J = 9.9, 4.4 Hz, 1H), 3.74 (dd, J = 9.9, 7.7 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 4.48 (d, J = 12.9 Hz, 1H), 4.63 (d, J = 7.7 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H) ppm.

Ethyl 3-(3,4-methylenedioxyphenyl)acrylate



The title compound was prepared according to the method described by Freudenburg *et al.* [169] Piperonal (4.0 g, 27 mmol) was combined with malonic acid monomethyl ester [168] (5.14 g, 35 mmol) in pyridine (10 mL) and piperidine (1 mL) and the reaction was warmed to 100°C and stirred for 4 hours. The cooled reaction mixture was poured into HCl (2M, 60 mL) and the resulting solid collected by filtration. Recrystallisation from ethanol and water provided the title compound as a white solid (5.23 g, 23.8 mmol, 88%). Spectroscopic data were consistent with those described in the literature [248].

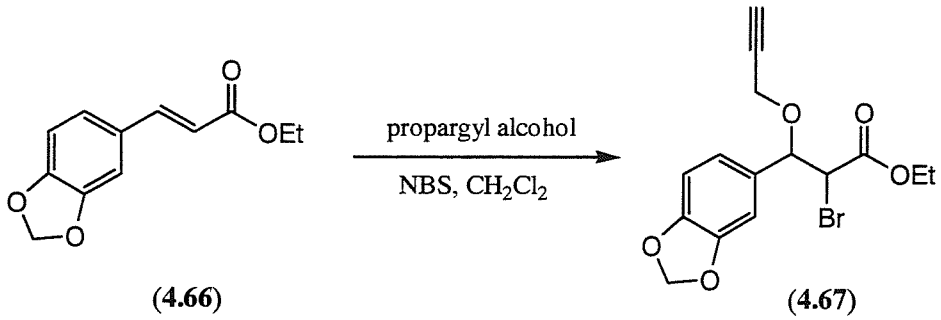
MP 70-71°C (ethanol/ water) (lit. 67-69°C [248]).

FT-IR (CH_2Cl_2) 2982, 2901, 1704, 1633, 1604, 1176 cm^{-1}.

^1H NMR (300MHz, $CDCl_3$) 1.30 (t, J = 6.9 Hz, 1H), 4.23 (q, J = 7.0 Hz, 1H), 5.97 (s, 2H), 6.25 (d, J = 15.8 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 7.57 (d, J = 15.8 Hz, 1H) ppm

^{13}C NMR (75 MHz, $CDCl_3$) 14.48 (CH_3), 60.51 (CH_2), 101.69 (CH_2), 106.56 (CH), 108.64 (CH), 116.289 (CH), 124.52 (CH), 128.99 (C), 144.39 (CH), 148.45 (C), 149.68 (C), 167.29 (C) ppm.

Ethyl 2-bromo-3-(3',4'-methylenedioxy)phenyl-3-propargyloxypropionate (4.67)

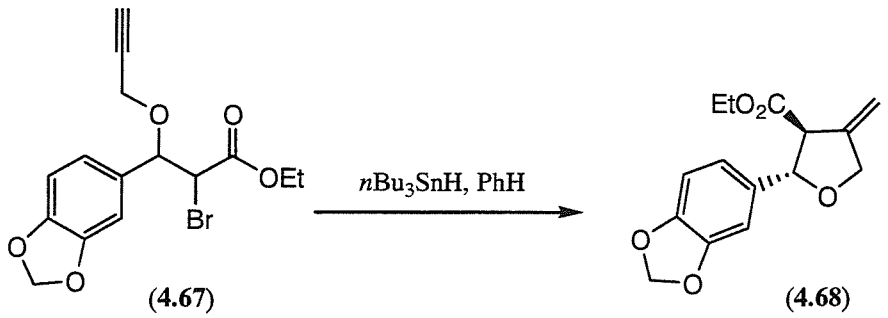


(4.66) **(4.67)**

The title compound (**4.67**) was prepared according to the method described by Chandra Roy *et al.* [249] A suspension of *N*-bromosuccinimide (6.0g, 34 mmol) and propargyl alcohol (6.87g, 6.6 mL, 113 mmol) in dichloromethane (20 mL) was cooled to -15°C with stirring, under an atmosphere of nitrogen. A solution of the alkene (**4.66**) (5.0g, 23 mmol) in dichloromethane (20 mL) was added by dropwise addition whilst maintaining the temperature at -15°C. After allowing to warm to room temperature the reaction was stirred at room temperature for 4 hours before adding a further aliquot of *N*-bromosuccinimide (2.0g, 21 mmol) and propargyl alcohol (2.08g, 2.0 mL, 34 mmol). The reaction was warmed to reflux for 24 hours before cooling and diluting with dichloromethane (100 mL). The organic phase was washed with sodium hydrogen carbonate (aq.), sodium hydroxide (1.0M), water and brine (50 mL each). After drying and removal of solvent the crude mixture was purified by chromatography on silica gel loading in toluene and eluting with 10% ethyl acetate in hexane. The title compound (**4.67**) was isolated as an oil (3.65g, 10.3 mmol, 45%). Another fraction containing a mixture of diastereoisomers was isolated but decomposed prior to analysis (2.93g). Spectroscopic data were consistent with those reported previously [249].

FT-IR (CH_2Cl_2)	3301, 2982, 2903, 2123 1740, 1610, 1504, 1488, 1444, 127, 1040 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	1.34 (t, *J* = 7.4 Hz, 3H), 2.44 (t, *J* = 2.6 Hz, 1H), 3.87 (dd, *J* = 15.8, 2.2 Hz, 1H), 4.12 (dd, *J* = 15.5, 2.6 Hz, 1H), 4.21 (d, *J* = 9.9 Hz, 1H), 4.25-4.38 (m, 2H), 4.86 (d, *J* = 9.9 Hz, 1H), 6.00 (s, 2H), 6.80-6.89 (m, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	14.1 (CH_3), 47.7 (CH), 56.4 (CH_2), 62.3 (CH_2), 75.2 (CH), 78.7 (C), 80.8 (CH), 101.5 (CH), 107.8 (CH), 108.2 (CH), 122.9 (CH), 129.9 (C), 141.2 (C), 148.5 (C), 168.6 (C) ppm.
LRMS	(EI) *m/z* (relative intensity) 299/ 301 (70) $[M\text{-}C_3H_4O]^{\bullet+}$.

(2S*, 3R*) 2-(3',4'-Methylenedioxyphenyl)-3-ethoxycarbonyl-4-*exo*-methylene tetrahydrofuran (4.68)



(4.67) (4.68)

The title compound (**4.68**) was prepared according to the method described by Chandra Roy *et al.* [249] The bromo derivative (**4.67**) (3.1g, 8.7 mmol) was dissolved in dry benzene (240 mL) along with tri-*n*-butyltin hydride (2.88g, 2.69 mL, 10 mmol) and AIBN (20 mg). The reaction was stirred under an atmosphere of nitrogen and warmed at reflux for 1 hour. After cooling the reaction was concentrated (to approximately 100 mL) and treated with a saturated aqueous solution of potassium fluoride (30 mL) before stirring overnight at room temperature. The resulting solid was separated by filtration and the filtrate washed with brine and dried before evaporating to dryness. The crude product was purified by chromatography on silica gel loading in benzene and eluting with a mixture of 50% dichloromethane in hexane. The product was isolated as an oil (1.4g, 5.2 mmol, 60%). Spectroscopic data were consistent with those reported previously [249].

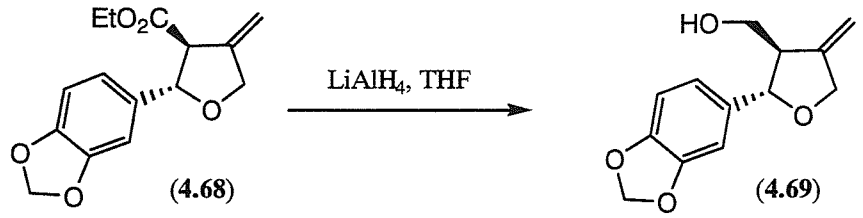
FT-IR (CH_2Cl_2) 3011, 2982, 2899, 1729, 1740 (s), 1665, 1633, 1610 (w), 1500, 1490, 1370 and 1176 cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$) 1.19 (t, J = 7.4 Hz, 3H), 3.42-3.46 (m, 1H), 3.87 (dq, J = 13.2, 2.6 Hz, 1H), 4.26 (dq, J = 10.8, 7.4 Hz, 1H), 4.49 (dq, J = 13.2, 2.6 Hz, 1H), 4.63 (d, J = 12.9 Hz, 1H), 5.10 (q, J = 2.2 Hz, 1H), 5.16 (d, J = 8.8 Hz, 1H), 5.18 (q, J = 2.2 Hz, 1H), 5.95 (s2H), 6.77 (d, J = 8.1 Hz, 1H), 6.86 (dd, J = 8.1, 1.5 Hz, 1H), 6.89 (d, J = 1.5 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 14.4 (CH_3), 57.3 (CH), 61.3 (CH_2), 71.6 (CH_2), 83.5 (CH), 101.2 (CH_2), 106.5 (CH_2), 106.7 (CH), 108.3 (CH), 120.0 (CH), 133.9 (q), 146.6 (C), 147.6 (C), 148.0 (C), 170.8 (C) ppm.

LRMS (CI) *m/z* (relative intensity) 277 (30) $[M+H]^+$, 276 (55) $[(M-H_2O)+NH_4]^+$.

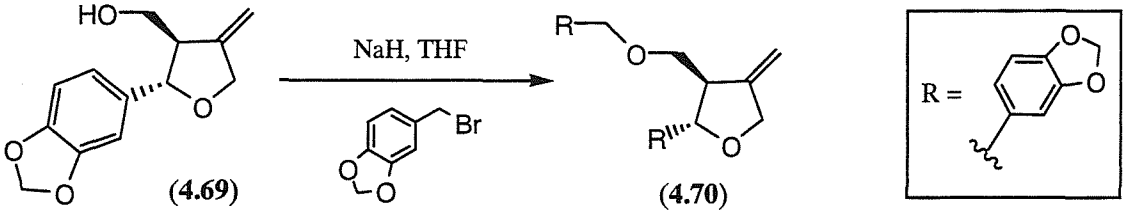
(2S*, 3R*) 2-(3',4'-Methylenedioxyphenyl)-3-hydroxymethyl-4-*exo*-methylene tetrahydrofuran (4.49)



The title compound (**4.69**) was prepared according to the method described by Chandra Roy *et al.* [249] The ethyl ester (**4.68**) (1.61g, 5.6 mmol) in dry THF (15 mL) was added by dropwise addition to a suspension of lithium aluminium hydride (429 mg, 11.3 mmol) in THF (15 mL) whilst stirring at rt under a flow of nitrogen. The reaction was warmed to reflux and stirred for 2 hours. After cooling the reaction was sequentially treated with water (0.43 mL), 15% sodium hydroxide (0.43 mL) and water (1.3 mL). The resulting solid was removed by filtration through celite and the filtrate collected and evaporated to dryness. The crude product was purified by chromatography on silica gel (6 x 4 cm) loading and eluting with 20% ethyl acetate in hexane followed by 40% ethyl acetate in hexane. The purified title compound (**4.69**) was collected as a colourless oil (1.32g, 5.6 mmol, 100%). Spectroscopic data were consistent with those reported previously [249].

FT-IR (CH_2Cl_2)	3612, 3456, 3011, 2884, 1504, 1489, 1445, 1249, and 1040 cm^{-1}.
^{1}H NMR	2.69-2.79 (m, 1H), 1.79-1.86 (m, exchange in D_2O, 1H),
(300MHz, $CDCl_3$)	3.66-3.76 (m, collapses to 3.71, dd, J = 11.0, 4.0 Hz in D_2O, 1H),
	3.79-3.89 (m, collapses to 3.83, dd, J = 11.0, 5.2 Hz in D_2O, 1H),
	4.40 (dq, J = 13.6, 2.2 Hz, 1H), 4.60 (d, J = 13.2 Hz with additional unresolved coupling, 1H), 4.75 (d, J = 7.4 Hz, 1H),
	5.06 (q, J = 2.2 Hz, 1H), 5.10 (d, J = 2.2 Hz, 1H), 5.95 (s, 2H),
	6.78 (d, J = 8.1 Hz, 1H), 6.84 (dd, J = 8.1, 1.5 Hz, 1H),
	6.86 (d, J = 1.5 Hz, 1H).
^{13}C NMR	54.2 (CH), 62.0 (CH_2), 71.5 (CH_2), 83.5 (CH), 101.2 (CH_2),
(75 MHz, $CDCl_3$)	105.3 (CH_2), 106.9 (CH), 108.3 (CH), 120.2 (CH), 135.2 (C),
	147.4 (C), 148.1 (C), and 148.8 (C).
LRMS	(CI) *m/z* (relative intensity) 235 (10) $[M+H]^+$, 187 (100).

(2S*, 3R*) 2-(3',4'-Methylenedioxyphenyl)-3-[(3",4"-methylenedioxyphenyl)-methyloxy methyl]-4-*exo*-methylene tetrahydrofuran (4.70)



A 50% dispersion of sodium hydride in oil (274 mg, 5.7 mmol) was washed with dry pentane in oven dried apparatus. The solvent was removed by decantation and replaced with dry tetrahydrofuran (10 mL) and the suspension stirred under nitrogen. A mixture of the alcohol (**4.69**) (1.16g, 4.7 mmol) and 3,4-methylenedioxyphenylmethyl bromide (1.22g, 5.7 mmol) in THF (10 mL) were added by slow dropwise addition at room temperature. After complete addition the reaction was warmed to reflux and stirred for 3 hours. After cooling the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). Re-extraction of the aqueous phase was followed by washing the combined extracts with water (20 mL), followed by brine (20 mL). After drying and removal of solvent *in vacuo* the crude product was subjected to column chromatography loading in toluene (10 mL) and eluting with 10% ethyl acetate in petroleum ether followed by 20% ethyl acetate in petroleum ether. The title compound (**4.70**) was isolated as a viscous oil (1.50g, 3.8 mmol, 82%).

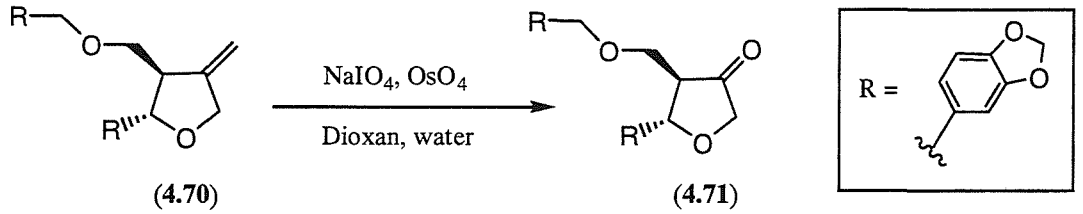
FT-IR (CH_2Cl_2) 2980, 1504, 1489, 1444, 1265, 1040, and 935 cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$) 2.80-2.90 (m, 1H), 3.56 (dd, J = 9.8, 5.5 Hz, 1H), 3.59 (dd, J = 9.8, 6.3 Hz, 1H), 4.38-4.40 (ABq, J = 11.8 Hz, 2H), superimposed on 4.42 (dq, J = 13.2, 2.2 Hz, 1H), 4.58 (d with additional unresolved coupling, J = 13.2 Hz, 1H), 4.75 (d, J = 7.0 Hz, 1H), 5.06 (q, J = 2.2 Hz, 1H), 5.04 (q, J = 2.2 Hz, 1H), 5.07 (q, J = 2.6 Hz, 1H), 5.96 (s, 2H), 5.97 (s, 2H), 6.72-6.83 (m, 5H), and 6.84 (, d, J = 1.5 Hz, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 51.9 (CH), 70.1 (CH_2), 71.5 (CH_2), 73.2 (CH_2), 84.1 (CH), 101.2 (2 x CH_2), 105.2 (CH_2), 107.0 (CH), 108.2 (CH), 108.6 (CH), 120.1 (CH), 121.4 (CH), 132.1 (C), 135.5 (C), 147.2 (C), 147.9 (C), 149.1 (C) ppm.

LRMS (ES+ve) *m/z* (relative intensity) 120 (100), 386 (25) $[M+NH_4]^+$.

(2S*, 3R*) 2-(3',4'-Methylenedioxyphenyl)-3-[(3",4"-methylenedioxyphenyl)-methyloxymethyl]-4-oxotetrahydrofuran (4.71)



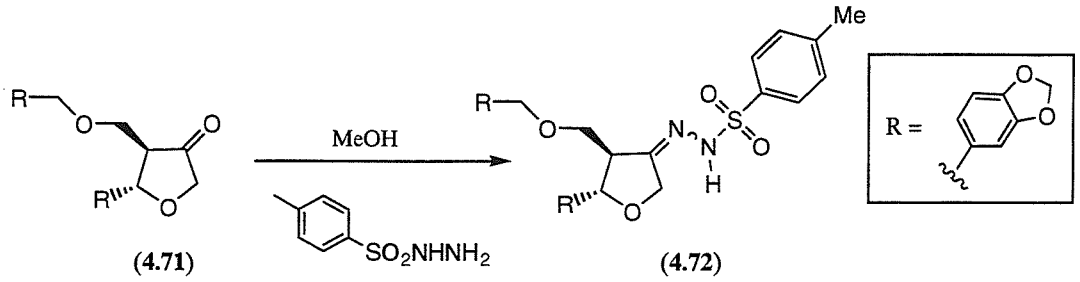
(4.70) **(4.71)**

The alkene (**4.70**) (1.17g, 3.2 mmol) was dissolved in dioxan, (25 mL) and water added (10 mL) according to the method described by Iwata *et al.* [170] A 5% solution of osmium tetroxide in water (0.6 mL, 0.12 mmol) and the reaction was stirred at room temperature prior to adding sodium metaperiodate (1.5 g, 7.0 mmol) by portionwise addition. The heterogeneous reaction was stirred for 3 hours at room temperature. The mixture was poured into diethylether and water (70 mL each) and the organic phase separated and washed with water (2 x 50 mL). The combined aqueous phases were re-extracted with diethyl ether (50 mL) and the combined organic phases dried and evaporated to dryness. The title compound (**4.71**) a colourless oil (967 mg, 82%) was found to be pure enough for further elaboration.

FT-IR (CH_2Cl_2)	2893, 1763, 1610, 1504, 1488, 1447, 1251, 1040, and 936 cm^{-1}.
^1H NMR (300MHz, $CDCl_3$)	2.42 (1H, dd with additional fine coupling, J = 6.6, 3.3 Hz), 3.51 (1H, dd, J = 9.9, 3.3 Hz), 3.85 (1H, dd, J = 9.6, 3.7 Hz), 3.98 and 4.33 (2H, ABq, J = 17.1 Hz), 4.34 and 4.45 (2H, ABq, J = 11.8 Hz), 5.12 (1H, d, J = 9.9 Hz), 5.97 (2H, s), 5.98 (2H, s), 6.72-6.84 (5H, m), and 6.88 (1H, d, J = 1.5 Hz) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	55.9 (CH), 64.5 (CH_2), 72.3 (CH_2), 73.4 (CH_2), 81.5 (CH), 101.2 (CH_2), 101.3 (CH_2), 106.7 (CH), 108.2 (CH), 108.4 (CH), 108.6 (CH), 120.2 (CH), 121.5 (CH), 131.7 (C), 133.6 (C), 147.4 (C), 147.8 (C), 147.9 (C), 148.2 (C), and 214.0 (C) ppm .
LRMS	(CI) *m/z* (relative intensity) 388 (20) $[M+NH_4]^+$, 758 (100) $[M+NH_4]^+$.

Note: Using a diethyl ether/ water mixture as solvent in the above reaction resulted in only a 17% conversion to the desired ketone after reaction for 24 hours at room temperature. 80% of the starting material was recovered.

4-Methylphenylsulfonylhydrazone of (2S*, 3R*) 2-(3',4'-methylenedioxyphenyl)-3-[(3",4"-methylenedioxyphenyl)methyloxymethyl]-4-oxotetrahydrofuran (4.72)

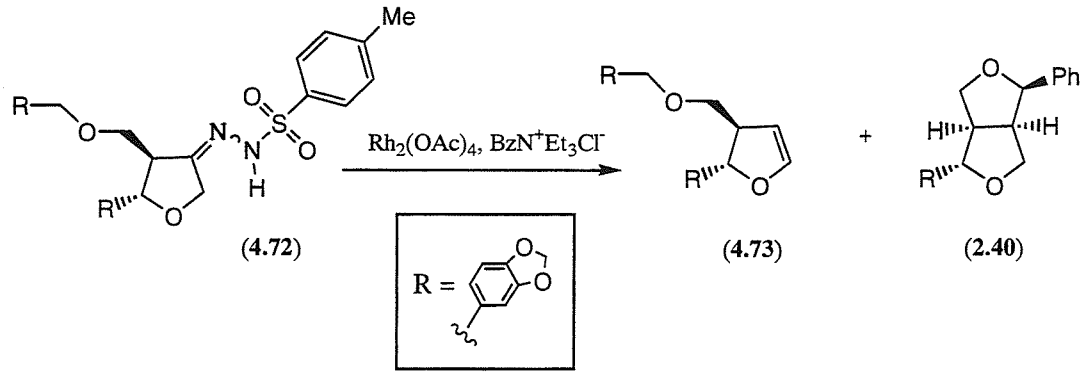


(4.71) (4.72)

The ketone (**4.71**) (496 mg, 1.34 mmol) was dissolved in methanol (10 mL) and treated with 4-methylphenylsulfonyl hydrazine (249 mg, 1.34 mmol) according to the method of Paquette *et al.* [171] The reaction was stirred at room temperature for 3 hours. After removal of solvent in vacuo the crude material was purified by chromatorgraphy on silica gel (30g; 5 x 3 cm) loading in dichloromethane and eluting with 20% ethyl acetate in petroleum ether followed by 50% ethyl acetate in petroleum ether. The product was initially recovered as a foam which was recrystallised to provide pale brown crystals (630 mg, 1.15 mmol, 86%). The title compound (**4.72**) was isolated as a mixture of hydrazone isomers. NMR data is recorded for the major isomer only (ratio of 9:1).

MP	150-1°C (CH_2Cl_2/ hexane).
CHN	Calcd. for $C_{27}H_{26}N_2O_8S$: C, 60.22; H, 4.87; N, 5,20. Found C, 59.85, H, 4.59; N, 5.23.
FT-IR (CH_2Cl_2)	3673, 3141, 2870, 1598, 1490, 1445, 1347, 1248, and 1040 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	The NMR was complicated by regioisomerism around the hydrazone N=N bond. The isomer ratio was approximately 9:1 and was not improved on crystallisation. The resonances quoted are for the major isomer only: 2.43 (s, 3H), 3.00-3.07 (m, 1H), 3.50 (d, J = 9.2 Hz, 1H), 3.57 (dd, J = 9.2, 4.8 Hz, 1H), 4.23 to 4.59 (m, 5H) which includes 4.39 (d, J = 11.4 Hz, 1H), 4.52 (d, J = 7.7 Hz, 1H), 5.95-5.99 (m, 4H), 6.60- 6.95 (m, 6H), 7.27 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), and 9.76 (s, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	21.8 (CH_3), 48.8 (CH), 69.3 (CH_2), 70.0 (CH_2), 74.0 (CH_2), 83.1 (CH), 101.5 (CH_2), 106.8 (CH), 108.5 (CH), 108.9 (CH), 120.1 (CH), 122.3 (CH), 127.9 (CH), 129.9 (CH), 133.1 (C), 136 (C), 143.9 (C), 148.0 (C), 148.2 (C), 148.3 (C), and 159.2 (C) ppm.
LRMS	(CI) *m/z* (relative intensity) 539 (100) $[M+H]^+$, 1077 (60) $[2M+H]^+$.

2-(3',4'-Methylenedioxyphenyl)-3-[(3",4"-methylenedioxyphenyl)methoxymethyl]-2,3-dihydrofuran (4.73)

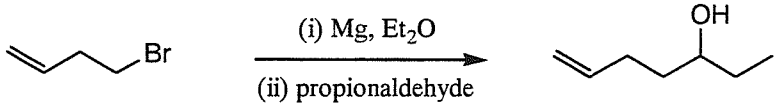


A 50% dispersion of sodium hydride (9 mg, 0.18 mmol) was suspended in freshly distilled dimethoxyethane (2 mL) after removal of the oil by washing in pentane. Hydrazone (**4.72**) (100 mg, 0.18 mmol) was added in one portion causing immediate evolution of hydrogen. After stirring at room temperature for 5 minutes TLC indicated no change. Dirhodium tetraacetate (10 mg, 7 mol%) was added and the reaction warmed to reflux. After 6 hours stirring at reflux another portion of dirhodium tetraacetate (10 mg, 7 mol%) was added along with benzyltriethylammonium chloride (10 mg, 20 mol%) and stirring continued at reflux for 36 hours whereupon consumption of starting material was complete. The reaction was allowed to cool before partitioning between ethyl acetate and water (30 mL each). After re-extraction of the aqueous phase the combined organics were dried and the solvent removed by evaporation in vacuo. Radial chromatography (2mm plate, loading in dichloromethane, eluting with 20% ethyl acetate in hexane) after prefiltering through silica provided the title compound (**4.73**) as the main product (22mg, 40%) with asarinin (**2.40**) isolated as a byproduct (2 mg, 3%). Data for the major product is outlined below:-

FT-IR (CH_2Cl_2)	2893, 1610, 1503, 1498, 1442, 1249, 1040 and 937 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	3.10-3.17 (m, 1H), 3.42 (dd, J = 9.2, 8.0 Hz, 1H), 3.49 (dd, J = 8.9, 5.2 Hz, 1H), 4.43 (s, 2H), 4.87 (t, J = 2.5 Hz, 1H), 5.19 (d, J = 6.2 Hz, 1H), 5.93 (s, 2H), 5.95 (s, 2H), 6.47 (dd, J = 2.7, 2.0 Hz, 1H), and 6.73- 6.81 (m, 6H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	51.9 (CH), 72.9 (CH_2), 73.0 (CH_2), 85.7 (CH), 100.3 (CH), 101.5 (2 x CH_2), 106.2 (CH), 108.1 (CH), 108.4 (CH), 119.0 (CH), 121.3 (CH), 132.1 (C), 136.6 (C), 146.4 (C), 147.1 (C), 147.2 (C), and 147.9 (C) ppm.
LRMS	(CI) *m/z* (relative intensity) 355 (85) $[M+H]^+$, 726 (65) $[2M+NH_4]^+$.

7.3 Experimental Details of Laurencin Preparations

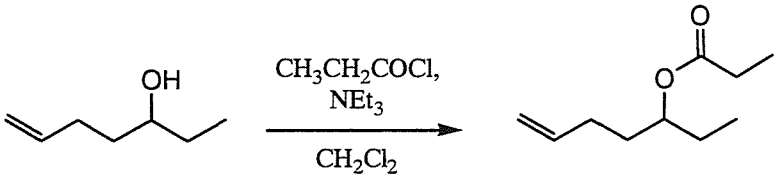
5-Hydroxyheptene



A suspension of magnesium turnings (0.59 g, 23 mol) in dry diethyl ether (20 mL) was treated with as crystal of iodine followed by dropwise addition of 4-bromobutene (3.06 g, 23 mmol). On completion of the exothermic reaction the resultant grey solution was transferred to propionaldehyde (1.27 g, 1.57 mL, 22 mmol) in diethyl ether (10 mL) *via* a cannula whilst at 0°C. The reaction was then allowed to warm to RT and stirred for 15 minutes. The reaction mixture was poured into iced HCl (2M, 50 mL), the phases separated and the aqueous phase re-extracted with diethyl ether (30 mL). The combined extracts were washed with brine and dried ($MgSO_4$). The product was purified by chromatography on silica gel (9 x 4.5 cm) eluting with 15% ethyl acetate in hexane. The title compound was isolated as an oil (0.58 g, 4.8 mmol, 22%).

FT-IR (ATR)	3336, 2934, 1641, 1459, 1275 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	0.94 (t, J = 7.7 Hz, 3H), 1.38-1.70 (m, 5H), 2.04-2.30 (m, 2H), 3.55 (tt, J = 7.4, 4.7 Hz, 1H), 4.96 (d, J = 10.3 Hz, 1H), 5.05 (dq, J = 17.3, 1.5 Hz, 1H), 5.84 (ddt, J = 17.3, 10.3, 6.6 Hz, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	10. 0 (CH_3), 30.1 (CH_2), 30.3 (CH_2), 36.1 (CH_2), 72.9 (CH), 114.7 (CH_2), 138.7 (CH) ppm.

1-Ethylpent-5-enyl propionate

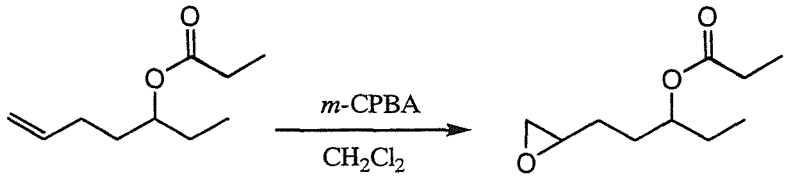


The alcohol (0.54 g , 4.78 mol) was dissolved in dry dichloromethane (5 mL) under an atmosphere of nitrogen. The solution was treated with catalytic DMAP, triethylamine (0.58 g, 0.80 mL, 5.70 mmol) and finally propionyl chloride (0.33 g, 0.49 mL, 5.7 mmol). The reaction was stirred RT for 30 minutes before diluting with dichloromethane (20 mL) and washed sequentially with sodium hydrogen carbonate (sat. aq.), water and brine (50 mL each) before drying ($MgSO_4$). The crude product was purified by chromatography

on silica gel (8 x 3 cm) eluting with 10% diethyl ether in hexane. The title compound was isolated as an oil (0.57 g, 3.35 mmol, 63%).

FT-IR (ATR)	2976, 1734, 1641, 1275, 1189 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	0.88 (t, J = 7.4Hz, 3H), 1.15 (t, J = 7.7Hz, 3H), 1.52-1.72 (m, 5H), 1.97-2.11 (m, 2H), 2.34 (q, J = 7.7Hz, 2H) superimposed on 2.40 (s, 1H), 4.85 (quint, J = 6.6Hz, 1H), 4.89-5.04 (m, 2H), 5.79 (ddt, J = 17.3, 10.3, 6.6Hz, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	9.45 (CH_3), 9.67 (CH_3), 27.14 (CH_2), 28.02 (CH_2), 29.79 (CH_2), 32.99 (CH_2), 74.76 (CH), 114.93 (CH_2), 138.11 (CH), 174.42 (C) ppm.
LRMS	(CI) *m/z* (relative intensity) 97 (100), 171 (75) $[M+H]^+$, 188 (40) $[M+NH_4]^+$.

1-Ethyl-3-oxiranylpropyl propionate (6.7)



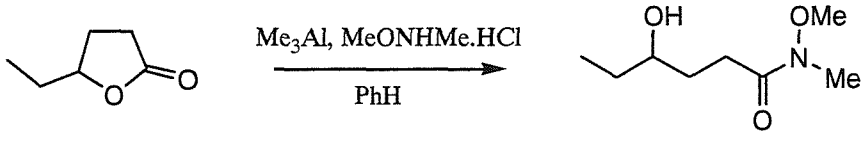
(6.7)

The alkene (0.47 g, 2.8 mmol) was dissolved in dry dichloromethane (5 mL). *m*-CPBA (50%, 1.24 g, 3.6 mmol) was added after cooling to 0°C and stirring for 16 hours. The reaction was diluted with dichloromethane (20 mL) and washed sequentially with sodium hydrogen carbonate (sat. aq.), water and brine (30 mL each) before drying ($MgSO_4$). The crude product was purified by chromatography on silica gel (4 x 3 cm) eluting with 25% ethyl acetate in hexane. The title compound (**6.7**), a 1:1 mixture of diastereoisomers, was isolated as an oil (0.35 g, 1.9 mmol, 67%).

FT-IR (ATR)	2970, 1731, 1189 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	0.81 (t, J = 7.7 Hz, 3H), 1.10 (t, J = 7.7 Hz, 3H), 1.36-1.73 (m, 6H), 2.27 (q, J = 7.4 Hz, 2H), 2.43-2.46 (m, 1H), 2.67-2.74 (m, 1H), 2.82-2.91 (m, 1H), 4.80-4.88 (m, 1H) ppm.

^{13}C NMR	9.36 (CH_3), 9.64 (CH_3), 27.11 (CH_2), 27.18 (CH_2), 27.90 (CH_2),
(75 MHz, $CDCl_3$)	28.37 (CH_2), 28.69 (CH_2), 29.88 (CH_2), 30.04 (CH_2),
	47.10 (CH_2), 47.19 (CH_2), 51.85 (CH), 52.07 (CH), 74.43 (CH),
	74.78 (CH), 174.31 (C), 174.36 (C) ppm.
LRMS	(CI) *m/z* (relative intensity) 113 (100), 187 (90) $[M+H]^+$.

4-Hydroxy-*N*-methoxy-*N*-methylhexanamide (6.9)

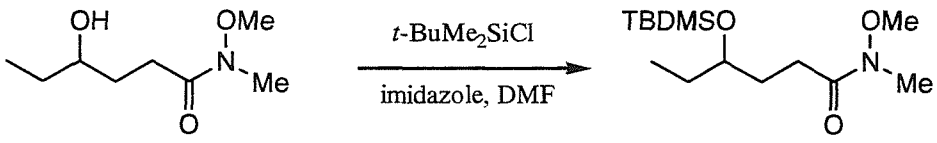


(6.9)

The title compound (**6.9**) was prepared according to the method described by Baxter *et al.* [220] Dimethylhydroxylamine. HCl (764 mg, 8.0 mmol) was suspended in sodium dried benzene (8 mL) whilst under an atmosphere of nitrogen. The suspension was treated with a solution of trimethylaluminium in hexane (2.0M, 4 mL, 8 mmol) by dropwise addition. After the evolution of methane had stopped the homogeneous solution was stirred at room temperature for 2 hours. 5-Methylbutyrolactone (455 mg, 442 μL, 4 mmol) in benzene (8 mL) was added dropwise and the reaction stirred at room temperature overnight. The reaction was quenched with sodium hydrogen carbonate (sat. aq., 8 mL) and the resultant heterogeneous mixture filtered through celite. The filtrate was washed with brine (20 mL) and dried ($MgSO_4$) to give a crude oil (611 mg). Purification was accomplished on silica gel (3 x 3 cm) loading and eluting with 50% ethyl acetate in hexane to provide the title compound (**6.9**) as a colourless oil (575 m, 3,3 mmol, 82%) which was separated from the starting lactone (90 mg, 0.7 mmol, 18%).

FT-IR (ATR)	3422, 2963, 2933, 1642, 1561, 1419, 1388, 993 cm^{-1}.
^{1}H NMR	0.90 (t, J = 7.4 Hz, 3H), 1.45 (app. quint., J = 7.0 Hz, 2H), 1.66
(300MHz, $CDCl_3$)	(dq, J = 14.0, 7.0 Hz, 1H), 1.79 (ddt, J = 14.3, 7.3, 3.3 Hz, 1H),
	2.50-2.65 (m, 2H), 2.94 (br s, 1H), 3.14 (3H, s),
	3.48-3.54 (m, 1H), 3.65 (s, 3H) ppm.
^{13}C NMR	10.10 (CH_3), 28.61 (CH_2), 30.51 (CH_2), 31.24 (CH_2),
(75 MHz, $CDCl_3$)	32.32 (CH_3), 61.34 (CH), 72.86 (CH_3), 175.19 (C) ppm.
LRMS	(ES, +ve) no molecular ion observed.

4-(*tert*-Butyldimethylsiloxy)-*N*-methoxy-*N*-methylhexanamide (6.10)

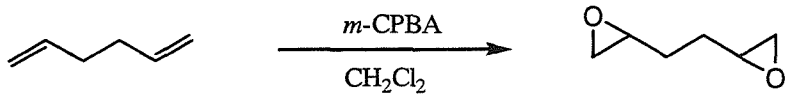


(6.9) **(6.10)**

The hydroxy compound (**6.9**) (175 mg, 1 mmol) was dissolved in dry DMF (1 mL) and treated with imidazole (81 mg, 1.2 mmol) followed by *tert*-butyldimethylsilyl chloride (182 mg, 1.2 mmol). The resulting mixture was stirred at room temperature for 16 hours before partitioning between ethyl acetate and water (20 mL each). After re-extraction of the aqueous phase the combined organic extracts where washed with water followed by brine before drying ($MgSO_4$). The crude material (390 mg) was filtered through silica gel to give the title compound (**6.10**) as a colourless oil (275 mg, 0.92 mmol, 92%).

FT-IR (ATR)	2959, 2929, 2856, 1671, 1463 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	0.90 (t, J = 7.4 Hz, 3H), 1.45 (app. quint., J = 7.0 Hz, 2H), 1.66 (dq, J = 14.0, 7.0 Hz, 1H), 1.79 (ddt, J = 14.3, 7.3, 3.3 Hz, 1H), 2.50-2.65 (m, 2H), 2.94 (br s, 1H), 3.14 (3H, s), 3.48-3.54 (m, 1H), 3.65 (s, 3H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	-4.46 (CH_3), -4.28 (CH_3), 9.66 (CH_3), 27.98 (CH_2), 29.93 (CH_2), 30.98 (CH_2), 32.36 (CH_3), 61.28 (CH), 72.83 (CH_3), 177.0 (C) ppm.
LRMS	(ES +ve) *m/z* (relative intensity) 146 (100), 290 (50) $[M+H]^+$, 312 (15) $[M+Na]^+$, 601 (30) $[2M+Na]^+$.

Hexa-1,5-diene *bis*epoxide (6.8)



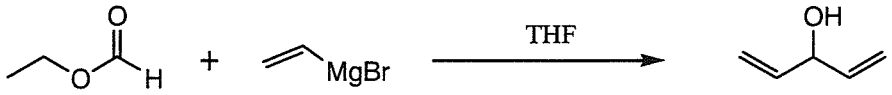
(6.8)

The title compound (**6.8**) was prepared according to the method of Baylon [218]. The diene (2.48g, 3.6 mL, 30 mmol) was dissolved in dry dichloromethane (60 mL) and cooled to 0°C under an atmosphere of nitrogen. *m*-CPBA (50% pure, 25.8 g, 75 mmol) was added in four separate portions over 30 minutes and the heterogeneous mixture stirred for 24 hours at room temperature. Sodium hydroxide (2M, 150 mL) was added to the reaction and the homogeneous biphasic mixture separated. The aqueous phase was repeatedly extracted

with dichloromethane (3 x 50 mL) and the combined organic extracts washed with sodium hydroxide (2M, 2 x 30 mL) followed by brine (30 mL). Drying ($MgSO_4$) and removal of solvent gave a crude product (3.4 g) that was purified by chromatography on silica gel (6 x 4 cm) loading eluting with 30% ethyl acetate in hexane. The product, a 1:1 mixture of diastereoisomers, was isolated as an oil (2.08g, 19.5 mmol, 65%) that had spectroscopic data consistent with that described in the literature [218].

FT-IR (ATR)	2987, 2923, 1411 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	1.54-1.84 (m, 4H), 2.48-2.52 (m, 2H), 2.73-2.82 (m, 2H), 2.89-3.05 (m, 2H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	29.1 (CH_2), 29.6 (CH_2), 47.4 (CH_2), 47.5 (CH_2), 52.0 (CH), 52.2 (CH) ppm.
LRMS	(CI) *m/z* (relative intensity) 115 (100) $[M+H]^+$.

Penta-1,4-dien-3-ol



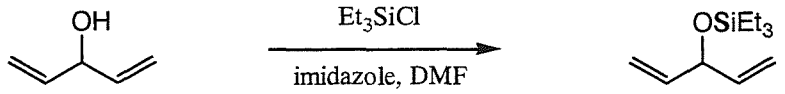
The title compound was prepared according to the method described by Normant [250]. Vinylmagnesium bromide in THF(1.0M, 300 mL, 300 mmol) was cooled to 0°C under an atmosphere of nitrogen. Ethyl formate (10.0 g, 10.9 mL, 135 mmol) in THF (30 mL) was added by dropwise addition over a period of 40 minutes. After complete addition the reaction was warmed to 40°C and stirred for 2 hours. The reaction was quenched with ammonium chloride (sat. aq.) which was added until the internally monitored exotherm ceased. The bulk of the THF was removed before diluting the material with diethyl ether (100 mL) and washing with water (100 mL). The organic phase was washed with brine and dried ($MgSO_4$). Purification by distillation at atmospheric pressure gave the title compound as a colourless oil (5.0 g, 59.4 mmol, 44%).

BP	110-120°C (760 mm Hg).
^{1}H NMR (300MHz, $CDCl_3$)	2.24 (br s, 1H), 4.61 (br s, 1H), 5.16 (dd, J =10.3, 0.9 Hz, 2H), 5.26 (dt, J = 17.3, 1.5 Hz, 2H), 5.89 (2H, ddd, J = 17.3, 10.3, 5.9 Hz) ppm.

^{13}C NMR 74.4 (CH), 115.9 (CH_2), 140.1 (CH) ppm.

(75 MHz, $CDCl_3$)

3-Triethylsiloxypenta-1, 4-diene (6.12)



(6.12)

The title compound was prepared according to the method described by Oppolzer *et al.* [221] The alcohol (2.0 g, 24 mmol) was dissolved in dry DMF (10 mL) along with imidazole (2.09 g, 29 mmol) whilst under an atmosphere of argon. The reaction was stirred at 0°C under an atmosphere of nitrogen during the addition of triethylchlorosilane (3.97 g, 4.47 mL, 26 mmol). The heterogeneous reaction was stirred at room temperature for 16 hours. After partitioning between diethyl ether and water (40 mL each) the organic phase was washed with water and brine (20 mL each) and dried ($MgSO_4$). The crude product (4.5 g) as purified by distillation at reduced pressure to provide the title compound (**6.12**) as a colourless oil (3.46 g, 17 mmol, 73%). Spectroscopic data was consistent with that from the literature [221].

BP 55-60°C (15 mm Hg)

FT-IR (ATR) 2952, 2875, 1003 cm^{-1}.

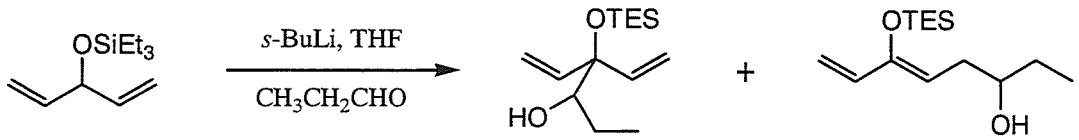
^{1}H NMR 0.56 (q, J = 7.5 Hz, 6H), 0.89 (t, J = 7.5 Hz, 9H),

(300MHz, $CDCl_3$) 4.53 (tt, J = 7.5, 1.5 Hz, 1H), 5.00 (dt, J = 10.0, 1.5 Hz, 2H),
5.15 (dt, J = 17.5, 1.5 Hz, 2H),
5.75 (ddd, J = 17.5, 10.0, 1.5 Hz, 2H) ppm

LRMS (ES +ve) *m/z* (relative intensity) no molecular ion: base peak 127 (100) $[M+NH_4]^+$ for starting material.

(CI) *m/z* (relative intensity) 169 (100), 199 (<1) $[M+H]^+$.

3-(Triethylsiloxy)octa-1,3-diene-6-ol (6.14)



(6.12) **(6.13)** **(6.14)**

The title compound was prepared according to the method described by Oppolzer *et al.* [221] The silyl ether (**6.12**) (1.0 g, 5.1 mmol) was dissolved in dry THF (5 mL) whilst under an atmosphere of nitrogen. The reaction mixture was cooled to -78°C and treated with *sec*-BuLi in THF (1.3M, 3.9 mL, 5.1 mmol) that was added by drop-wise addition over 5 minutes. The yellow solution of the anion was stirred at -78°C for 40 minutes before treating with freshly distilled propionaldehyde (325 mg, 400μL, 5.6 mmol). After stirring at -78°C for 45 minutes the reaction was quenched by the slow addition of ammonium chloride (sat. aq., 20 mL) that was added dropwise whilst allowing the reaction to warm to RT. The reaction was diluted with diethyl ether and water (40 mL of each) and the organic extract washed with water followed by brine (40 mL of each). After drying ($MgSO_4$) the crude product (1.26 g) was purified by chromatography on silica gel (10 x 3 cm) using 10% ethyl acetate in hexane as eluent. The title compound (**6.14**) was isolated as an oil (0.84 g, 3.3 mmol, 64%). A major, less polar, by-product was the regioisomeric 3-(triethylsilanoxy)-3-vinyl-hexen-4-ol (**6.13**) also isolated as an oil (0.33 g, 1.3 mmol, 25%). Spectroscopic data was consistent with that from the literature [221].

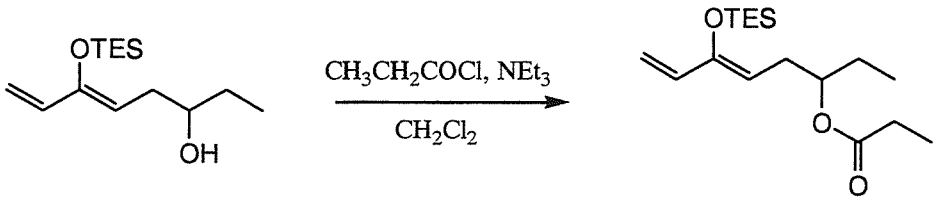
Data for 3-(triethylsilanoxy)octa-1,3-diene-6-ol (**6.14**).

FT-IR (ATR)	3407, 2957, 2877, 1604, 1459, 1053 cm^{-1}.
^{1}H NMR (300MHz, $CDCl_3$)	Data indicated presence of Et_3SiOH impurity. 1.38-1.45 (m, 2H), 1.70 (br s, 1H), 2.14-2.25 (m, 2H), 3.50 (br. s, 1H), 4.79 (t, J = 7.0 Hz, 1H), 4.92 (d, J = 10.5 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 6.13 (dd, J = 17.1, 11.0 Hz, 1H) ppm.
^{13}C NMR (75 MHz, $CDCl_3$)	5.60 (CH_2), 6.99 (CH_3), 10.39 (CH_3), 30.29 (CH_2), 33.84 (CH_2), 73.48 (CH), 112.74 (CH_2), 135.93 (CH), 151.38 (C) ppm.
LRMS	(CI and EI) *m/z* (relative intensity) no molecular ion detected.

Data for 4-triethylsilanyloxy-4-vinylhex-5-en-3-ol (**6.13**).

FT-IR (ATR)	3478, 2953,2874, 1411, 1001 cm^{-1}.
^{1}H NMR	0.54 (t, J = 8.0 Hz, 6H), 0.87 (t, J = 8.0 Hz, 9H), 0.91
(300MHz, $CDCl_3$)	(t, J = 7.5 Hz, 3H), 1.10 1.23 (m, 1H), 1.39-1.48 (m, 1H), 2.39 (br s, 1H), 3.27 (app. d, J = 8.0 Hz, 1H), 5.22 (d, J = 10.5 Hz, 2H), 5.28 (d, J = 18.6 Hz, 2H), 5.85-5.95 (m, 1H) ppm.
^{13}C NMR	5.21 (CH_3), 5.44 (CH_3), 9.73 (CH_3), 22.44(CH_2), 78.52 (CH),
(75 MHz, $CDCl_3$)	79.13 (C), 115.57 (CH_2), 115.85 (CH_2), 136.33 (CH), 137.71 (CH) ppm.
LRMS	(CI) *m/z* (relative intensity) 199 (100), 257 (<1) $[M+H]^+$, 239 (10) $[M-OH+H]^+$.

1-Ethyl-4-triethylsiloxyhexa-1,5-dienylpropionate (6.15) - method A



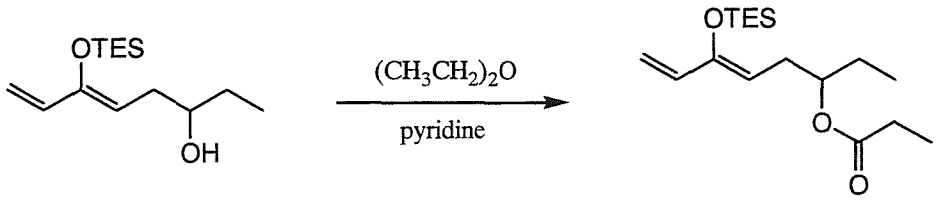
(6.14) **(6.15)**

The alcohol (**6.14**) (1.0 g, 3.9 mmol) was dissolved in dry dichloromethane (15 mL) under an atmosphere of nitrogen. The solution was cooled on ice and treated with triethylamine (0.59 g, 0.833 mL, 5.83 mmol) followed by catalytic DMAP (20 mg). Propionyl chloride (0.48 g, 0.40 mL, 5. 8 mmol) was added by drop-wise addition and the reaction allowed to warm to RT before stirring for 16 hours. The mixture was diluted with dichloromethane (50 mL) and washed with 0.2 M HCl, sodium hydrogen carbonate (sat. aq.), water and brine (50 mL) wash before drying (MgSO4). The crude material was purified by chromatography on silica gel (10 x 3 cm) eluting with 10% ethyl acetate in hexane. The title compound (**6.15**) was isolated as an oil (0.38 g, 1.24 mmol, 31%).

FT-IR (ATR)	2956, 1737, 1604, 1187 cm^{-1}.
^{1}H NMR	Data indicated presence of Et_3SiOH impurity. 0.63 (q, J =
(400MHz, $CDCl_3$)	8.0 Hz, 6H), 0.90 (t, J = 8.0 Hz, 9H), 1.10 (t, J = 7.5 Hz, 3H), 1.46-1.54 (m, 2H), 2.24 (q, J = 7.5 Hz, 2H), 2.31 (app t, J = 7.0 Hz, 2H), 4.65 (t, J = 7.0 Hz, 1H), 4.77 (app quint, J = 6.0 Hz, 1H), 4.90 (d, J = 11.1 Hz, 1H),

	5.22 (d, J = 17.1 Hz, 1H), 6.08 (dd, J = 17.1, 10.5 Hz, 1H) ppm.
^{13}C NMR	5.90 (CH_2), 7.30 (CH_3), 9.68 (CH_3), 27.15 (CH_2), 30.44 (CH_2),
(100 MHz, $CDCl_3$)	35.11 (CH_2), 75.09 (CH_2),110.28 (CH), 112.61 (CH_2),
	135.97 (CH), 150.98 (C), 174.65 (C) ppm.
LRMS	(EI and CI) no molecular ion observed.

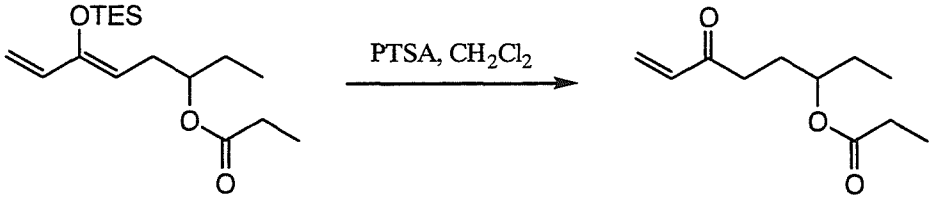
1-Ethyl-4-triethylsiloxyhexa-1,5-dienylpropionate (6.15) - method B



(6.14) **(6.15)**

The alcohol (**6.14**) (187 mg, 0.73 mmol) was dissolved in pyridine (1 mL) under an atmosphere of nitrogen. Catalytic DMAP was added whilst stirring followed by propionic anhydride (0.142 g, 0.140 mL, 1.1 mmol). The reaction was stirred at room temperature for 16 hours. The reaction mixture was diluted with diethyl ether (10 mL) and washed with 2.0M HCl (10 mL). The aqueous phase was re-extracted with diethyl ether (10 mL) and the combined organic phases washed with sodium hydrogen carbonate (sat. aq.), water and brine before drying ($MgSO_4$). The crude product was purified by chromatography on silica gel (10 g) eluting with 20% ethyl acetate in hexane. The title compound (**6.15**) was isolated as an oil (0.187 g, 0.63 mmol, 82%). On a larger scale acylation occurred along with concomitant hydrolysis of the silyl enol ether to provide ketone (**6.16**).

1-Ethyl-4-oxohex-5-enyl propionate (6.16)



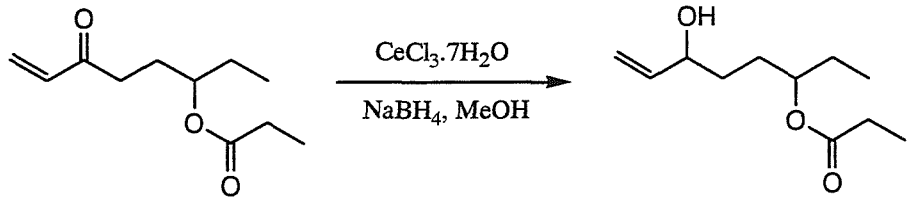
(6.15) **(6.16)**

The silylenol ether (**6.15**) (0.20 g, 0.6 mmol) was dissolved in dichloromethane and cooled to 0°C. The solution was treated with *p*-toluenesulfonic acid (0.12 g, 0.6 mmol) that was added in one portion. The mixture was stirred at 0°C for 20 minutes before washing the reaction with sodium hydrogen carbonate (sat. aq., 3 mL). The aqueous phase was re-

extracted with dichloromethane (10 mL) and the combined organic extracts washed with water and brine (20 mL each) before drying ($MgSO_4$). The crude material (0.175 g) was not purified further as triethylsilanol, the only impurity observed, co-eluted in all the chromatography solvents that were investigated.

FT-IR (ATR)	2970, 2878, 1732, 1703, 1683, 1191 cm^{-1}.
^{1}H NMR	Data indicated presence of Et_3SiOH impurity.
(400MHz, $CDCl_3$)	0.83 (t, J = 7.5 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H), 1.52 (dq, J = 7.5, ~7.5 Hz, 2H), 1.70-1.79 (m, 1H), 1.86 (ddt, J = 14.5, 7.5, 4.0 Hz, 1H), 2.24 (q, J = 7.5 Hz, 2H), 2.53 (t, J = 7.5 Hz, 2H), 4.77 (ddt, J = 8.5, 7.5, 4.0 Hz, 1H), 5.75 (dd, J = 10.5, 1.0 Hz, 1H), 6.12 (dd, J = 17.6, 1.0 Hz, 1H), 6.28 (dd, J = 17.6, 10.5 Hz, 1H) ppm.
^{13}C NMR	9.92 (CH_3), 11.79 (CH_3), 27,58(CH_2), 28.06 (CH_2), 28.21 (CH_2),
(100 MHz, $CDCl_3$)	35.94 (CH_2), 74.94 (CH), 128.48 (CH_2), 136.78 (CH), 174.71 (C), 200.19 (C) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 397 (<10) $[M+H]^+$, 419 (25) $[M+Na]^+$, 437 (100).

1-Ethyl-4-hydroxyhex-5-enyl propionate (6.18)



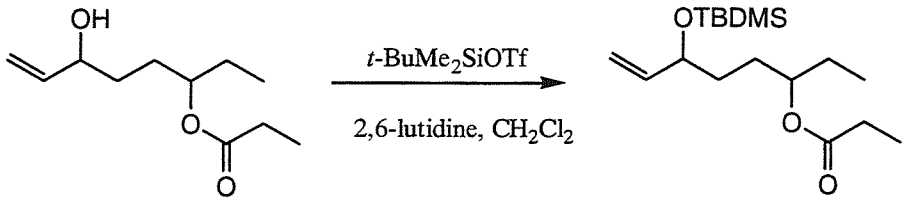
(6.16) **(6.18)**

The reduction was carried out according to the method of Luche *et al.* [222] The ketone (contaminated with 30% triethylsilanol) **(6.16)** (1.50 g, calculated at 5.3 mmol) was dissolved in methanol (25 mL) and the reaction treated with cerium chloride heptahydrate (2.36 g, 6.4 mmol) followed by sodium borohydride (0.24 g, 6.4 mmol) and the reaction stirred until evolution of hydrogen ceased. The reaction was treated with 2.0M HCl (20 mL) and stirred until the excess sodium borohydride had been destroyed. Dilution with diethyl ether and water was followed by repeated extractions of the aqueous phase. The combined organic extracts were washed with brine and dried ($MgSO_4$). Purification was accomplished by chromatography on silica gel (7.5 x 5) eluting with 15% ethyl acetate

in hexane. The title compound (**6.18**), a 1:1 mixture of diastereoisomers, was isolated as a colourless oil (0.67 g, 3.3 mmol, 67% adjusted yield).

FT-IR (ATR)	3425, 2967, 1728, 1712, 1187 cm^{-1}.
^{1}H NMR	0.81 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 8.0 Hz, 3H),
(400MHz, $CDCl_3$)	1.40-1.70 (m, 7H), 2.25 (qd, J = 7.5, 1.0 Hz, 2H),
	4.03 (app. quint., J = 6.5 Hz), 4.73-4.82 (m, 1H),
	5.04 (dd, J = 10.5, 1.0 Hz, 1H), 5.16 (dd, J = 17.1, 1.0 Hz, 1H),
	5.78 (t, J = 16.6,10.0, 6.1 Hz, 1H) ppm.
^{13}C NMR	9.69 (CH_3), 9.97 (CH_3), 27.44 (CH_2), 28.28 (CH_2), 29.77 (CH_2),
(100 MHz, $CDCl_3$)	29.90 (CH_2), 32.91 (CH_2), 32.99 (CH_2), 73.20 (CH_2),
	73.37 (CH_2), 75.31 (CH), 75.50 (CH), 115.25 (CH_2),
	115.30 (CH_2), 141.32 (CH), 141.35 (CH), 174.85 (C) ppm.
LRMS	(CI +ve) *m/z* (relative intensity) 127 (100), 201 (20) $[M+H]^+$.

1-Ethyl-4-*tert*-butyldimethylsiloxyhex-5-enyl propionate (6.19)



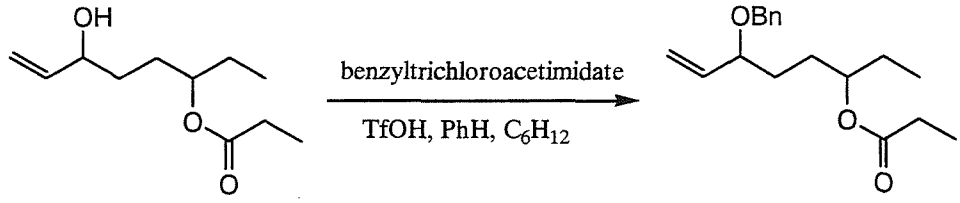
(**6.18**) (**6.19**)

The silyl ether (**6.19**) was prepared according to the method described by Corey *et al.* [251]. The hydroxy compound (**6.18**) (1.73 g, 8.65 mmol) was dissolved in dichloromethane (15 mL) and treated with 2, 6-lutidine (2.74 g, 2. 38 mL, 10 4 mmol) before cooling to 0°C whilst under an atmosphere of nitrogen. *tert*-Butyldimethylsilyl triflate (1.38 g, 1.51 mL, 12.9 mmol) was added over a period of 10 minutes. The reaction was allowed to warm to room temperature and stirred for 2 hours. After dilution with dichloromethane (50 mL) the mixture was sequentially washed with 2.0M HCl, sodium hydrogen carbonate (sat. aq.), water and brine (50 mL each). After drying ($MgSO_4$) the crude material was purified by chromatography on silica gel (6 x 4.5) eluting with 10% ethyl acetate in hexane. The title compound (**6.19**), a 1:1 mixture of diastereoisomers, was isolated as an oil (2.34 g, 7.4 mmol, 86%).

FT-IR (ATR) 2955, 2857, 1736, 1463, 1189, 835 cm^{-1}.

^{1}H NMR	0.00 (s, 6H), 0.84 (t, 3H) partially obscured by 0.86 (s, 9H), 1.11
(400MHz, $CDCl_3$)	(t, J = 7.5 Hz, 3H), 1.40-1.67 (m, H), 2.28 (q, J = 8.0 Hz, 2H), 4.04-4.11 (m, 1H), 4.79 (app. sextet, J = 6.0 Hz, 1H), 5.00 (1H, dt, J = 10.5, 1.5 Hz, 1H), 5.11 (dt, J = 17.1, 1.5 Hz, 1H), 5.74 (ddd, J = 17.5, 10.5, 6.0 Hz, 1H) ppm.
^{13}C NMR	8.30 (CH_3), 8.51 (CH_3), 24.80 (CH_3), 26.00 (CH_2), 26.02 (CH_2),
(100 MHz, $CDCl_3$)	26.88 (CH_2), 27.81 (CH_2), 28.04 (CH_2), 32,42 (CH_2), 32.57 (CH_2), 72.23 (CH), 72.51 (CH), 112.84 (CH_2), 112.89 (CH_2), 140.37 (CH), 140.39, (CH), 173.25 (C), 173.28 (C) ppm.
LRMS	(EI or CI +ve) *m/z* (relative intensity) no molecular ion observed.

1-Ethyl-4-benzyloxyhex-5-enyl propionate



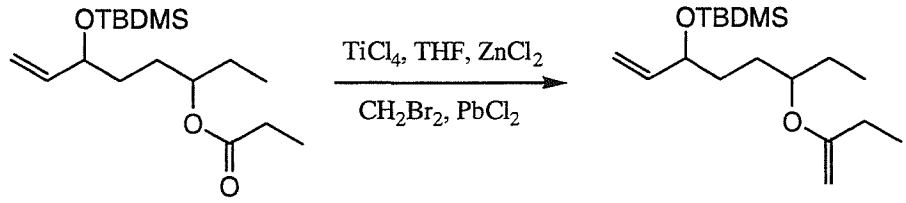
(6.18)

The benzyl ether was prepared according to the method described by Bundle and Iversen [143]. The alcohol (**6.18**) (73 mg, 0.36 mmol) was dissolved in dichloromethane (2 mL) and cyclohexane (4 mL) along with benzyltrichloroacetimidate [142] (109 mg, 0.43 mmol). The solution was stirred under an atmosphere of nitrogen whilst trifluoromethane sulfonic acid (25 μL) was added in one portion. After 6 hours at RT the reaction was diluted with dichloromethane (10 mL) and washed with water (2 x 10 mL) and brine (10 mL). After drying ($MgSO_4$) the crude material (57 mg) was purified by chromatography on silica gel (8 x 2 cm) eluting with 10% diethyl ether in hexane. The title compound, a mixture of isomers, was provided as an oil (20 mg, 0.07 mmol, 20%).

FT-IR (ATR)	1734 cm^{-1}.
^{1}H NMR	0.91 (t, J = 7.5 Hz, 6H), 1.40-1.60 (m, 4H), 1.68 (ddd, J = 14.8,
(400MHz, $CDCl_3$)	9.0, 5.6 Hz, 1H), 1.86 (ddd, J = 14.8, 5.3, 3.5 Hz, 1H), 2.25 (br. s, 2H), 3.47-3.50 (m, 1H), 4.25 –4.27 (m, 1H), 4.49 (d, J = 11.3 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 5.03 (dt, J = 10.5, 1.3 Hz, 1H), 5.18 (d, J = 17.3 Hz, 1.3Hz, 1H),

	5.81 (ddd, J = 16.3, 10.5, 5.7 Hz, 1H), 7.20-7.30 (m, 5H) ppm.
^{13}C NMR	11.48 (CH_3), 11.72 (CH_3), 29.17 (CH_2), 30.05 (CH_2), 31.44
(100 MHz, $CDCl_3$)	(CH_2), 31.87 (CH_2), 33.27 (CH_2), 33.38 (CH_2), 72.27 (CH_2), 76.99 (CH), 77.25 (CH), 82.21 (CH), 82.61 (CH), 119.52 (CH_2), 119.62 (CH_2), 127.85 (CH), 128.14 (CH), 128.73 (CH), 140.88 (CH), 140.94 (CH), 176.46 (C) ppm.
LRMS	(CI) *m/z* (relative intensity) 91 (100), 109 (75) $[PhCH_2OH+H]^+$, 291 (5) $[M+H]^+$.

2-(1-Ethyl-4-*tert*butyldimethylsiloxyhex-5-ene)oxybut-1-ene (6.34)



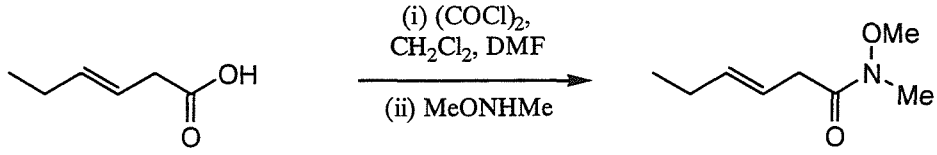
(6.19) **(6.34)**

The title compound (**6.33**) was prepared according the method described by Takai *et al.* [230] A solution of titanium tetrachloride in dichloromethane (1.0M, 4 mL, 4.0 mmol) was added to dry THF (8 mL) whilst stirring under an atmosphere of argon whilst at 0°C. The yellow heterogeneous solution that resulted was treated with TMEDA 0.93 g, 1.12 mL, 8.0 mmol) whereupon the mixture darkened. After 20 minutes zinc powder (0.59 g, 9.0 mmol) was added followed immediately by lead (II) chloride (15 mg, 0.05 mmol). An intense blue colouration formed in the reaction. Treatment with a mixture of the ester (**6.19**) (0.32 g, 1.0 mmol) and dibromomethane (0.43 g, 0.18 mL, 2.5 mmol) in THF (5 mL) that was added by drop-wise addition was followed by stirring at RT for 2 hours. Sodium hydroxide (2M, 2 mL) was added at 0°C and stirred at this temperature until gaseous evolution was complete. The reaction mixture was filtered through Celite® washing the filter cake well with diethyl ether. Removal of solvent was followed by chromatography on silica gel eluting with 20% diethyl ether in hexane containing 1% triethylamine. The main product fraction was isolated as a yellow oil which decomposed on storage (0.21 g, 0.67 mmol, 67%).

FT-IR (ATR) 2953, 1649, 1461, 1254, 1066 cm^{-1}.

^{1}H NMR	Data indicated presence of TBDMS-OH impurity.
(400MHz, d6-acetone)	0.00-0.10 (m, 6H), 0.97 (s, 9H), 0.90 (t, J = 7.5 Hz, 3H), 0.95-0.99 (m, 3H), 1.40-1.64 (m, 4H), 1.96-2.02 (app. q, 2H), 3.73-3.74 (m, 1H), 3.78 (s, 1H), 3.84-3.88 (m, 1H), 4.12-4.15 (m, 1H), 4.97 (d, J = 10.0 Hz, 1H), 5.12 (d, J = 7.5 Hz, 1H), 5.72-5.82 (m, 1H) ppm.
^{13}C NMR (100 MHz, d6-acetone)	5.52 (CH_3), 5.61 (CH_3), 17.50 (C), 24.73 (CH_3), 24.86 (CH_3), 25.35 (CH_2), 25.37 (CH_2), 27.86 (CH_2), 27.95 (CH_2), 32.96 (CH_2), 72.81 (CH), 72.95 (CH), 75.92 (CH), 75.97 (CH), 78.84 (CH_2), 112.61 (CH_2), 112.58 (CH_2), 141.23 (CH_2), 141.30 (CH_2), 162.69 (C) ppm.

***N*-methoxy-*N*-methylhex-3-enamide (6.20)**



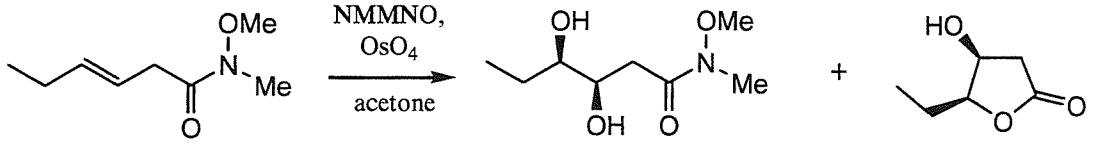
(6.20)

trans-Hex-3-enoic acid (2.0 g, 17.5 mmol) was dissolved in dry dichloromethane (20 mL). The solution was treated with oxalyl chloride (2.44 g, 1.67 mL, 19.2 mmol) and catalytic DMF. After gaseous evolution had ceased the mixture was allowed to continue stirring at RT for 2 hours at which point IR analysis of the reaction mixture revealed complete conversion to the acid chloride. This was treated with *N, N*-dimethylhydroxylamine. HCl (1.75 g, 18.0 mmol) followed by the drop-wise addition of triethylamine (1.80 g, 2.50 mL, 18.0 mL). The resulting mixture was stirred at RT for 10 minutes whereupon IR analysis revealed complete consumption of the acid chloride. Dilution of the reaction with dichloromethane (20 mL) was followed by washing the organic phase with sodium hydrogen carbonate (sat. aq.) (2 x 30 mL), water and brine (20 mL each) before drying ($MgSO_4$). The crude product (2.53 g) was purified by chromatography on silica gel (7 x 4.5 cm) eluting with 20% ethyl acetate in hexane. The title compound (**6.20**) was isolated as an oil (1.78 g, 11.30 mmol, 65%).

FT-IR (ATR)	2965, 1669, 1461, 1176 cm^{-1}.
^{1}H NMR	0.92 (t, J = 7.5 Hz, 3H), 1.87 (dq, J = 7.5, 7.4 Hz, 2H),

(400MHz, $CDCl_3$)	3.15 (s, 3H), 3.25 (s, 2H), 3.62 (s, 3H), 5.48 (dt, J = 15.6, 6.0 Hz, 1H), 5.54 (dt, J = 15.9, 5.0 Hz, 1H) ppm.
^{13}C NMR	13.86 (CH_3), 25.94 (CH_3), 36.45 (CH_2), 61.66 (CH_3), 121.77
(100 MHz, $CDCl_3$)	(CH), 136.26 (CH), 173.48 (C) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 158 (20) $[M+H]^+$.

3,4-Dihydroxy-*N*-methoxy-*N*-methylhexanamide (6.21)

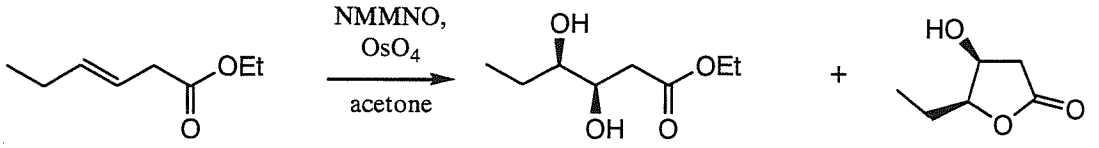


(6.20) **(6.21)** **(6.22)**

The title compound (**6.21**) was prepared according to the method described by Kelly *et al.* [252] The amide (**6.20**) (0.47 g, 3.0 mmol) and *N*-methyl morpholine-*N*-oxide (0.64 g, 3.3 mmol) were dissolved in acetone (5 mL) and water (2 mL). Catalytic osmium tetroxide (0.3 mol%) was added and the rapidly darkening reaction mixture stirred at room temperature for 16 hours. The reaction mixture was treated with sodium metabisulfite (0.20 g) and diluted with dilute HCl (2.0M, 20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) after saturating with sodium chloride. The combined organic extracts were washed with brine and dried ($MgSO_4$). Purification was achieved by chromatography on silica gel (6 x 2.5 cm) eluting with ethyl acetate. The title compound (**6.21**) was isolated as an oil as the minor component from the reaction (24 mg, 0.12 mmol, 4.0%) with the main product arising from lactonisation (**6.22**) (0.22 g, 1.65 mmol, 55%).

FT-IR (ATR)	3394, 2970, 1639 cm^{-1}.
^{1}H NMR	0.99 (t, J = 7.4 Hz, 3H), 1.48-1.67 (m, 2H), 2.65-2.70 (m, 2H)
(300MHz, $CDCl_3$)	superimposed on 2.60 (br s, 1H), 3.20 (s, 3H), 3.38 (dt, J = 7.4, 4.8 Hz, 1H), 3.70 (s, 3H), 3.91-3.94 (m, 1H) superimposed on 4.02 (br s, 1H) ppm.
^{13}C NMR	10.25 (CH_3), 26.57 (CH_2), 32.06 (CH_3), 35.19 (CH_2),
(75 MHz, $CDCl_3$)	61.47 (CH_3), 70.15 (CH), 75.42 (CH), 174.10 (C) ppm.
LRMS	(ES +ve) *m/z* (relative intensity) 192 (45) $[M+H]^+$, 214 (25) $[M+Na]^+$, 255 (100), 405 (30) $[2M+Na]^+$.

Ethyl 3,4-dihydroxyhexanoate (6.23)

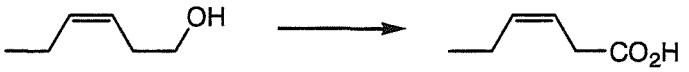


(6.23) **(6.22)**

The dihydroxylation reaction was carried out in the fashion described for the preparation of **6.21**. Thus, *trans*-ethyl hex-3-enoate (1.0 g, 7.0 mmol) was converted to the title compound (**6.23**) (0.61g, 3.5 mmol, 50%) and hydroxy lactone (**6.22**) (56 mg, 0.43 mmol, 6.0%).

FT-IR (ATR)	3431, 2971, 1731 cm^{-1}.
^{1}H NMR	1.01 (t, J = 7.5 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H),
(400MHz, $CDCl_3$)	1.47-1.65 (m, 2H), 2.54 (dd, J = 16.1, 4.0 Hz, 1H),
	2.61 (dd, J = 16.1, 8.5 Hz, 1H), 3.05 (br s, 2H), 3.38 (dt,
	J = 8.0, 4.5 Hz, 1H), 3.93 (dt, J = 8.5, 4.0 Hz, 1H),
	4.19 (q, J = 7.0 Hz, 2H) ppm.
^{13}C NMR	10.39 (CH_3), 14.51 (CH_3), 29.59 (CH_2), 38.77 (CH_2),
(100 MHz, $CDCl_3$)	61.23 (CH_2), 70.56 (CH), 75.48 (CH), 173.34 (C) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 161 (100), 199 (10) $[M+H]^+$.

***cis*-Hex-3-enoic acid**

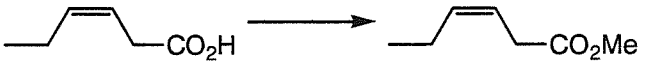


The title compound was prepared according to the method described by Azzena *et al.* [224] *cis*-Hex-3-enol (11.88 g, 14.0 mL, 120 mmol) was dissolved in acetone (200 mL) and treated with Jones' reagent [253] (8M in [O], 60 mL) by slow drop-wise addition ensuring that the reaction temperature stayed at <25°C. The orange colouration changed to green overnight. The supernatant was separated by decantation and the insoluble Cr(III) salts washed well with acetone. The bulk of the acetone was removed by evaporation in vacuo before partitioning the residue between diethyl ether (200 mL) and sodium hydrogen carbonate (sat. aq., 300 mL). The aqueous phase was acidified with 10% sulfuric acid and extracted with diethyl ether (3 x 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) and then dried ($MgSO_4$). The solvent was

removed to provide the title compound as a volatile liquid that was not purified further (8.88, 77 mmol, 65%). Spectroscopic data corresponded to literature values [224].

FT-IR (ATR)	1702 cm^{-1}.
^{1}H NMR	NMR indicated substantial impurities present.
(400MHz, $CDCl_3$)	1.01 (t, J = 7.5 Hz, 3H), 2.05-2.15 (m, 2H), 3.15-3.17 (m, 2H), 5.50-5.67 (m, 2H) ppm.
^{13}C NMR	14.22, 21.11, 32.99, 119.75, 136.09, 178.97 ppm.
(100 MHz, $CDCl_3$)	

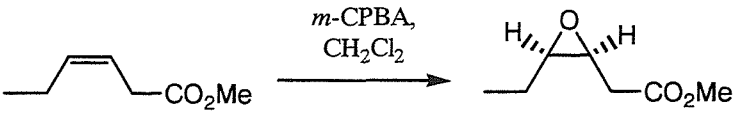
Methyl *cis*-hex-3-enoate



cis-Hex-3-enoic acid (5.50 g, 48 mmol) was dissolved in methanol (50 mL) and the solution treated with conc. sulfuric acid (2 mL). The reaction was warmed to reflux and stirred for 16 hours. After cooling the solvent was removed and the residue partitioned between dichloromethane (50 mL) and water (50 mL). Extraction of the aqueous phase with dichloromethane (2 x 30 mL) preceded washing the combined organic extracts with brine (30 mL). After drying ($MgSO_4$) and removal of solvent the residue was distilled at reduced pressure to give the title compound as a colourless liquid. Spectroscopic data corresponded to literature values [224].

FT-IR (ATR)	1724 cm^{-1}.
^{1}H NMR	0.98 (t, J = 7.5 Hz, 3H), 2.06 (app. quint., J = 7.5 Hz, 2H), 3.09
(400MHz, $CDCl_3$)	(d, J = 6.5 Hz, 2H), 3.68 (s, 3H), 5.52 (approx. dt, J = 10.5, 7.0 Hz, 1H), 5.57 ((approx. dt, J = 10.5, 7.0 Hz, 1H) ppm.
^{13}C NMR	14.42 (CH_3), 21.25 (CH_2), 33.19 (CH_2), 52.31 (CH_3), 119.76
(100 MHz, $CDCl_3$)	(CH), 134.85 (CH), 172.18 (C) ppm.

(3S*, 4R*) Methyl 3,4-epoxy-4-ethyl hexanoate (6.24)

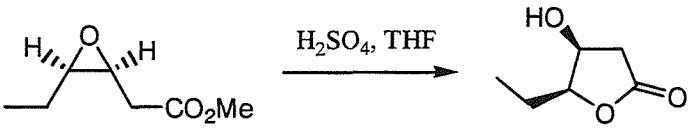


(6.24)

Methyl hex-3-enoate (8.82 g, 69.0 mmol) was dissolved in dichloromethane (650 mL) and treated with sodium acetate (17.0 g, 210.0 mmol) whilst mechanically stirring at 0°C. *m*-CPBA (65%, 23.8 g, 90.0 mmol) was added portion-wise over 45 minutes before allowing to warm to room temperature and stirring overnight. The reaction mixture was filtered through Celite® and the filter cake washed with dichloromethane (100 mL). The filtrate was washed with sodium sulfite (sat. aq., 300 mL) sodium hydrogen carbonate (sat. aq., 300 mL) and brine (200 mL) before drying over ($MgSO_4$). The solvent was removed by evaporation in vacuo and used without further purification. The title compound (**6.24**) was a colourless oil (9.90 g, 69.0 mmol, 100%).

FT-IR (ATR)	2970, 1735 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$)	0.98 (t, J = 8.0 Hz, 3H), 1.38-1.55 (m, 2H), 2.46 (dd, J = 16.6, 6.0 Hz, 1H), 2.55 (dd, J = 16.6, 6.0 Hz, 1H), 2.85-2.92 (m, 1H), 3.21-3.28 (m, 1H), 3.66 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	10.73 (CH_3), 21.51 (CH_2), 33.84 (CH_2), 52.21 (CH), 52.90 (CH), 58.04 (CH_3), 171.34 (C) ppm.
LRMS	(CI, +ve) *m/z* (relative intensity) 145 (80) $[M+H]^+$, 162 (100) $[M+NH_4]^+$.

(4S*, 5S*) 5-Ethyl-4-hydroxydihydrofuran-2-one (6.22)



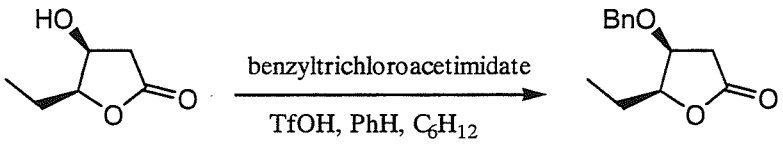
(6.24) **(6.22)**

The epoxide (**6.24**) (9.60 g, 67 mmol) was suspended in 3% sulfuric acid (70 mL) with the addition of THF (3 mL) to allow for complete dissolution. After stirring the reaction mixture at room temperature for 16 hours it was saturated with sodium chloride. The aqueous phase was then extracted with dichloromethane (6 x 100 mL). The combined organic phases were dried ($MgSO_4$) before purifying with dry suction chromatography on

silica gel (150 g) eluting with 50% diethyl ether in hexane rising to neat diethyl ether. The title compound (**6.22**) was isolated as a colourless oil (6.48 g, 50.0 mmol, 75%). Spectroscopic data was consistent with literature values [254].

FT-IR (ATR)	3430, 2973, 1759 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$)	1.02 (t, J = 7.4 Hz, 3H), 1.75 (d quint., J = 14.7, 7.4 Hz, 1H), 1.87 (d quint., J = 14.0, 7.4 Hz, 1H), 2.51 (d, J = 16.9 Hz, 1H), 2.78 (dd, J = 17.6, 5.5 Hz, 1H), 3.21 (br s, 1H), 4.29 (ddd, J = 8.1, 6.6, 3.7 Hz, 1H), 4.44-4.47 (m, 1H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	10.25 (CH_3), 21.59 (CH_2), 39.70 (CH_2), 68.62 (CH), 87.06 (CH) 176.93 (C) ppm.
LRMS	(CI, +ve) *m/z* (relative intensity) 130 (50) $[M-H+H]^+$, 148 (100) $[M+NH_4]^+$.

(4S*, 5S*) 5-Ethyl-4-benzyloxydihydrofuran-2-one (6.26)



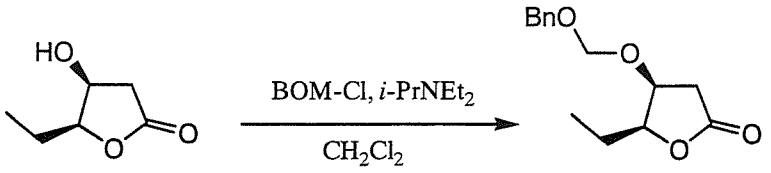
(**6.22**) (**6.26**)

The benzyl protection of the hydroxyl compound (**6.22**) was accomplished according to the method described by Bundle and Iversen [143]. Thus, **6.22** (0.89 g, 6.8 mmol) was dissolved in dichloromethane (5 mL) and cyclohexane (10 mL) along with benzyltrichloroacetimidate [142] (2.05 g, 8.1 mmol) whilst under an atmosphere of nitrogen. Trifluoromethane sulfonic acid (100 μL) was added and the resultant heterogeneous reaction mixture stirred at RT for 2 hours. The reaction was diluted with dichloromethane (50 mL) and washed with water and brine (25 mL). After drying ($MgSO_4$) the solvent was removed to give a residue that was triturated with dichloromethane/ hexane to provide the by-product trichloroacetamide as a crystalline solid. The filtrate was concentrated and purified by chromatography on silica gel (7 x 3 cm) eluting with 20% ethyl acetate in hexane. The title compound (**6.26**) was isolated as an oil (1.02 g, 4.6 mmol, 68%).

FT-IR (ATR)	2976, 1775, 1727 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$)	0.93 (t, J = 7.5 Hz, 3H), 1.69-1.89 (m, 2H), 2.54 (dd, J = 17.6, 5.0 Hz, 1H), 2.61 (dd, J = 18.1, 2.5 Hz, 1H), 4.09 (td, J = 4.5, 2.0 Hz, 1H), 4.26 (ddd, J = 7.6, 5.0, 4.5 Hz, 1H), 4.32 (d, J =

	12.0 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 7.15-7.30 (m, 5H) ppm.
^{13}C NMR	11.43 (CH_3), 23.41 (CH_2), 37.50 (CH_2), 72.14 (CH_2), 76.79
(100 MHz, $CDCl_3$)	(CH), 87.62 (CH), 129.87 (CH), 130.24 (CH), 130.77 (CH), 139.54 (C), 177.80 (C) ppm.
LRMS	(CI, +ve) m/z (relative intensity) 221 (10) $[M+H]^+$, 238 (100) $[M+NH_4]^+$.

(4S*, 5S*) 5-Ethyl-4-(benzyloxymethoxy)dihydrofuran-2-one (6.27)

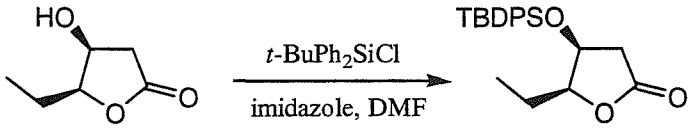


(6.22) **(6.27)**

The lactone (**6.22**) (215 mg, 1.65 mmol) was dissolved in dry dichloromethane (5 mL) and treated with *N,N*-di*iso*propylethylamine (255 mg, 344 μL, 1.98 mmol), followed by benzyloxymethyl chloride (60%, 510 mg, 408 μL, 1.98 mmol). The reaction was stirred under nitrogen for 2 hours at room temperature. The reaction was diluted with dichloromethane (10 mL) and washed with HCl (2M), sodium hydrogen carbonate (sat. aq.), water and brine (20 mL each). After drying ($MgSO_4$) the crude material was purified by chromatography on silica gel (5 x 3 cm) eluting with 40% diethyl ether in hexane. The title compound (**6.27**) was isolated as an oil (130 mg, 0.52 mmol, 31%).

FT-IR (ATR)	1777 cm^{-1}.
^{1}H NMR	0.97 (t, J = 7.0 Hz, 3H), 1.64-1.72 (m, 1H), 1.74-1.84 (m, 1H),
(400MHz, $CDCl_3$)	2.59-2.61 (m, 2H), 4.24-4.30 (m, 1H), 4.34-4.36 (m, 1H), 4.54. (s, 2H), 4.71 (q, J = 7.0 Hz, 2H), 7.21-7.31 (m, 5H) ppm.
^{13}C NMR	9.79 (CH_3), 21.65 (CH_2), 36.55 (CH_2), 69.93 (CH_2), 73.45 (CH),
(100 MHz, $CDCl_3$)	85.22 (CH), 93.51 (CH_2), 127.63 (CH), 127.78 (CH), 128.29 (CH), 136.97 (C), 174.86 (C) ppm.
LRMS	(CI, +ve) m/z (relative intensity) 130 (100), 268 (35) $[M+NH_4]^+$.

(4S*, 5S*) 5-Ethyl-4-(*tert*butyldiphenylsiloxy)dihydrofuran-2-one (6.25)

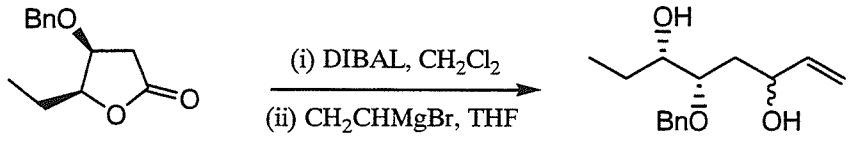


(6.22) (6.25)

The lactone (**6.22**)(1.00 g, 7.70 mmol) was dissolved in dry DMF (10 mL) under an atmosphere of nitrogen. Imidazole (1.15 g, 6.90 mmol) and *tert*butyldiphenylsilyl chloride (2.32 g, 2.20 mL, 8.50 mmol) were added to the solution. The reaction was stirred at RT for 6 hours before pouring into water and diethyl ether (70 mL each). The organic phase was washed with water and brine (30 mL each) before drying ($MgSO_4$). The crude material was purified by chromatography on silica gel (11 x 3 cm) eluting with 25% diethyl ether in hexane. The product was isolated as an oil that crystallised on standing to give the title compound (**6.25**) as a colourless crystalline solid (2.26 g, 6.1 mmol, 80%).

MP	78-79°C (hexane).
CHN analysis	Calcd. for $C_{22}H_{23}O_3Si$: C, 71.70; H, 7.66. Found: C, 71.61; H, 7.77.
FT-IR (ATR)	1765 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$)	1.02 (t, J = 7.5 Hz, 3H), 1.07 (s, 9H), 1.74-1.85 (m, 1H), 1.95 (d quint., J = 14.5, 7.0 Hz, 1H), 2.37-2.38 (m, 2H), 4.17 (dt, J = 8.5, 4.5 Hz, 1H), 4.46 (app. q, J = 4.5 Hz, 1H), 7.37-7.49 (m, 6H), 7.60 (t, J = 7.0 Hz, 4H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	10.67 (CH_3), 19.70 (q), 22.64 (CH_2), 27.26 (CH_3), 39.36 (CH_2), 70.93 (CH), 86.84 (CH), 128.33 (CH), 128.36 (CH), 130.57 (CH), 130.59 (CH), 132.91 (CH), 133.52 (CH), 136.14 (CH), 136.18 (CH), 175.64 (C) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 759 (100) $[2M+Na]^+$, 1127 (30) $[3M+Na]^+$.

(3S*, 4S*, 6RS) 3,6-Dihydroxy-4-benzyloxyoctene (6.30)

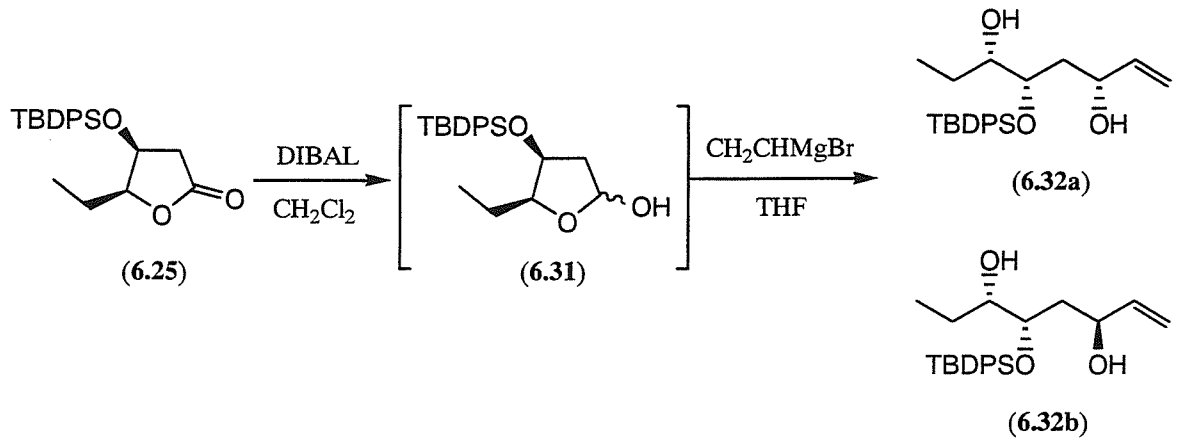


(6.26) **(6.30)**

The lactone (**6.26**) (0.110 g, 0.5 mmol) was dissolved in dry dichloromethane (5 mL) under nitrogen. The mixture was cooled to -78°C and treated with DIBAL (1.0M in tolene, 1.2 mL, 1.2 mmol). After stirring for 3 hours at -78°C the reaction was treated with methanol (1 mL) followed by 2.0M HCl (1 mL) and allowed to warm to room temperature. The organic layer was separated and dried ($MgSO_4$). Removal of solvent gave the crude lactol that was redissolved in dry THF (5 mL) and treated with vinyl magnesium bromide at -10°C. After 2 hours at this temperature the reaction was quenched with 2.0M HCl and the isolated by extraction into diethyl ether (20 mL). After drying (MgSO4) the crude material was purified by chromatography on silica gel (6 x 2 cm) loading and eluting with 50% diethyl ether in hexane. The title compound (**6.30**) (0.012 g, 0.05 mmol, 10%) was isolated as an oil.

FT-IR (ATR)	3369, 2952 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$)	0.90 (t, J = 7.5 Hz, 3H), 1.32-1.43 (m, 1H), 1.50-1.61 (m, 1H), 1.77 1.90 (m, 2H), 3.50-3.58 (m, 1H), 3.65 (dt, J = 8.0, 4.0 Hz, 1H), 4.52 (s, 2H), 4.99 (dd, J = 10.5, 1.0 Hz, 1H), 5.12 (dd, J = 10.5, 1.0 Hz, 1H), 5.21 (dd, J = 17.1, 1.0 Hz, 1H), 5.30 (dd, J = 17.1, 1.0 Hz, 1H), 5.82 (dd, J = 17.1, 10.5 Hz, 1H), 5.86 (dd, J = 17.1, 10.5 Hz, 1H), 7.21-7.28 (m, 5H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	11.60 (CH_3), 26.97 (CH_2), 41.42 (CH_2), 73.13 (CH_2), 75.78 (CH), 76.63 (C), 80.75 (CH), 113.57 (CH_2), 114.49 (CH_2), 129.17 (CH), 129.75 (CH), 138.93 (C), 143.87 (CH), 144.11 (CH) ppm.
LRMS	(CI, +ve) *m/z* (relative intensity) 91 (100), 108 (40) $[PhCH_2OH+H]^+$, 233 (10) $[M-H_2O+H]^+$, 250 (<5) $[M-H+H]^+$.

(3S*, 4S*, 6RS) 3,6-Dihydroxy-4-*tert*butyldiphenylsiloxyoctene (6.32)



(6.25) (6.31) (6.32a) (6.32b)

The title compounds were prepared according the method described by Holmes *et al.* [223] Thus, lactone (**6.25**) (0.76 g, 2.1 mmol) was dissolved in dry dichloromethane (10 mL) under an atmosphere of nitrogen. The reaction mixture was cooled to -78°C and treated with a solution of DIBAL in toluene (1.0M, 4. 2 mL, 4.2 mmol) by dropwise addition. The reaction was stirred at this temperature for 90 minutes before quenching with methanol (1.0 mL). After stirring for 10 minutes the solution was treated with HCl (2M, 5 mL) and immediately allowed to warm to RT. The reaction was diluted with dichloromethane and washed with HCl (2M) and brine (20 mL) of each. After drying ($MgSO_4$) the solvent was removed and the resulting 1-ethyl-2-(*tert*butyldiphenyl)silanoxy-5-hydroxytetrahydrofuran (**6.31**) (0.68 g, 1.83 mmol, 88%), a single compound by TLC (50% diethyl ether in hexane), was used directly in the next reaction.

6.31 (0.63 g, 1.72 mmol) was dissolved in dry THF (10 mL) and stirred whilst under an atmosphere of nitrogen. After cooling to -25°C vinyl magnesium bromide in THF (1.0M, 4 mL, 4.0 mmol) was added at such a rate that the reaction temperature did not exceed -15°C. After addition, it was allowed to warm to room temperature and and stirred for 2 hours. The reaction was recooled to -40°C and treated with HCl (2.0M, 5 mL) ensuring that the reaction temperature remained below -10°C. The resulting mixture was partitioned between diethyl ether and water (50 mL) each with the organic phase subsequently being washed with water and brine (30 mL each) and dried ($MgSO_4$). Partial purification was accomplished by chromatography on silica gel (10 x 3 cm) eluting with 30% ethyl acetate in hexane providing the title compound (**6.32**) as a 3:2 mixture of diastereoisomers (0.49 g, 1.24 mmol, 71%). The diastereoisomers were separated by a combination of further chromatography and crystallisation from hexane.

Least polar isomer

MP	100-101°C (hexane).
CHN analysis	Calcd. for $C_{24}H_{34}O_3Si$: C, 72.31; H, 8.60. Found: C, 72.01; H, 8.72.
FT-IR (CH_2Cl_2)	3183, 2950, 1425, 1089 cm^{-1}.
^1H NMR (400MHz, $CDCl_3$)	0.81 (t, *J* = 6.3 Hz, 3H), 1.08 (s, 9H), 1.42-1.54 (m, 3H), 1.75 (ddd, *J* = 14.6, 7.5, 3.0 Hz, 1H), 2.34 (br s, 2H), 3.46 (ddd, *J* = 7.0, 5.0, 2.0 Hz, 1H), 3.87-3.90 (m, 1H), 4.25-4.27 (m, 1H), 4.94 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.05 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.59 (ddd, *J* = 17.1, 10.5, 5.5 Hz, 1H), 7.36-7.46 (m, 6H), 7.65-7.69 (m, 4H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	10.75 (CH_3), 19.91 (q), 27.45 (CH_2), 27.57 (CH_3), 41.93 (CH_2), 68.93 (CH), 73.08 (CH), 75.59 (CH), 114.32 (CH_2), 128.06 (CH), 128.18 (CH), 130.29 (CH), 130.38 (CH), 133.65 (C), 134.14 (C), 136.42 (CH), 141.07 (CH) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 194 (100), 399 (5) $[M+H]^+$, 421 (5) $[M+Na]^+$, 797 (25), $[2M+H]^+$, 819 (25) $[2M+Na]^+$.

most polar isomer

MP	93-94°C (hexane).
CHN analysis	Calcd. for $C_{24}H_{34}O_3Si$: C, 72.31; H, 8.60. Found: C, 72.21; H, 8.75.
FT-IR (ATR)	3219, 2927, 1425, 1098 cm^{-1}.
^1H NMR (400MHz, $CDCl_3$)	0.89 (t, *J* = 7.5 Hz, 3H), 1.07 (s, 9H), 1.38-1.49 (m, 1H), 1.51-1.63 (m, 2H), 1.79 (ddd, *J* = 14.5, 9.5, 5.5 Hz, 1H), 2.09 (br s, 2H), 3.48 (dt, *J* = 9.0, 3.5 Hz, 1H), 3.86 (app. dd, *J* = 9.5, 5.5 Hz, 1H), 3.89-3.96 (m, 1H), 4.92 (d, *J* = 9.5 Hz, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 5.57 (ddd, *J* = 16.5, 10.0, 6.0 Hz, 1H), 7.37-7.46 (m, 6H), 7.69 (t, *J* = 8.5 Hz, 4H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$)	10.80 (CH_3), 17.92 (q), 26.08 (CH_2), 27.50 (CH_3), 39.04 (CH_2), 68.39 (CH), 72.46 (CH), 73.96 (CH), 112.52 (CH_2), 126.09 (CH), 126.23 (CH), 128.26 (CH), 128.39 (CH), 131.77 (C), 132.15 (C), 134.39 (CH), 139.23 (CH) ppm.
LRMS	(ES, +ve) *m/z* (relative intensity) 194 (100), 399 (5) $[M+H]^+$, 421 (15) $[M+Na]^+$, 797 (50), $[2M+H]^+$, 819 (100) $[2M+Na]^+$.

Chapter 8

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