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Development and application of the vinylepoxide – dihydrofuran rearrangement

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Development and Application of the Vinylepoxide – Dihydrofuran Rearrangement

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Declaration

This work was conducted in the Department of Chemistry at the University of Durham between October 1996 and September 1999. A three month CASE placement was taken in the Medicinal Chemistry Department of Rhône-Poulenc Rorer, at the Dagenham Research Centre in Essex, between July 1998 and September 1998. The work has not been submitted for a degree in this, or any other university. It is my own work, unless otherwise indicated.

Acknowledgements

Abbreviations

Ac	: acetyl
Ar	: aromatic
b.p.	: boiling point
Boc	: *tert*-butylcarbonate
br	: broad
Bu	: butyl
BuLi	: butyl lithium
CAN	: ammonium cerium (IV) nitrate
CI	: chemical ionisation
d	: doublet
DCC	: N,N'-dicyclohexylcarbodiimide
DCM	: dichloromethane
de	: diastereomeric excess
DIBAL	: diisobutylaluminium hydride
DMAP	: 4-dimethylaminopyridine
DMF	: N,N-dimethylformamide
DMSO	: dimethylsulfoxide
EDC	: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	: enantiomeric excess
EI	: electron impact ionisation
Et	: ethyl
FVP	: flash vacuum pyrolysis
GC	: gas chromatography
GC-MS	: gas chromatography – mass spectrometry
HPLC	: high performance liquid chromatography

IR	: infrared
Kcal	: kilocalories
LC-MS	: liquid chromatography – mass spectrometry
LDA	: lithium diisopropylamide
m	: multiplet
*m*CPBA	: *meta*-chloroperoxybenzoic acid
Me	: methyl
MeLi	: methyl lithium
m.p.	: melting point
Ms	: methanesulfonyl
MS	: mass spectrometry
NMP	: *N*-methylpyrrolidinone
NMR	: nuclear magnetic resonance
PDC	: pyridinium dichromate
Ph	: phenyl
q	: quartet
s	: singlet
t	: triplet
Tf	: trifluoromethanesulfonyl
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	: trimethylsilyl
Ts	: toluenesulfonyl
p-TsOH	: *para*-toluenesulfonic acid

Abstract

Development and Application of the
Vinylepoxide – Dihydrofuran Rearrangement

William Martin Dutton
Ph.D. 2000

The vinylepoxide – dihydrofuran rearrangement offers a route to substituted 2,3-dihydrofurans with a high degree of diastereoselectivity. The rearrangement proceeds via an ylide-type intermediate arising from the thermolysis of a carbon-carbon epoxide bond. This thesis discusses work aimed at developing the rearrangement, introducing asymmetric control, and application of the dihydrofuran products in target molecule synthesis.

Synthesis of the vinylepoxide rearrangement precursors is described, and development of the rearrangement to achieve a moderate scale rearrangement process is discussed. Alternative rearrangement technologies are also explored.

Asymmetric induction into the rearrangement was approached by the use of chiral auxiliaries and in particular C2 symmetric amines. A novel synthesis of (S,S)-2,5-diphenylpyrrolidine and (S,S)-2,6-diphenylpiperidine is reported. High degrees of enantiomeric purity were achieved through the application of an effective oxazaborolidine catalyst in the reduction of dibenzoylethane and dibenzoylpropane. Use of this chiral reduction catalyst on further diketones is described.

Application of the dihydrofuran products in the synthesis of several 2,6-disubstituted-3,7-dioxabicyclo[3.3.0]octanes. These compounds, commonly termed furofuran lignans exhibit a wide range of biological properties. The dihydrofuran products were combined with a range of dimethylacetals, in a one pot synthesis, with high degrees of stereocontrol, by a Noyori type transacetalisation. Further derivatisation of these bicyclic compounds was accomplished and is discussed.

Finally, with the vinylepoxide – dihydrofuran rearrangement established a preliminary exploration of the related vinylaziridine – 2-pyrroline rearrangement is reported.

Contents

Section A: Introduction

Chapter 1:   Introduction and Background

1.1 Introduction

This thesis is concerned with the exploration of the vinylepoxide - dihydrofuran rearrangement, Scheme 1.
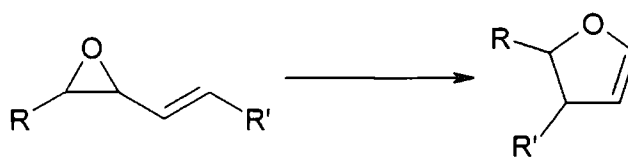
Scheme 1

The dihydrofuran structural motif occurs in a number of natural products, for example. 6β-acetoxy-10βH-furanoexmohilan extracted from *Lopholaena dregeana* and zederone isolated from *Curcuma zedoaria*, Scheme 2.[1]
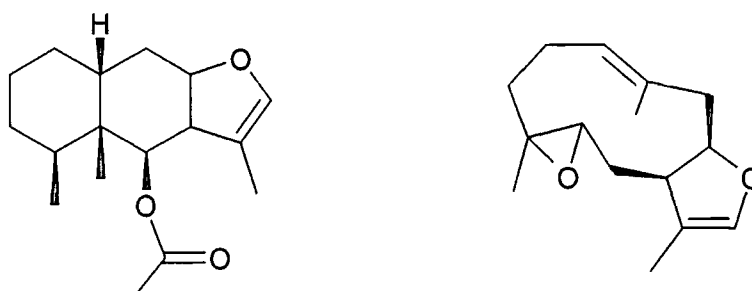
6β-Acetoxy-10βH-furanoexmohilan   Zederone

Scheme 2

This rearrangement is comparable to the well-known vinylcyclopropane – cyclopentene rearrangement which is discussed in outline in this section. Furthermore, this rearrangement can be extended to corresponding aziridine and thiirane analogues and while much less studied, these are also described.

In particular our research is focused on the development of a protocol amenable to large scale synthesis, approaches for the incorporation of asymmetry and the application of the dihydrofuran products in target synthesis. These subjects are covered in chapters 2-4. In addition, work towards the vinylaziridine – dihydropyrrole rearrangement, has been undertaken and is described in chapter 5.

The remainder of this chapter describes the background to the work, focusing on the properties, synthesis, mechanisms and previous applications of these rearrangements. Finally the goals of the project are described.

1.2 Properties and mechanisms of small ring rearrangements

The chemistry of small rings has risen in prominence over the last few decades. In particular they have seen much use as synthetic intermediates, owing to their tendency to undergo ring opening, driven by the release of ring strain.

Epoxides, aziridines and cyclopropanes all have similar C-X-C bond angles compared to the thiirane.[2] Similarly the C-X bond length for the first three ring systems is smaller than the thiiranes and consequently the thiirane has less strain energy in the ring, Table 1.[3]
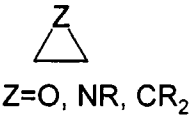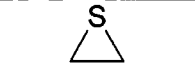
	Bond Angle	Bond Length	Strain Energy
Z, Z=O, NR, CR$_2$	58-61°	1.44-1.51 Å	27 kcalmol^{-1}
S	48°	1.82 Å	20 kcalmol^{-1}

Table 1

These differences in properties can be accounted given sulfur uses the $3p$ orbitals in bonding. As a result of these differences in geometry and activation energies, vinylthiirane rearrangements show considerably different reactivity profiles from

3

vinylepoxides and vinylaziridnes and have not been explored in the scope of this thesis. They do, however, represent a possible direction for future research.

Owing to the recent growth in the use of small ring rearrangements in synthesis, there have been considerable efforts to elucidate the mechanistic pathways for these rearrangements. To date, three possible mechanisms have been identified that lead to five membered rings.[4]

A $[2\sigma_s + 2\pi_s]$ concerted rearrangement into a five membered ring, Scheme 3.
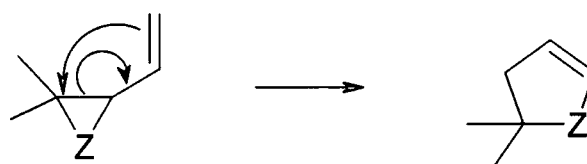
Scheme 3

B Heterolytic fission of the three membered ring to give an ylide-type intermediate which produces a five membered ring on electrocyclic closure, Scheme 4.
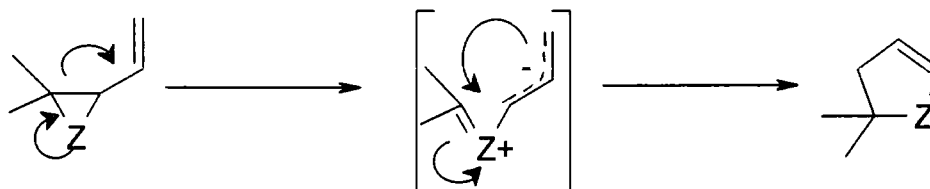
Scheme 4

C Diradical fission of the three membered ring, followed by recombination to a five membered ring, Scheme 5.

Scheme 5

4
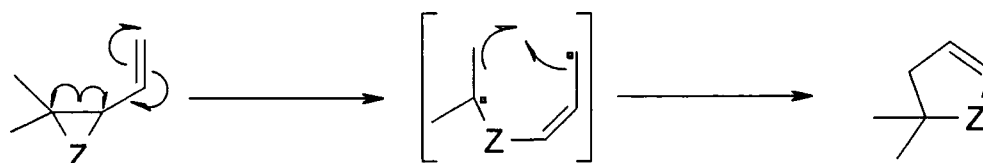
The pathway which is followed depends upon the reaction conditions, precise structure, (vinylcyclopropane, epoxide, or aziridine) and the type and configuration of substituents around the molecule.

This situation is further complicated by other competing processes, both intermolecular processes and a spectrum of intramolecular rearrangements can occur, Scheme 6.[5]

The [3+3] divinylcyclopropane Cope rearrangement (A), nucleophilic facilitated opening (B), aza-Wittig rearrangement[6] (C), and [1,5] sigmatropic hydrogen shifts (D) are important processes of much current interest.

$Z = CH, O.$
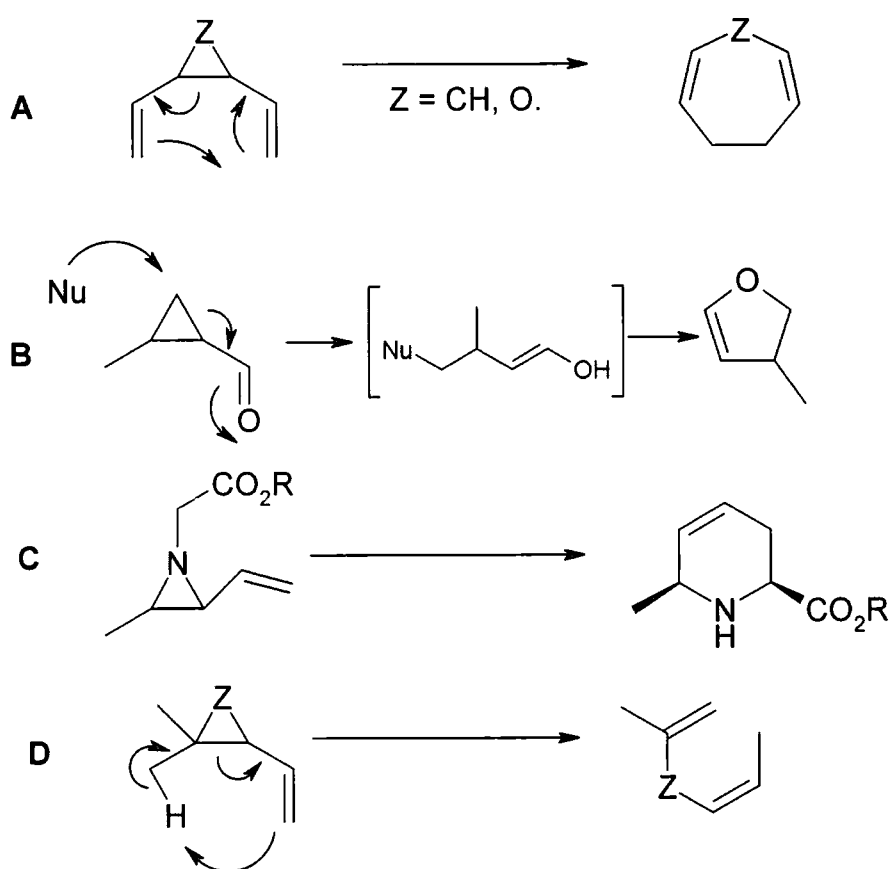
Scheme 6

For example, the thermolysis of *trans*-divinylepoxide (1) gives a 7:3 mixture of dihydrofuran (2) and oxepin (3), Scheme 7.

(2)   170-200°C   (1)   170-200°C   (3)

Scheme 7
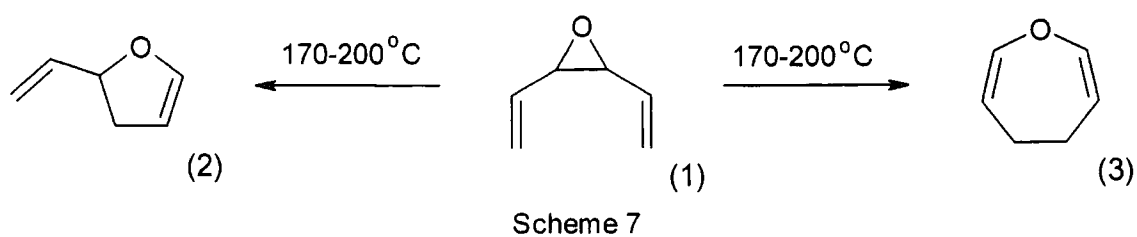
However, given the size of this field and the specific subject of this thesis, a comprehensive survey is not feasible and the reader is directed to the reviews listed in the references above.

In the rest of this section we discuss the effects of conditions and substituents on the well-known vinylcyclopropane – cyclopentene rearrangement, the developing vinylepoxide rearrangement and the as yet relatively unexploited vinylaziridine rearrangement.

1.3 Vinylcyclopropane - cyclopentene rearrangement

The rearrangement of vinylcyclopropanes to cyclopentenes was discovered in 1959 by Neureiter.[7] Vinylcyclopropane contains strain energy in the cyclopropane ring (found to be 27.5 kcal mol^{-1}),[3] which, while considerably less than the calculated value (104 kcal mol^{-1}), is responsible for the species' reactive properties.[8]

The precise orientation, nature of substituents and reaction conditions determine which rearrangement pathway occurs on thermolysis. Examples of all three relevant mechanisms have been put forward for vinylcyclopropane derivatives.

In Scheme 8, a vinylcyclopropane undergoes rearrangement at 260°C to the *cis* alkene exclusively, via a [1,5] sigmatropic hydrogen shift,[9] with an activation energy of 30 kcal mol^{-1}.[10]

6
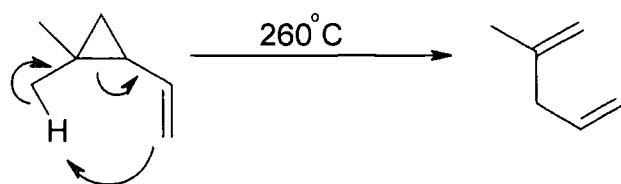
Scheme 8

In the majority of other rearrangements the experimental evidence indicates a diradical-type cleavage of the vinylcyclopropane system and a reclosure of the allylic diradical, Scheme 9.[11]
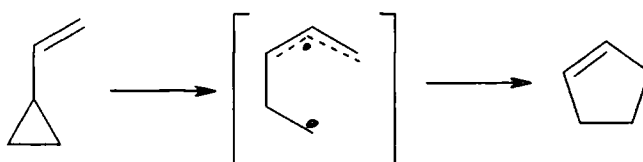
Scheme 9

This is supported by the lower activation energy for the diradical pathway,[12] which is on average 45 kcal mol^{-1} compared to 50 kcal mol^{-1} for the competing concerted process.[13]

Further support of the diradical pathway comes from investigations into substituent effects on the activation energy of the rearrangement. Experiments show that any substitution on the vinyl portion of the molecule has little effect, however, radical-stabilising groups such as heteroatoms and olefins on the cyclopropane ring tend to lower the activation energy, Scheme 10.

$E_a = 44$ kcal mol^{-1}

(4)

$E_a = 39$ kcal mol^{-1}

(5)
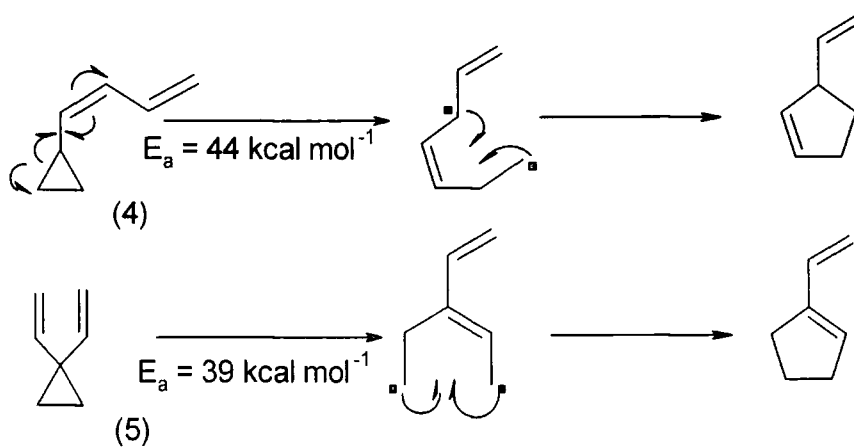
Scheme 10

Thus, the lower activation energy observed for divinylcyclopropane (4)[14] compared with the equivalent substituent on the vinyl group as in (5)[15] can be accounted for by the stabilisation of forming a dienyl radical compared with an allyl radical.

Consistent with this observation, further reductions in the activation energy are observed for the rearrangements of the cyclopropane with 2-methoxy (6)[12] and 2-dimethylamino substituents (7), Scheme 11.[16] This again is attributed to the stabilisation of a developing radical centre at C-2 due to the lone pairs of the heteroatoms.

$E_a = 39 \text{kcalmol}^{-1}$

$E_a = 32 \text{kcalmol}^{-1}$

Scheme 11
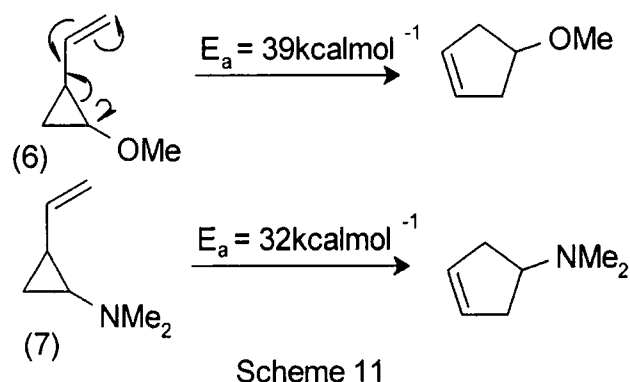
It has also been proposed that in these cases considerable ionic character may develop on the hetero atom in an ylide-type mechanism. There is evidence for anionic assistance in the literature, for example, 2-vinyl cyclopropanol undergoes a rearrangement at room temperature, Scheme 12.[5]
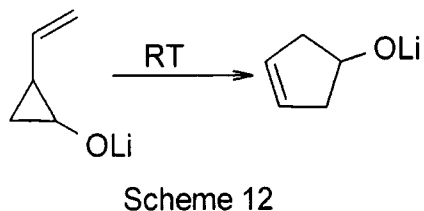
Scheme 12

Recently, further more elaborate examples of these oxyanion accelerated process have been reported. Again these occur at low temperature and exhibit high stereoselectivity, Scheme 13.[17]
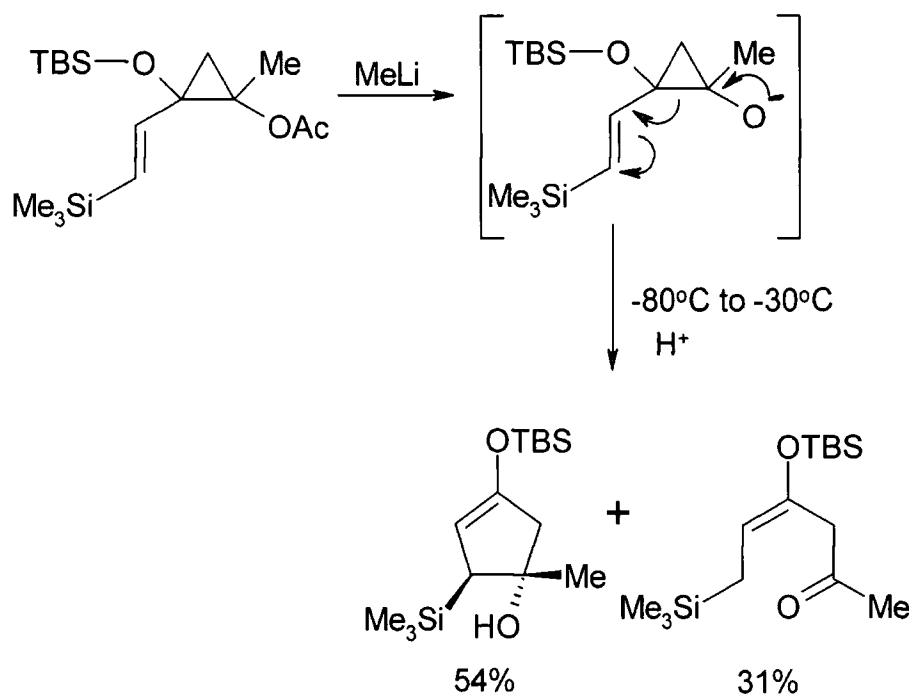
Scheme 13

Although a diradical pathway could lead to loss of stereochemical conformation, frequently a high degree of stereoselectivity can be observed in the rearrangement of enantiomerically pure vinylcyclopropanes. For example, the enantiomerically pure cyclopropane (8) undergoes thermal rearrangement to give all four possible isomers with the *trans* compound (-)-(9) being produced in 86% ee, Scheme 14.[18]
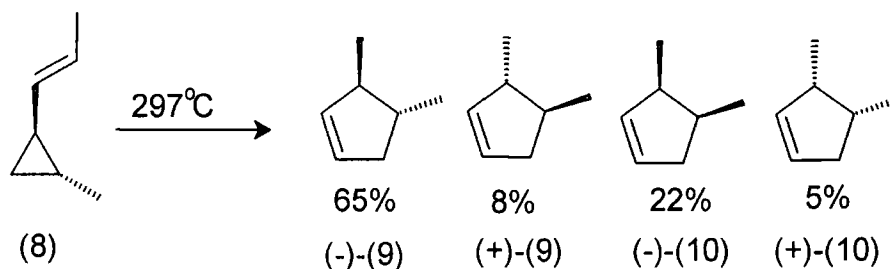
Scheme 14

Since the formation of the *cis* isomers (-)-(10), (+)-(10) would be forbidden following a concerted process their presence supports a diradical mechanism. However, the high

degree of retention of optical purity suggests a concerted process. It is proposed that both the $[2\sigma_s + 2\pi_s]$, concerted rearrangement and diradical fission process may occur simultaneously to different extents.

In conclusion it seems that in the majority of vinylcyclopropane rearrangements the most likely mechanism is the diradical pathway and further evidence for this can be found in detailed kinetic studies.[19] However, owing to the stereoselectivity that can be observed, a concerted $[2\sigma_s + 2\pi_s]$ mechanism cannot be ruled out and it may be that both pathways occur simultaneously.

1.4 Vinylepoxide - dihydrofuran rearrangement
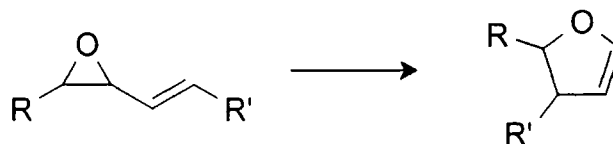
Scheme 15

1.4.1 Introduction

The rearrangement is analogous with the previously described vinylcyclopropane - cyclopentene rearrangement with two main exceptions: Firstly, the vinylepoxide rearrangement has a lower activation energy and hence proceeds under milder conditions. Secondly it is thought to proceed through an ylide-type intermediate unlike the favoured diradical intermediate in the majority of cyclopropane rearrangements. This has major implications for the stereochemistry as discussed below.

1.4.2 Mechanism and stereochemistry

The mechanism of the rearrangement has been under scrutiny for a number of years, with a proposal that homolytic ring cleavage at the C-C bond, forming a diradical species does not usually lead to formation of 2,3-dihydrofuran species.

The stated exception to this is divinylepoxide (1) where the ability to form the stabilised diradical (11) facilitates the alternative mechanism, Scheme 16.[20]

11
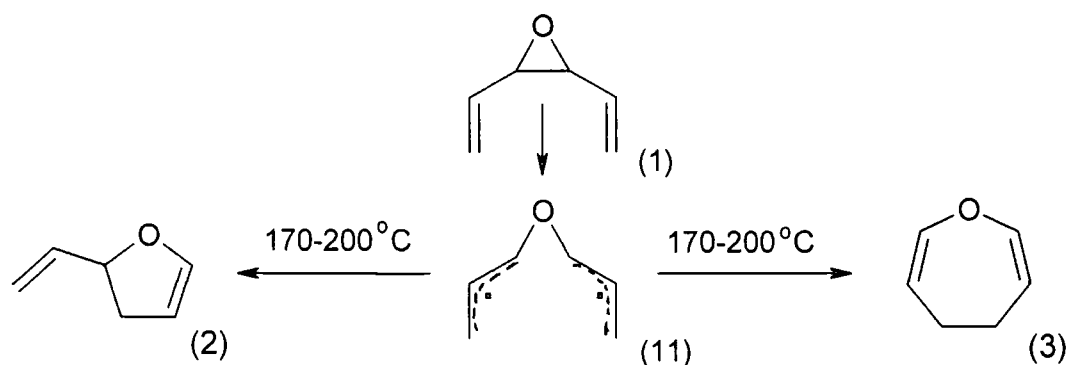
Scheme 16

However, the C-C cleavage to form an ylide-type species, Scheme 17, has become the favoured intermediate with electrocyclic ring closure giving the dihydrofuran species.
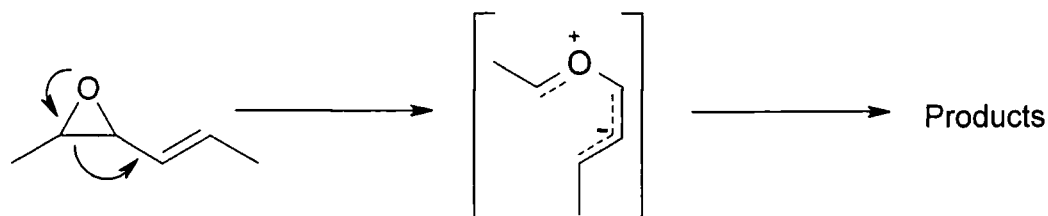
Scheme 17

Kinetic studies on the gas phase pyrolysis of vinylepoxide were carried out by Crawford et al.[21] Enantiomerically pure 2-vinylepoxide was synthesised from the isopropylidene derivative of D-glyceraldehyde. These studies showed that isomerisation of enantiomerically pure vinylepoxide occurred six times faster than the rearrangement to 2,3-dihydrofuran at a temperature range of 270°C - 310°C, Scheme 18. Additionally, similar studies with deuterium labelled substrates indicated that it was the epoxide C-C bond that cleaves opposed to the C-O bond.

Starting Material k_1 / k_{-1} k_{-1} / k_1 **Racemised Material**

k_2

$k_{-1} > k_1 > k_2$

k_2 = r.d.s.

Product
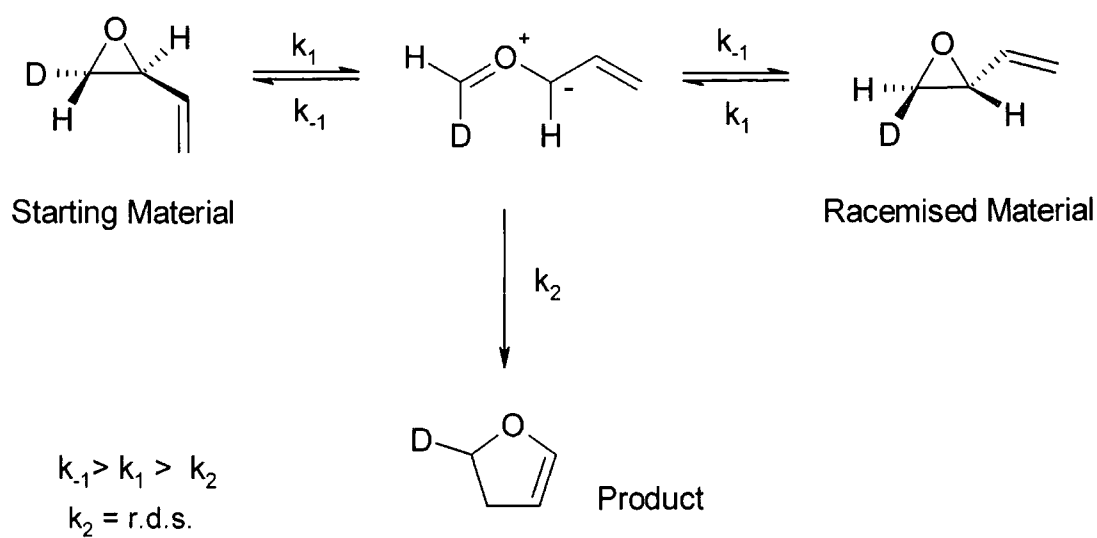
Scheme 18

The now generally accepted rearrangement pathway was published by Eberbach[22] and demonstrates how the stereocentres in the starting material are destroyed giving intermediates that lead to the allowed disrotatory ring closures. The intermediates described rationalise the findings that the stereoselectivity of the rearrangement is independent of the initial stereochemistry of the epoxide ring. The predominantly (90%) *cis* dihydrofuran product (12), can be accounted for by the configuration of the intermediate prior to ring closure. Steric interactions between the substituents disfavour the intermediate leading to the minor, (10%) *trans* product (13), Scheme 19.
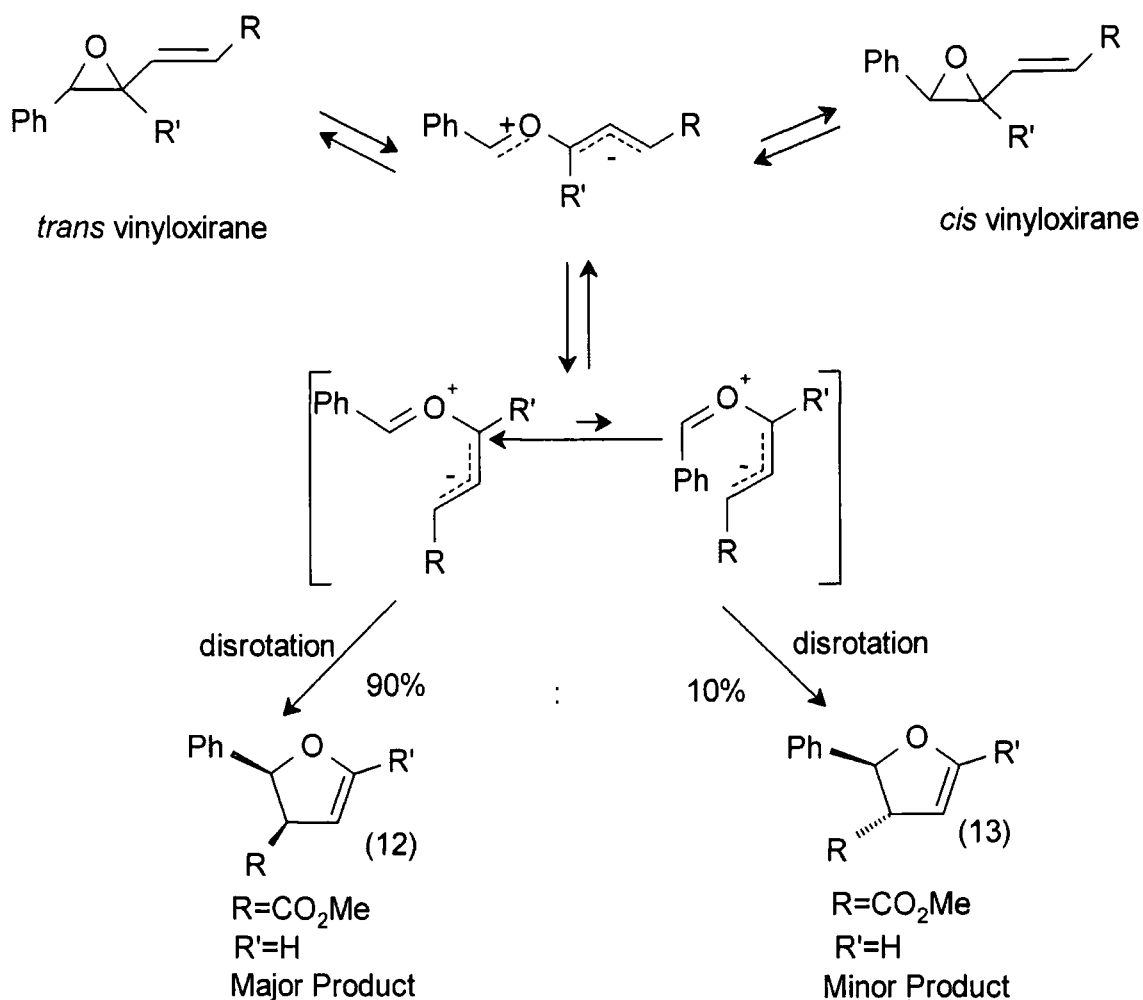
Scheme 19

However, in a similar study the dimethylester vinylepoxide rearranged to an equal mixture of *trans* and *cis* isomers, Scheme 20. Eberbach suggests a diradical mechanism for this particular epoxide should not be ruled out. Other possible explanations are either the intermediate for the ring closure is less sterically hindered by the ester group than a phenyl ring or the product may have epimerised after rearrangement due to the additional acidic proton, not unreasonable at such high temperatures.
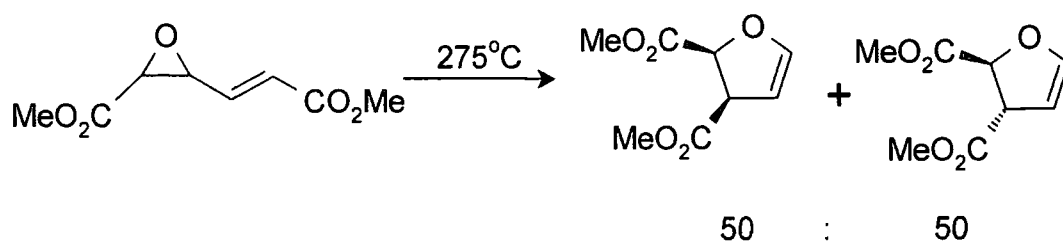
Scheme 20

50 : 50

1.4.3 Other competing process

Further to the work on vinylepoxides, Eberbach demonstrated some competing processes with epoxy dienes (14), (15) having the potential to undergo similar thermal rearrangements to dihydrofurans and oxepins. Using only *trans* epoxides, and varying the nature of the first vinyl group between *cis* and *trans* he established the *cis* double bonded species (15) could lead to oxepins or dihydrofurans, whereas the *trans* double bonded species gave only dihydrofurans, Scheme 21.[23]

(14) *trans, trans*

(15) *trans, cis*

200°C

200°C

Scheme 21
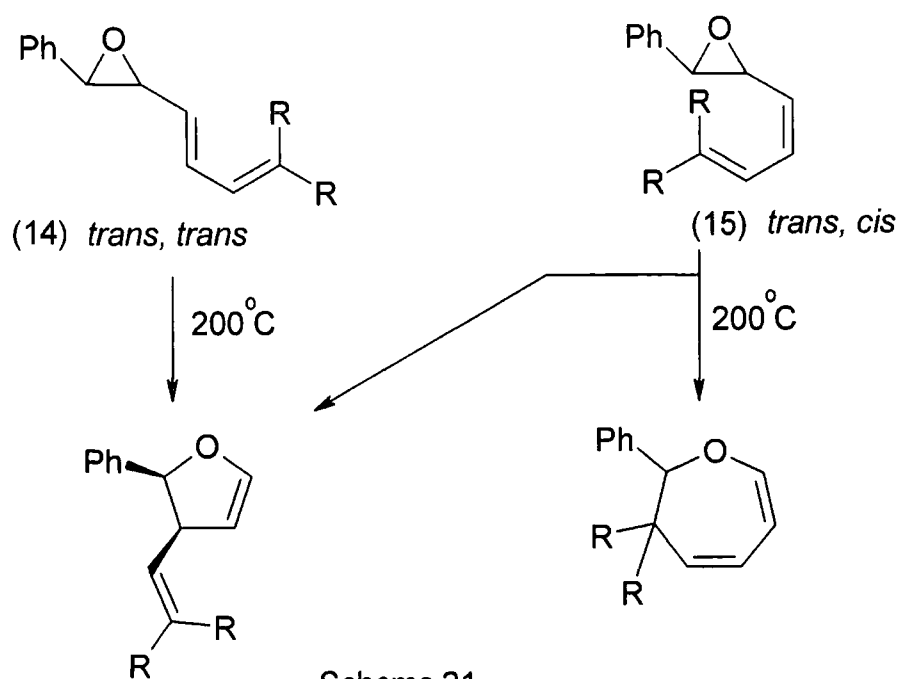
Hudlicky also studied these rearrangements, varying the flash vacuum pyrolysis temperature profile.[24] These studies indicated that the oxepin pathway is favoured by lower temperatures and dihydrofuran can be obtained by using higher temperatures, Scheme 22.
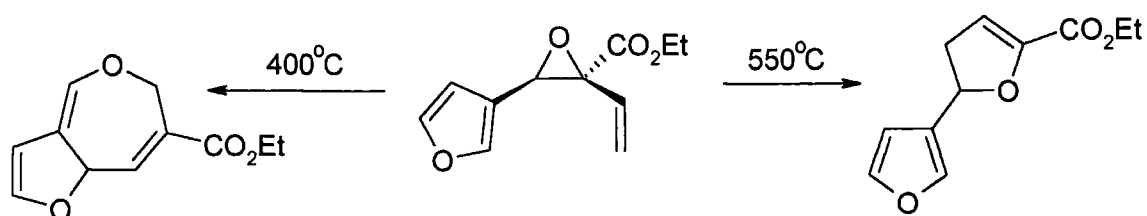
Scheme 22

Construction of dihydrofuran moieties fused to another ring have also been demonstrated as viable rearrangement substrates, Scheme 23.[25]
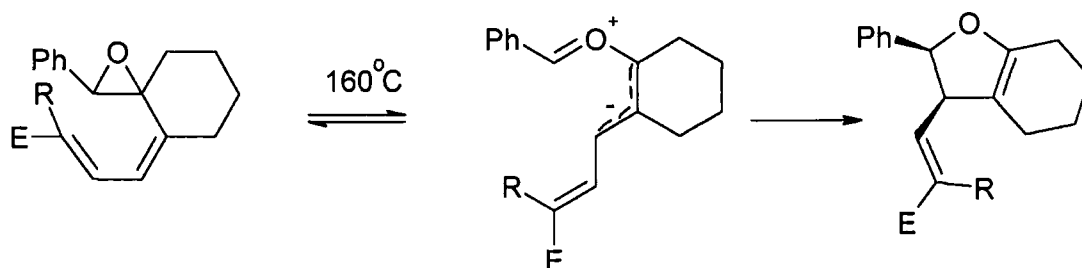
Scheme 23

Whilst the rearrangement does lead to loss of stereochemical configuration, more recent work in our own group has shown that the use of a simple chiral auxiliary does lead to moderate asymmetric induction in the process, (see section 1.7.2) Scheme 24.
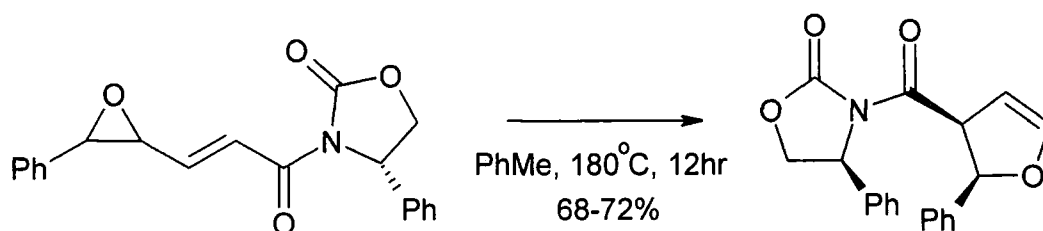
Scheme 24

1.5 Vinylaziridine - pyrroline rearrangement

Vinylaziridines undergo thermal rearrangement comparable to the rearrangement of vinylcyclopropanes and epoxides. However, considerably less research has been conducted on these species producing a number of rearrangement products. Specifically, *N*-vinylaziridines undergo rearrangement to give a mixture of 1- and 2-pyrroline, Scheme 25.

1-pyrroline
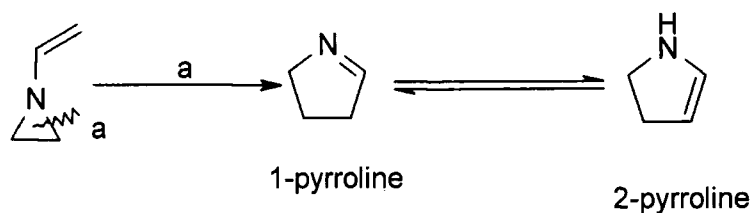
2-pyrroline

Scheme 25

The corresponding 2-vinylaziridines also undergoes rearrangement to give 2-pyrroline presenting an analogous rearrangement to the vinylepoxide rearrangement described above. 2-vinylaziridine can also rearrange with cleavage of the C-N aziridine bond to give 3-pyrroline, Scheme 26.

2-pyrroline
(16)
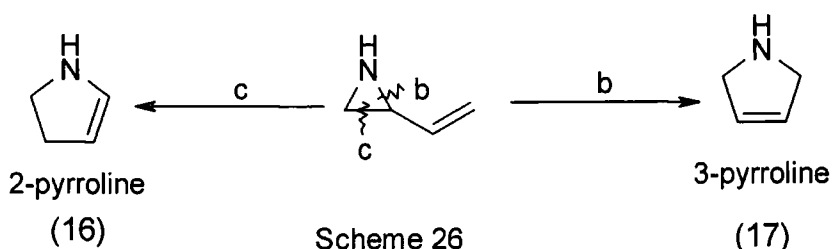
Scheme 26

3-pyrroline
(17)

Rearrangement to give 3-pyrrolines (17) is well precedented.[26] This is unsurprising since the process is favoured by the relatively low C-N bond strength compared to the C-C bond.

Borel *et al* described vinylaziridine rearrangements giving a variety of products, including the desired 2-pyrrolines (16).[27] Which rearrangement occurred depended on

the substituents on the aziridine ring. For the production of 2-pyrrolines (16) it was found necessary for C-3 of the aziridine to possess a phenyl ring substituent, Scheme 27.

A.

B.

70% cis (21)   30% trans (21)
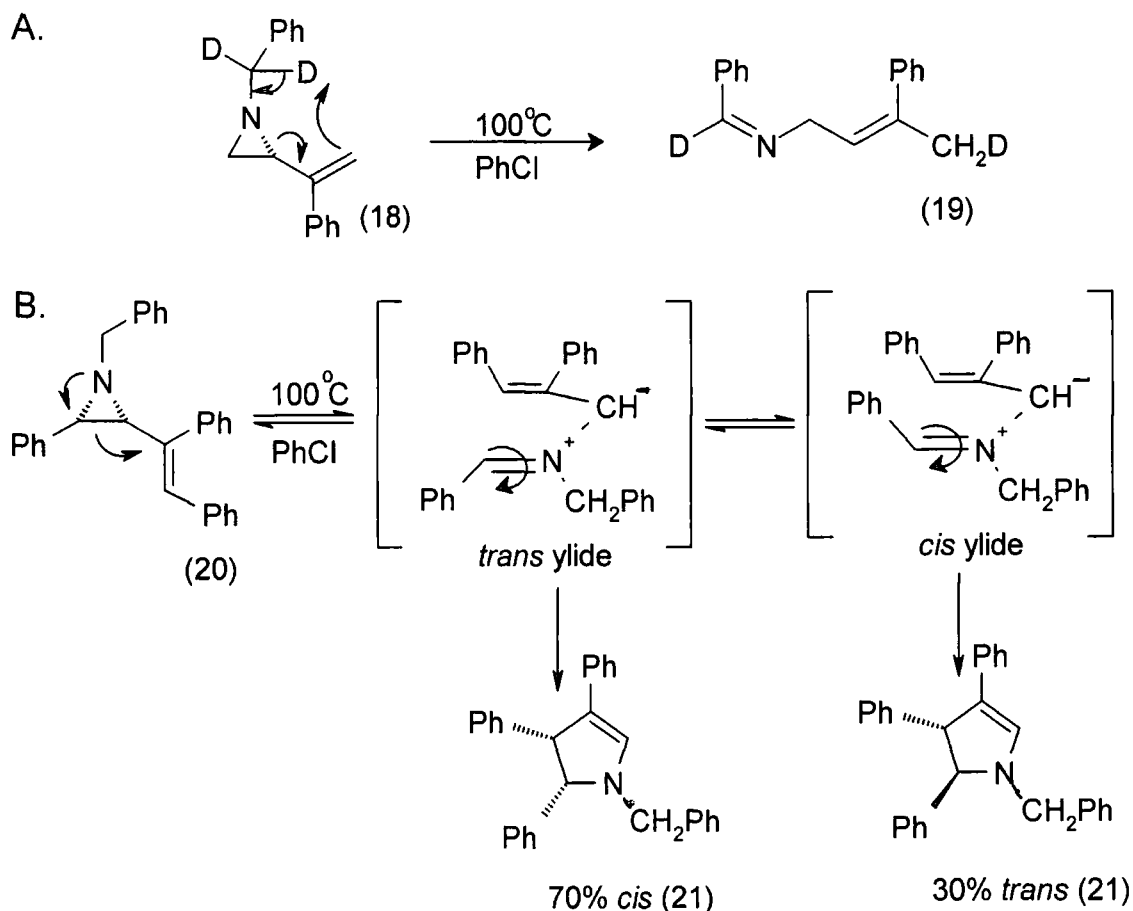
Scheme 27

Lack of a phenyl ring on the C-3 of the aziridines (18) led to ene type reaction (Pathway A), where hydrogen / deuterium extraction from the benzyl group gives rise to the ring opened imine-alkene (19) via C-N bond cleavage of the aziridine. The presence of a C-3 phenyl substituent (20) facilitates stabilisation of the required ylide - type intermediate obtained via the C-C bond cleavage of the aziridine.

The rearrangement was found to be diastereoselective, with a de of 40% for cis isomer of the pyrroline (21). A radical intermediate does not account for this stereoselectivity, a 50/50 mixture of cis and trans products would be the expected

outcome. The isomerisation between *cis* and *trans* ylides is in competition with concerted disrotatory ring closure and the benzyl group on the aziridine nitrogen in each of these cases is likely to stabilise the ylides due to conjugation. The more stabilised the ylides, the more likely they are to isomerise to the corresponding *cis* form prior to cyclisation and therefore give more *trans* product. The *trans* ylide is favoured over the *cis* due to the steric effects of the terminal phenyls.

In conclusion the vinylaziridine – 2-pyrroline rearrangement requires a phenyl group on C3 of the aziridine, and undergoes thermal rearrangement via an ylide-type intermediate, akin to the vinylepoxide – dihydrofuran rearrangement. This demonstrates the fact that the conditions and substituents play a pivotal role in determining the reaction outcome. Beyond these few examples, relatively little work on this rearrangement has been reported.

1.6 Synthetic applications

Owing to the large variation in substitution patterns possible, application of these rearrangements in a number of synthetic applications of cyclopentene systems have been reported and the interested reader is directed to the review by Hudlicky.[5] Two illustrative examples are shown below.

The vinylcyclopropane – cyclopentene was exploited in a thermolysis of vinylcyclopropane (22), yielding exclusively the triquinane (23) in a synthesis of the sesquiterpene, Hirsutene, (24), Scheme 28.[28] As usual for the cyclopropane series the diradical pathway is most likely, stereochemical control is observed, as a result of the ring fused structure.
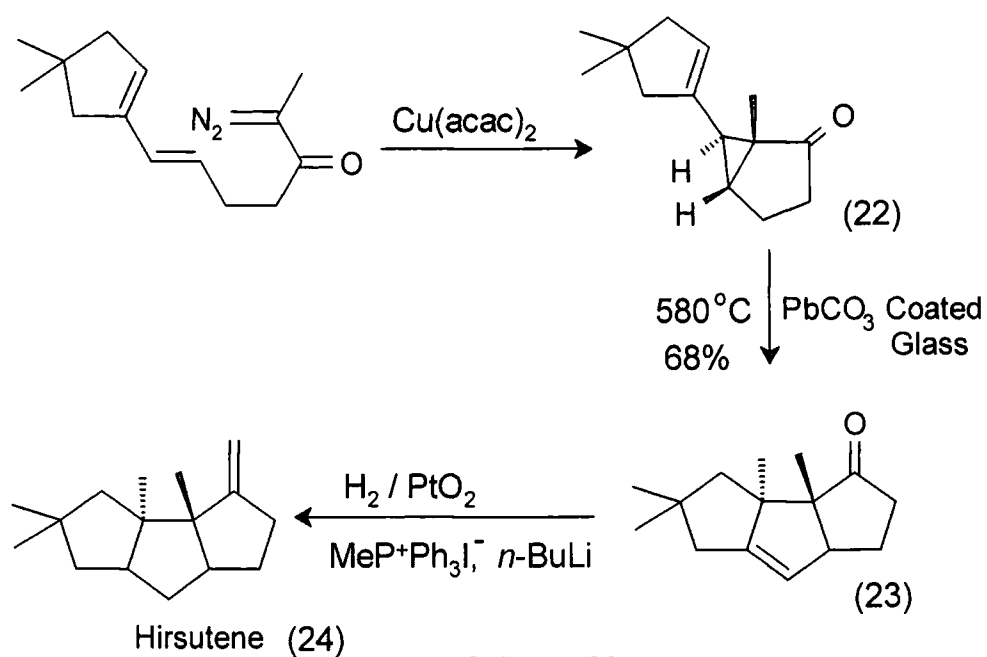
Scheme 28

The vinylepoxide – dihydrofuran rearrangement represents a useful synthetic methodology and has found a number of applications. One example is the synthesis of Ipomeamarone, Scheme 29, in which flash vacuum pyrolysis (fvp) of the vinylepoxide (25) leads to dihydrofuran (26) in 49% yield.

Scheme 29   Ipomeamarone
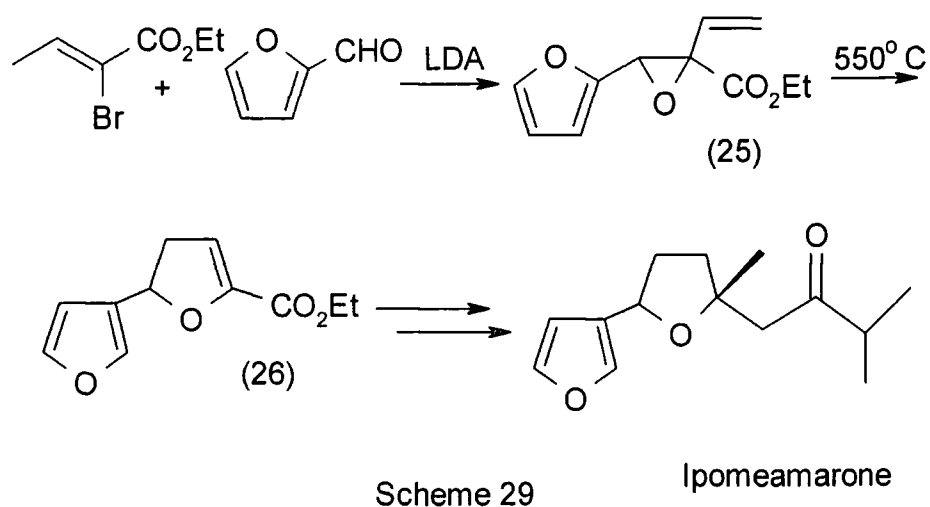
The rearrangement was also carried out on the related 1-phenylepoxide (27) to give the expected product in 95% yield, Scheme 30.[29]

Scheme 30
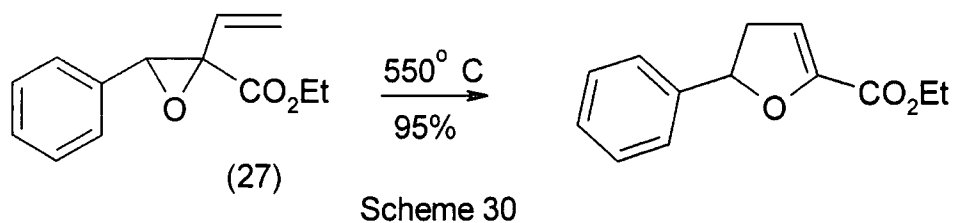
The vinylaziridine – pyrroline rearrangement has not been as widely exploited in natural product synthesis although a number of examples do exist. Hudlicky utilised the rearrangement in a synthesis towards Isoretronecanol (28), with the key transformation illustrated in Scheme 31.[30]
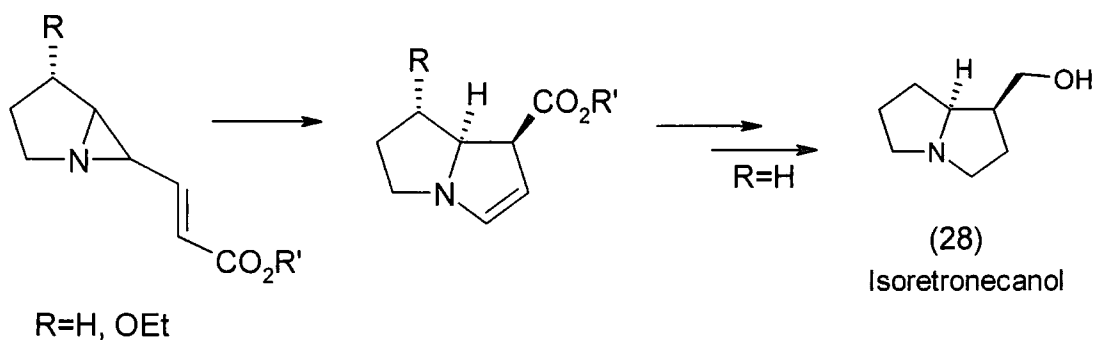
Scheme 31

1.7 Previous work in our group

1.7.1 Vinylepoxides

Following the research in recent decades, outlined previously in this section, which explored the mechanism, characteristics and scope of the rearrangement, our group first became interested in vinylepoxide rearrangements in search for a route to enantiomerically pure substituted dihydrofurans for the construction of stereoregular polymers. The required vinylepoxide substrate had been previously prepared by Eberbach,[22] as the methyl ester by two methods. In the first approach a vinylogous Darzen reaction uses benzaldehyde and ester (29)[31] to prepare a 7:3 mixture of *trans* (30a) and *cis* (30b) epoxides in an overall yield of 68%, Scheme 32.[32]
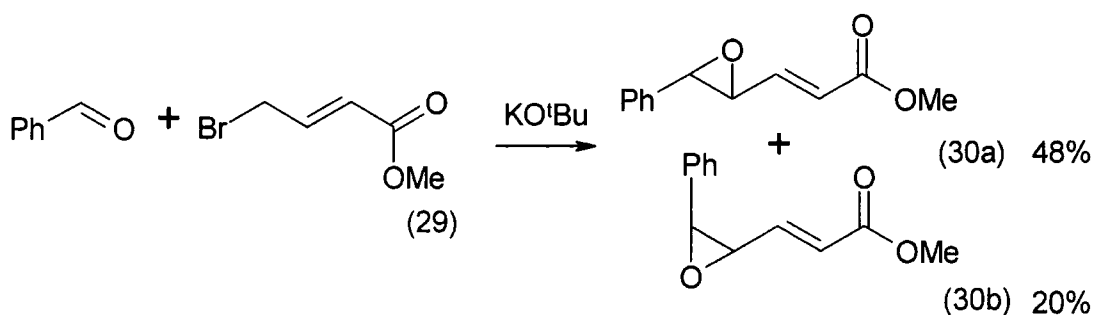
Scheme 32

The *trans* epoxide (30a) had also been selectively prepared using *m*CPBA on the relevant *E,E* diene (31), Scheme 33.[33]
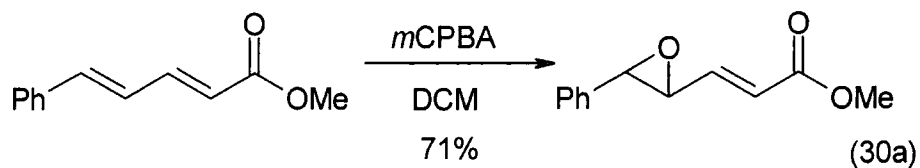
Scheme 33

These processes led to effective, but not the most efficient route available and our group therefore sought more convenient access to these compounds.

A vast number of epoxidation methods are available in modern organic synthesis, and some initial research as to suitable methods for the required precursor was carried out in our laboratories. Synthesis of the vinylepoxy ester (33) commences with a *m*CPBA (*m*-chloroperoxybenzoic acid) epoxidation of cinnamyl alcohol. Subsequent SO$_3$.pyridine activated DMSO oxidation[34] furnished the desired epoxy aldehyde (32) in overall yield of 51% with expected 100% *trans* epoxide stereochemistry, Scheme 34. Attempts to perform the oxidation by standard Swern and PDC methods failed.
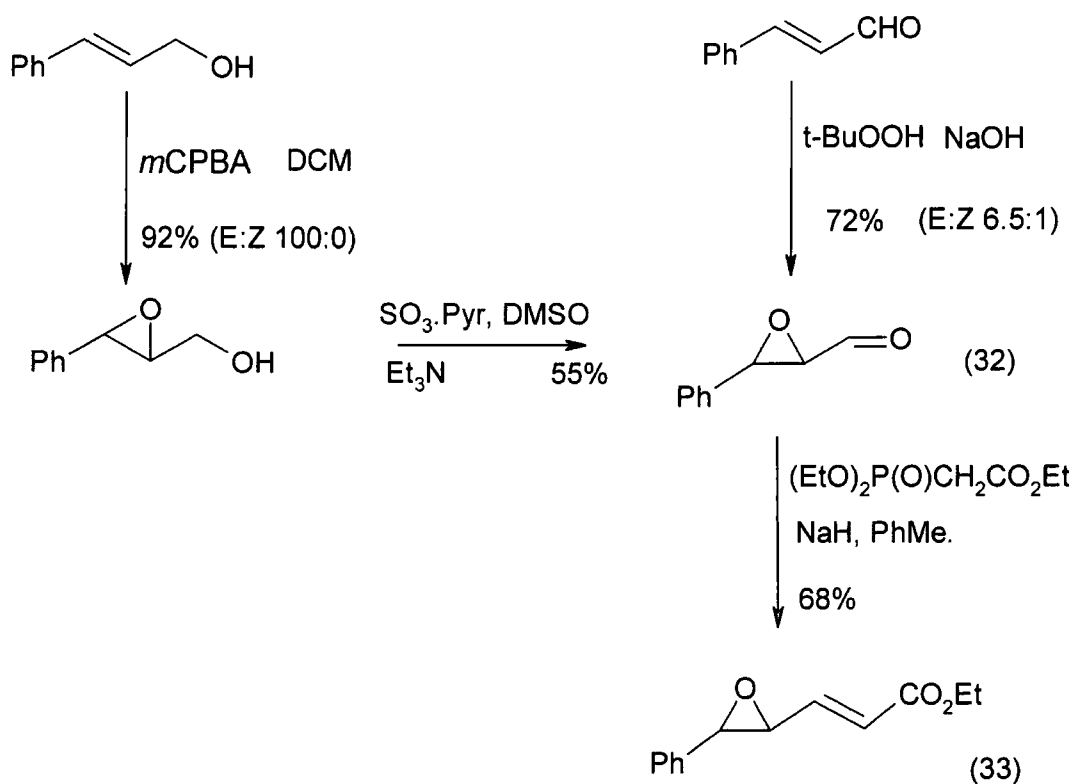
Scheme 34

An alternative procedure following a protocol developed by Payne,[35] using a base mediated *tert*-butyl hydroperoxide epoxidation of *trans*-cinnamaldehyde was then explored. Stereochemistry at the epoxy centre was found to favour the *trans* over the *cis*, (6.5:1) and routinely tendered an overall yield of 72%. Since the epoxide stereochemistry is destroyed in the rearrangement process, this was the favoured, more efficient route to (33), Scheme 34.

With the aldehyde in hand a Wadsworth Emmons reaction using triethylphosphonoacetate then afforded the vinylepoxy ester (33) with 100% *trans* olefin selectivity in 68% yield. Use of the equivalent Wittig reagent proved non-selective and no more efficient. From this development work the rearrangement precursor was available from cinnamaldehyde in 58% yield.

The thermal rearrangements of the vinylepoxide were undertaken using Carius tubes and flash vacuum pyrolysis (FVP) following the same techniques as used by previous researchers.[21,22] The use of Carius tubes allowed small quantities (500mg) to be rearranged to the expected dihydrofuran in good yield and diastereoselectivity whilst FVP allowed the rearrangement of slightly larger quantities albeit with lower selectivity, and less reliability, Scheme 35.
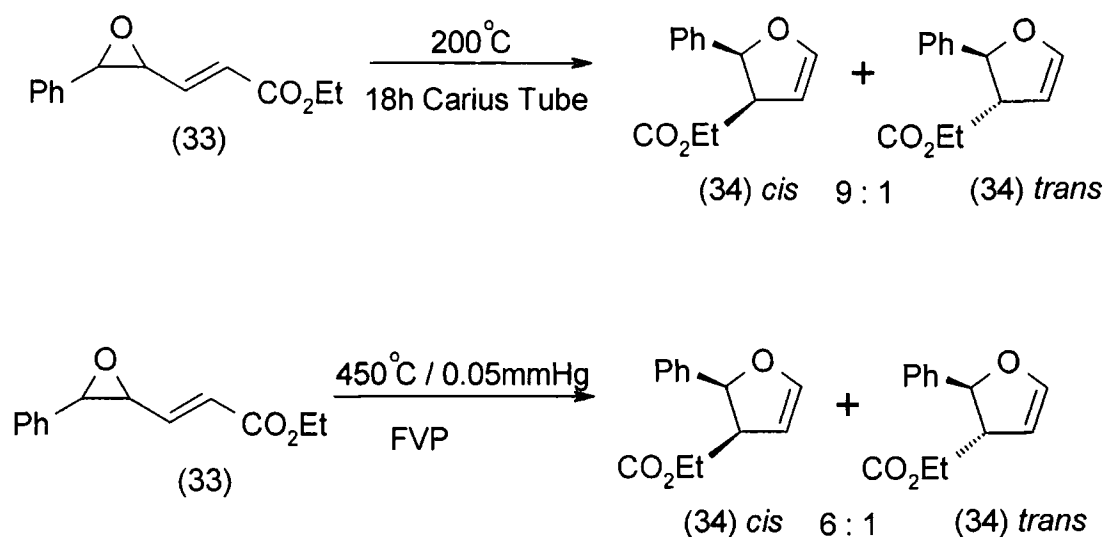
Scheme 35

Attempted application to some alternative substrates, showed FVP to be unsuccessful and thus the Carius tube method appeared to represent the method of choice.[36]

1.7.2 Asymmetric induction

Given the prochiral nature of the proposed ylide-type intermediates, it was envisaged that incorporation of a chiral auxiliary would favour one of the transition states and lead to high levels of asymmetric induction. Given the enolate type intermediate in the rearrangement, an Evans type auxiliary was proposed and explored in previous work within our research group, Scheme 36.

Ylide type intermediates   Evans auxiliary
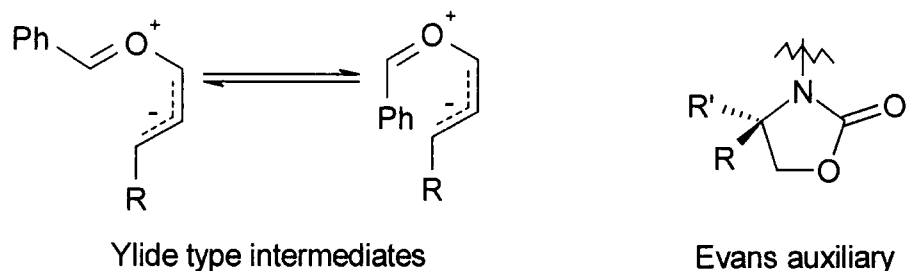
Scheme 36

Coupling was achieved between several oxazolidinones and the required vinylepoxide carboxylic acid (35), using a mixed − anhydride derived from trimethylacetyl chloride in good yields, Scheme 37.[36]

(35)

36a; R=H, R'=H   36b; R=H, R'=i-Pr
36c; R=Ph, R'=H   36d; R=H, R'=Ph
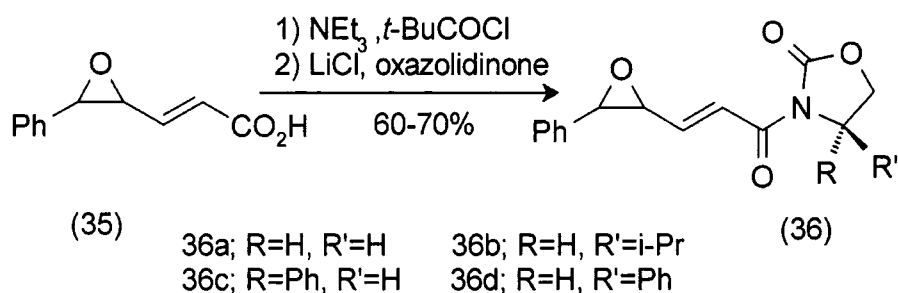
Scheme 37

Fvp of the oxazolidinones (36) proved disappointing with extensive decomposition occurring. However, heating in a sealed Carius tube proceeded smoothly yielding the same stereochemical mixture as with (33).

Treatment of (36c) and (36d) afforded modest diastereoselectivity, Scheme 38, while (36a) and (36b) were essentially non-selective.

37i:37ii:37iii:37iv = 57:33:6:4
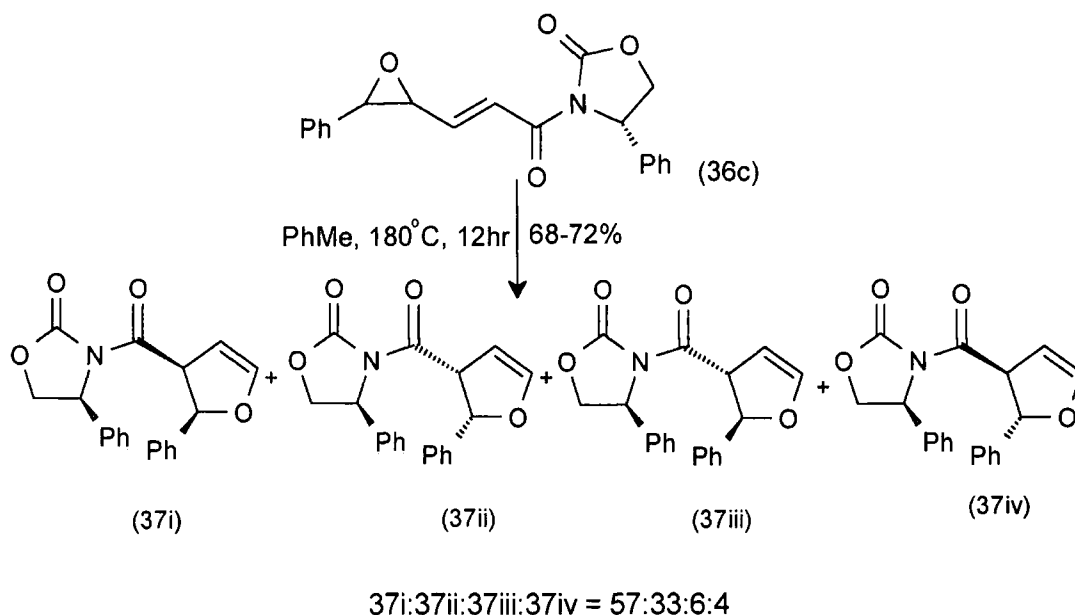
Scheme 38

In order to account for the modest diastereoselectivity, it was suggested that due to the high reaction temperatures there was relatively even population of the two intermediates (38a), (38b) which can be interconverted by rotation around the N-CO bond, Scheme 39. These intermediates are key to determining the selectivity in which the dihydrofuran enantiomers are formed with (38a) proposed to give greater selectivity. Therefore a greater energy difference between the possible transition states was sought.
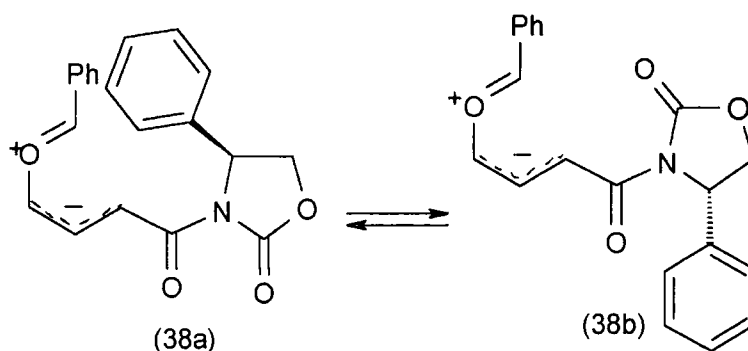
Scheme 39

In an attempt to increase the potential for π facial shielding (+)-phenylmenthol was employed as the chiral auxiliary. Standard N,N'-dicyclohexylcarbodiimide (DCC) coupling with the free acid (35) afforded the desired ester (39), Scheme 40. On heating in Carius tubes the compound rearranged smoothly, however no improvement in diastereoselectivity was obtained.
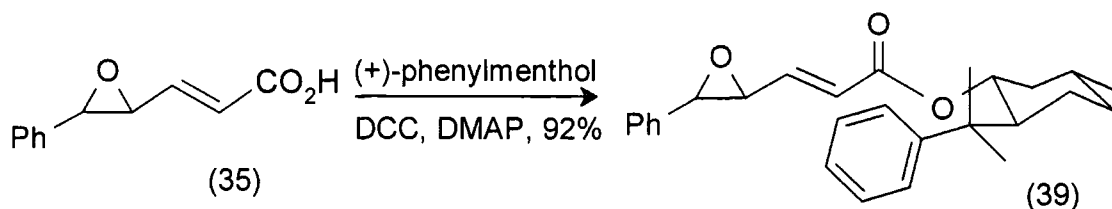
Scheme 40

1.7.3 Vinylaziridines

Many methods are available to generate aziridines.[37] A number of these feature the formation of a nitrene and subsequent reaction with an alkene, Scheme 41. This method is effective in the synthesis of aziridines with substituents on the nitrogen that are not easily prepared from the cyclised, free aziridine.[38]

Scheme 41

Many approaches involve an intramolecular displacement, for example amino alcohols or azide alcohols which are readily available from the corresponding epoxide.

The hydroxy group can be activated via mesylation / tosylation to allow intramolecular displacement to occur resulting in the aziridine with inverse stereochemistry to the original epoxide, Scheme 42.

X=Ms, Ts, etc.
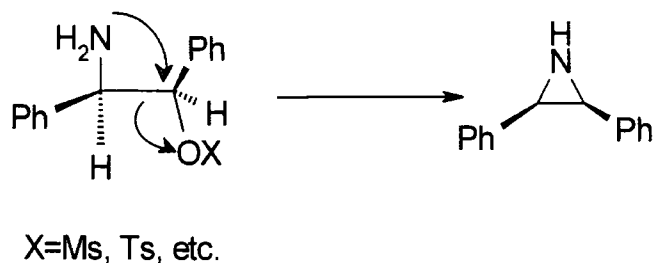
Scheme 42

A more general reaction involves 1,3-dipolar addition of azides to olefins giving triazoles which eliminate nitrogen on pyrolysis or photolysis, and can give a mix of stereochemistry, as in Scheme 43. This method is useful for preparation of *N*-aryl, vinyl, and arenesulfonyl aziridines.
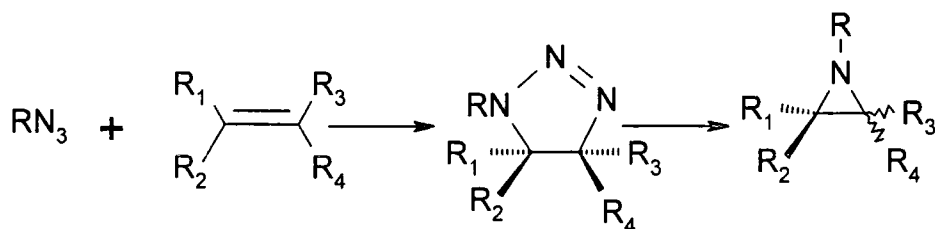
Scheme 43

Using this methodology, synthesis of vinylaziridines would commence from the relevant diene, which presents problems of regioselectivity. Alternatively, formation of the aziridine ring, on in our case, cinnamaldehyde or cinnamalcohol, followed by oxidation and olefination would subject the relatively fragile aziridine ring to basic and oxidative conditions.

There are relatively few literature examples of vinylaziridine synthesis. However, Coldham, *et al.* describe a route to the vinylaziridine of interest via an azide alcohol

(40) intermediate.[39] This route was successfully employed by our group, producing the desired aziridine, albeit in low yields. Some optimisation work was carried out, but without success.
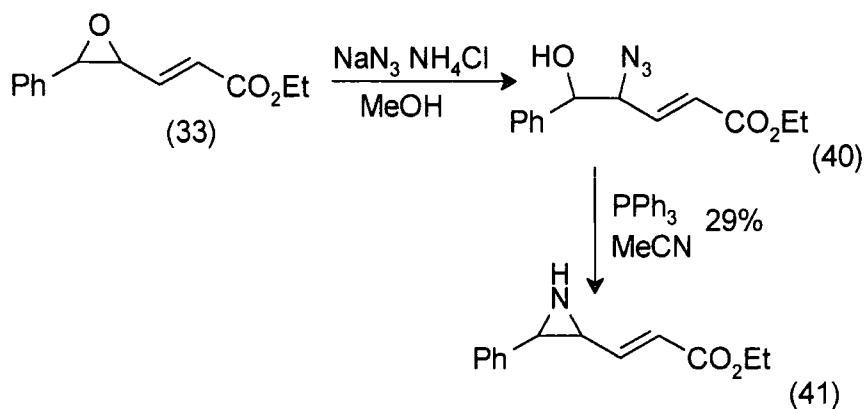
Scheme 44

In the above synthesis, Coldham *et al* isolated products arising from straight chain imine (42) formation when refluxing in acetonitrile in order to promote ring closure to the aziridine (41), Scheme 44.
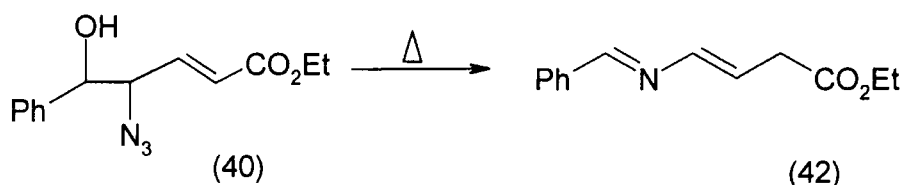
Scheme 45

This pathway occurs despite the conclusions of Borel *et al.* stating a phenyl ring on C-3 of the aziridine inhibits straight chain imine formation, see section 1.5.

In our laboratories, an undergraduate project was concerned with initial work on the rearrangement. The free vinylaziridine was found to decompose on heating, therefore it was decided to protect the aziridine NH to inhibit decomposition. The aziridine was treated with di-*tert*-butyldicarbonate in the presence of DMAP to yield the Boc protected aziridine (43) in 77% yield, Scheme 46.

Attempts at rearranging this compound failed and alternative protecting groups were sought. Benzyl protection via benzyl bromide was attempted but resulted in decomposition. Benzoyl chloride and DMAP was used to treat aziridine (44) in an attempt to produce benzoyl-*N*-aziridine (43). At the time it was concluded the reaction was successful and the *N*-benzoyl aziridine had been obtained.
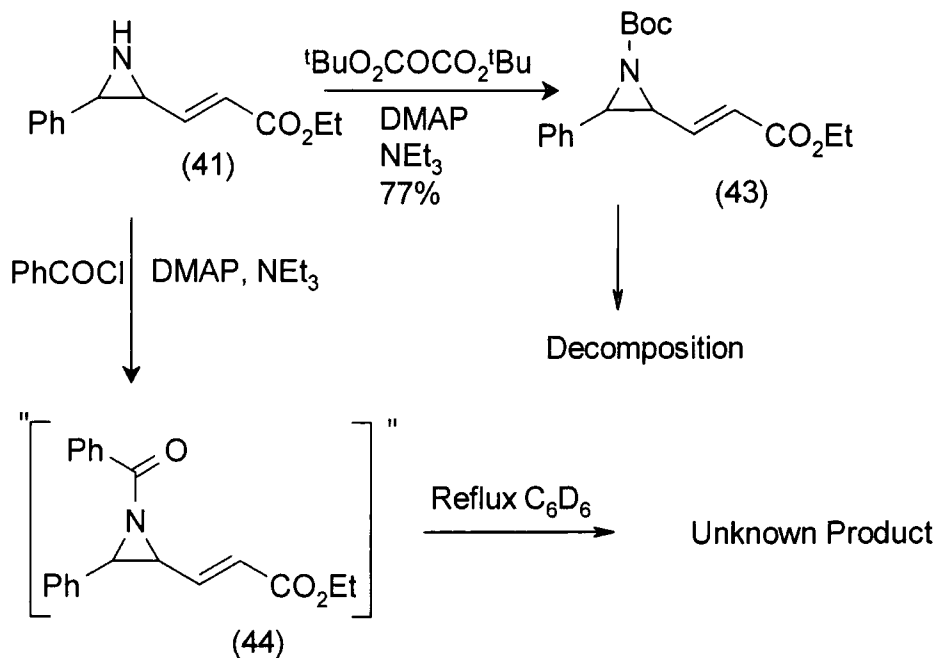
Scheme 46

Thermolysis of this compound on a small scale gave a product which was tentatively assigned as a 2-pyrroline. However insufficient material was prepared to fully characterise the product.

1.8 Project intentions

It was our intention to develop further the established synthesis of the required vinylepoxide precursor, identify improvements to the rearrangement technologies described and pilot new methods with a view to increasing diastereoselectivity, yields and the scale on which the reaction can be performed. Milder conditions or techniques and investigation of the use of catalysts would also be explored.

Given the early results with chiral auxiliaries it was postulated that the rotation around the amide bond limits the effectivity of the auxiliary. It was therefore proposed to utilise a C_2 symmetric chiral auxiliary, in order that the two intermediates, which are thought to be rapidly interconverting, would be identical despite this rapid rotation around the C-N bond. A common C_2 symmetric auxiliary is 2,5-dimethylpyrrolidine,[40] as featured in a recent review of such auxiliaries.[41]

An auxiliary such as this would lead to the intermediate being identical in nature, despite rapidly rotating around the N-CO bond, Scheme 47. This results in the single intermediate and not the two, previously described in Scheme 39.

Synthesis of a suitable chiral auxiliary was to be explored and the rearrangement carried out with the C_2 symmetric chiral auxiliary attached.

Given the reported success of the aziridine rearrangement it was proposed to optimise the route to vinylaziridines, and subsequently investigate the conditions, characteristics and substituent effects on the rearrangement itself.
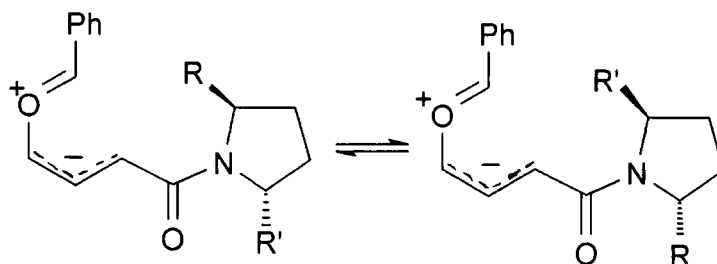
Scheme 47

Finally it is proposed to apply the rearrangement in the synthesis of compounds of interest, for example, suitable target molecules include the diaryl substituted furofuran lignans, Scheme 48.[42]
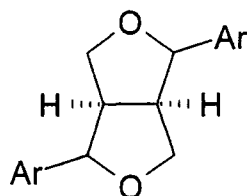
Scheme 48

Section B: Results and Discussion

Chapter 2:   Development of the Vinylepoxide –
Dihydrofuran Rearrangement

2.1   Introduction

This chapter is concerned with the synthesis of vinylepoxides and our subsequent work on the relevant rearrangement processes. Following from the previous work in our group we describe our development of the synthesis and exploration of new rearrangement technologies.   Finally remaining areas for development are highlighted.

2.2   Synthesis of vinylepoxide precursor
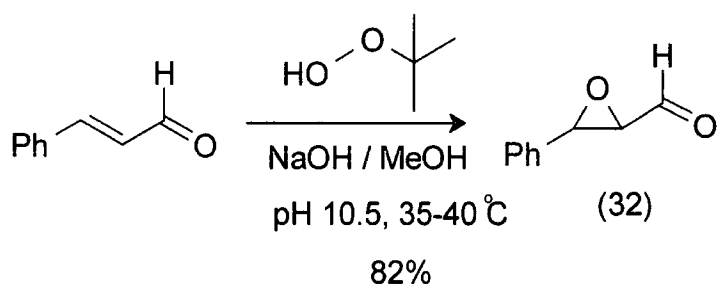
Scheme 49

Following the precedent established in the group by Byerley, we commenced this study by an optimisation of the conditions required for the base promoted epoxidiation of cinnamaldehyde.[35] In this *trans*-cinnamaldehyde is added dropwise to a stirred solution of the *tert*-butyl hydroperoxide in methanol maintained at a constant pH of 10.5 by the addition of sodium hydroxide. However, initial attempts gave low yields and enhanced yields were only obtained with the use freshly distilled *trans*-cinnamaldehyde, and 2.1 equivalents of *tert*-butyl hydroperoxide and under these

conditions an 86% yield was obtained. Prolonged reaction times did not appear to have any significant effect on the reaction yield and the product could be purified by distillation as a colourless liquid.

Evidence for generation of the epoxide was obtained from the mass spectrum which gave the required molecular ion. Confirmation of the product was obtained from the ^{1}H NMR spectra which showed an absence of vinylic signals and exhibited two isomeric aldehyde peaks, δ = 9.18, 9.09, indicating a 6.5:1 *trans:cis* ratio. Separate samples of the *cis* and *trans* isomers could be obtained by flash chromatography, although this was not routinely carried out.
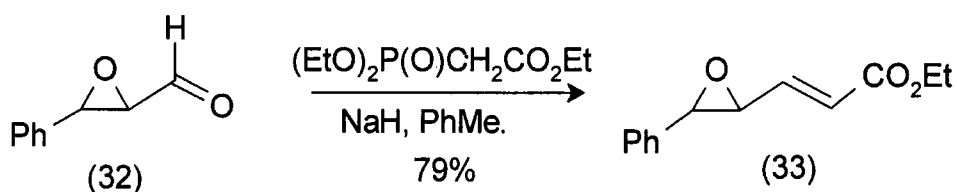
Scheme 50

Byerley had previously shown that the conversion of aldehyde (32) to the required alkene was best achieved using Horner-Wadsworth-Emmons methodology, however this conversion had never been achieved on significant scale. Repeating these early conditions, that is adding aldehyde (32) dropwise to a solution of the anion of triethyl phosphonoacetate (generated by dropwise addition to a cooled, stirred suspension of sodium hydride in toluene) resulted in low yields due to competing polymerisation and decomposition. In an attempt to avoid this, the concentration of the anion was progressively lowered in subsequent experiments, Table 2.

Mass aldehyde (32)	Qty aldehyde (32)	Solvent	Molarity of (32)	Yield
3.0g	0.02mol	35ml toluene	0.58M	26%
3.0g	0.02mol	60ml toluene	0.33M	51%
7.0g	0.05mol	150ml toluene	0.31M	61%
18.5g	0.125mol	300ml tol/THF	0.42M	37%
23g	0.155mol	550mol toluene	0.28M	72%
50g	0.338mol	1000ml toluene	0.34M	79%

Table 2

These findings indicate that toluene is an adequate solvent for the reaction, but the concentration must be less than 0.35M to avoid polymerisation or decomposition. Under these conditions it proved possible to prepare the ester on a 50g scale, in 79% yield following purification by vacuum distillation.

Inspection of the ^{1}H NMR showed the required vinylic proton signals (δ = 6.81, 6.18) (δ = 6.46, 5.95 for *cis* epoxide isomer) indicating exclusive production of the *trans* olefin production (J=15Hz), with the epoxide isomer ratio still 6.5:1. The absence of a signal in the δ = 9-10 ppm region indicates complete consumption of aldehyde. Although the isomers could be separated by flash column chromatography, this was not routinely carried out, as each isomer produces the same products on thermolysis.

2.3 Vinylepoxide – dihydrofuran rearrangement

2.3.1 Thermal Rearrangements

Carius Tubes
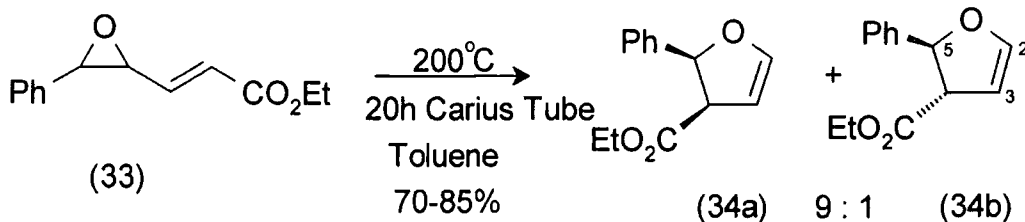
Scheme 51

The rearrangement was carried out cleanly as described by Byerley at 200°C in toluene in a Carius tube.[36] Crude proton NMR showed the *cis / trans* ratio of products (34a), (34b) to be 9:1, as expected from the rationale explained on p14. Flash chromatography partially separated the *cis* from the minor *trans* compound giving yields of between 70 and 85%. The best results were obtained when the starting epoxide (33) was freshly columned and the resultant solution thoroughly degassed by a freeze-thaw process prior to sealing the experiment for heating. Reaction times were varied between 16 and 25 hours, and temperatures of 180°C, and 200°C were tested. Optimum conditions, providing complete conversion of starting material with minimum decomposition, were 200°C for 18 hours with a concentration of 0.12M in toluene. More concentrated mixtures lead to incomplete conversion or high percentages of decomposed material. Proton NMR showed the shift in vinyl signals to $\delta = 6.7$, 5.1 and the C4 proton at $\delta = 4.1$, C5 proton at $\delta = 5.8$. The expected molecular ion was observed by mass spectrometry.

In search of more convenient and potentially milder conditions, a series of experiments to attempt the thermal rearrangement of the precursor (33) in a variety of solvents, under nitrogen / argon atmospheres, at varying time periods were conducted. The solvents used were all of high boiling point, and varying polarity; *N-*

methylpyrrolidinone (NMP, 202°C), diphenyl ether (PhOPh, 260°C), o-dichlorobenzene (180°C). As a control for comparison with the Carius tube experiments toluene was also tried (bp. 110°C). However, in all cases the material recovered was merely starting material or decomposed products. A second variable is the pressure generated in the thermolysis. Using Carius tubes it has not been possible to measure the pressure generated, although using the ideal gas equation, the theoretical maximum pressure is about 75 atmospheres. However, the glass Carius tubes are thought to hold a maximum pressure of no more than 30 atmospheres and consequently this calculation has some obvious limitations. Furthermore, this technology is limited by scale, with only 500mg being rearranged per experiment. FVP had proved to be an unreliable alternative providing less than 100% conversion, poorer diastereoselectivity and ineffective in the rearrangement of further substrates. Given this knowledge and the rudimentary FVP apparatus in our laboratories we elected to pursue stainless steel bomb technology to scale up the rearrangement from our 500mg turnover. This work is described in the next section.

Use of stainless steel bomb technology

As discussed above, we sought to examine the effect of pressure on the vinylepoxide – dihydrofuran rearrangement. The ideal technique appeared to be stainless steel bomb technology which offered increased maximum working pressures, and also a larger scale of reaction. They are also available for use in laboratories not equipped for Carius tube experiments. Initially, to simulate the Carius tube experiments, a pressure gauge attached to a 100ml capacity stainless bomb was used to measure the pressure induced by 20ml toluene being heated to an external temperature of 205°C with a maximum of 2 atmospheres being recorded. Given that Carius tubes are of a similar volume (80-100ml), it seems the pressure generated in the Carius

tubes were unlikely to exceed 3 atmospheres. This enabled some basic thermodynamic characteristics of the reaction solvent to be investigated to discover how much pressure was generated for given volumes of toluene, Table 3.

Toluene/ml	No. Moles Toluene	Temperature/°C	Pressure generated/atm.
35ml	0.33	163	3
35ml	0.33	180	5
35ml	0.33	200	7
90ml	0.85	205	30

Table 3

Given the maximum working pressure of the stainless steel bomb in question was 300 atmospheres, a measured pressure of 30 atmospheres was quite acceptable. With these pressure / volume limitations clarified, we were able to develop optimum conditions for the thermal rearrangement in stainless steel bombs, Table 4.

Run	Toluene /ml	Substrate (33) /g	Temp. /°C	Pressure /atm	Reaction Time/hr	Yield (33)
1	50	1.4	200	10	22	10%
2	90	5g	208	35	17	40%
3	90	5g	205	30	8	68%
4	92	5g	205	62	9	69%
5	85	5g	205	10	9	68%
6	92	5.2g	210	60	6	68%
7	88	8g	205	40	9	63%
8	90	7g	205	30	8	71%

Table 4

Initially similar reaction time and temperatures to the Carius tube experiments were used but these were found to yield mainly decomposed material with only small quantities of the desired product (runs 1 and 2). By halving the reaction time, the yield was increased to a respectable 68% (run 2, to 3). A doubling of the pressure generated from 30 to 62 atmospheres (in runs 3 to 4) produced no change in the reaction yield. Similarly a decrease to 10 atmospheres did not alter the results.

In the optimum experiment (run 9) 7g of vinylepoxide was converted to the dihydrofuran in 71% yield, in 8 hours. That is equivalent to 14 Carius tube experiments over 20 hours, which due to our limited Carius tube facilities would take at least about 6 working days with the previous technique.

Diastereoselectivity was monitored from crude ^1H NMR and found to be consistently 9:1 *cis:trans* with all data being identical to the product found by Carius tube rearrangement.

A change in laboratories with different stainless steel bomb guidelines required that the bomb be only 1/3 filled. The best result with 35ml toluene and 5g of substrate at 200°C gave a yield of 38%. In a subsequent experiment the starting pressure was increased by addition of nitrogen, to 30 atmospheres pressure. Heating the same experiment under the same conditions generated a total pressure of 50 atmospheres, and gave the desired product in a yield of 47%. This arrangement was less than ideal, and it seems our optimum conditions require a moderate pressure of toluene vapour. This could be due to a negative volume of activation for the reaction, and hence some pressure is required for the reaction to proceed. The negative volume of activation indicates that ring closure to the furan product is the rate determining step, and not the opening of the epoxide ring. In conclusion, we have developed the rearrangement in stainless steel bombs, enabling a larger scale reaction, producing up to 5.7g in one reaction. This gave us sufficient material for further work on the rearranged product – see chapter 4.

2.3.2 Alternative methods for the promotion rearrangement.

Microwave technology

In microwave promoted reactions energy transfer operates through dielectric loss rather than thermal convection or conduction, and hence heating efficiency is largely solvent dependant.[43] It is suggested that DMF and acetonitrile with significant dipole moments produce greater heat transfer than solvents such as toluene and hexanes.

(33)

Solvent = Toluene
DMF
Neat

Scheme 52

(34)
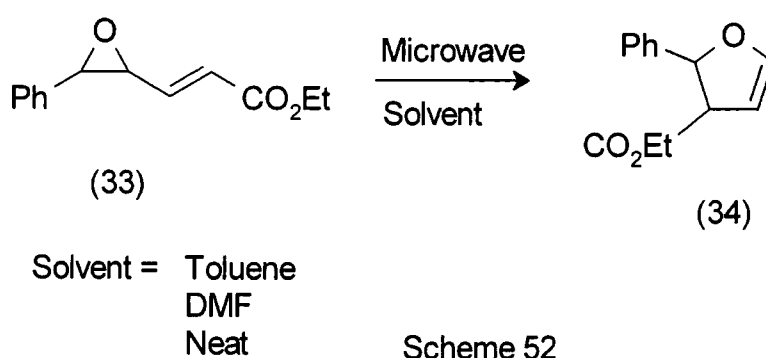
For our experiments a Pyrex conical flask was used, capped with a narrow bore funnel to limit evaporation. Three reactions were carried out, in toluene (20ml), DMF (20ml), and neat. In each case the epoxy ester (33) was subjected to irradiation for 2 minutes before allowing the reaction to cool over 1 minute, before repeating the cycle, 9 times. No change was observed by TLC, and on NMR analysis no evidence of rearrangement or isomerisation was observed. This cycle of rapid heating and cooling is a problem associate with domestic microwaves, which is overcome with a commercial "*continuous microwave reactor*" (CMR), which allows efficient cooling and better control of heating temperature. A reactor such as this would have allowed more intense, greater controlled reaction conditions.

Ultrasonication

Again as a more recent technique, sonication was explored as a method of inducing the rearrangement. Reactions occur as micro hot-spots develop within the solution when it is ultrasonicated, with temperatures as high as 15,000°C occur in the minute energy bubbles that rapidly appear, expand and relax creating high energy zones. A variety of solvents were tested in our survey, in attempts to perform the rearrangement on epoxy ester (33). In each case the sample was subjected to 90 minutes of ultrasonication treatment in a room temperature water bath using a standard laboratory sonicator. The solvents tested were; acetonitrile, methanol, chloroform, toluene and DMF. The reaction was also attempted neat. In each case starting material was recovered with no evidence of isomerisation occurring. Given our limited resources and expertise in the area a more in depth investigation by another research group is warranted. However our brief experiment showed there was no effect on straightforward sonication, more specialised apparatus is required to reach higher energy conditions.

Lewis Acid facilitated rearrangements

Given that the intermediate involved in the thermal rearrangement is of an ylide-type nature, it was hypothesised that access to this intermediate may be possible through Lewis acid catalysis. It was anticipated that the desired process requires co-ordination to the ester moiety, which would decrease the energy barrier for C-C bond cleavage of the epoxide. Although it is expected that the Lewis Acid may favour binding to the epoxide and the resulting competing process is ring opening at the C-O bond, facilitating access to the relevant diol or hydroxy halide compound, Scheme 53.

Desired Process

Competing Process

Scheme 53
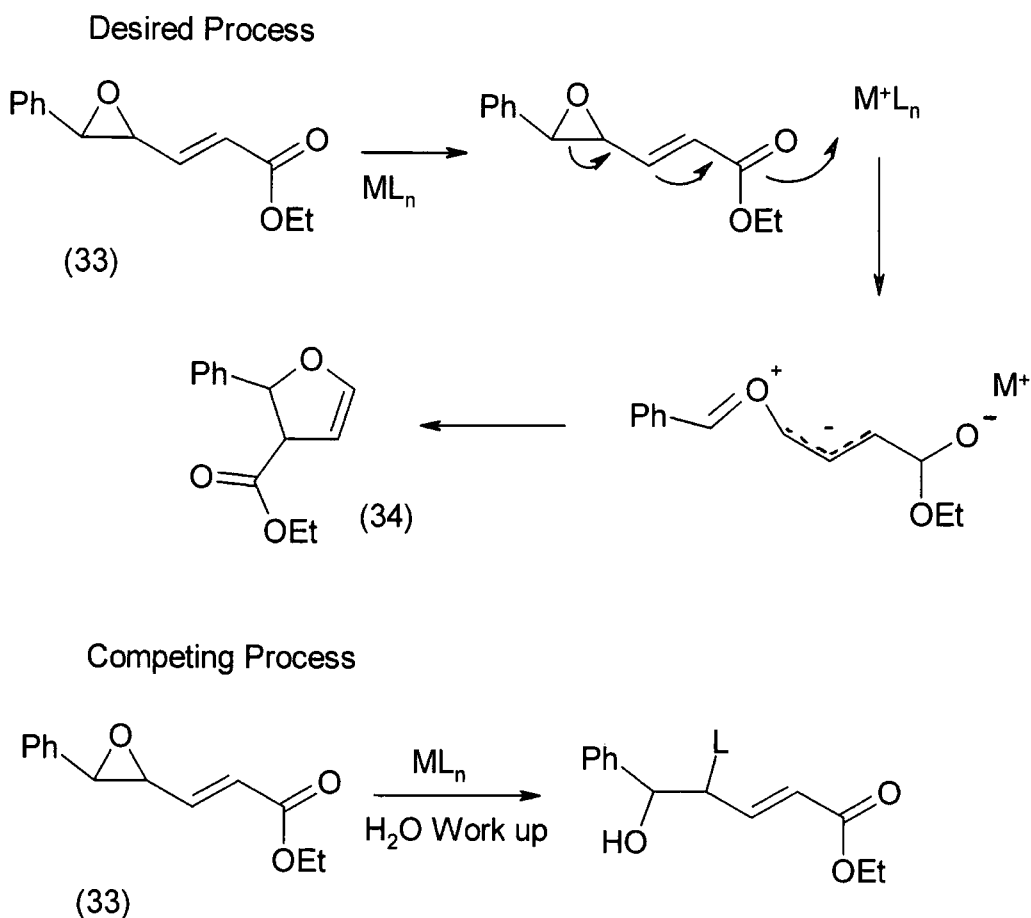
We chose to conduct a survey of potential Lewis acids, with a broad range of metals/cations and various counter ions in a variety of solvents for each Lewis acid. All reactions were conducted at 30°C in a waterbath, and monitored by TLC. Using library techniques, a total of 39 Lewis acids, and similar compounds (silica, zinc powder, triflic acid, and various salts) were surveyed in six solvents; tetrahydrofuran, dichloromethane, diethyl ether, acetonitrile, toluene and DMF.

In each experiment 0.1mmol of epoxy ester (33) was shaken with 0.1mmol of Lewis acid in the solvent, at 30°C for 96 hours in anhydrous conditions. After workup using Jones tubes for rapid work up of multiple samples, those displaying no change by TLC were analysed by ^{1}H NMR and found to contain only starting material (33). The remainder, showing some change by TLC (summarised in Table 5), were analysed by LC-MS.

Lewis Acid	Solvent					
	THF	DCM	EtOEt	MeCN	Tol	DMF
AgCl						
Al(O^{i}Pr)$_3$						
AlBr$_3$	✓	✓	✓	✓	✓	✓
AlCl$_3$	✓	✓	✓	✓	✓	✓
AlMe$_2$Cl						
BCl$_3$						
BF3.OEt$_2$	✓	✓	✓	✓	✓	✓
B(OMe)$_3$						
CaCl$_2$	✓	✓	✓			
Ce(SO$_4$)$_2$		✓			✓	
CsCl						
CuCl						
CuCl$_2$						
FeCl$_3$	✓	✓	✓	✓	✓	✓
LaCl$_3$						
La(OTf)$_3$	✓	✓	✓			
LiBr						
LiCl						
LiClO$_4$						
MgCl$_2$						
Sc(OTf)$_3$		✓	✓	✓	✓	✓
Silica						
SiCl$_4$	✓	✓	✓	✓	✓	✓
SnCl$_2$	✓	✓	✓	✓	✓	
TeCl$_4$	✓	✓	✓	✓	✓	✓
Ti(iPrO)$_4$		✓	✓	✓	✓	✓
TiCl$_4$	✓	✓	✓	✓	✓	✓
TMSOTF	✓	✓	✓	✓	✓	✓
Triflic Acid	✓	✓	✓	✓	✓	✓
Yb(OTf)$_3$	✓	✓	✓			
Zinc Powder						
Zn(OTf)$_2$		✓	✓			
ZnBr$_2$		✓				
ZnCl$_2$						
ZnI$_2$		✓				
Zr(^{t}BuO)$_4$						
ZrCl$_4$						

✓ = Change observed by TLC

Table 5

However, problems with the LC-MS occurred which were attributed to unreliable machinery and residues of Lewis Acids in the samples which prevented suitable analysis. Analysis by ^{1}H NMR showed no trace of desired product (characteristic ^{1}H NMR peak at 0.8ppm (Me of ester) not present), some starting material was clearly present but the majority appeared to be decomposed / polymeric material with no significant quantities of any identifiable product materials, Table 5.

Cleavage of the epoxide ring is thought to have occurred in most of these processes, particularly in DCM, where the presence of trace quantities of HCl would lead to the chloro hydrin being obtained. This limited study surveyed a broad range of Lewis acids, with a number of solvents but at only one reaction time and temperature.

This brief work demonstrates the epoxide ring seems to be favoured strongly by the Lewis acids surveyed, and if the area is to be explored in future work, then a different substrate, with more favourable binding properties to the carbonyl of compound (33) eg, compound (45), Scheme 54, should be investigated. This is more likely to promote the required rearrangement.
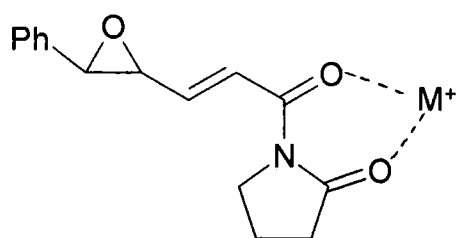
(45)

Scheme 54

2.4 Summary: The vinylepoxide – dihydrofuran rearrangement

The vinylepoxide rearrangement proceeded as expected in good yield. We have developed the rearrangement in stainless steel bombs in order to scale up the reaction and obtain sufficient diastereomerically pure material for the study of its application in the synthesis of target molecules (chapter 4). Alternative technologies and Lewis acid mediated access to the dihydrofurans have been investigated, albeit with no success to date. However, there is some foundation work that has been covered in this area and these represent the future work for development. Investigation into the application of the rearrangement to other substrates is in a suitable position to proceed with these refined conditions. Molecules such as the 3'-4'-methoxyphenyl derivative (46) may facilitate lower activation energy access to the necessary ylide-type intermediate.
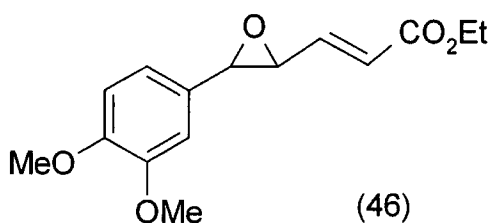
Scheme 55

Chapter 3:   Chiral Auxiliary Synthesis and Application

3.1 Introduction

This chapter is concerned with the work undertaken in attempting to achieve enantioselectivity in the vinylepoxide – dihydrofuran rearrangement. Previous work undertaken in our laboratories is detailed and our strategy explained in the background material. Results of the synthesis of a variety of chiral auxiliaries, and our application of them into the rearrangement are described.

3.2 Background – Chiral Auxiliaries

As discussed in chapter 1, it was proposed to synthesise a suitable C_2 symmetric chiral amine to lessen the problem of rapid rotation of the chiral auxiliary around the amide bond, Scheme 56.
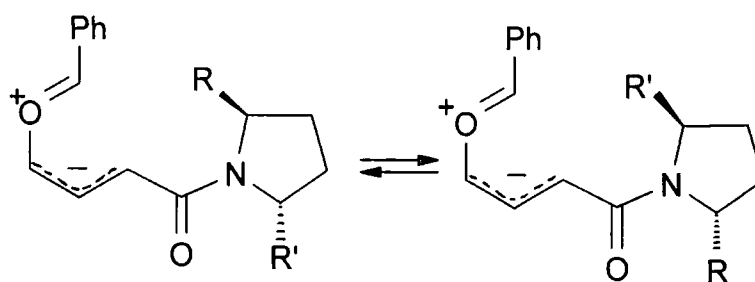
Scheme 56

The simplest candidate was thought to be 2,5-dimethylpyrrolidine (47) and has been used in the past as an effective chiral auxiliary, for example on a vinylogous urethane enolate, Scheme 57.[44]
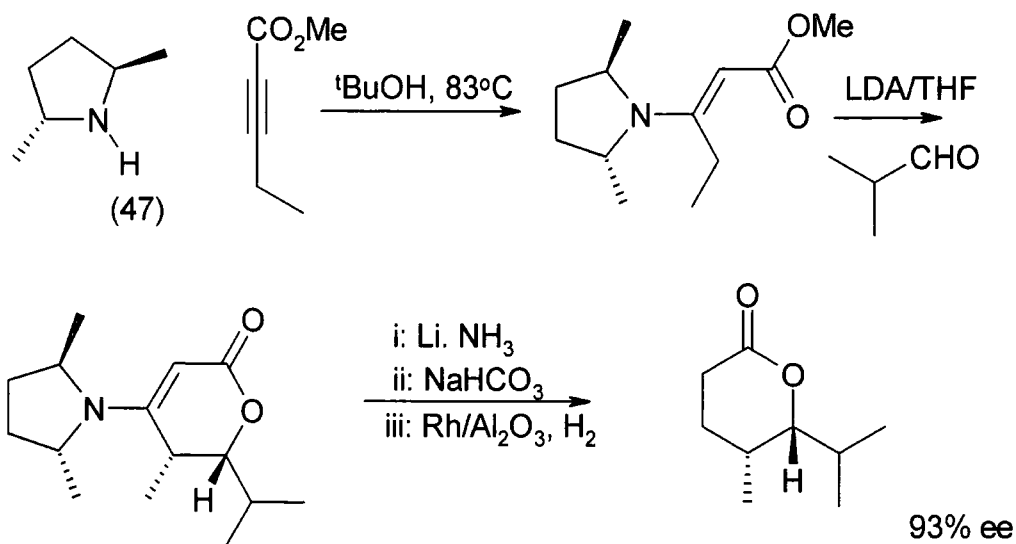
Scheme 57

Strategies towards 2,5-dimethylpyrrolidine

Adopting this approach required access to the chiral auxiliary. Although common, routes to 2,5-dimethylpyrrolidine were traditionally challenged by the tendency for many reactions to form the *cis* (meso) diastereomer. Early methods have utilised resolution, such as the protocol by Whitesell, in which the amine was resolved by forming salts with mandelic acid.[45] Other methods utilising a convenient bakers yeast reduction of hexan-2,5-dione described by Lieser[46] were limited to a yield for the reduction of 50%, and only the (S,S)-hexanediol (48) was accessible. Commonly, the ring closure was effected by mesylation, and benzylamine to yield the protected *N*-benzyl-(R,R)-dimethylpyrrolidine (49) with good ee, typically 96%, Scheme 58.[47]
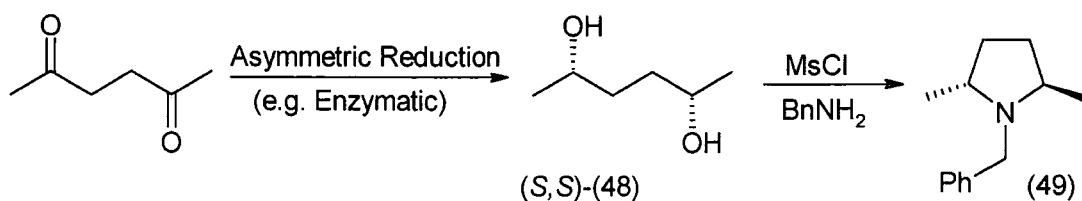
Scheme 58

Alternative methods have sought to utilise the chiral pool of amino acids to access (R,R) and (S,S)-dimethylpyrrolidine (47). This has been achieved using either D- or L-alanine in overall 44% yield, by Schlessinger, Scheme 59.[48]
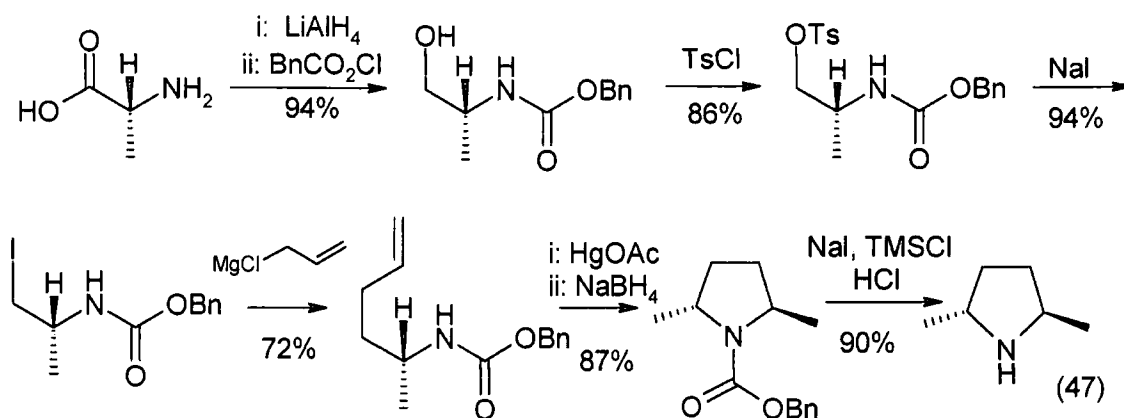
Scheme 59

More recently Beak reported a method of generating (S,S)-2,5-dimethylpyrrolidine (47), through asymmetric deprotonation utilising s-butyllithium in the presence of (-)-sparteine as a chiral ligand, Scheme 60.[49]
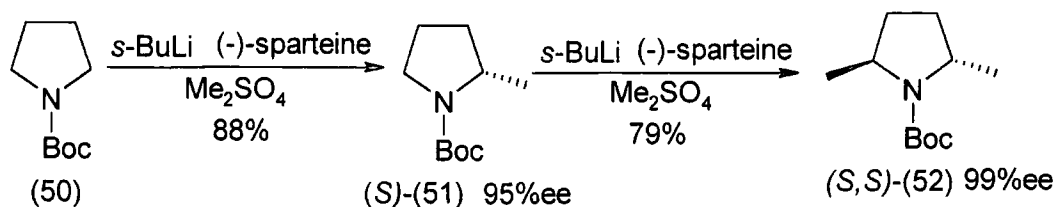
Scheme 60

Given the high enantiomeric excess found in this reaction, and the good yields over what is essentially a two-step process, it was decided to pursue this methodology in our synthesis of trans-2,5-dimethylpyrrolidine.

3.3 Synthesis of *trans*-2,5-dimethylpyrrolidine by asymmetric deprotonation

Boc-pyrrolidine (50), was prepared from di-*tert*-butyl dicarbonate (Boc anhydride), with pyrrolidine and base. Protection proceeds cleanly and the desired compound can be distilled to provide the product (50) in 92% yield. The product was characterised by a carbonyl stretch in the IR (1690 cm^{-1}), assigned proton spectra and the molecular ion seen by mass spectrometry.
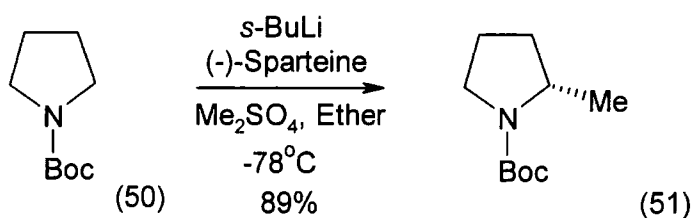
Scheme 61

With this carbamate in hand we examined the asymmetric deprotonation. This requires access to pure sparteine. With commercially available material, it was difficult to obtain reproducible results with this material. Ultimately it was found to be more reliable and cheaper to access this cleanly from the corresponding sulfate pentahydrate, by addition of base to release the free amine. Organic extraction followed by distillation from calcium hydride yielded the desired chiral ligand (53) in 89% yield. Sparteine (53) was characterised only by boiling point and optical purity was checked before proceeding with deprotonation of *N*-Boc-pyrrolidine (50), Scheme 61.

The deprotonation complex (54) was prepared first, as described by Beak. We also found it essential to age the complex (54) for 30 minutes in order to obtain good yields. After 6 hours the dimethylsulfate was added and reaction stirred for 12 hours.

We obtained better yields with 1.1 equivalents of dimethylsulfate, than with the prescribed 1.5 equivalents used by Beak. After work up, purification by flash column chromatography yielded the (S)-N-Boc-2-methylpyrrolidine (51) in 89%. The optical rotation closely matched the pure (S)-N-Boc-2-methylpyrrolidine literature value. Proton NMR confirmed the methylation had taken place with a suitable CH_3 signal at δ = 1.16, and mass spectrometry revealed the expected molecular ion.

Preliminary attempts at this reaction were thwarted due to difficulties maintaining the required anhydrous conditions. Using freshly distilled ether, and dimethylsulfate distilled from calcium hydride ensured the success of subsequent attempts. Temperature control was also important with a constant -78°C throughout the reaction improving the yield as did using only a 1.1 equivalents of dimethylsulfate.

The stereochemical outcome is attributed to the asymmetric deprotonation of pyrrolidine with fixed coordination of the lithium – sparteine complex (54) to the nitrogen and carbonyl of the Boc-pyrrolidine. This allows directed addition of the electrophile, with retention of configuration of the C-Li bond to C-Me, Scheme 62.
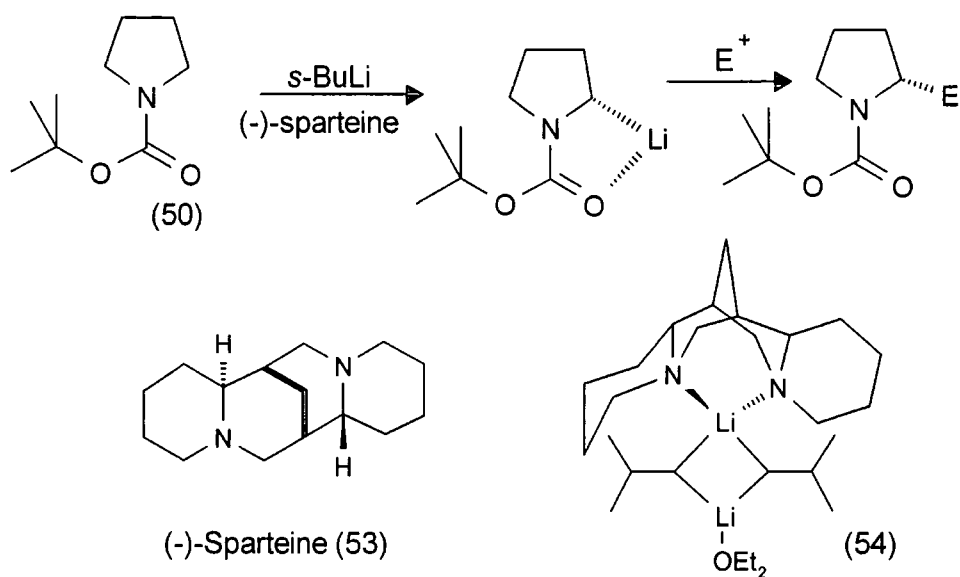
Scheme 62

Continuing with Beak's method we conducted the second deprotonation on Boc-2-methylpyrrolidine (51) following the same procedure as before. This proceeded well with freshly distilled, dry solvent and reagents.

$$s\text{-BuLi} \ -78°C$$
$$(-)\text{-Sparteine}$$
$$\xrightarrow{\hspace{2cm}}$$
$$Me_2SO_4, \ Ether$$
$$72\%$$
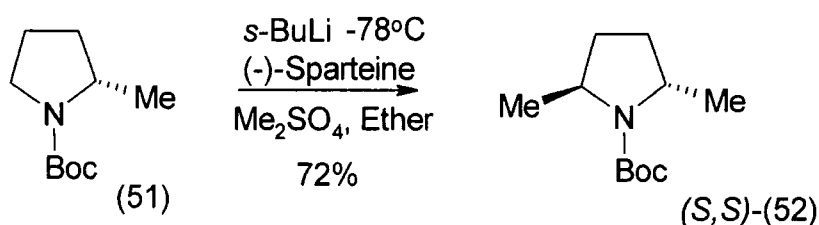
Scheme 63

Yields were initially low (ca 30%) but the starting Boc-2-methylpyrrolidine (51) could be recovered by flash chromatography and reused. It was found that the proportion of sec-BuLi, sparteine and dimethylsulfate was important in determining the success of the reaction. The reaction yields improved when the ratio of dimethylsulfate to starting Boc-2-methylpyrrolidine was 1.1 rather than 2. On a small scale, using up to 1g of Boc-2-methylpyrrolidine (51), it was found that 4 equivalents of sparteine (53) and sec-butyllithium were required to give a 63% yield. However, in the large scale synthesis (4.5g of Boc-2-methylpyrrolidine), 2 equivalents of sparteine and sec-butyl lithium at -70°C were sufficient to produce a 72% yield. Separation from starting material was achieved by flash chromatography and the proton NMR indicated the product was the dimethyl species due to the disappearance of a signal at δ = 3.35 for CH_2N, and the increase in intensity of the signal at δ = 1.12 for the methyl groups. Optical rotation again closely matches that found in the literature, and ^{13}C spectra gave only 6 carbon signals indicating only one isomer present. Mass spectrometry indicated the expected molecular ion.
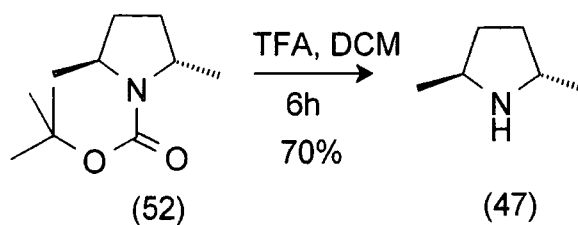
Scheme 64

Trifluoroacetic acid was used to remove the Boc group from the *N*-Boc-2,5-dimethylpyrrolidine yielding the free (*S,S*)-2,5-dimethylpyrrolidine (47) which due to its volatility could not be subjected to flash chromatography and instead was purified by vacuum transfer. The product was confirmed by proton NMR, no longer displaying the intense singlet at δ = 1.4 for the Boc group, and showing a doublet at δ = 1.3 for the two methyl groups. A broad NH signal is also apparent at δ = 1.4-1.3, and the mass spectrum shows the mass ion.

Although free dimethylpyrrolidine could be obtained and handled as a DCM solution, the volatility rendered the compound difficult to manage and handle. Additionally we were concerned as to how efficiently it could be coupled with the epoxy acid (35), and subsequently recovered.

3.4 Alternative chiral auxiliary; 2,5-diphenylpyrrolidine

These concerns were shared in the literature where an alternative auxiliary, 2,5-diphenylpyrrolidine was suggested as an alternative. This had been synthesised by Chong and co-workers using an asymmetric reduction of dibenzoylethane, and an effective route via the dimesylate to the *N*-allyl protected pyrrolidine.[50] The enantiomeric excess achieved would be reliant on the asymmetric induction achieved in the reduction of the diketone. Chong utilised the (-)-diisopinocampheylchloroborane

(Ipc$_2$BCl) reduction as developed by Brown.[51] The overall Scheme from dibenzoylethane is shown in Scheme 65.
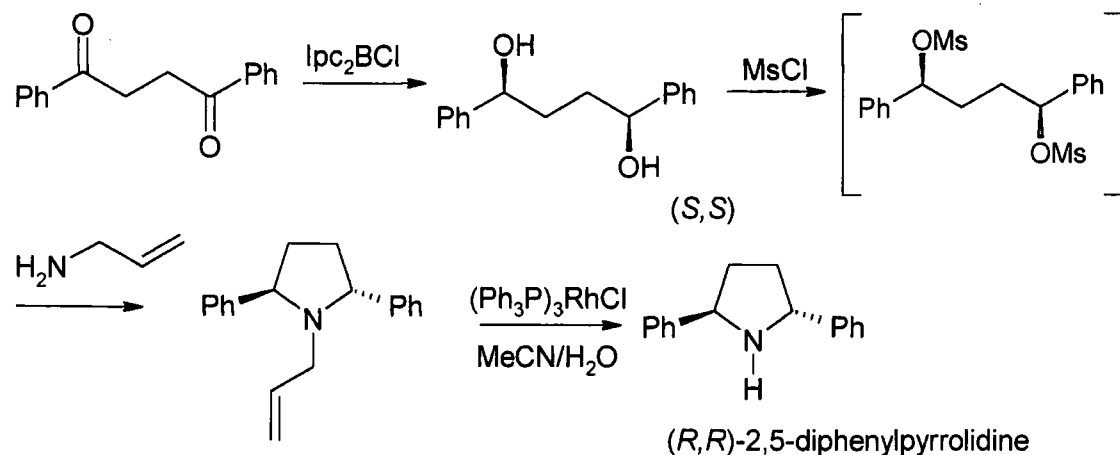
Scheme 65

Related reductions of diketones with a range of substituents have been carried out by Quallich *et al.* using diphenyl oxazaborolidine to yield other 1,4-diols in varied enantiomeric excess, Scheme 66.[52]
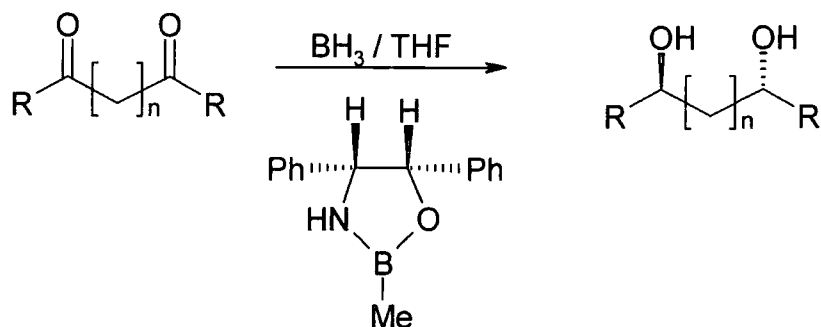
Diketone:	Meso / R,R + S,S	%ee, S,S.
R = Ph, n = 2.	16 / 84	99
R = Me, n = 2.	31 / 69	17
R = ^{t}Bu, n = 2.	20 / 80	97

Scheme 66

Whilst both of these represented attractive routes it would still be necessary to prepare the chiral reductant, which can be a non-trivial operation requiring a 18 hour

premix of the chiral auxiliary and borane. Furthermore, good diastereoselectivity and enantioselectivity requires stoichiometric amounts of the oxazaborolidine.

On further examination of the literature, we became aware of a report detailing the use of 0.05 equivalents of the amino alcohol, diphenylprolinol (55), to reduce mono-ketones asymmetrically, with borane.[53]

With trimethylborate, the prolinol forms oxazaborolidine (56), Scheme 67 and on application the reduction of acetophenone proceeds in above 90% yield resulting in an ee of 98%.
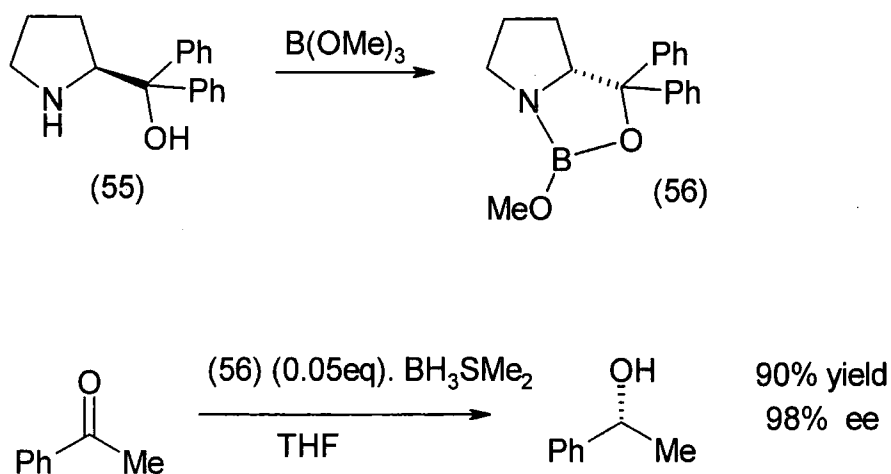
Scheme 67

Amino alcohol (55) is readily available commercially (either enantiomer), and with a ready source of the required amino alcohol we decided to use this reduction on dibenzoylethane and pursue a synthesis of 2,5-diphenylpyrrolidine from the resulting diol. We also decided to extend this reduction to several 1,4-diketones with a view of creating the enantiomerically pure diols, to explore this as a key step in a route to 2,5-disubstitued pyrrolidines.

3.5 Synthesis of 1,4-diols and 2,5-diphenylpyrrolidine

As described in the previous section, our route to 2,5-diphenyl pyrrolidine requires access to dibenzoylethane. Although this is commercially available it is expensive and we sought an in-house synthesis. A Friedel-Crafts reaction between benzene and fumaryl chloride is precedented and provides access to dibenzoylethene (57).[54]
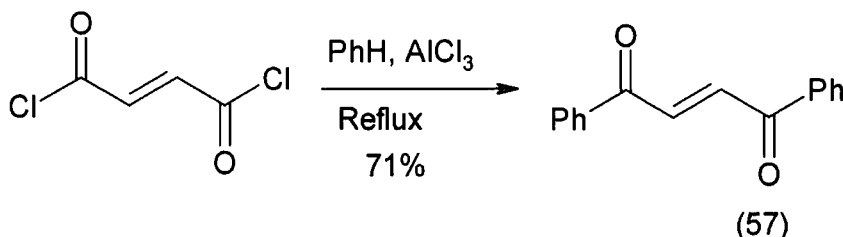
Scheme 68

Success of the Friedel-Crafts reaction relied on the use of freshly distilled fumaryl chloride, being added to a pre-prepared suspension of aluminium chloride in an excess of benzene. After extraction and drying the bright yellow needle-like crystals of dibenzoylethene (57) were obtained in good yield and without need for any further purification, Scheme 68. The product (57) was characterised with a carbonyl and olefin stretch in the IR, (1654, 1597 cm^{-1}), suitable carbonyl ^{13}C signal (192ppm), and all carbon signals were above 130ppm. ^{1}H spectra indicated only aromatic and vinyl protons (8.1-7.4ppm and 7.2ppm) and the melting point matched the literature value.

Reduction of the double bond was then required, and a search of the literature showed conjugated α,β-unsaturated ketones, could be converted to the relevant saturated ketones using sodium dithionite, Scheme 69.[55]
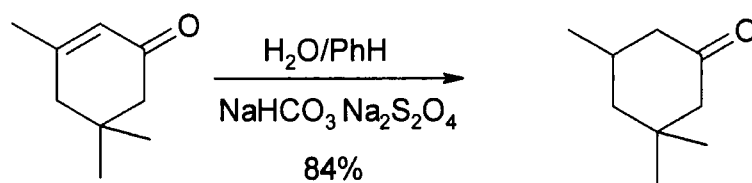
Scheme 69

Given the nature of the double bond in dibenzoylethene we thought this compound to be an ideal candidate for this reduction, Scheme 70.
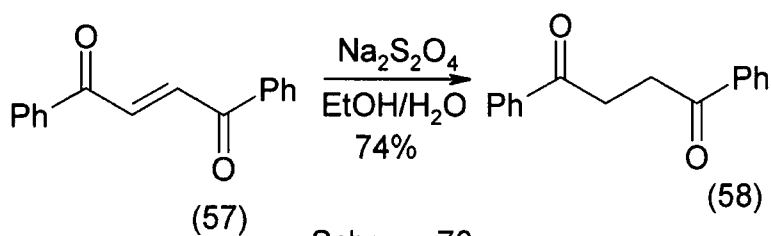
Scheme 70

With (57) in hand, we followed the precedented method for reduction by swift addition of (57) in boiling aqueous ethanol to a stirred solution of sodium dithionite in boiling water. After 30 minutes the reaction is cooled and resulting precipitate recrystallized to provide the saturated dibenzoylethane (58) in good yield, Scheme 70. Slight deviations from this method such as prolonged heating lead to no precipitate being collected. Characterisation showed the loss of the alkene stretch but persistence of carbonyl stretch at 1676 cm^{-1}. A suitable carbonyl ^{13}C signal at 200ppm, aromatic peaks and the ethane moiety were observed with a signal at 35ppm. The mass ion was observed in mass spectrometry, and proton spectra showed the loss of vinyl protons and the addition of alkane protons at 3.47ppm. The melting point matched the literature value (144°C).

Despite producing respectable yields the dithionate reduction was unreliable and required large quantities of carcinogenic benzene. Therefore an alternative route to dibenzoylethane was sought. A search of the literature highlighted the possibility of using ammonium cerium (IV) nitrate (CAN) as a single electron reducing reagent to

couple two trimethylsilylenol ethers, and we commenced a route with this method, Scheme 71.[56]
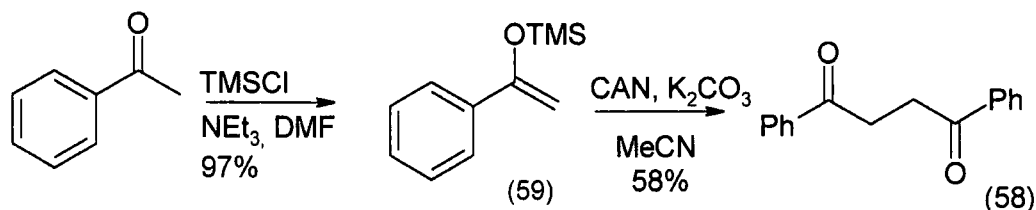
Mechanism
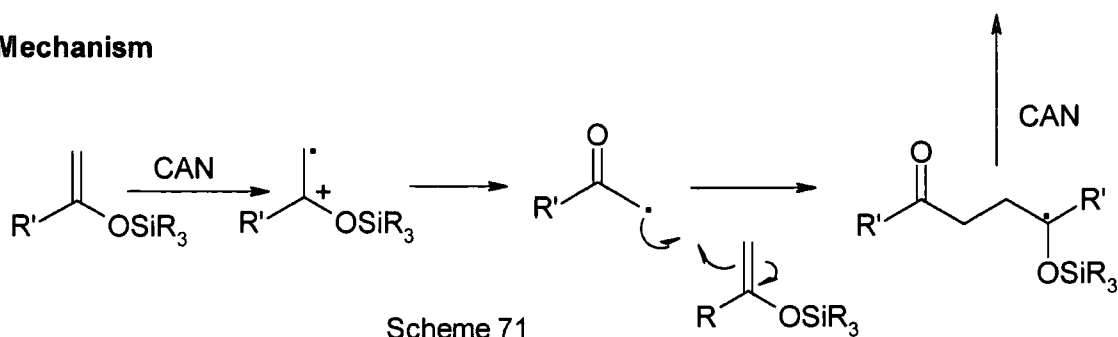
Scheme 71

Generation of the TMS enol ether of acetophenone proceeded in excellent yield following the literature precedent.[57] The silyl enol ether (59) was characterised by two gem alkene ^{1}H signals and the appearance of a 9 proton singlet at 0.03ppm signifying the presence of the TMS group. ^{13}C NMR also displayed suitable aromatic signals and the two vinyl carbons at 156 and 91ppm.

The CAN reaction was carried out by adding the enol ether in solution, dropwise to a stirred solution of CAN and base under an argon atmosphere. The inorganic residues that result from the reaction cause problems when trying to separate the phases and required the use of extensive repeated extraction with DCM to recover the product (58). Following a simple recrystallisation the product was obtained in 56% yield compared with the previous method of 53%. More importantly, the second method proved more reliable and consequently became the method of choice.

With the diketone in hand, the asymmetric reduction was examined, Scheme 72.

Following the literature precedent for mono-ketones, the oxazaborolidine was prepared by stirring the 0.09 equivalents of the required chiral amino alcohol with trimethylborate in THF for one hour prior to addition of the dissolved diketone. After a further hour the reaction is quenched slowly with hydrochloric acid, and the required diol obtained by simple extraction.
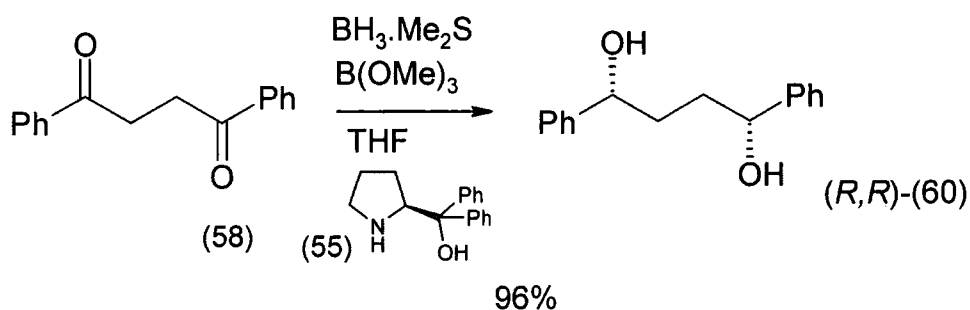
Scheme 72

Purification by flash column chromatography gave the 1,4-diphenylbutan-1,4-diol (60) in 96% yield. Characterisation showed appearance of the OH stretch and loss of carbonyl stretch in the IR. ^{13}C NMR also confirmed the loss of the benzoyl carbonyl and along with the ^1H spectra was suitably assigned. The mass ion was observed in the mass spectra.

Given the simplicity and success of this reduction method, on reasonable scale, we were encouraged to continue towards the target of diphenylpyrrolidine but also to investigate the application of this particular reduction to other diketones which would potentially lead to candidates for alternative disubstituted pyrrolidines. These are discussed in section 3.6.

Following protocols established by Chong, the chiral diol was added to a stirred solution of methanesulfonyl chloride, and uncomplicated mesylation was complete within 2 hours. Due to instability (a tendancy to form diphenyltetrahydrofuran) the mesylate (61) was precipitated out using hexane, and filtered before quickly

recrystallizing from ethyl acetate to give white crystals in good yield, 85%. Brief analysis by ^{1}H NMR confirmed the product to have similar data to that reported by Chong. After treatment with allyl amine and flash chromatography to achieve separation of a small fraction of *cis* diphenylpyrrolidine gave the desired (*S,S*) enantiomer of *N*-allyl-2,5-diphenylpyrrolidine (62) in 75% yield, Scheme 73.
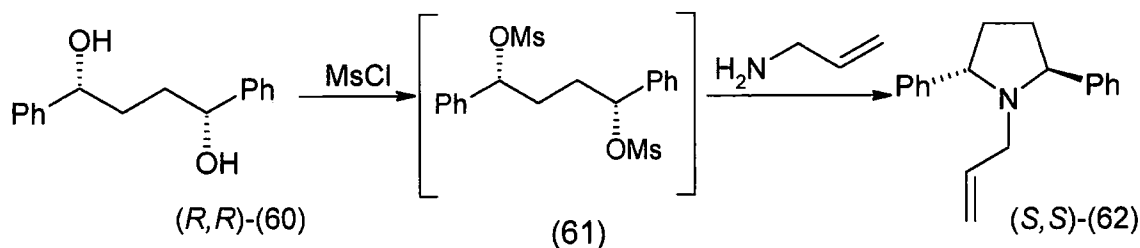
Scheme 73

Characterisation of compound (62) showed the presence of the allyl group in ^{1}H NMR spectrum at 5.7-5.55 and 4.92-4.87ppm, and 1603cm^{-1} in the IR spectrum. Optical rotation for the allyl protected pyrrolidine matched the literature value for this compound.

With this achieved the remaining step involved deprotection by removal of the *N*-allyl group. The procedure followed is described by Laguzza and is effected with Wilkinson catalyst under nitrogen.[58]

Scheme 74

60
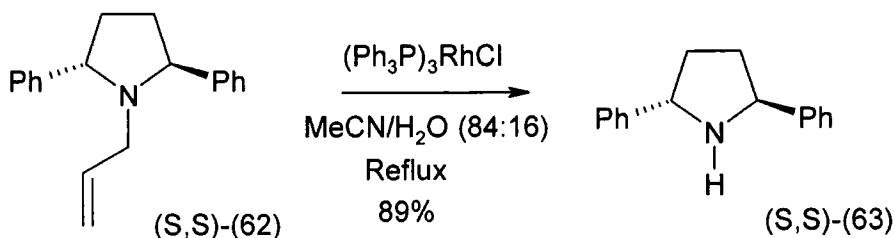
The catalyst (0.5mol%), allylamine and solvent are warmed in an azeotropic distillation, removing the aldehyde by-product over 5 hours as the solvent level is maintained using a dropping funnel. Organic extraction followed by flash chromatography yielded the pure (S,S)-2,5-diphenylpyrrolidine (63) which solidified on standing. Characterisation showed the N-H stretch in the IR, and consistent ^{1}H and ^{13}C NMR spectra. Comparison of the optical rotation of the product with literature values showed that stereochemistry had been maintained throughout the deprotection.[50]

The application of the Masui and Shioiri reduction to dibenzoylethane and following a predescribed methodology for conversion of the resultant 1,4-diol to 2,5-diphenylpyrrolidine (99% ee) provided a route to the desired chiral auxiliary. This proceeded in 53% yield from the diketone. Dibenzoylethane has been accessed in two syntheses, overall offering a viable, economic synthesis of chiral (S,S)-2,5-diphenylpyrrolidine.

3.6 Further application of oxazaborolidine reduction

Given the above success it was decided to expand the application of the asymmetric reduction to the preparation of analogous compounds, and for those reductions which were successful, their conversion into related chiral auxiliaries, Scheme 75.
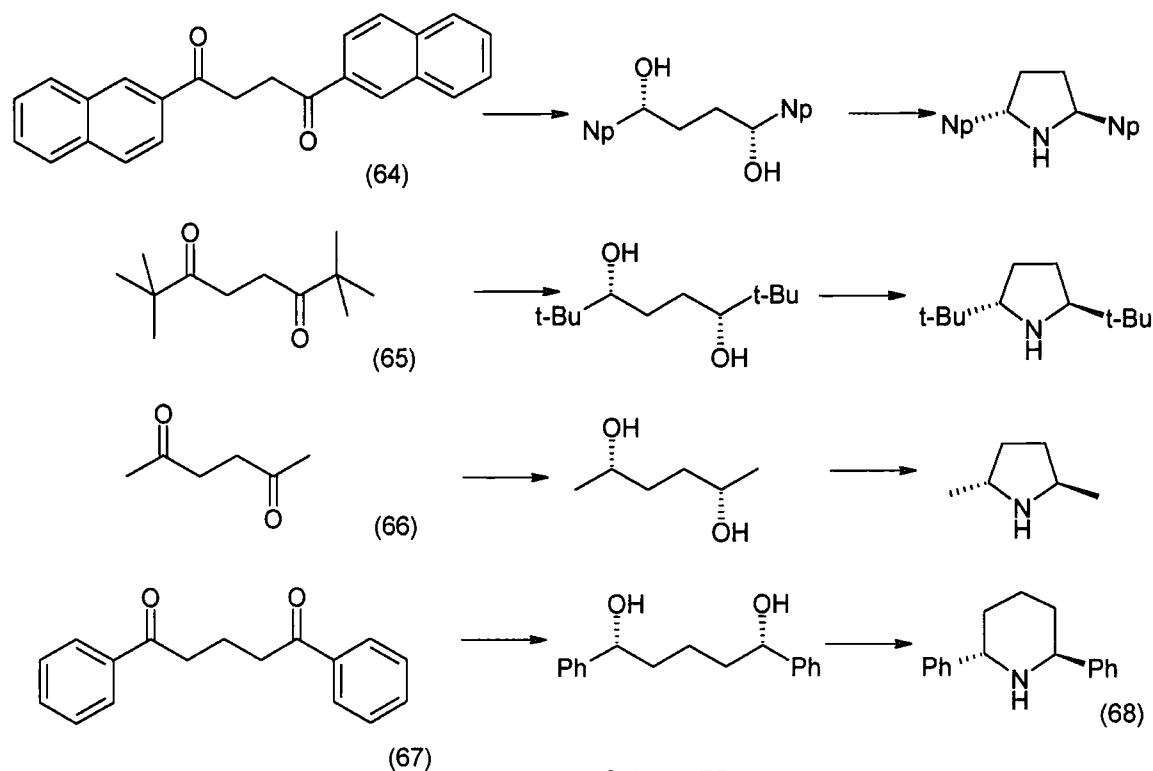
Scheme 75

Ideally the dinaphthyl ketone (64), would allow access to a more hindered diaryl substituted pyrrolidine, and with the tetramethyloctandione (65), would expand our range of reductions to alkyl substituted diketones. The hexanedione (66) was chosen for comparison with the asymmetric deprotonation method described and achieved earlier in this section, while the dibenzoylpropane (67) would allow exploration of application of the Chong protocol to make piperidine chiral auxiliaries such as (68).

Compounds (64) and (65) are not commercially available and synthesis from the silyl enol ethers and a CAN coupling was thought to be an appropriate route, Scheme 76.
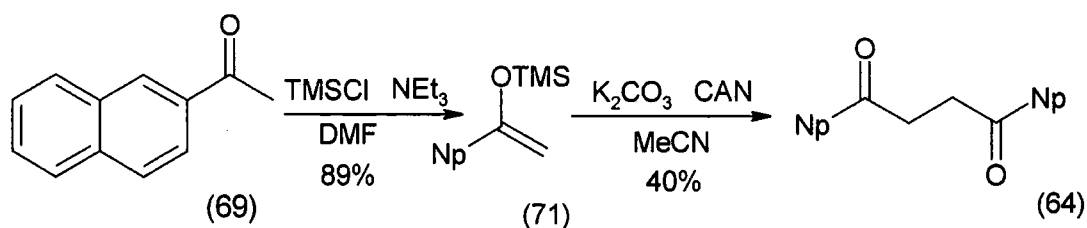
Scheme 76

The silyl enol ether of acetonaphthone (71) was prepared as described for the analogous phenyl compound, giving the silyl enol ether in good yield following purification by distillation. Characterisation confirmed the identity with the *gem* alkene protons providing signals in the ^{1}H NMR at 4.76 and 4.24ppm, and ^{13}C signals at 157 and 92 ppm. The mass ion was observed at 242 by mass spectrometry.

The CAN reaction was first carried out on 2g scale as described in the previous example, but yielded only 22% of the desired ketone (72). Slightly better yields could be obtained (40%) on a large scale. It is not clear why this seemingly analogous reaction to the phenyl example should proceed less efficiently. However, given that sufficient material was obtained to explore the asymmetric reduction, no attempts were made to optimise the result. The white crystalline solid was characterised by microanalysis, and the carbonyl stretch at 1679 cm^{-1} in the IR. The ^{13}C NMR features the carbonyl carbon at an unusually high value of 209ppm. This high value could be due to some π-stacking from the aromatic rings shielding the carbonyl groups. The melting point matched that given in the literature.

Synthesis of the silyl enol ether of pinacolone (72) proceeded under the same conditions described above, for acetophenone, and was successfully distilled to yield the product (73) in 65% yield. Characterisation confirmed the identity with proton spectra showing only 4 signals, in a ratio of 1:1:9:9. Consistent with this, the carbon

spectra showed 5 signals, clearly assigned to the vinyl carbons (167 and 86 ppm), quaternary (36ppm) and methyl carbons (28 and 0ppm).

The CAN coupling method as used previously was attempted twice on this substrate only poor yields being obtained ($\leq$5% yield). Further examination of the literature suggested a copper coupling type process may be more effective, Scheme 77.[59]
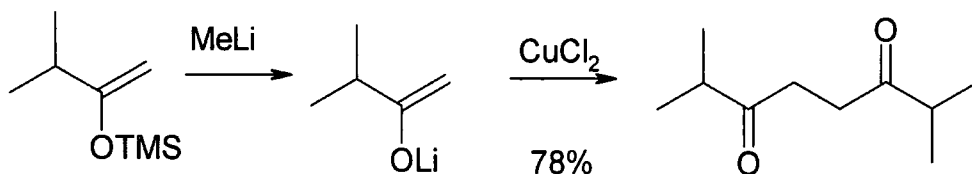
Scheme 77

In this protocol, copper (II) chloride is added to the silyl enol ether (which had been exchanged with methyllithium). Care was required to maintain absolute dryness as addition of copper chloride was difficult due to low solubility in DMF. After 10 minutes the reaction was complete, quenched with dilute sulphuric acid and workup commenced.
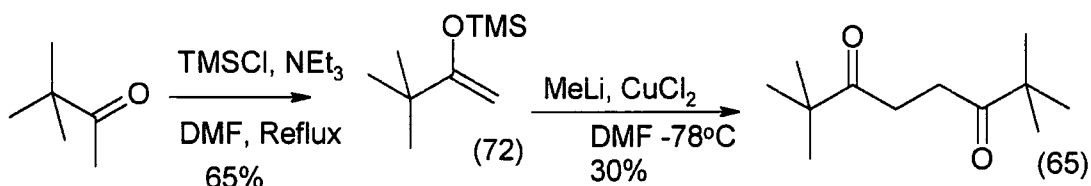
Scheme 78

The method was applied to the silyl enol ether of pinacolone (72) and after purification by flash chromatography the product was confirmed as the desired diketone (65) in 30% yield, Scheme 78. Characterisation included microanalysis, carbonyl stretch in the IR (1703 cm^{-1}) and proton NMR spectra which showed only two signals. The carbon NMR spectra showed a carbonyl carbon at a rather high value of 215ppm.

A similar procedure as for the diphenyl compound was followed for the oxazaborolidine reduction, with no success. The dinaphthyldiketone (64) was less soluble in THF, but heating to 45°C aided solubility. The reaction was attempted twice, without success, and 70% recovery of starting material, Scheme 79.
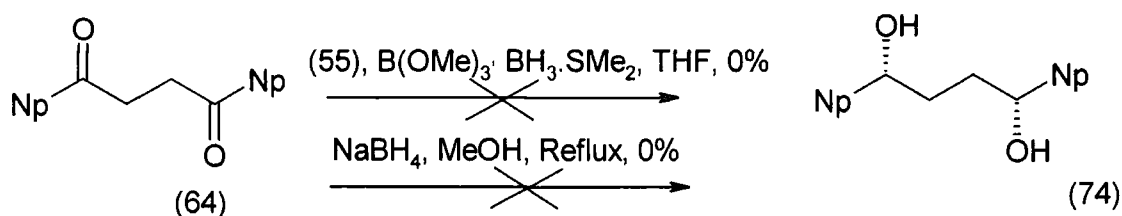
Scheme 79

One possible cause may be intramolecular π-stacking between the aromatic nucleus and carbonyl group inhibiting binding of the catalyst shielding the reaction centre from reducing agents. However, this only accounts for shielding over one face of the structure and indicated by insolubility of the compound it is envisaged the stacking is more than intramolecular and occurs between individual molecules to form a polymeric stack, by intermolecular interactions. The carbon NMR of the starting material had the carbonyl at 209ppm, which was a comparatively high value compared to the dibenzoyl equivalent compound with a value of 200ppm and that of acetophenone (198ppm). With this in mind, a sodium borohydride reduction was attempted in refluxing methanol. With no reduction occurring under these conditions, it was noted the desired compound has not been reported in the literature and in our hands, the diketone (64) was resistant to these initial attempts at reduction.
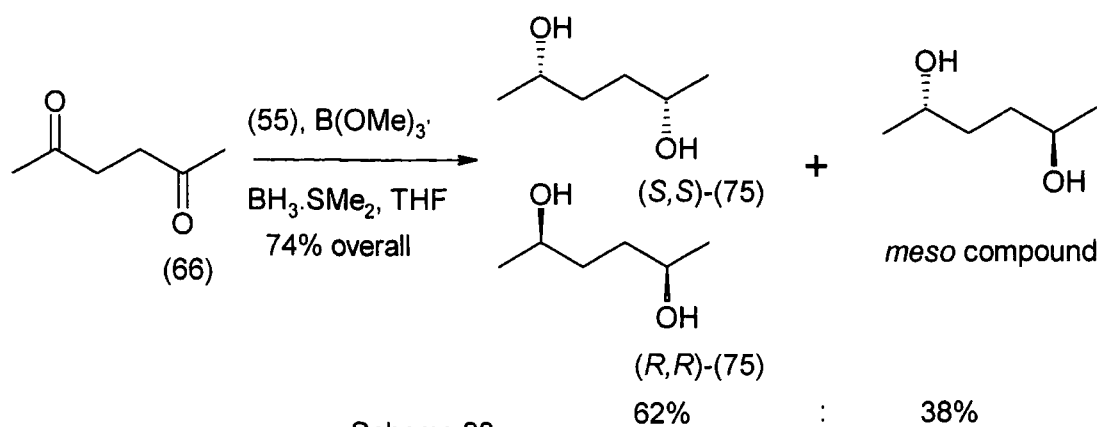
Scheme 80

We then extended the protocol to non-aryl diketones. Commencing with the same oxazaborolidine reduction procedure in THF as described above on 2,5-hexandione (66), followed by flash chromatography on the reaction product gave 2,5-hexanediol (75) in 74% yield. GC showed there to be 38% of the *meso* compound present, which was confirmed by the integrated diastereomeric signals in ^{13}C NMR; 23.80 / 23.46 CH_3; 35.97 / 34.98 CH_2.

Optical rotation indicated the ee obtained to be small, (especially compared to the previously referred to synthesis with bakers yeast providing an ee of 98%),[47] and also that the major enantiomer present was the (R,R)- isomer. This was surprising as the relative stereochemistry produced was opposite to all the other diols synthesised by us in this fashion. At present it remains unclear as to the exact reason for this change but it seems most likely the methyl group is sterically insignificant when compared to the joining 2 carbon chain between the two ketones. With such a modest ee (32%), this route was not pursued further as more competitive methods exist for the compounds synthesis.

66
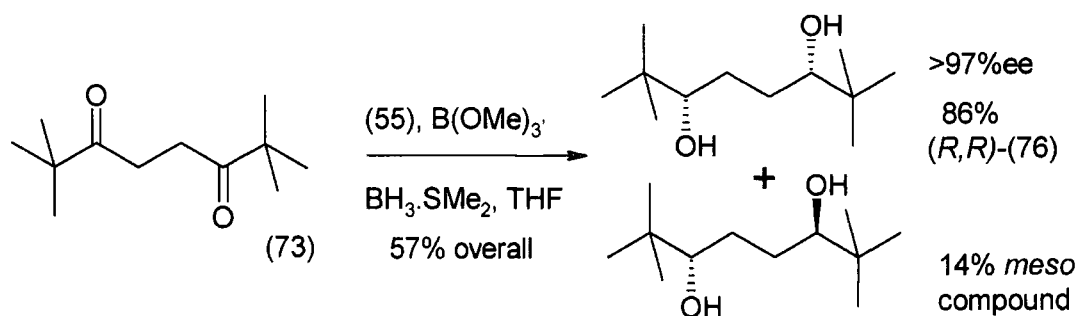
Scheme 81

Following the pre-described oxazaborolidine procedure, the diketone (73) was reduced within an hour, and the diol (76) was recovered as a white solid in reasonable yield, Scheme 81. Analysis confirmed the identity with a matching microanalysis, and broad alcohol stretch in the IR (3417 cm^{-1}). ^{13}C NMR showed there to be 14% of the meso compound present, and the mass ion at 203 was observed in the mass spectrum. Suitably assigned proton and carbon spectra completed the characterisation. The optical rotation value was +37, which was compared to the literature values for the (S,S) isomer.

The literature has two values both reported in the same solvent and concentration as we conducted our measurement, but the values do differ substantially, -34.3,[54] and –44.4.[60] Allowing for the 14% of the meso compounds present in our sample, the optical rotation recorded for (76) corresponds to an ee of 97% (taking the literature value of 44.4). Unfortunately the meso isomer was not separated from the chiral compound and a more accurate measure of ee was not obtained. The oxazaborolidine reduction of this type appears to perform well on this substrate, despite a moderate (57% unoptimised) yield, and 14% of the product being the meso form. This indicates the reaction was not hindered by the steric bulk of tert-butyl group but there was sufficient bulk to assist in asymmetric reduction.
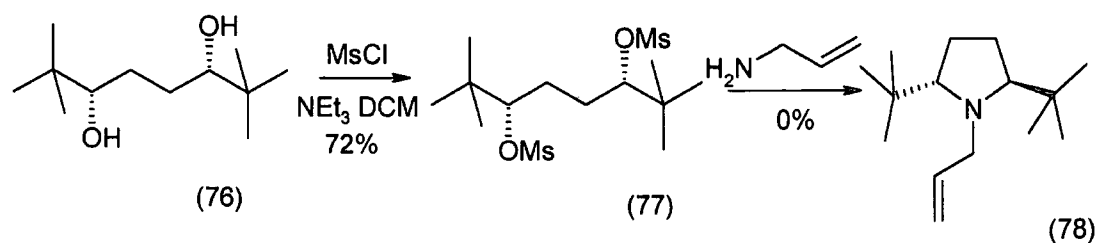
Scheme 82

Following the previous success with mesylation and subsequent cyclisation with allylamine, the pre-described method of adding a solution of the asymmetric diol to a stirred solution of mesylation chloride was attempted. After just under two hours TLC showed no starting material remained, and so the reaction was worked up and the product carefully crystallised from ethyl acetate using hexane and cooling. The resulting solid was recovered by filtration in 72% yield and added to a solution of allylamine and stirred overnight. The allylamine was removed and residue dissolved in ether for washing with sodium bicarbonate solution. The recovered compound was the starting mesylate. The reaction was repeated, but without success. We propose that this inability to cyclise is due to steric hindrance and that the desired pyrrolidine is probably very strained as a species. There were no occurrences of compound (78) in the literature and due to time constraints we did not investigate any further cyclisation methods.

Application of the pre-described oxazaborolidine reduction to the commercially available 1,5-diphenylpentan-1,5-dione (67) substrate proceeded smoothly, and the product purified by column chromatography crystallised to a white solid, in 91% yield, Scheme 82.
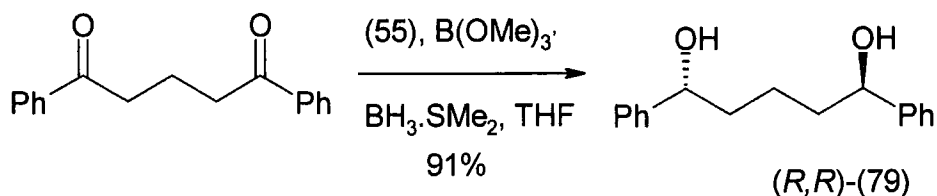
Scheme 83

Characterisation confirmed the structure as (79), from microanalysis and the required alcohol stretch in the IR at 3321cm^{-1}. Carbon NMR showed the loss of the carbonyl groups and a consistent proton spectra was obtained. Optical rotation was recorded in methanol (c=1.0, $[\alpha]_D^{25}$ = +20) comparing well with the literature value for the (S,S) isomer (c=1.0, $[\alpha]_D^{25}$ = -22.8).[52] The lower optical rotation obtained was due to a small quantity of the *meso* form being present. This reduction showed our method is applicable to 1,5-diketones with aromatic substituents in excellent yield and continues the trend set by the equivalent 1,4 diketone (67). Given the balance of high yield, good ee, and steric bulk of the phenyl groups, it was decided to convert the 1,5-diphenylpentan-1,5-diol (79) into the relevant piperidine (68).
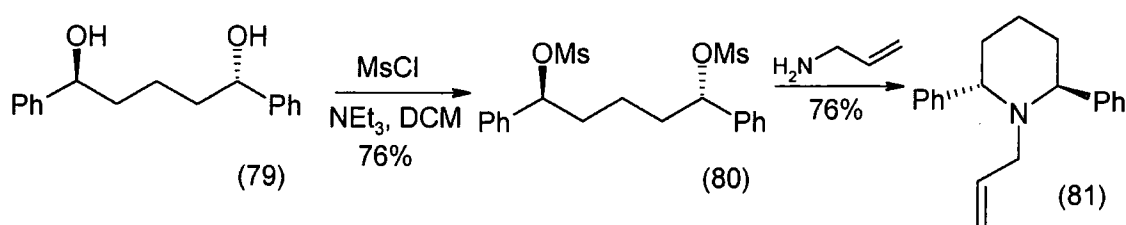
Scheme 84

The asymmetric diol was added dropwise to a stirred solution of mesylchloride as previously described. After 2 hours there was no trace of starting material and the reaction was worked up. The dimesylate was then successfully crystallised from ethyl acetate using hexane, and the resulting solid was recrystallized from the same system. The dimesylate was recovered by filtration as a white crystalline solid in 76% yield. The unstable mesylate was characterised by proton NMR, showing the proton shifts for the incorporated SO$_2$CH$_3$ group (6H, 2.02ppm) and absence of the broad OH signal, seen in compound (79).

The mesylate (80) was dissolved in allylamine and stirred overnight, allowing to warm from 0°C to room temperature. After workup the crude product was isolated as a yellow oil, which after chromatography gave the required (S,S)-N-allyl-*trans*-2,6-diphenylpiperidine (81), and also the *cis* isomers, (S,R) (R,S)-N-allyl-*cis*-2,6-

diphenylpiperidine, as a colourless liquid in 72% yield. Full characterisation confirmed the identity, with optical rotation matching the literature value, and GC-MS showing the molecular ion, for *cis* and *trans* samples in a 5.7% *cis*, 94.3% *trans* ratio at 277. These results correspond to a de of 89%, with this considered the concentration of substrate in the optical rotation measurement of (*R*,*R*)-Allyl-1,5-diphenylpentan-1,5-diol (81) gives a rotation of (c=0.94, $[\alpha]_D^{25}$ = +19), and the HPLC shows no trace of the (*S*,*S*) enantiomer. Microanalysis matched the calculated values, and proton spectra showed the presence of the allyl moiety with signals at 4.98 and 5.7 ppm, as did the ^{13}C spectra with signals at 138 and 116 ppm. The route to *trans*-2,6-diphenylpiperidine had successfully followed the example of the previously synthesis pyrrolidine analogue.

Following the previous protocol, the *N*-allyl deprotection was performed with Wilkinson's catalyst, (Ph₃P)₃RhCl was stirred in an azeotropic mixture of acetonitrile and water, to which the allylamine was added. The level of the solvent in the vessel was maintained through additions with the dropping funnel as the resulting aldehyde by-product was distilled.
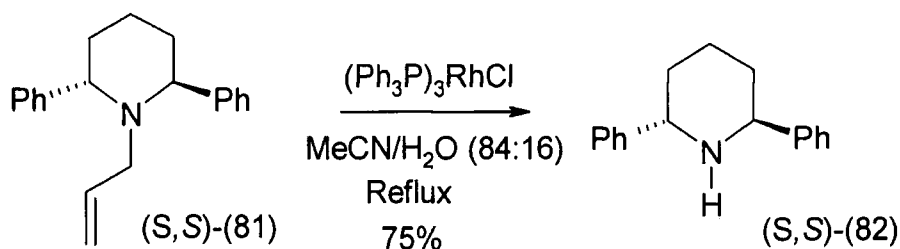
Scheme 85

After 5 hours the reaction was complete, and after work-up the resulting residue was purified by flash chromatography, to yield the desired product as a yellow solid. Analysis confirmed the product to be the amine (82) with a matching microanalysis and broad *N*-H stretch in the IR at 3359 cm⁻¹. There was an absence of the allyl

signals in the proton spectrum and broad *N*-H signal at 2.2ppm. ^{13}C NMR confirmed loss of the allyl group and the required molecular ion was found by mass spectrometry.

It was concluded that our oxazaborolidine did not perform as satisfactorily on small alkyl substituted 1,4-diketones and there were more efficient methods of accessing 2,5-dimethylpyrrolidines.

3.7 Summary of asymmetric chiral auxiliary synthesis work

We have successfully followed the method of Beak, *et al* to synthesise dimethylpyrrolidine in high ee and good yield. The asymmetric reduction we have introduced using the oxazaborolidine did not prove efficient in enantiomeric reduction on this substrate, more suitable methods for obtaining the asymmetric diol in this case already exist. Our first synthetic pathway for this compound, we believe, continues to offer the best solution to dimethylpyrrolidine.

The dinaphthyl diketone failed to reduce under various conditions, and it is our opinion there are intermolecular stacking interactions, shielding the carbonyl groups and thus preventing the reduction of this compound.

The *tert*-butyl diketone reduced well with good ee to give the desired diol. This we found difficult to cyclise in our brief attempts and the sterically hindered diol should now be subjected to different cyclisation methods such as benzylamine, and ammonia to see if its reluctance to form is due to product ring strain or steric hindrance prevents ring closure.

Diphenylpiperidine and diphenylpyrrolidine have both been prepared with success: High ee, excellent yield and separation of the pure *trans* isomer.

3.8 Preparation of vinyl amides

Hydrolysis of the ester (33) to the free acid (35) was carried out at room temperature using lithium hydroxide monohydrate (LiOH.H₂O) in tetrahydrofuran / water (5:1). On addition of the LiOH.H₂O to a solution of colourless ester (33) the solution turned pale yellow. Following acidification and extraction, the acid (35) was obtained in crude yield of 69% as a mixture of isomers. Recrystallization from ether/petrol afforded only the *trans* isomer in 30% yield.

Scheme 86
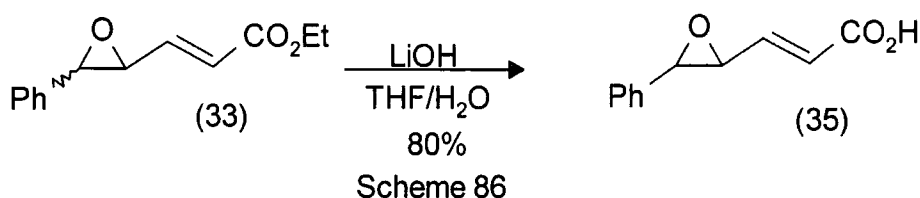
Further refinements involving carrying out the initial addition at 0°C, before allowing the mixture to return to room temperature while stirring and following workup with sodium bicarbonate, careful re-acidification with ice-cold HCl to pH3 prior to extraction led to 80% recrystallized yield of the *trans, trans* product (35). Prior to recrystallization evidence of the *cis* product can be seen in the crude ¹H NMR with a ratio of *trans:cis* of 14:1. The acid was identified from the loss of ethyl peaks at $\delta = 4.2$ and 1.3 in the ¹H NMR, and a broad O-H stretch at 3500-3280 cm^{-1} in the infra red supported by a molecular ion observed in the mass spectrum.

With the free vinylepoxide acid in hand we set about coupling the pre-synthesised chiral auxiliaries (the pyrrolidines described above) to this rearrangement precursor. The first chosen route was simple DCC mediated coupling as is standard in amide bond synthesis.

The reaction is catalysed by 4-dimethylaminopyridine (DMAP) acting as an acyl transfer reagent. The DCC and DMAP (10mol%) was added in solution by cannula to the volatile dimethylpyrrolidine (47) at room temperature. The free acid (35) was then added, and after 24 hours there was no more starting material (35) by TLC.

Work up including a wash with dilute hydrochloric acid to remove any remaining free amine, resulted in what we believe to be the desired product (83) but also urea (84), the DCU by-product. These proved co-polar by flash chromatography and impossible to separate in our hands, Scheme 87.

Scheme 87
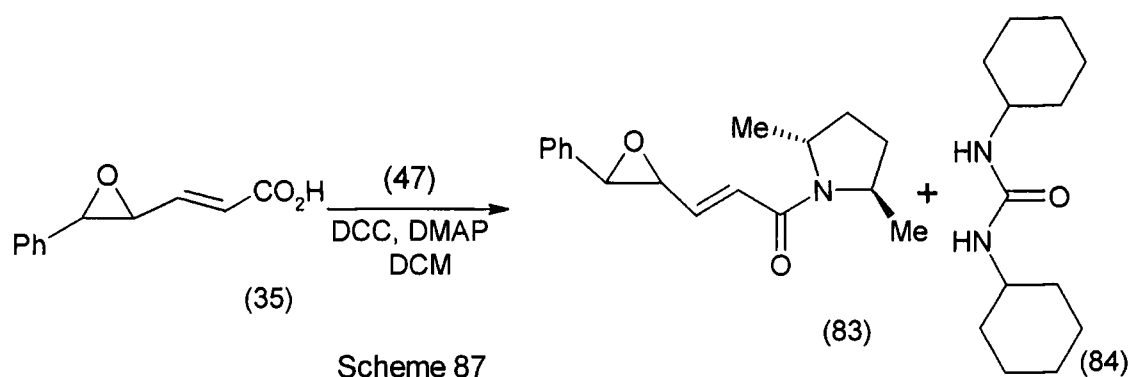
It was important we could obtain the target rearrangement precursor (83) cleanly for use in the Carius tubes as it was known a small amount of impurity would prevent rearrangement. Alternative methods such as EDC, where the urea side product is water-soluble were considered but given the success in our laboratories with the mixed anhydride method of coupling, with the oxazolidinones (see section 1.7.2), we pursued this synthetic route as a method to attach our chiral auxiliaries to the free carboxylic acid (35), Scheme 88.
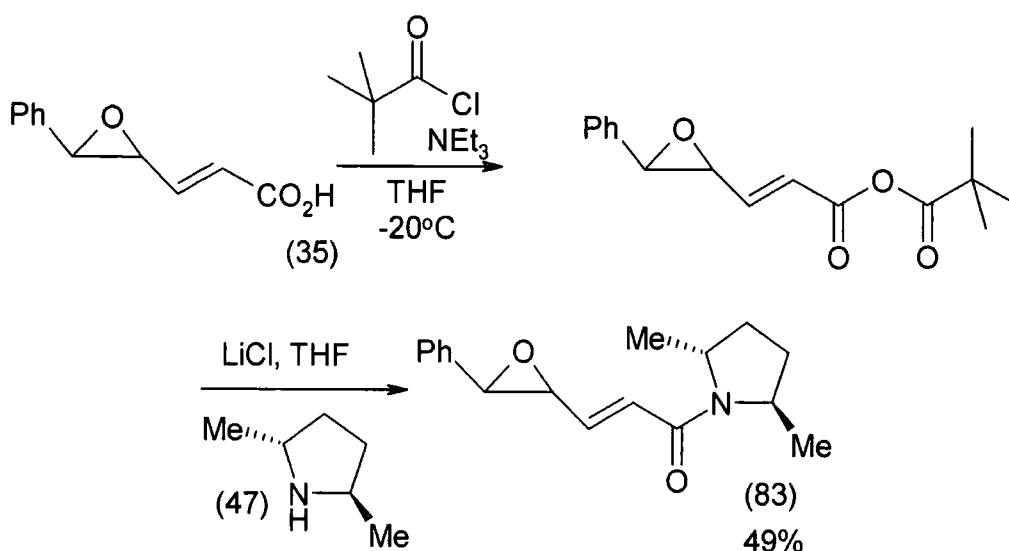
Scheme 88

The trimethylacetyl chloride was added to a pre-prepared solution of triethylamine and the free acid (35) at -20°C. After about 2 hours, LiCl and the 2,5-dimethylpyrrolidine (47) were added and the reaction stirred overnight. Complete consumption of starting material by TLC was observed, and the reaction worked up. Flash chromatography yielded the coupled product (83) as a yellow solid. The moderate yield is attributed in part to the volatility of 2,5-dimethylpyrrolidine. The difficulties associated with satisfactorily removing solvent from such a low boiling liquid mean it is difficult to obtain homogeneous amine (47). The use of an excess would ensure high conversion and any remaining amine is lost in the work up, but in this case the amine is inherently precious being of high chiral purity. Characterisation showed the obtained product to be the title compound, with carbonyl and alkene stretches in the IR at 1662 and 1608 cm⁻¹. The expected signals from the amide were found in the proton NMR and the carbon provided 13 assignable signals. The mass ion was observed by mass spectrometry.

Given this problem, and the precious nature of the chiral auxiliary, we chose to optimise conditions, and prepare sufficient material of a model pyrrolidine amide (84)

to investigate the rearrangement potential of these compounds prior to committing precious chiral auxiliary to the thermolysis, Scheme (89).

Scheme 89
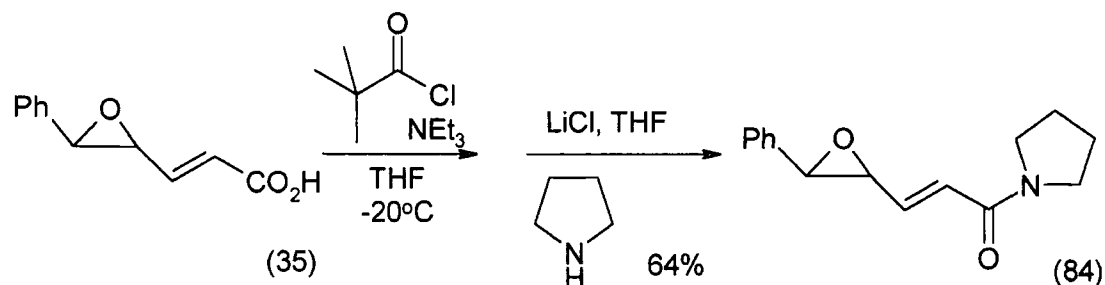
Following the previous method, but with addition of excess pyrrolidine, the desired product (84) was obtained as a pale yellow solid in reasonable yield (64%). Characterisation confirmed the product structure, with carbonyl and alkene stretches in the IR and expected signals from the amide in the proton NMR and the carbon provided 11 assignable signals. Interestingly, the two carbon signals for the amide ring carbons are observed as 2 sets of singlets (46.86, 46.19; and 26.33, 24.55) This provides further structural confirmation as the doubling up of signals are due to the two different rotamers, putting the 2-α carbons in different environments, one shielded by the carbonyl. This distinction occurs due to hindered rotation about the amide bond due to conjugation between the amide lone pair and the carbonyl. The mass ion was observed in the mass spectrum. With this model compound in-hand we proceeded with preparing the 2,5-diphenylpyrrolidine derivative as studies into applying the model compound to the rearrangement began.

Following the predescribed protocol, but with 1 equivalent of chiral auxiliary per carboxylic acid equivalent, and purificiation by flash chromatography yielded the coupled product (85) as a light brown crystalline solid in acceptable yield (55%).
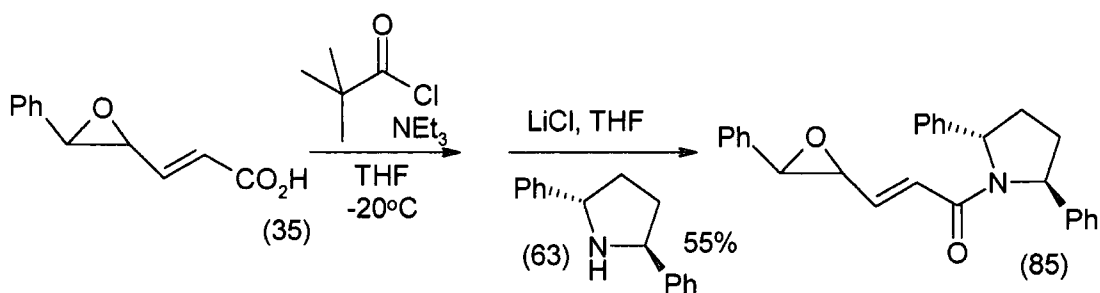
Scheme 90

Characterisation proved the product to be the title compound with carbonyl and alkene stretches in the IR at 1661 and 1617 cm^{-1} respectively. A consistent proton NMR spectrum was obtained and the carbon spectra provided the two carbon signals for the amide ring carbons are observed as two sets of singlets (47.90, 47.04; and 25.57, 23.85). Microanalysis data was found to match the calculated values.

3.9 Attempted rearrangement of coupled products

With the vinylepoxide – dihydrofuran rearrangement established in our laboratories we sought to apply the rearrangement to substrates with amide functionality with the view to induce asymmetry through the use of chiral pyrrolidines. Carius tubes had provided the most reliable, cleanest form of rearrangement and these were examined first.
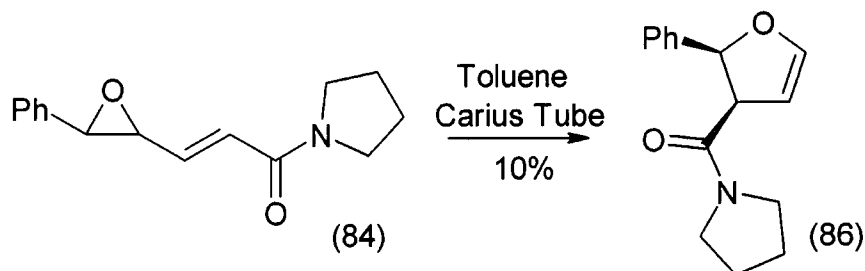
Scheme 91

We examined the reaction shown in Scheme 91. In each case, the Carius tubes were 100ml capacity and the material to be rearranged was dissolved in 20ml of dry

toluene. The reaction mixtures were degassed, and the tubes sealed. A variety of heating times and temperatures were attempted, but only in a single case could any of the desired material be obtained, Table 6.

Qty (84) / mg	Temp / °C	Time / hr	Results.
50	180	12	Starting material recovered
90	180	20	Starting material (44%), Product (86), 9.5mg, 10%.
80	200	12	Starting material recovered
50	200	20	Decomposition products only

Table 6

After flash chromatography 9.5mg of product obtained was characterised, and is thought to show evidence only for the *cis* product. The IR showed evidence of a carbonyl stretch and the alkene stretch at 1719, and 1598 cm^{-1} respectively. Proton spectra indicated aromatic protons, and signals consistent with the dihydrofuran ring and an intact pyrrolidine ring. The carbon spectra showed relevant signals for the carbonyl carbon and ring carbons at 171, 138, 99, 85 and 48ppm as expected with the pyrrolidine ring carbons being observed as rotamers centred on 47 and 25ppm. From this evidence we concluded the rearrangement is difficult using Carius tube methodology and consequently we decided to apply the stainless steel bomb technology in the knowledge that shorter reaction times are required for the standard epoxide rearrangement and therefore, decomposition would not occur quite so readily.

The stainless steel bomb was charged with the substrate dissolved in 35ml toluene, and degassed as described previously. The sealed bomb was then heated, with a number of experiments being conducted with varying temperatures and times, Table 7.

Qty (84) / mg	Temp / °C	Time / hr	Results.
100	200	10	Decomposed material only
80	180	16	Decomposed material
50	180	10	Starting material recovered 50% Remainder decomposed material
80	180	6	Starting material recovered 96%

Table 7

None of the desired dihydrofuran product (86) was recovered. The rearrangement of this substrate did not appear to be amenable to our thermal rearrangement methods, if achievable at all.

Despite the disappointing results in attempting to apply the rearrangement to epoxy vinyl amides, we decided to attempt the rearrangement with our already synthesised chiral compounds, Scheme 92.
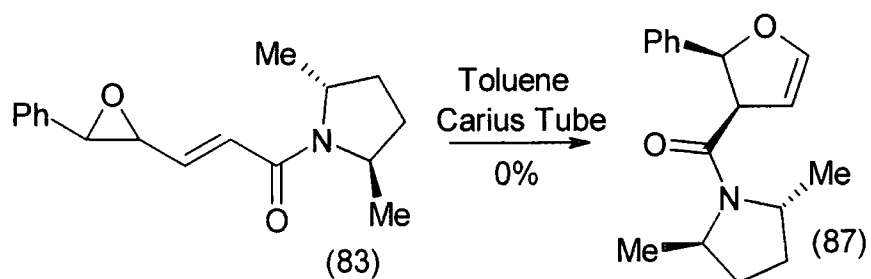
Scheme 92

Due to limited availability of starting material only 2 Carius tube experiments were attempted on (83), Scheme 92, and following the results of the model study of (84) rearranging, they were conducted at 180°C, for 20hr and 18hr. Both produced only decomposed material.

Two rearrangements were attempted with compound (85) in Carius tubes and several in stainless steel bombs, Scheme 93.
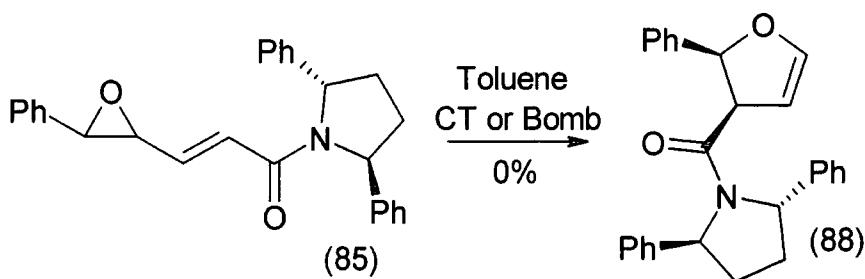
Scheme 93

The Carius tubes were prepared as before, with 80mg of substrate (85), dissolved in 20ml of toluene and sealed prior to heating. The bombs were prepared with 35ml toluene dissolving 100mg of substrate (85) prior to degassing and the last experiment detailed was conducted under 50atm of N_2 gas in order to conduct higher pressure experiments. Various temperatures and reaction times were tested, without success in isolating any product other than decomposed material, Table 8.

Temp / °C	Time / hr	Type	Result
200	20	CT	Decomposed material only
180	18	CT	Starting material 20%, rest decomposed
180	10	Bomb	Starting material 95%
180	20	Bomb	Decomposed
180	15	Bomb	Starting material 20%, rest decomposed
180	15	Bomb	Decomposed (High pressure experiment)

Table 8

Given this reluctance for the chiral amides to rearrange, we considered the possibility of increasing the rigidity of the system, instead of relying on C_2 symmetry in our chiral auxiliary. For this we returned to the oxazoline type structures but with a view of forming the oxazoline onto the vinyl group of our rearrangement precursor. We reasoned these compounds may favour the required transition state more than the

amide compounds, and allow attachment of steric groups on two pseudo-symmetrical positions, Scheme 94.
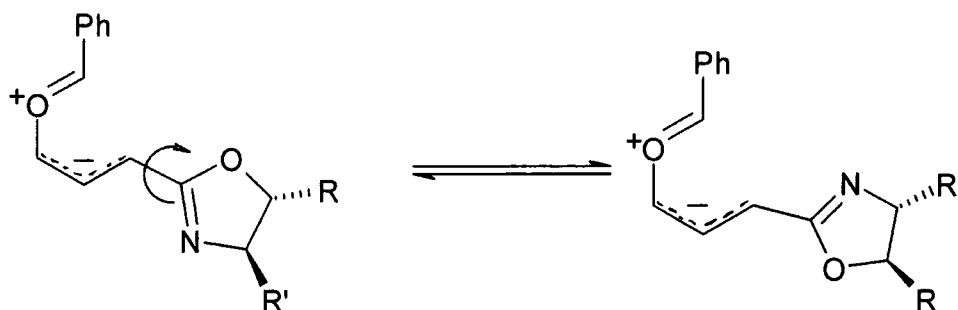
Scheme 94

Examination of the literature suggested a coupling of the carboxylic acid (35), with a chiral amino alcohol such as (89).[61] The reaction is proposed as a one-pot solution, however in our hands despite the one-pot formula of amino alcohol, carboxylic acid and triphenylphosphine in acetonitrile/pyridine for 2 hours followed by addition of the carbon tetrachloride, we isolated the intermediate (90) in 73% yield as a white fibrous solid after flash chromatography, Scheme 95.

Scheme (95)
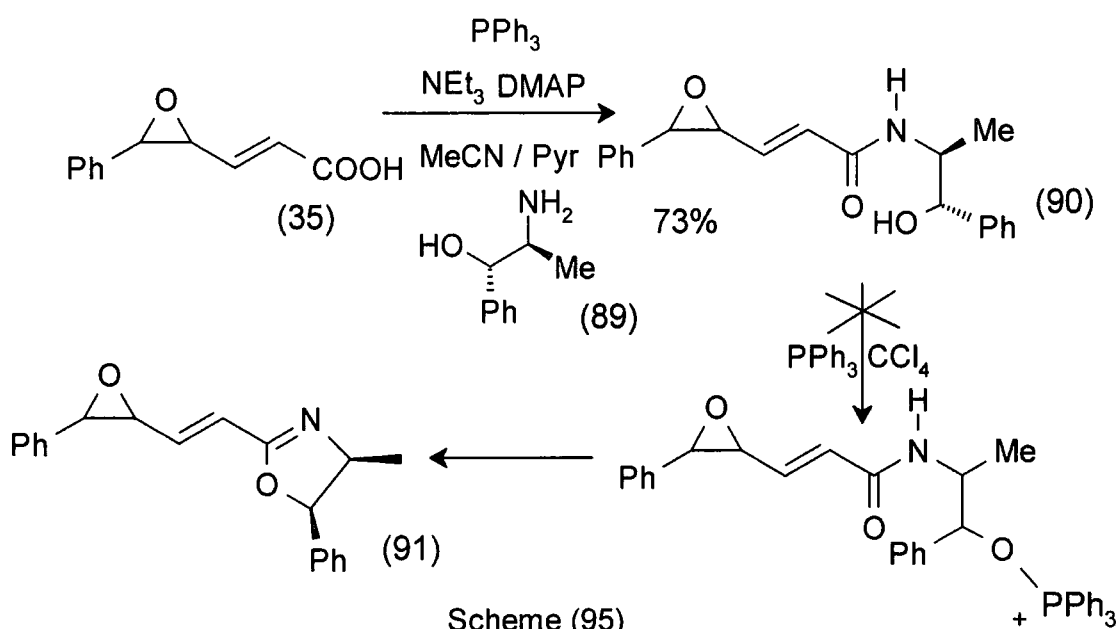
The compound was characterised by a matching microanalysis and decoupling experiments on the proton NMR confirmed ring closure had not taken place and the existence of the exchangeable protons on OH and NH were seen by D_2O shake experiments at 3.6ppm and 4.9ppm respectively, and the mass ion observed in the mass spectrum.

In an attempt to complete the ring closure step the product (90) was mixed with triphenylphosphine and carbon tetrachloride in acetonitrile/pyridine. The reaction yielded some decomposed material and starting material only.

Further examination of the literature suggested the use of ethyl chloroformate with the carboxylic acid, to generate the mixed anhydride.[62] Reaction of the mixed anhydride with the relevant amino alcohol and ring closure with $SOCl_2$ led to oxazoline (92), Scheme 96.[63]
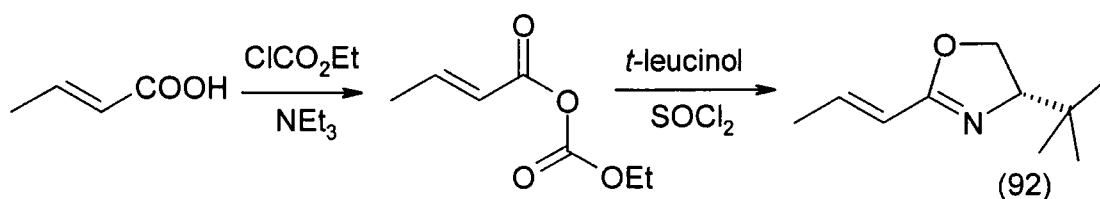
Scheme 96

We applied the literature protocol to our vinylepoxide, but obtained only decomposed material, Scheme 97. It seems likely that the conditions involved, especially $SOCl_2$ are too harsh for the vinylepoxide substrate.

Scheme 97
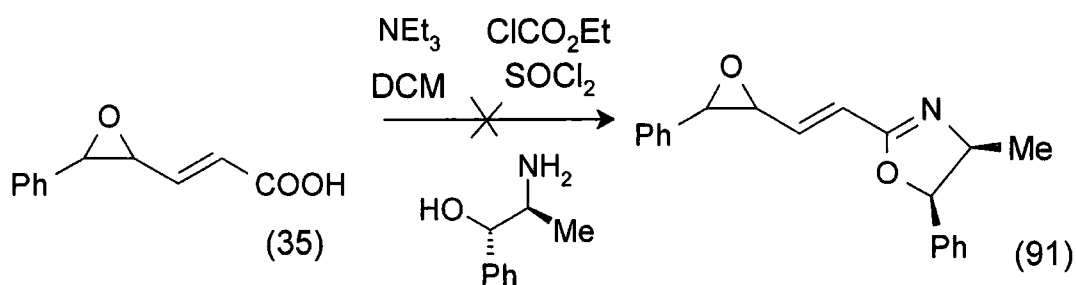
Limited by time for the project, this avenue is yet to be fully explored with future work. Development of the ring closure step conditions could lead to a viable synthesis of (91), and subsequent rearrangement attempts.

3.10 Summary of attempted rearrangements

Our attempts to induce asymmetry into the rearrangement through the use of pyrrolidines as C_2 chiral auxiliaries have failed due to the instability of the substrates and/or products in the harsh conditions leading to them decomposing either on rearrangement or before rearrangement occurs. A variety of techniques, substrates and conditions have been tested, though there is more scope for further research into different solvents. In an attempt to rationalise these observations with the oxazolidinone work conducted prior to this project, (section 1.7.2) the principle difference appears in the electronics that occurs in the two auxiliaries. In the oxazolidinones, the nitrogen lone pair is in conjugation with the carbonyl group of the auxiliary, leaving the amide carbonyl free to partake in the movement of electrons, from the epoxide C-C bond through the vinyl group to the amide carbonyl. We propose it is this effect which allows the rearrangement to occur, especially given the milder conditions used, which when our amines were subjected to these conditions, we recovered starting material.

With amide based auxiliaries the nitrogen lone pair is free to conjugate with the amide carbonyl, thus reducing the stability otherwise provided to the vinyl group by conjugation with the carbonyl bond, Scheme 98.

Required intermediate
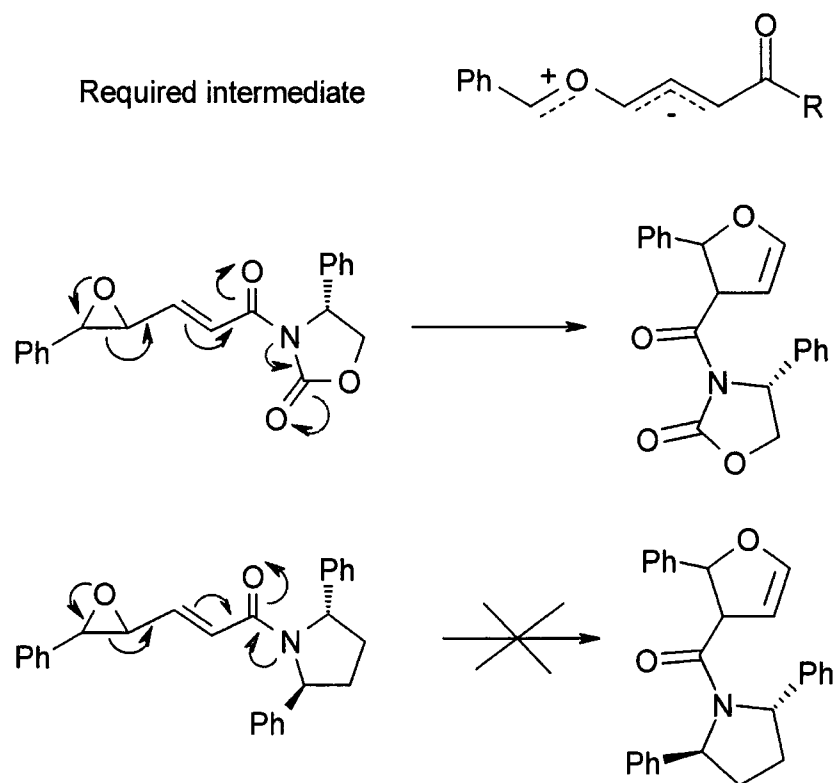
Scheme 98

Preliminary attempts at the synthesis of oxazoline (91) have been unsuccessful but we have as yet to complete the exploration of this area, limited by the timescale of the project.

Chapter 4: Application of dihydrofuran products to synthesis of furofuran lignans

4.1 Introduction

Having developed the vinylepoxide – dihydrofuran thermal rearrangement to give a reliable yield with good diastereoselectivity at a reasonable scale as described in chapter 2, we embarked on the application of our dihydrofurans in the synthesis of a class of target molecules with interesting biological properties.

The class of compounds chosen was the furofuran lignans characterised by a 2,6-diaryl-3,7-dioxbicyclo[3.3.0]octane skeleton, Scheme 99.
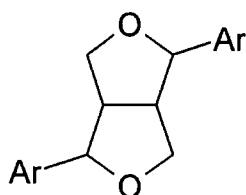
Scheme 99

4.2 Furofuran lignans

There have been considerable reports of the diverse range of biological properties, structural diversity and synthesis of these compounds.[64] Biological properties that have been reported include, regulation of cholesterol levels, PAF antagonist properties and antioxidant, anticancer, and antiviral activity.[65]

The reported structures include a wide variety of substituents around the furofuran ring system, varying in nature and stereochemistry. All illustrated lignans are naturally occurring, Scheme 100.

Sesamin

Epieudesmin

Diyangambin

2'-Hydroxyasarin
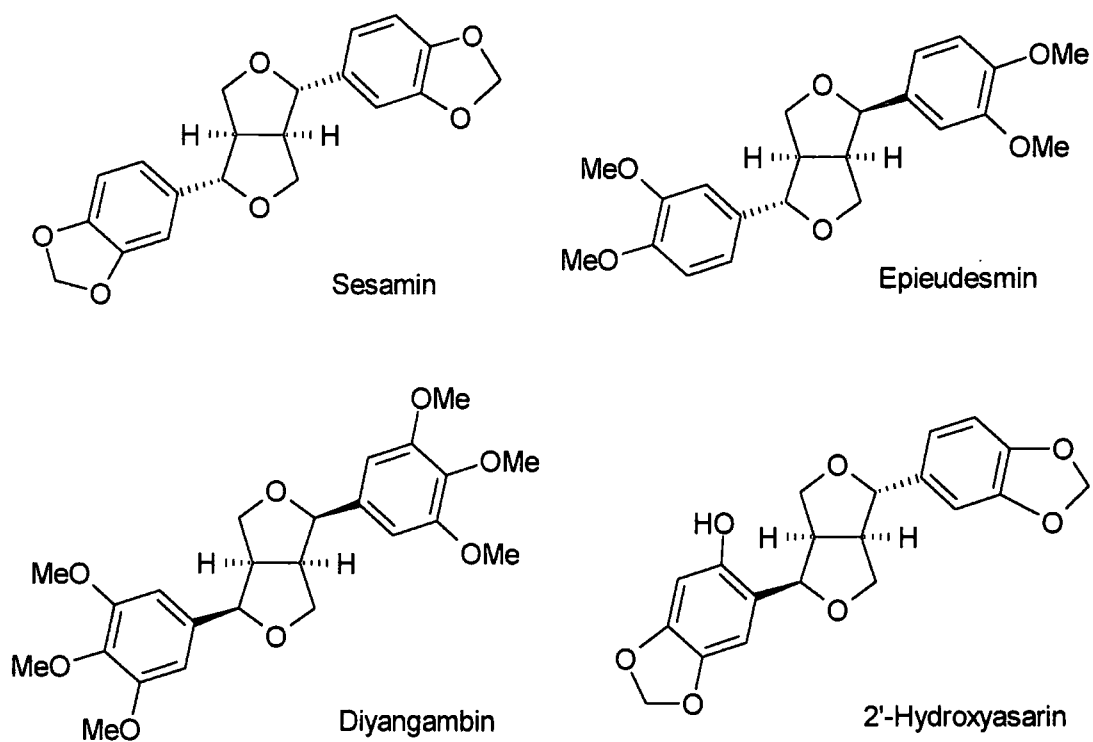
Scheme 100

4.3 Biosynthesis of 2,6-diaryl-3,7-dioxbicyclo[3.3.0]octanes

Biosynthesis of furofuran lignans is thought to occur through a bimolecular phenoxy radical coupling.[66] The precise stereo- and regio- control is thought to originate from enzymatic binding of the radical intermediate and associated proteins. Thus different enantiomers of the same lignan are commonly found in related organisms. For example, Scheme 101, shows the biosynthetic pathway of (+)-pinoresinol, from the species *Forsythia suspensa*.[67] This is not the only isomer of this compound to be found naturally occurring as (-)-pinoresinol occurs in a similar organism, *Xanthoxylum ailanthoides*.[68]

E-Conniferyl alcohol

Enzyme bound intermediate
78kD protein from *Forsythia suspensa*

(+)-Pinoresinol

Scheme 101
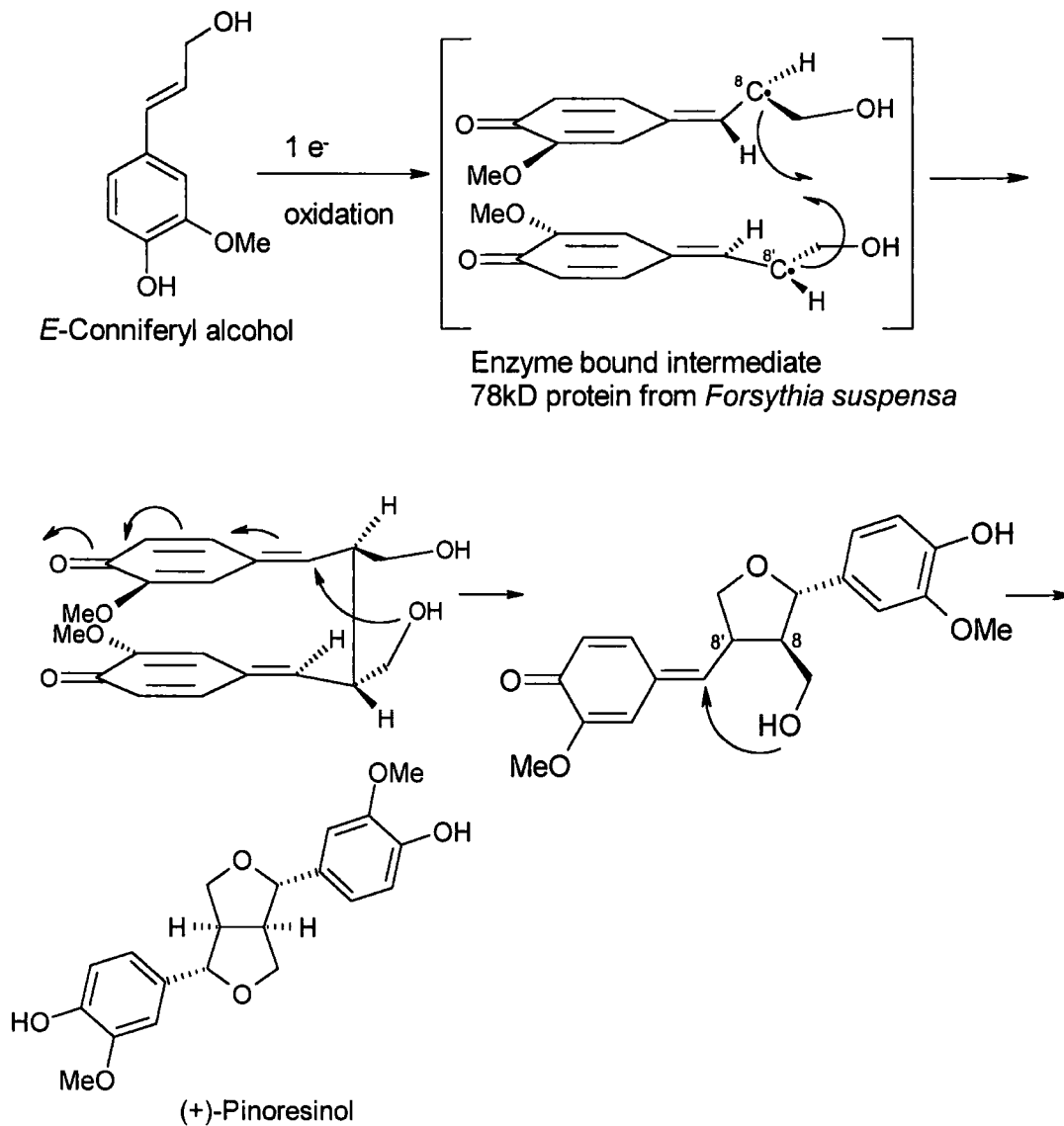
4.4 Previous synthetic strategies

Due to the medicinal potential of the furofurans, there has been considerable interest in their extraction and synthesis. Several strategies have centred on the use of a preformed furan template, usually obtained with some form of selectivity. Ward approached the furofuran lignans via the related lactone, summarised in Scheme 102.[69] The synthesis of lactone (93a) proceeds in 33% yield separable from isomer

(93b) by trituration. The dilactone (94) is obtained under similar conditions and finally reduced to the desired structure, (95).
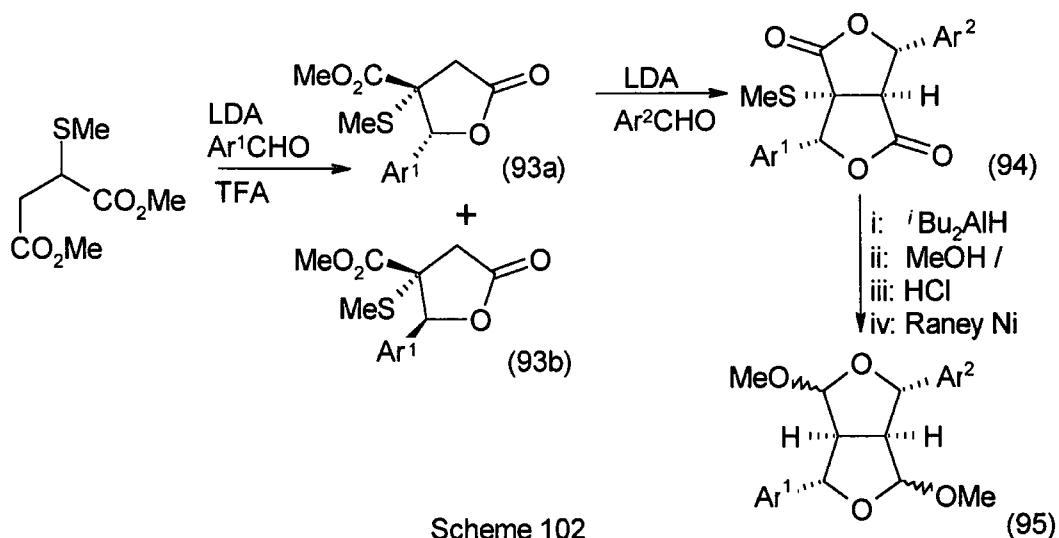
Scheme 102

Knight, *et al* used the Claisen – Ireland rearrangement to generate the functionalised furan ring prior to cyclisation to the relevant lignan, Scheme 103.[70]

Scheme 103
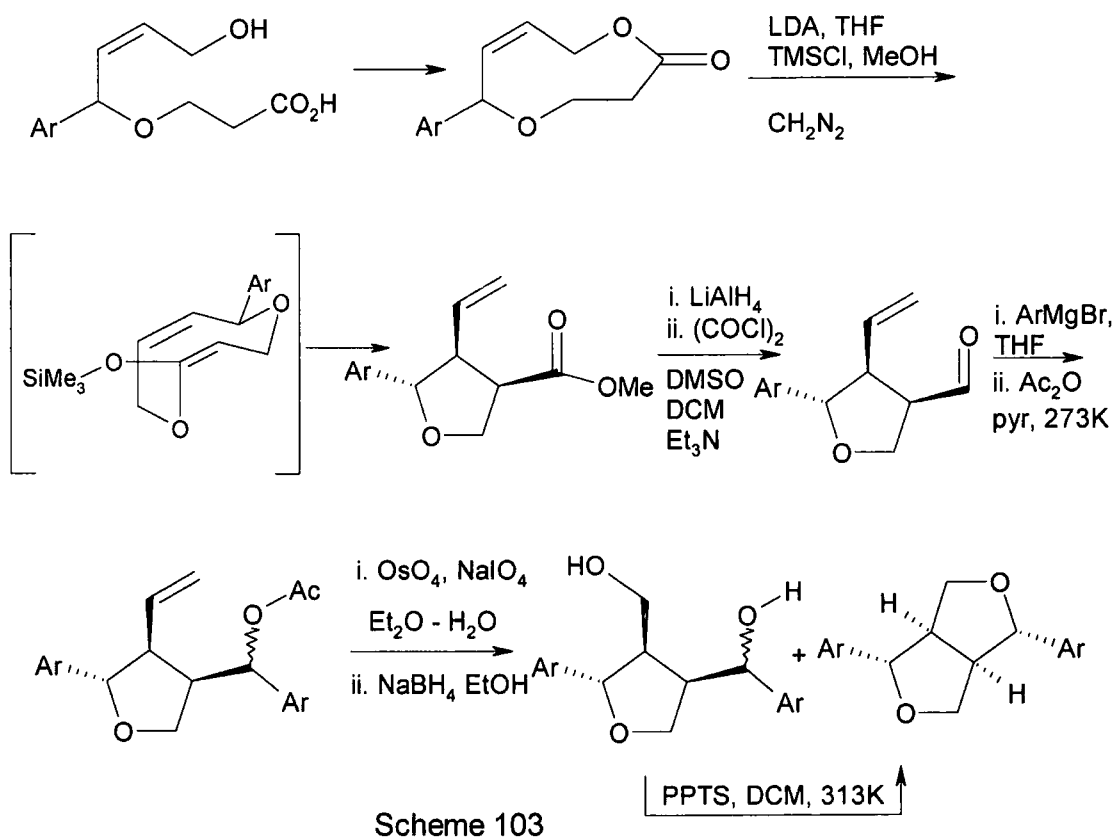
Whiting *et al* also proceed by the furofuran lactone, to give the furofuran framework with opposite stereochemistry to the above examples using the intramolecular

Mukaiyama reaction to perform a ketene acetal ring closure. [71] The ring closure is accomplished with TiCl$_4$ on the trimethylsilyl ether (97) to give single isomer (98a), or with TMSOTf on the acetal (96), to give mixture of compounds (98a) and (98b). Progression to the reduced furofuran structure is by way of reduction with LiAlH$_4$ and ring closure with acid, Scheme 104. [72] This route presented an effective but multi-pot route to access a number of reported furofuran lignans in racemic form. For further discussion on previously reported furofuran lignan syntheses, the reader is directed to the list of references. [73]
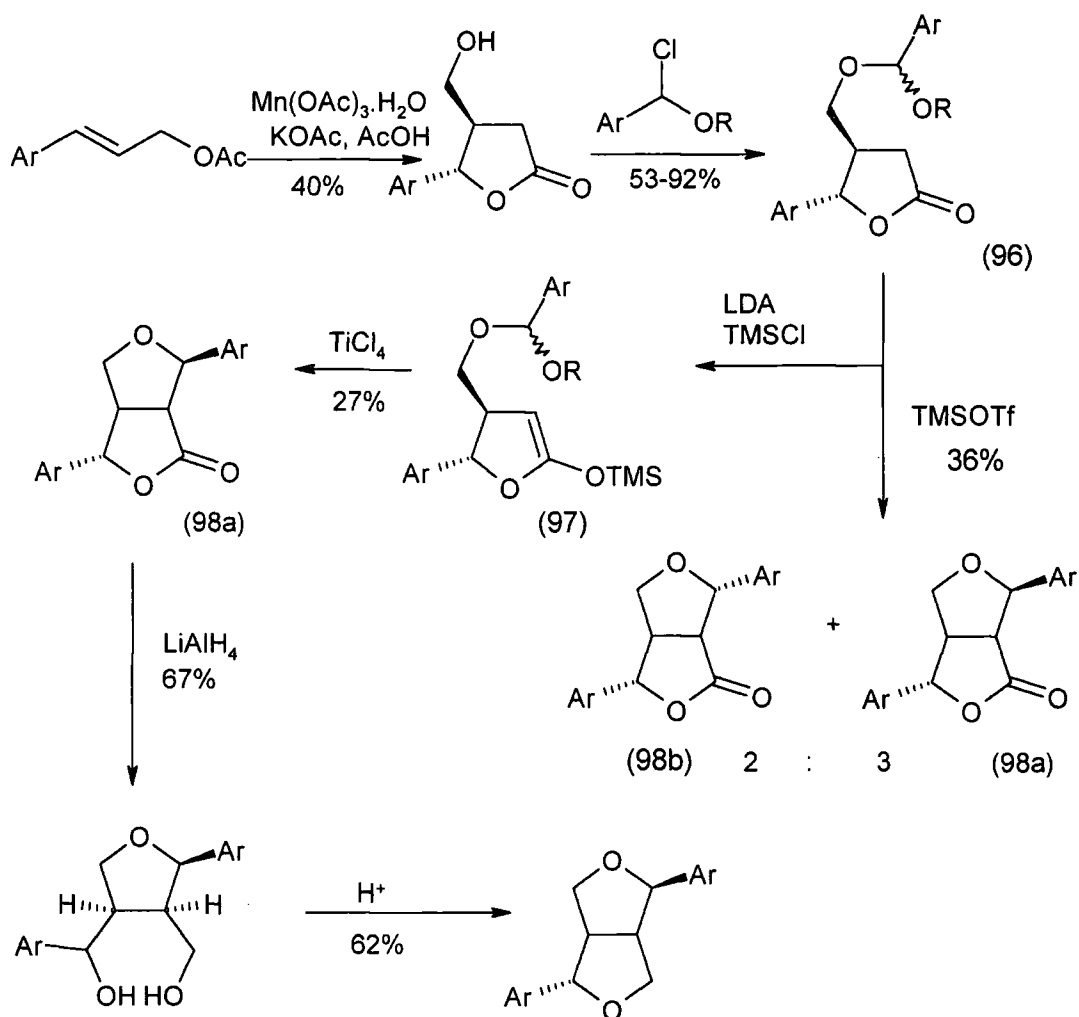
Scheme 104

4.5 Intended strategy

Using our efficient diastereoselective route to the dihydrofuran ester (34), we reasoned we had a suitable starting material for the furofuran lignans. We envisaged a cationic cyclisation of the vinyl ether unit onto a proximal oxacarbenium ion generated as an intermediate in a Noyori type transacetalisation, Scheme 105.[74]
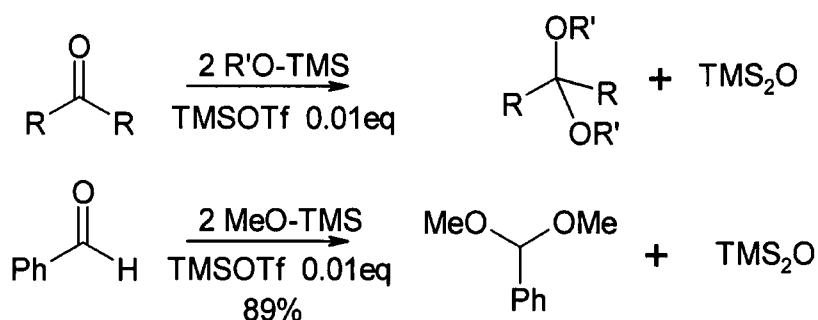
Scheme 105

We anticipated easy access to the silyl ether, and subsequent cyclisation with some stereochemical control, from rapid closure of the second furan ring relying on a geometrically rigid first dihydrofuran, Scheme 106.
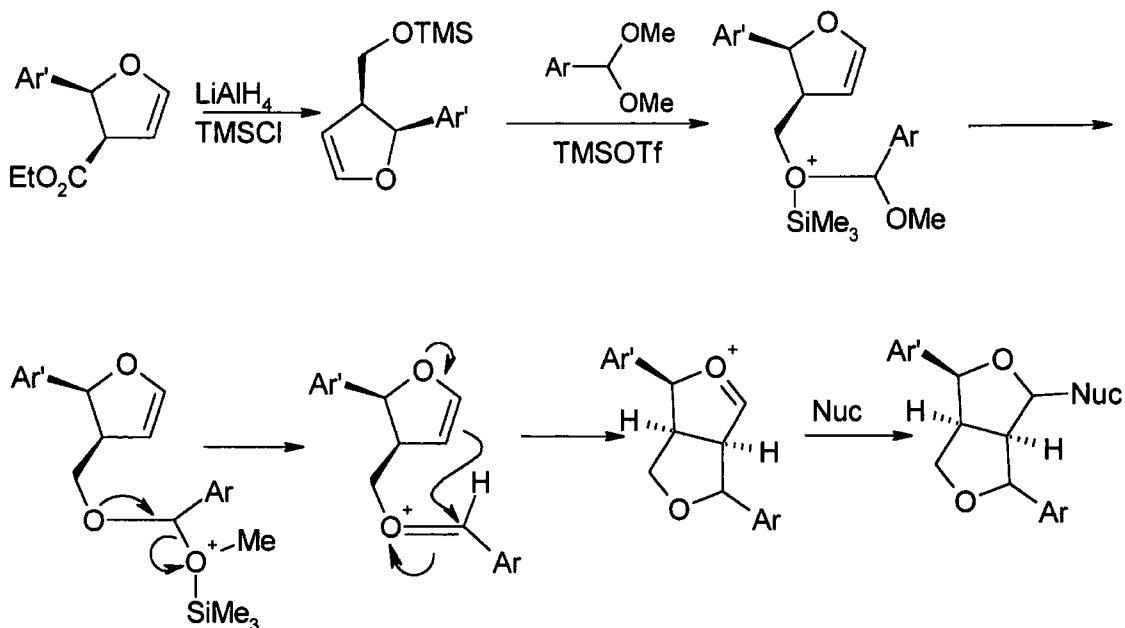
Scheme 106

We expected to be able to apply a variety of acetals, varying the functionality on Ar, and a series of nucleophiles in the quenching stage.

4.6 Furofuran lignan synthesis

With the dihydrofuran ester in hand from our previously described thermal rearrangement studies, we were careful to select a sample of pure *cis* dihydrofuran for our study of the transacetalisation reaction. This can be obtained by separation using flash chromatography on the crude thermal rearrangement product. Access to the furan alcohol, (99) was first approached with 2 equivalents of DIBAL-H in THF at -78°C, following standard procedures. This led only to decomposition. Our next approach was to use LiAlH$_4$ and after some studies, optimised the reaction temperature to −30°C in ether and with a controlled quench of the LiAlH$_4$ achieved 94% yield for the desired *cis* alcohol after rapid chromatography, Scheme 107.
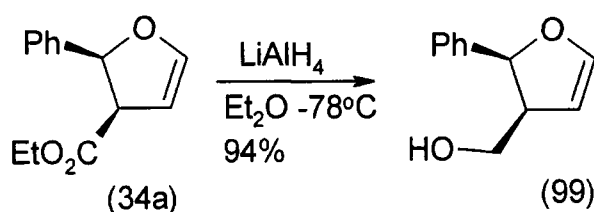
Scheme 107

Characterisation confirmed the identity of the product. The IR presented a broad O-H stretch at 3332, and a C=C bond at 1616, and the proton NMR showed loss of the ethyl group and appearance of a broad OH signal at 3.35-3.05ppm. The carbon NMR showed 9 signals, and demonstrated the loss of carbonyl and ethyl groups. The alcohol was found to be unstable at room temperature but could be stored for about 12 hours under argon at -20°C before decomposition to polymeric material occurred. The alcohol was, however routinely carried through to the following stages immediately after flash column chromatography.

In order to utilise the Noyori approach it was necessary to generate the corresponding trimethylsilyl ether (100). This proved surprisingly difficult with TMSCl as the original choice, being added to a stirred solution of the furan alcohol and DMAP, at 0°C, before warming to room temperature and quenching with sodium bicarbonate. This only gave decomposed material, Scheme 108.
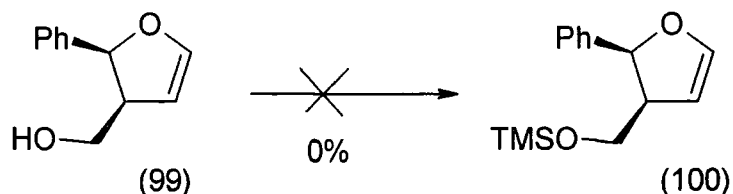
Scheme 108

A second attempt was made with trimethylsilyl trifluoromethanesulfonate (TMSOTf), a strong Lewis acid silylating agent, which would be present later in the reaction pathway. TLC showed disappearance of starting material, however, after workup only decomposed products were apparent.

Finally a method where the by-product was a solid or gas for easy removal was required. Of the reagents available, trimethylsilylcyanide offered a gaseous side product – but with the hazards associated with such chemicals we turned to the *N,N'*-*bis*(trimethylsilyl)urea offering a method of protecting alcohols and carboxylic acids, leaving the urea by-product to be simply filtered off, Scheme 109.[75]
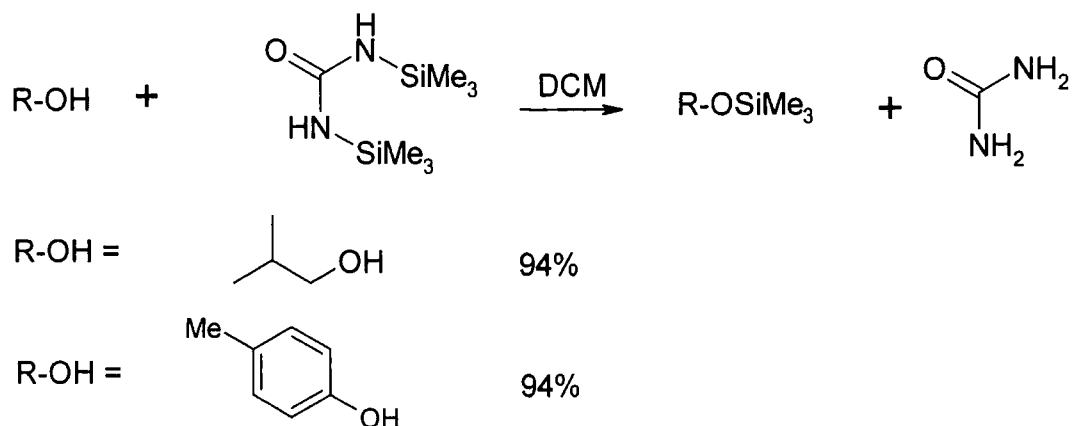
Scheme 109

Following this precedent the reaction proceeded, showing disappearance of starting material and appearance of urea. However on workup, only a small quantity of the residual solid urea by-product was obtained and analysis of the remaining material was decomposed products.

Given this lack of success it was decided to attempt to silylate the alcohol *in situ*, by addition of the alcohol to a mixture of the required acetal, and 1.1 equivalents of TMSOTf with the expectation that the small excess would be sufficient to catalyse the transacetalisation.

As outlined above, our strategy was revised at this stage, to generate the silyl ether in the presence of a preformed oxonium ion. 1.1 equivalents of TMSOTf were added to a stirred solution of 1.0 equivalents of 4-methoxybenzaldehyde dimethyl acetal, leading almost immediately to a deep purple colour change which was taken to signify the appearance of the required oxonium ion. Whilst maintaining the reaction at -20°C, a pre-cooled solution of the furan alcohol (99) was added. The 1.1 equivalents of TMSOTf added would silylate the furan alcohol rapidly forming the reactive intermediate (100), which would quickly react with the preformed oxonium ion and in turn resulted in formation of the cyclised intermediate (101).

Addition of methanol, with the temperature of the reaction maintained at -20°C, followed by addition of sat. NaHCO₃ gave the product, 4-methoxy-6-endo-(4'-methoxyphenyl)-2-endo-phenyl-3,7-dioxabicyclo[3.3.0] octane as the isomer illustrated, Scheme 110, (102) was formed. With optimised reaction times and dry conditions, the reaction was able to give the furofuran (102) in 81% yield.
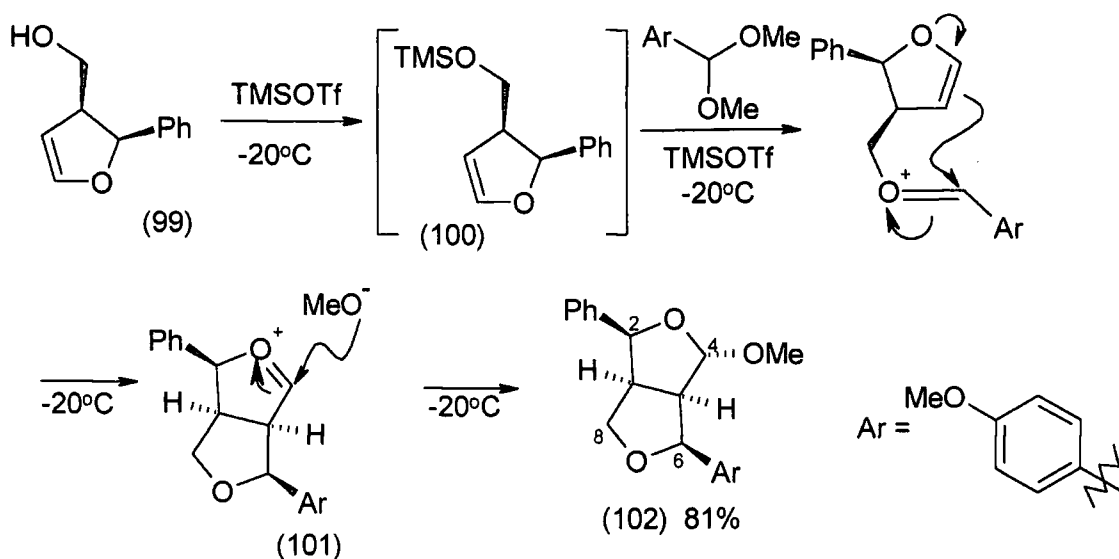
Scheme 110

Characterisation of the product confirmed the identity as that of (102): Microanalysis matched the calculated values, IR showed no outstanding functionality, and the mass ion was found at 326 using mass spectrometry. High field NMR experiments were required to elucidate the stereochemistry and exact assignment of the signals. HSQC, COSY, and NOESY experiments were conducted to assign the structure. Scheme 112 shows the prominent NOESY couplings occurring between protons on C1 and C2, C1 and C5, C1 and C8, C6 and C5, and the two protons on C8 couple also. The protons on C4 is a singlet with no W coupling across the ring with H-C2 which further suggests the compound is the isomer illustrated (102).

To our surprise, when the reaction was repeated without the addition of methanol to quench, the same product was obtained, suggesting that methoxy source is not in fact the methanol added to quench, but from the methoxy acetal. This could be verified by the use of a diethyl acetal in future work.

When the completed reaction was allowed to warm to room temperature prior to quenching with methanol / bicarbonate, the product obtained differed from that previously synthesised. The product was obtained as a white solid, in 68% yield, and the reaction is summarised in Scheme 111. Complete characterisation showed there is extensive similarity between the two compounds with only the NMR spectra

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displaying any significant differences. This suggested the change in quenching temperature had led to a different isomeric form of the previously described furofuran, (102).
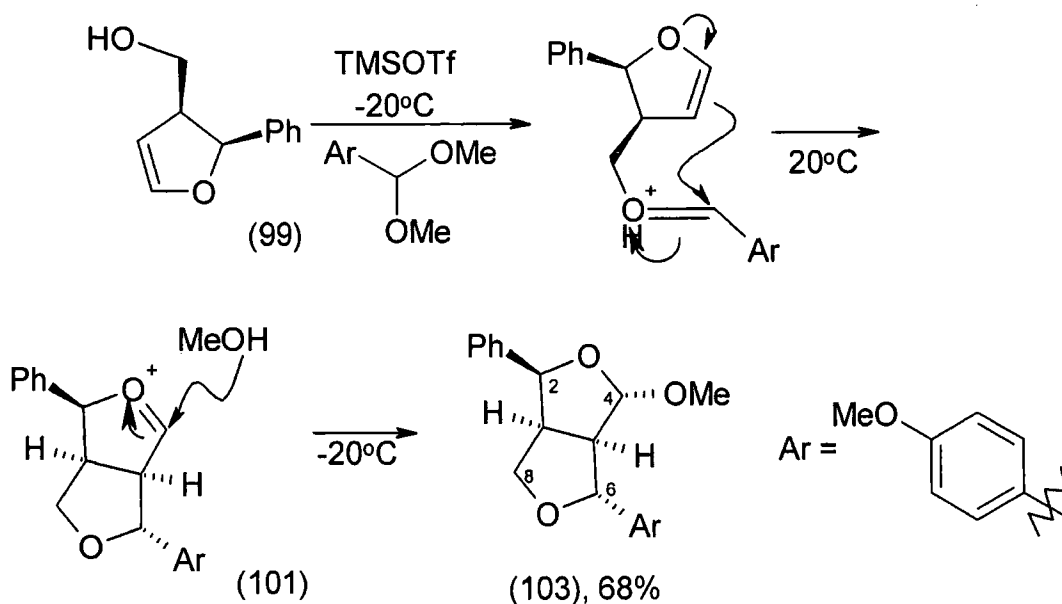
Scheme 111

Extensive NMR experiments were conducted to enable stereochemical assignment and the product stereochemistry elucidated to be furofuran lignan (103). Proton couplings are seen between C8 and C1, C1 and C2, C1 and C5 and the two protons on C8 couple to one another. The prominent NOESY correlations for the two products (102) and (103) are illustrated in Scheme 112 for comparison.

(102)   Scheme 112   (103)
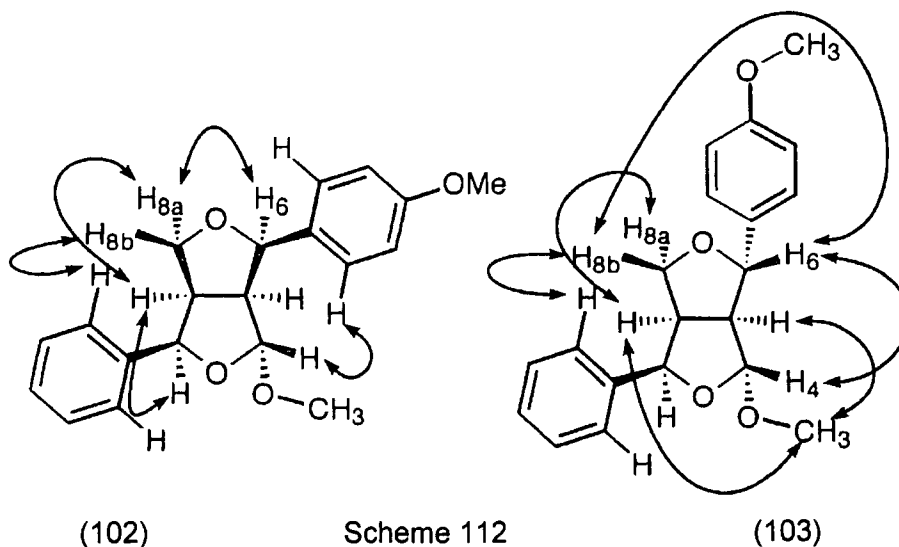
The previously described procedure was repeated using 4-methoxybenzaldehyde in place of the acetal however no reaction occurred. 4-methoxybenzaldehyde was recovered and it was taken from this, in line with the general trend of reactivity that the free aldehyde was not sufficiently reactive for the transacetalisation. In order to study the suitability of this method for the synthesis of a furofuran lignans with a broad range of substituents, it was necessary to synthesis a range of the required acetals before trying to incorporate them into the framework.

We elected to try the reaction with a variety of acetals as illustrated in Scheme 113.
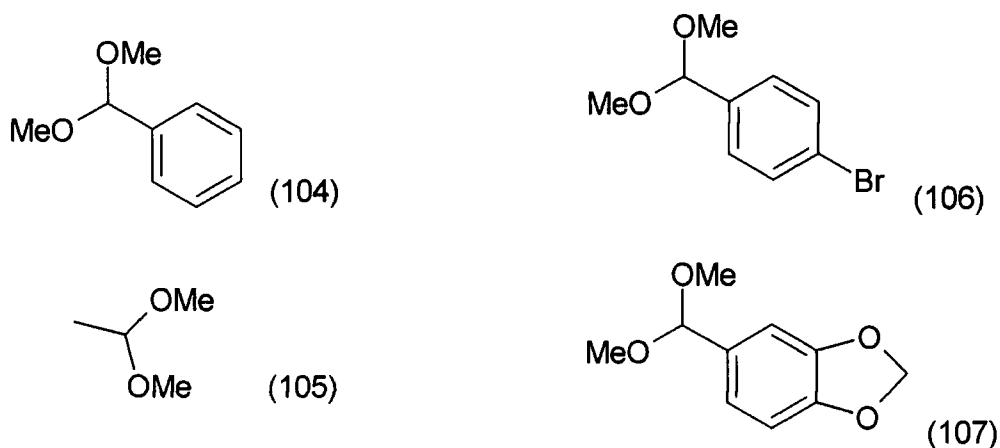
Scheme 113

Benzaldehyde dimethyl acetal (104) was chosen to provide access to a "symmetrical" furofuran lignan and, if successful, would allow access to the simplest diaryl furofurans.

Ethanal dimethyl acetal (105) would allow us to investigate the application of our method to alkyl acetals. The 4-bromobenzaldehyde (106) would provide a lignan with versatile functionality on the aryl ring and explore the application of the route to more electron-poor acetals. Finally the piperonal (107) derivative would provide an opportunity to put an electron rich aryl ring into the system which is commonly found in natural furofuran lignans.

Compounds (104) and (105) are commercially available. Whereas both (106) and (107) had to be synthesised from the corresponding aldehyde.

Using trimethyl orthoformate with p-toluenesulfonic acid in methanol, the 4-bromobenzaldehyde was heated under reflux for 24 hours. After workup the required acetal (106) was obtained as a light brown liquid in 96% yield, Scheme 114.
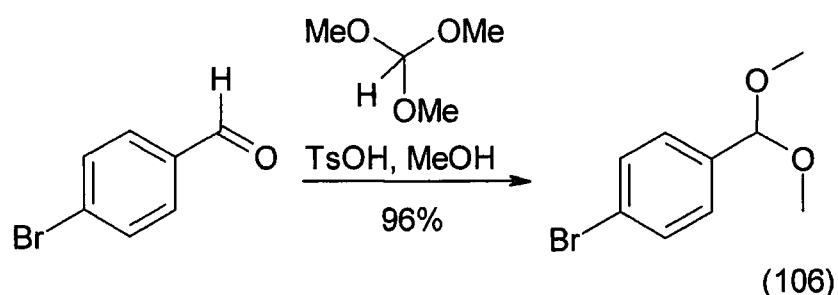
Scheme 114

Piperonal (3,4-methylenedioxybenzaldehyde) was subjected to the same conditions used to synthesise the acetal of 4-bromobenzaldehyde, but the product appeared to cleave on workup. An alternative method was found completing the reaction almost instantaneously using a cerium catalyst.[76]
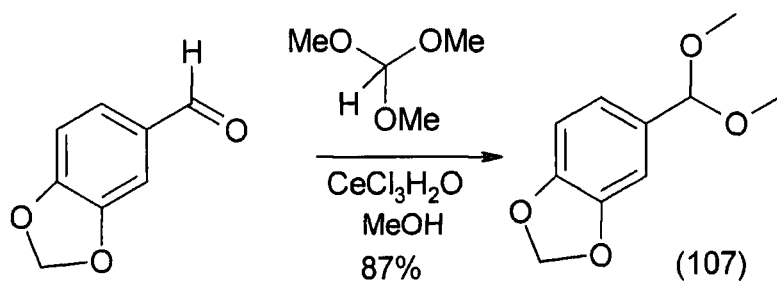
Scheme 115

Piperonal (3,4-methylenedioxybenzaldehyde) in dry methanol was added to trimethyl orthoformate and cerium chloride in methanol, Scheme 115. After 10 minutes at room temperature the reaction mixture was washed with sodium bicarbonate, before extracting into ether and drying with sodium sulfate. Removal of solvent gave the acetal (107) as a yellow solid in excellent yield, 87%.

Characterisation of this compound was achieved by proton NMR only, showing the complete loss of aldehyde protons, 3 aromatic protons, the methylene protons at 5.96ppm, acetal proton (5.29ppm) and the methyl groups at 3.32ppm.

4.7 Synthesis of further furofuran lignans
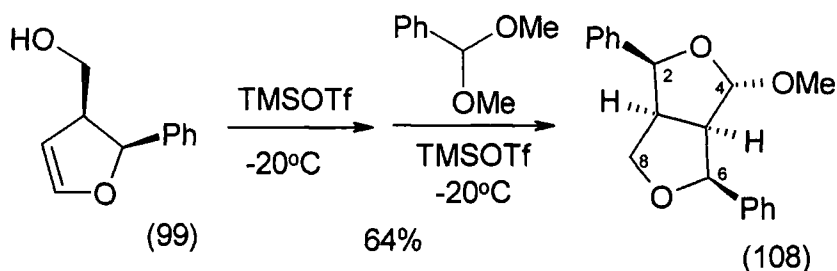
Scheme 116

Using the same method as for the 4-methoxyphenyl derivative (102), the diphenyl lignan (108) was synthesised in good yield (64%) as a white solid, Scheme 116. Characterisation gave microanalysis matching the calculated values, and the mass ion at 296 by mass spectrometry. Extensive NMR experiments, COSY, HSQC, NOESY enabled stereochemical assignment. The proton couplings for C1 to C2, C1 to C8, C8 to C8, C5 to C6 were prominent, and showed this to be the illustrated isomer (108).

The reaction was repeated, allowing the mixture to warm to room temperature prior to quenching, however this resulted in the same compound, (108) being isolated in 57% yield. Thus, for the phenyl derivative only the kinetic isomer was accessible, but in our first example the 4-methoxyphenyl (electron rich) derivative had given the kinetic (102), and thermodynamic (103) isomers.
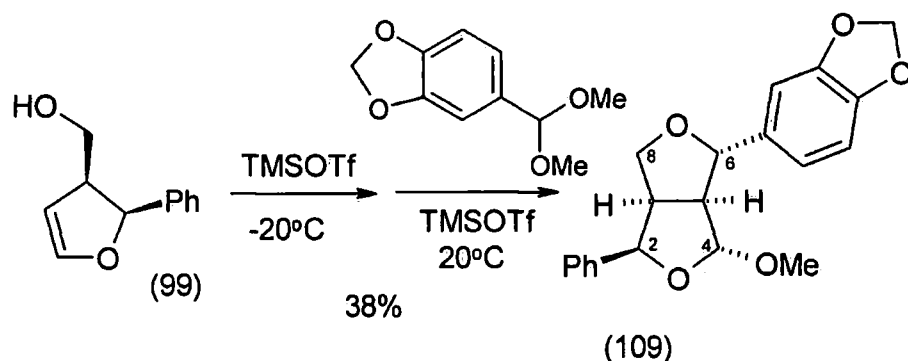
Scheme 117

Using the same method as for the 4-methoxyphenyl derivative (103), warming to ambient temperature prior to quenching, the piperonal derived lignan (109) was synthesised as a white solid, in 38% yield, Scheme 117. Characterisation gave microanalysis matching the calculated values, extensive NMR experiments, COSY, HSQC, NOESY enabled stereochemical assignment. The proton couplings for C1 to C2, C1 to C8, C8 to C8 were prominent, and showed this to be the illustrated, thermodynamic isomer (109). This is expected due to the highly electron rich piperonal group enabiling equilibration via a stabilised cation (discussed later in this section). We then repeated the reaction, but maintaining -20°C prior to quenching, leading to a mixture of the previously isolated isomer (109) (9%), and the kinetic isomer (110) (27%) being obtained, Scheme 118.
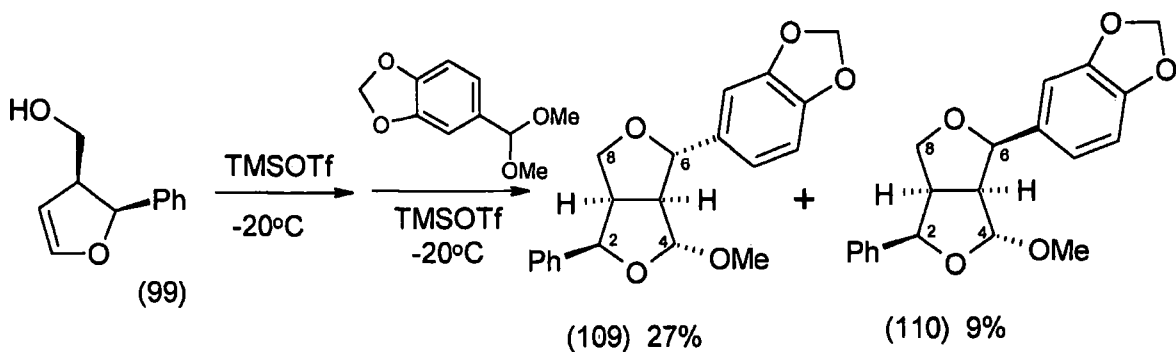
Scheme 118

When repeated at -40°C the two compounds were obtained again (109) in 5% yield, and (110) in 22% yield. The kinetic isomer was again characterised by extensive NMR experiments.

Using the same method as for the 4-methoxyphenyl derivative (102), the 4-bromophenyl lignan (111) was synthesised as an amorphous yellow solid, Scheme 119.

Scheme 119
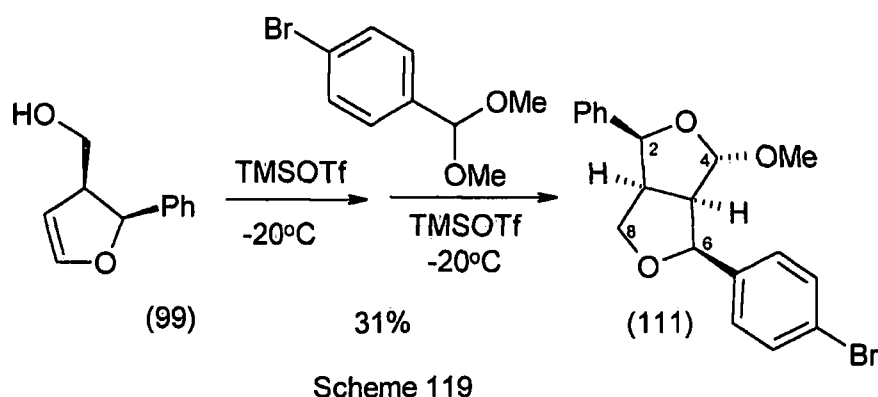
Characterisation gave microanalysis matching the calculated values, and the mass ion at 345 / 343 by MS (EI) with characteristic bromine isotope pattern. Extensive NMR experiments, COSY, HSQC, NOESY enabled stereochemical assignment. The proton couplings for C1 to C2, C1 to C8, C8 to C8, C5 to C6 were prominent, and showed the illustrated isomer (111), Scheme 119.

We then repeated the reaction, but allowed the mixture to warm to room temperature prior to quenching. This resulted in the same compound, (111) being isolated in 27% yield. Thus, for the 4-bromophenyl derivative, only the kinetic isomer was accessible.

Using the same method as for the 4-methoxyphenyl derivative (102), the previously unreported methyl substituted lignan (112) was synthesised as an amorphous white solid, Scheme 120.

(99) (112)

30%

Scheme 120
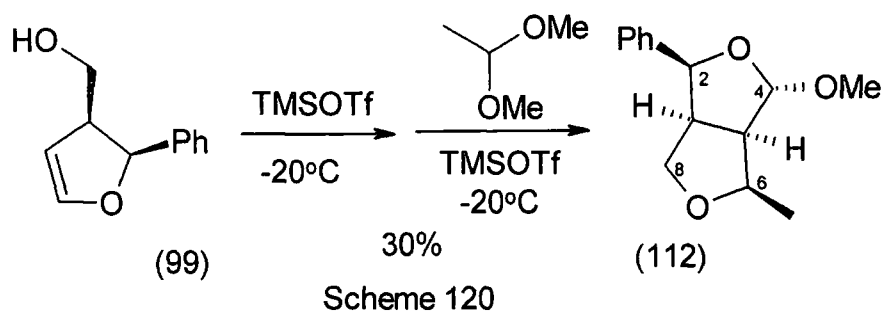
Characterisation gave microanalysis matching the calculated values, and the required mass was observed by mass spectrometry. Extensive NMR experiments, COSY, HSQC, NOESY enabled stereochemical assignment. The proton couplings for C1 to C2, C1 to C8, C8 to C8, C5 to C6 were prominent, and showed this illustrated isomer, (112).

We then repeated the reaction, but allowed the mixture to warm to room temperature prior to quenching. This resulted in the same compound, (112) being isolated in 28% yield. Thus, for the methyl derivative, only the kinetic isomer was accessible. This showed our method allowed access to not just diaryl lignans but also the introduction of alkyl substituents into the framework.

Explanation for isomeric variation

Our developed methodology represents a one-pot route from the starting furan alcohol to the completed bicyclic framework. We have demonstrated the synthesis of a number of the furofuran methyl glycosides and in some cases achieved stereocontrol through the use of varying temperature. A summary of the reactions reported follows, Table 9 and 10.

Kinetic Conditions.

Quenching the reaction at -20°C, gave access to the 5 examples of *endo, endo* isomer with stereochemistry as described by A, Scheme 121.
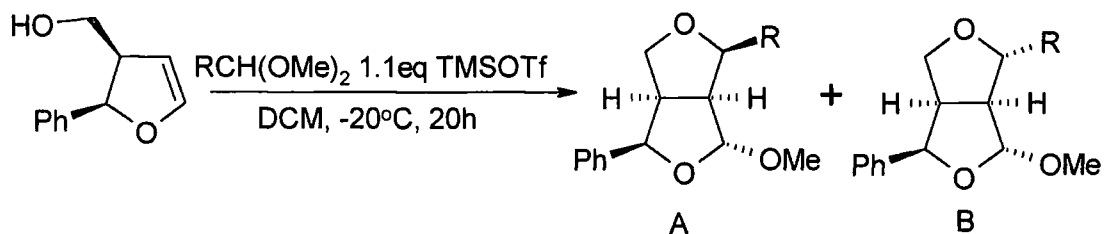
Scheme 121

Entry	RCH(OMe)$_2$	Yield A	Yield B
1	MeO—⟨⟩—CH(OMe)$_2$	81%	-
2	⟨⟩—CH(OMe)$_2$	64%	-
3	piperonyl-CH(OMe)$_2$	27%	9%
4	Br—⟨⟩—CH(OMe)$_2$	31%	-
5	CH$_3$CH(OMe)$_2$	30%	-

Table 9

Only the electron rich piperonal derivative produced mixed stereochemistry at -20°C.

Thermodynamic Conditions

Allowing the reaction mixture to reach room temperature before quenching with methanol and sodium bicarbonate, gave access to some of the lignans with stereochemistry B, while the remainder produced the previously described isomer A, in lower yields than under the kinetic conditions, Scheme 122.

Scheme 122
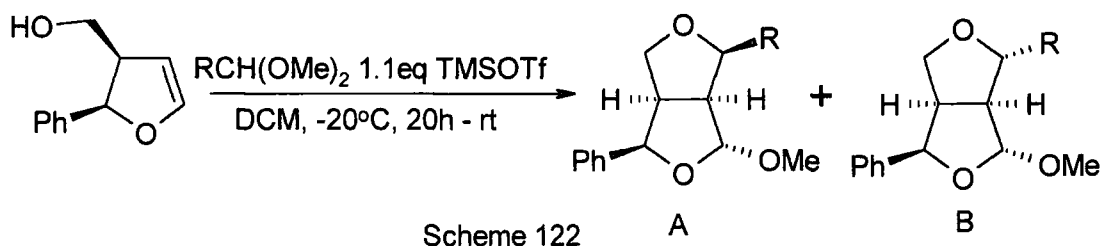
Entry	RCH(OMe)$_2$	Yield A	Yield B
1	MeO—〈 〉—CH(OMe)$_2$	-	68%
2	〈 〉—CH(OMe)$_2$	57%	
3	(methylenedioxyphenyl)—CH(OMe)$_2$	-	38%
4	Br—〈 〉—CH(OMe)$_2$	27%	
5	CH$_3$—CH(OMe)$_2$	28%	

Table 10

To account for these outcomes it is proposed the initially formed oxacarbenium ion, has an *E* configuration and cyclisation occurs through an *endo* type transition state (113), giving access to the *endo, endo* isomers, Scheme 123.

The alternative, *exo* transition state which is required for access to the *endo, exo* isomers is unlikely to be favoured due to the steric interactions between Ar and C3 proton (114).
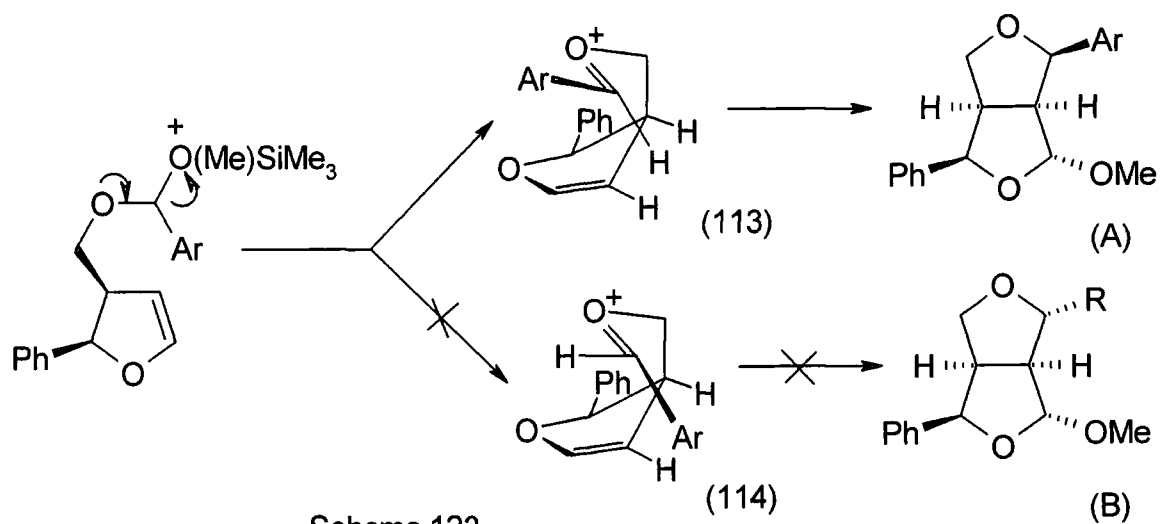
Scheme 123

The alternative possibilities for this pathway may involve an S_N2 type displacement (115) (path X), Scheme 124 or the formation of a stabilised oxacarbenium ion (116), Scheme 125. The first seems unlikely with the proximity of the oxygen lone pair, to stabilise the required intermediate for (113) (path Y, as before Schemes 123, 124),
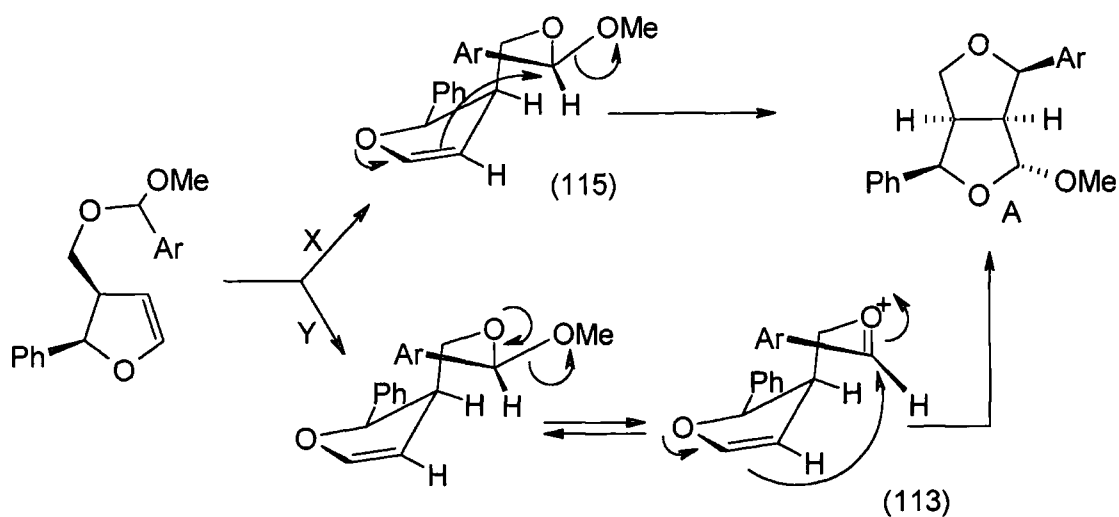
Scheme 124

Although the later (Scheme 125), is certain to provide the intermediate for the isomerisation to the thermodynamic isomer, it is not likely to partake in the *endo, endo* lignan route, with the success reported of substrates which are electron poor, (108), (111), (112).

Scheme 125
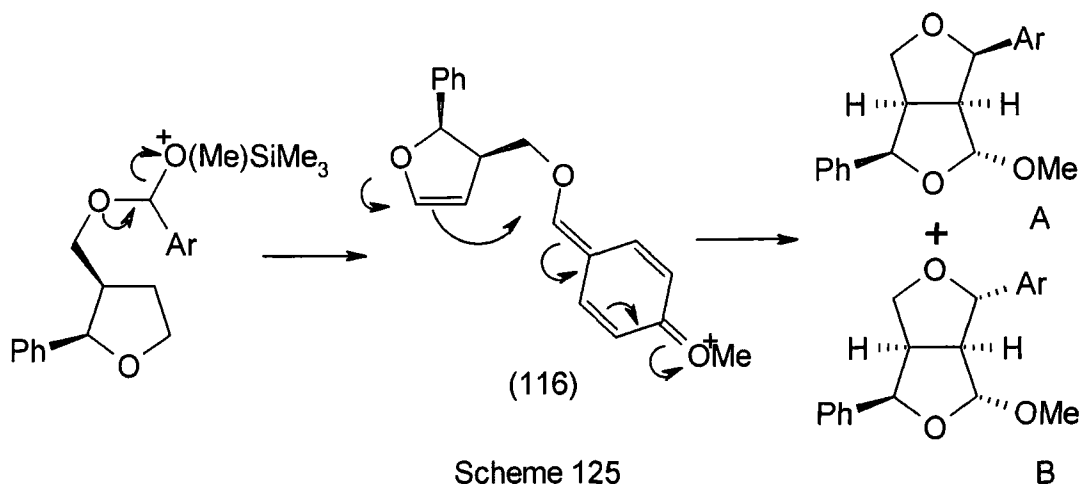
The formation of the thermodynamic isomers (103), (109), with stereochemistry described in structure B, at higher temperatures reflects the equilibration via cation (116) to place all the substituents on the less crowded exterior of the structure, Scheme 125.

4.8 Further derivatisation of the furofuran framework.

From our method of creating the [3,3,0]-dioxaoctane framework, we had easy access to the methyl glycoside furofuran lignans. We decided to use the methoxy centre as a site for further functionisation of the framework, reasoning that attack with a Lewis acid allows its potential replacement with a range of nucleophiles.

A search of the literature revealed Ward had used BF_3 etherate and triethylsilane on a number of furofuran lignan acetals with varying results. Simple examples were successful in reduction to the corresponding cyclic ethers, though with some disruption of stereochemistry, Scheme 126.[77]

We reasoned that this disruption of the stereochemical centre was due to the electron rich properties of the 3,4-dimethoxyphenyl substituent. Given the 3,4-methylenedioxyphenyl group was untouched we subjected our furofuran lignans to the described conditions.
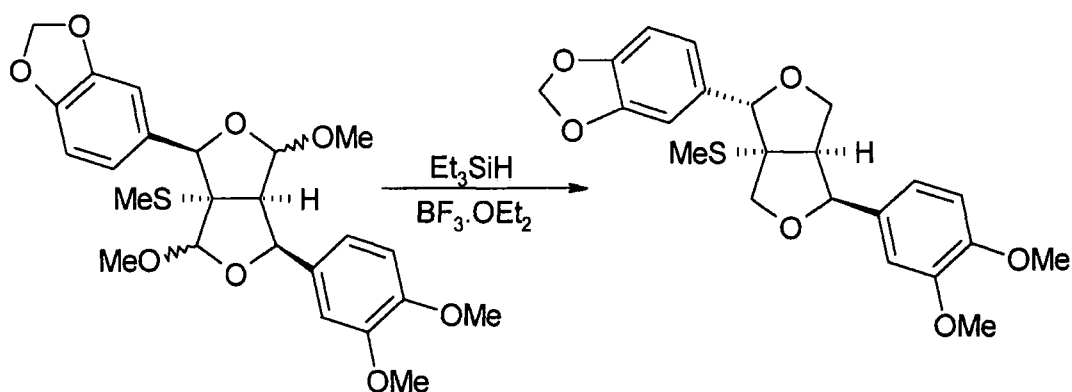
Scheme 126

To probe this possibility and to further confirm the stereochemistry of our synthesised lignans we aimed to reduce the diphenyl furofuran acetal (108) to the highly symmetrical cyclic ether (117). To this end the diphenyl furofuran was premixed with 50 equivalents of triethylsilane (Et₃SiH), and then treated, with boron trifluoride diethyl ether complex, with the solution immediately becoming dark green in colour, taken to be indicative of the oxonium ion. After stirring at room temperature overnight the desired symmetrical lignan (117) was obtained, in 61% yield, Scheme 127.
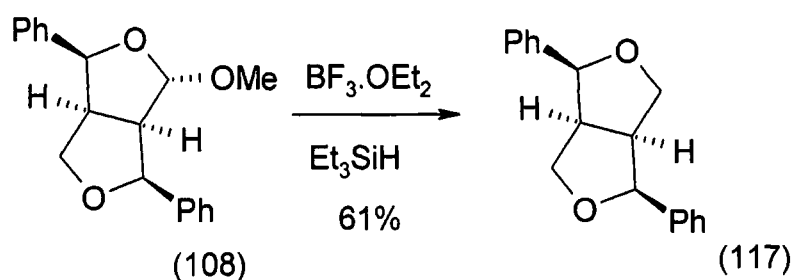
Scheme 127

Evidence for the product was given by the correct mass ion on MS, a matching microanalysis and a fully assignable, and simplified NMR. The proton spectra showed the loss of the methoxy group and the carbon revealed only 7 signals. This is expected, and indeed further confirms the assigned stereochemistry of the starting material as the compound is highly symmetrical with only 7 magnetically different carbons.

Using this successful method, the *para*-methoxy lignan (102) was similarly treated, obtaining the expected furofuran lignan (118) in 68% yield, Scheme 128.
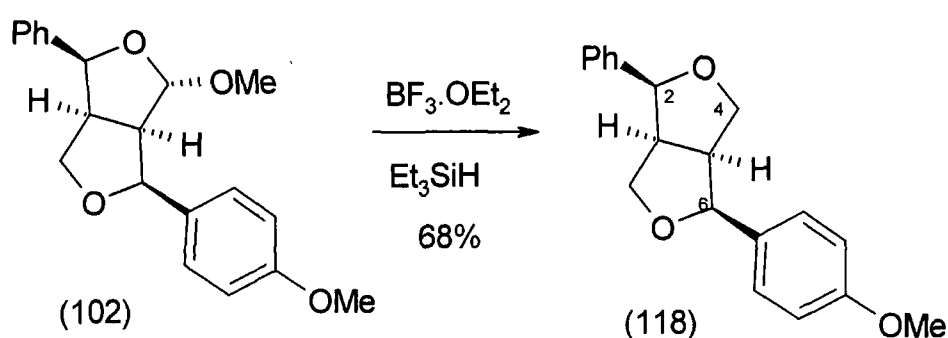
Scheme 128

In the ^{13}C NMR there was no evidence of epimerisation at the C-6 centre where potential scrambling of the stereocentre was envisaged due to Lewis Acid interaction with the *para*-methoxy phenyl group. This further confirms the proposed mechanistic pathway, as the alternative equilibrium pathway that would have led to scrambling at this centre has not occurred as there was no evidence of the thermodynamic product (103), Scheme 129. The product was confirmed by the presence of the correct mass ion and through clear loss of the one methoxy group in the ^{1}H NMR spectra.
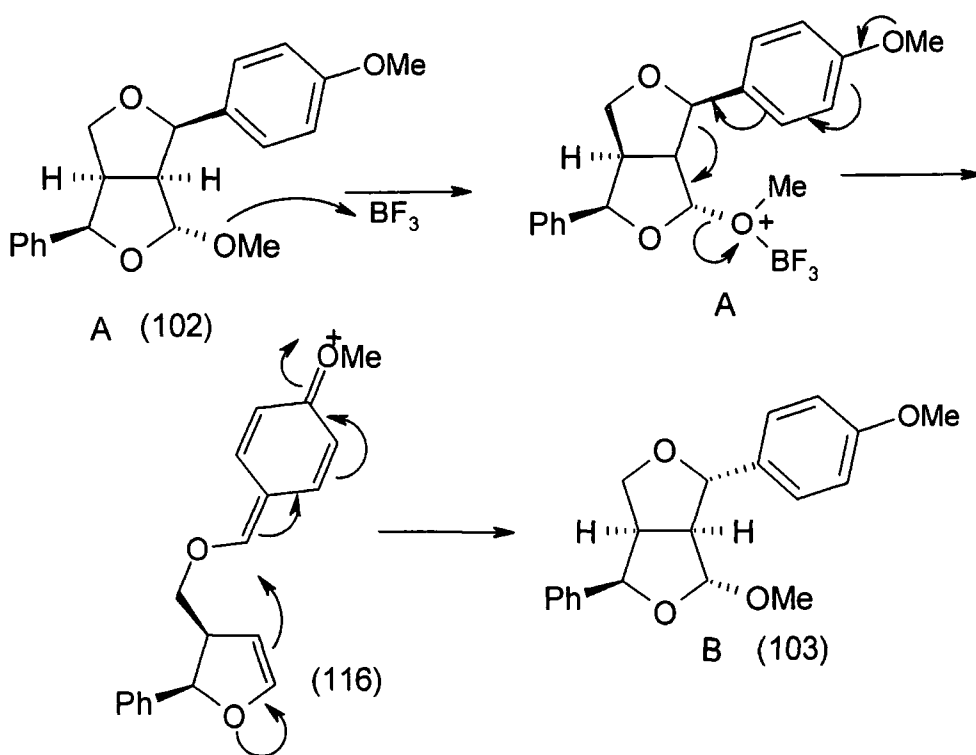
Scheme 129

A series of nucleophiles were then tested against lignan (102), in experiments following the same protocol that had been used with these silane reactions. The results are collated in Table 11

A variety of conditions were tried with stirring for several days, while monitoring by TLC, and a range of temperatures were tested. Other than the allyl and Et₃SiH examples, the work up resulted in recovery of decomposition products or starting material. It seemed the IPA was too bulky and even in large excess we could not displace the Lewis acid activated methoxy group. It could be that small quantities of methoxy were present, albeit in low concentrations, but in all the reactions methoxy would have been sterically small enough to beat the substrates to the cationic sites immediately after formation. On one reaction the IPA did indicate traces of a possible product but the yield was small and the quantities low. Repeating the reaction did not allow us access to the desired product.
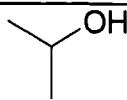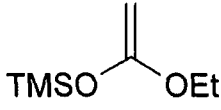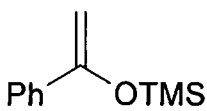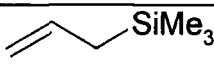
Run	Nucleophile	Yield with (102)
1	Et$_3$SiH	68%
2	![OH structure]	-
3	PhSiMe$_3$	-
4	TMSO⟍⟍OEt	-
5	Ph⟍⟍OTMS	-
6	⟍⟍SiMe$_3$	56%

Table 11

Extensive work and varying conditions were used in a concentrated effort to succeed with synthesis of the allyl compound. Only after considerable efforts were the conditions set to 48 hours stirring at 0°C and the desired product was obtained. The other substrates are yet to have further conditions applied to them, but it seems this method may be limited by the bulk of the nucleophiles. Molecular sieves were used to attempt to absorb any free methoxy during the reaction, but with no change in the reaction outcomes. The diphenyl lignan (108) was also tried in runs 2, 4 and 5, but with no evidence of the desired product. Why there should be a loss of starting material in runs 3 , 4 and 5 on extended reaction times is at this point is unclear.

The allyl substituted lignan was purified by flash chromatography to give a yellow non-crystalline solid. The product was characterised in full, producing a matching microanalysis, and the expected mass ion (336). The NMR spectra showed loss of a methoxy group and the presence of the allyl moiety. COSY and NOESY experiments were run and the stereochemistry of the incorporated allyl group showed to be in the same configuration as the methoxy group had been. There were traces of the other (C-4) isomer, but these were never separated from the main, illustrated isomer (119), Scheme 130.
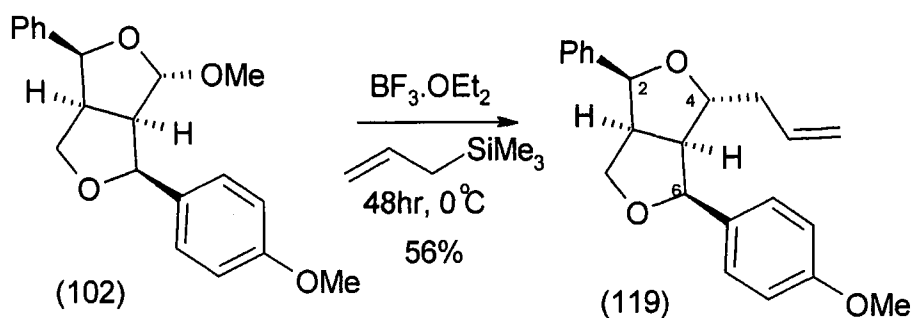
Scheme 130

In an attempt to discover how labile the methoxy group was we attempted to hydrolyse the acetal to the glycoside compound using aqueous hydrochloric acid on the diphenyl lignan (108). To our surprise the acetal was resilient and was recovered after 36 hours with no evidence of hydrolysis.

Further examination of the recent literature highlighted the possibility that the Lewis Acid facilitated exchange we were attempting may be less facile than we thought. Comparison of compounds (120) and (121) by Rousseau demonstrated the methoxy group to be much more stubborn to displace by allyl-TMS than other substrates, Scheme 131.[78]
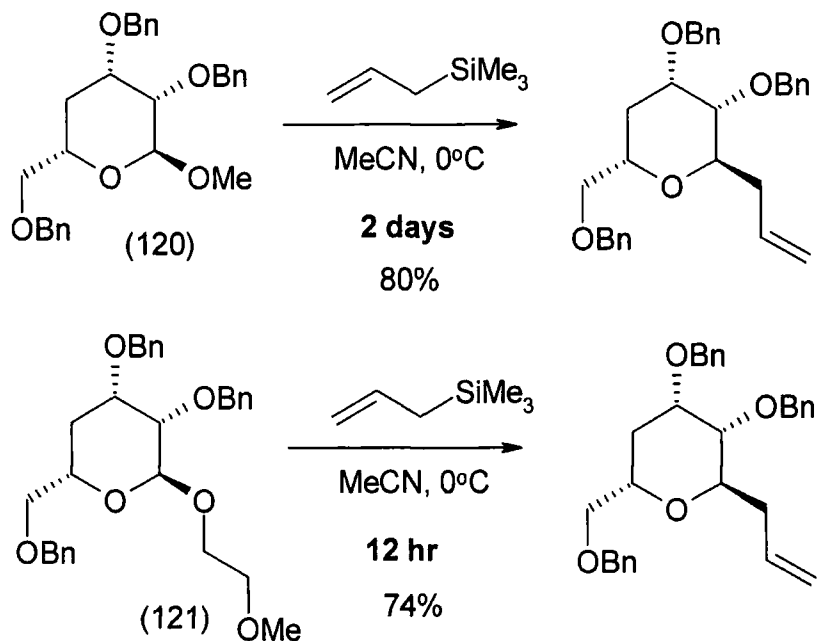
Scheme 131

With this in mind, future work should investigate the incorporation of a differing acetal group (other than OMe), in order to confirm the source of this functionality and to investigate the ease of displacement with allyl and other nucleophiles.

Our final work was to attempt the transacetalisation with a secondary or tertiary furan alcohol to introduce some substituents on C8 of the furofuran ring system. We reasoned that Grignard attack on the dihydrofuran ester (34) would give access to a tertiary alcohol (122). This in turn would be treated to our lignan synthesis protocol, in an attempt to access the highly substituted framework (123), Scheme 132.
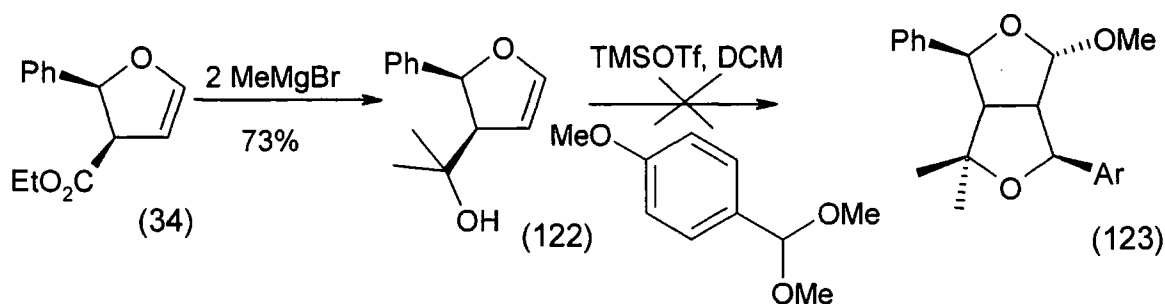
Scheme 132

The Grignard reagent, methyl magnesium bromide, was added to a solution of the ester (34) in diethyl ether. After 2 hours, the reaction was quenched with ammonium chloride and flash chromatography led to the desired tertiary alcohol in 73% yield. This was characterised by a broad OH stretch in the IR and a fully assigned proton spectra with two methyl singlets at 0.88 and 0.85ppm and the ^{13}C NMR showing the same methyl groups at 28 and 27ppm. The unstable alcohol was then subjected to the predescribed lignan synthesis using p-anisaldehyde dimethyl acetal. Several attempts at this reaction were made, only resulting in decomposed material and recovery of 4-methoxybenzaldehyde. From these results we reasoned the intermediate formed on the initial transacetalisation may be too constrained by the dimethyl substituents to form the desired transition state (124), or that indeed, the

product contains too much strain energy due to the conformation of the newly formed substituted furan ring that the reaction will not occur.
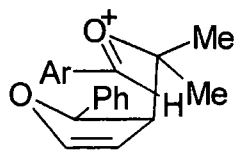
(124)

Scheme 133

Following these results we elected to attempt the reaction using the secondary alcohol in a hope that it would ring close with ease to form the relevant furofuran lignan (128). It was envisaged that the secondary alcohol could be accessed through the corresponding Weinreb amide, a technique commonly used as route between esters and secondary alcohols in transformations such as in Scheme 134.[79]
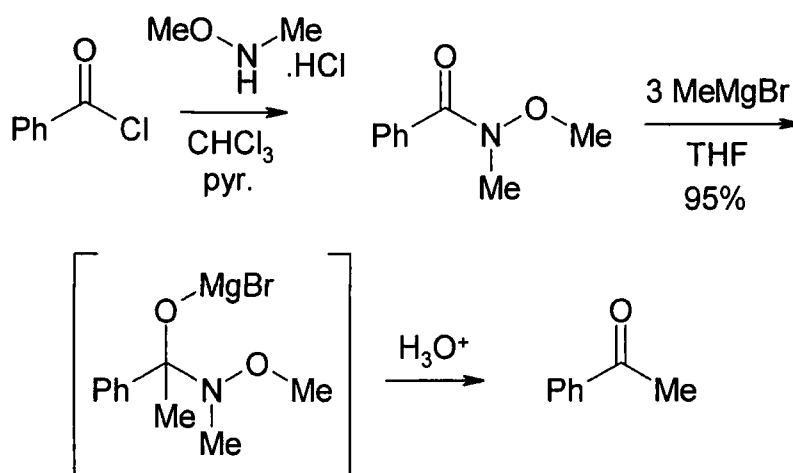
Scheme 134

Our attempts to synthesis the Weinreb amide (125) commenced with the preparation of the reactive aluminium complex (126), according to an established literature procedure.[80] The complex is prepared using $AlMe_3$ in DCM with the N,O-dimethylhydroxylamine. This is added to a solution of ester (34), but in our case led only to decomposed products.
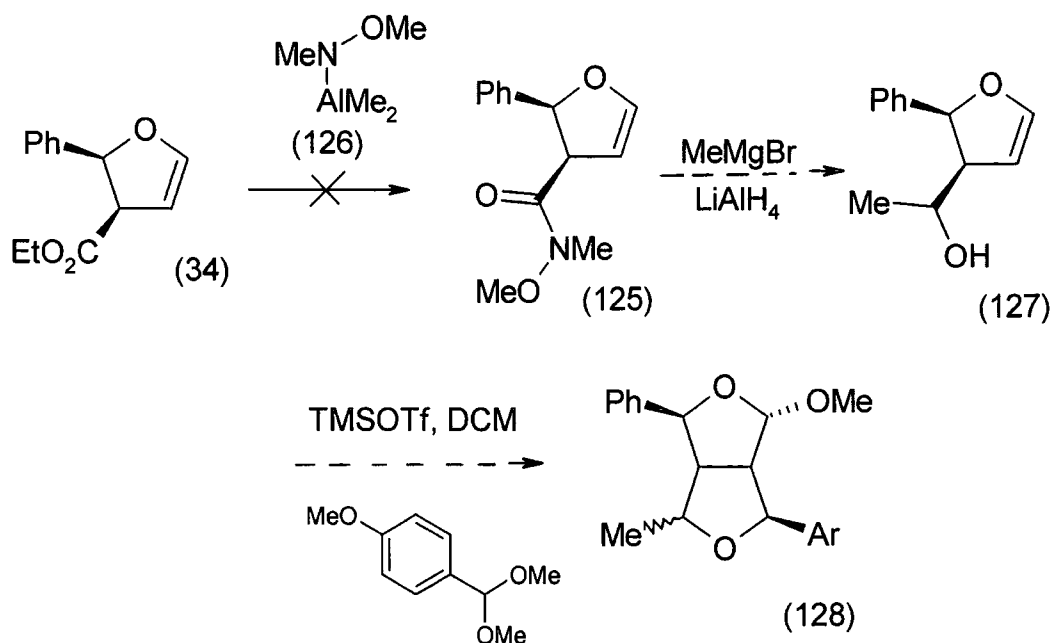
Scheme 135

We then chose to hydrolyse the ester to the dihydrofuran carboxylic acid (129) and make the mixed anhydride using the previously described protocol for coupling the chiral auxiliaries to our vinylepoxide. This, we reasoned would be of similar reactivity to the acid chloride, and we proposed to complete the coupling by the addition of the N,O-dimethylhydroxylamine, Scheme 136.
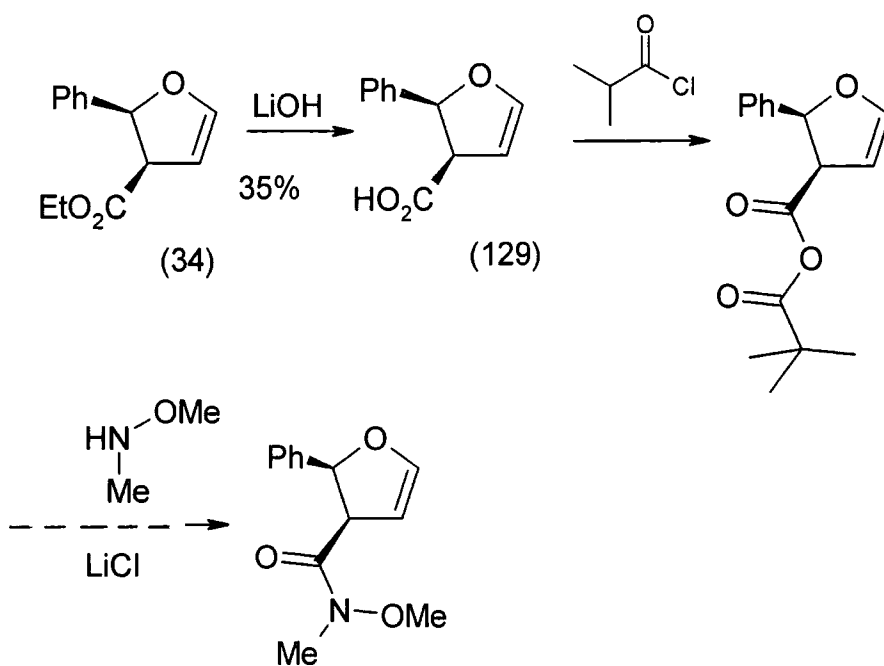
Scheme 136

The hydrolysis was conducted on the dihydrofuran using the successful method developed for the vinylepoxide. The reaction was conducted only once and the modest yield (35%) reflects the unoptimised conditions. However, with sufficient material in hand we proceeded with the mixed anhydride coupling reaction, but obtained only decomposed material. With this lack of success in synthesis of the Weinreb amide in the short time available for this section of our research we have been unable to synthesise the proposed multisubstituted lignan (128). This presents obvious opportunities for future work with the many literature methods of synthesising the required amide available, including the use of 2-chloro-1-methylpyridinium iodide,[81] or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP).[82]

4.9 Conclusions to furofuran lignan studies

We have successfully applied our dihydrofuran product to the synthesis of potentially bioactive molecules in a convenient one-pot synthesis of a variety furofuran lignans. The method allows diversity in the nature of the 2,6- substituents and, to some degree, control of stereochemistry. Work has been carried out to convert the resulting acetals to the corresponding substituted cyclic ethers with some success, and with future possibilities of more work in this area. With the route established, the use of different dihydrofurans (varying in both aryl substituents and secondary alcohols) can be investigated with time.

Chapter 5:   Vinylaziridine – 2-Pyrroline
rearrangement

5.1 Introduction

Having successfully developed a large scale synthesis and subsequent rearrangement of the vinylepoxide we then turned to examine the analogous vinylaziridine - pyrroline rearrangement. As discussed in chapter 1, preliminary work in the group had formally identified a synthetic route from the vinylepoxide, albeit in poor and unreliable yields on a small scale. The goals of this section of the project were to improve the synthesis and explore the possibility of the rearrangement of the vinylaziridine.

5.2 Synthesis of vinylaziridine precursor

Preliminary attempts followed our groups previous efforts and used dry reaction conditions. Under an argon atmosphere, dry methanol was used as the solvent for vinylepoxide, (33) to which sodium azide and ammonium chloride was added, heated slowly to reflux over 90 minutes, before filtering and concentrating down for analysis. The yield by this method was only 42%, and we sought to optimise the reaction, Scheme 137.
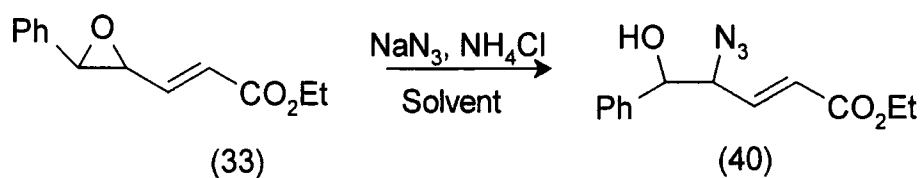
Solvent	Yield
Dry methanol	42%
DMF	18%
Methanol/water (5:2)	63%
Ethanol/water (5:2)	67%
Ethanol/water (7:1)	84%

Scheme 137

We thought that a more polar, aprotic solvent may be required to aid solvation and the reaction was tried at 20°C in DMF. No reaction occurred in 24 hours, and so heat was applied. Within thirty minutes (90°C) the reaction had gone black and the mixture was worked up. Flash column chromatography yielded 18% of the desired azide alcohol (40), from the remaining polymeric and decomposition material.

Whilst conducting the investigation into suitable solvent system for the azide alcohol production it was noticed in the literature that Crotti *et al.* had used a procedure for azidolysis of 1,2-epoxides using 1.5 equivalents $LiClO_4$ as a catalyst for attack by sodium azide, Scheme 138.[83] The reaction was attempted on our more hindered 2,3-substituted vinylepoxide, but resulted in decomposition after 3 hours of refluxing at 80°C.
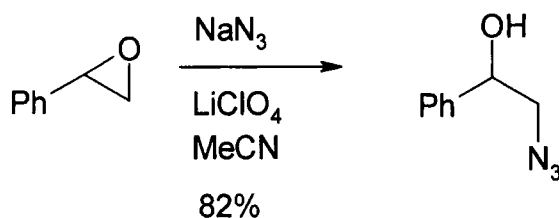
Scheme 138

Following this experiment we decided to try addition of water to the reaction in an attempt to aid solubility especially of the inorganic reagents and side products. Methanol/water (2.5:1) was used with work up involving removal of all solvent and the

organic material being washed from the inorganic residue with methanol. This gave the azide alcohol in more respectable 63% yield.

Further examination of the literature revealed that while Coldham *et al.* had conducted their azide alcohol syntheses in methanol/water,[6] it was noted that Fritch and Wipf had carried their reaction in ethanol on a similar epoxide (130) obtaining 85% yield, scheme 139.[84]

(130)　　　NaN$_3$. NH$_4$Cl　　EtOH, reflux　85%　→　OH　O　OEt　N$_3$　(132)
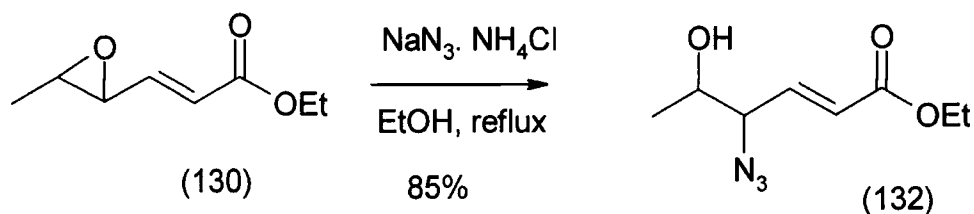
Scheme 139

Therefore ethanol/water was tried in the same 5:2 ratio, obtaining 67% yield. Scale up, changing the ratio of ethanol/water to 7:1, in order to improve homogeneity and adding the inorganic reagents dissolved in the aqueous portion of the solvent mixture gave yields of 84%. In each case the product was obtained from flash column chromatography. In our case the use of ethanol/water drastically improved the yield and we offer this as a superior protocol for azidolysis of the α, β unsaturated epoxide. ^{1}H NMR shows loss of epoxide and generation of HCN$_3$ at δ = 4.48, and PhHCOH at δ = 4.83. The molecular ion was observed by mass spectrometry. The infra red shows a broad O-H stretch at 3440 cm^{-1}, and azide stretches at 2495, 2102 cm^{-1}.

Ring closure of the azide alcohols to aziridines has been carried out routinely in the literature by treatment with triphenylphosphine (PPh$_3$) in anhydrous acetonitrile, Scheme 140.[84]
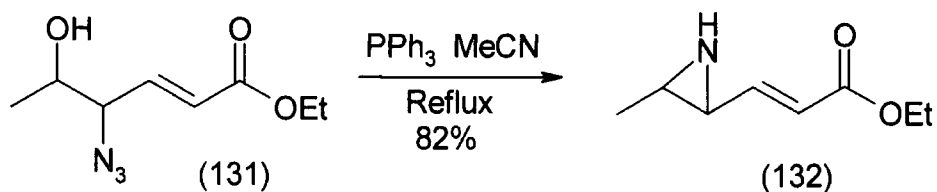
Scheme 140

Heating the reaction was considered, and indeed Wipf and Fritch[84] heated the reaction to reflux with their similar aziridine but Coldham had found that heating the azide alcohol in question had resulted in immediate decomposition to the imine (133), Scheme 141.[6]
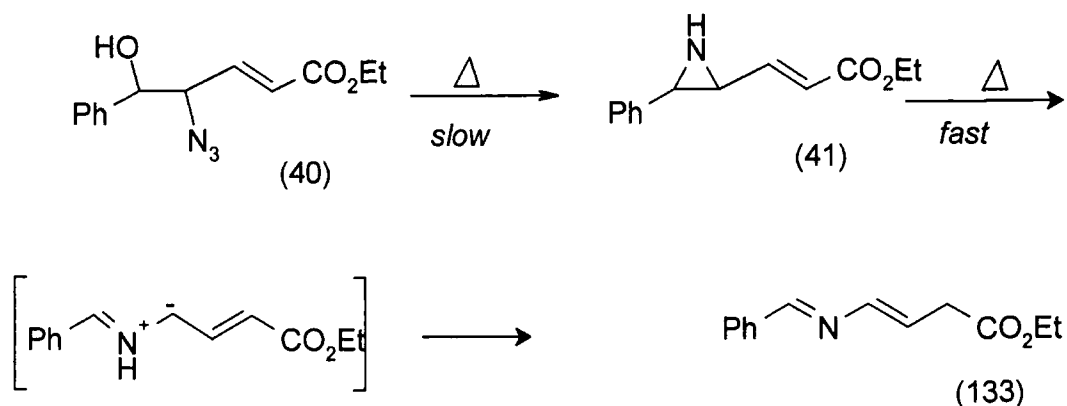
Scheme 141

In our hands, after 3 hours of stirring the azide alcohol (40) with triphenylphosphine, in MeCN at room temperature the aziridine (41) was isolated in 22% yield. Freshly distilled MeCN (from CaH_2) and recrystallized PPh_3 were tried to improve the yield and 33% was achieved. The majority of the crude product is polymerised or decomposed material, and at room temperature there is no evidence of the imine.

The exact nature of the mechanism was investigated to see how optimisation might be achieved. The mechanism proposed is based to on the report of Pöchlauer who isolated the intermediate for 2,3-diphenyl aziridine (134), Scheme 142.[85]

Scheme 142
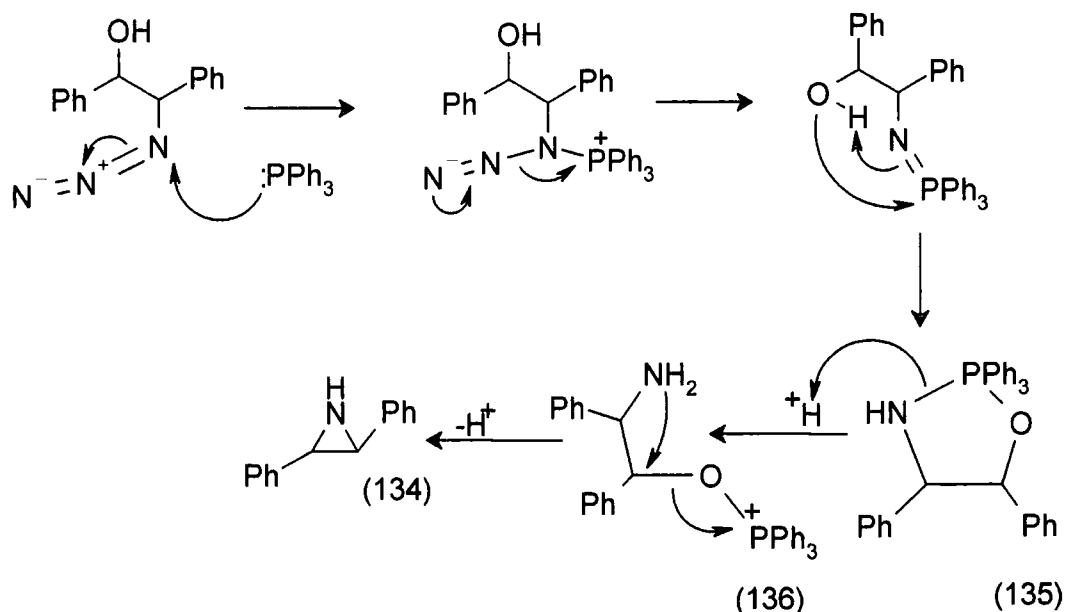
The mechanism shows the catalytic addition of a proton, (135) to (136), and it was decided to attempt the ring closure again, using the method of Pöchlauer with a catalytic quantity of acetic acid.

Consequently, the azide alcohol was stirred with PPh_3 in dichloromethane (DCM) (distilled from CaH_2) and a catalytic quantity of dry acetic acid. The reaction goes yellow-orange and after 1 hour, total consumption of starting material was observed by TLC. Following neutralisation with $NaHCO_3$ a standard work up to give the desired aziridine (41) in 46% yield, Scheme 143.

Scheme 143
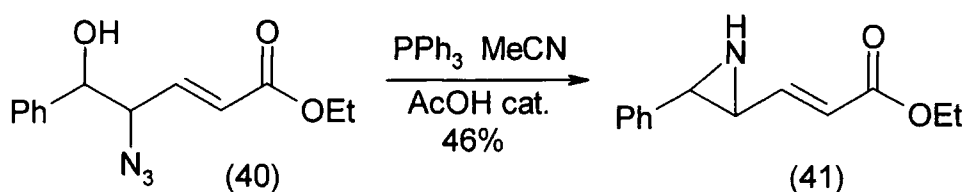
The formation of the aziridine (41) was confirmed by ^1H NMR displaying vinylic proton signals (δ = 6.59 (dd), 6.08 (d)), aziridine peaks (δ = 3.1 (d), 2.6 (dd)), and the ethyl signals (δ = 4.2 (q), 1.3 (t)) a secondary amine proton was observed δ=1.6, and the

infra red shows N-H stretch at 3288 cm^{-1}, with carbonyl and vinyl signals at 1703 cm^{-1} and 1643 cm^{-1} respectively. Mass spectrometry gave the molecular ion.

The low yield could be attributed to the instability of the aziridine under the conditions of this reaction. Acetic acid may easily have ring opened the aziridine leading to decomposition due to the sensitive nature of the aziridine group. Careful monitoring or temperature optimisation may lead to better yields but with sufficient material in hand to progress with the study into the rearrangement we commenced our examination of the rearrangement process.

5.3 *N*-Protected aziridines

As described earlier in chapter 1, previous work in the group had ascertained that attempting to rearrange the unprotected aziridine led to decomposition.

It was also thought that protection with an electron donating group will help stabilise the ylide-type intermediate. Although it had not proved possible to achieve this transformation, with the free N-H aziridine in hand we undertook an attempt at *N*-benzyl protection of the aziridine, Scheme 144.
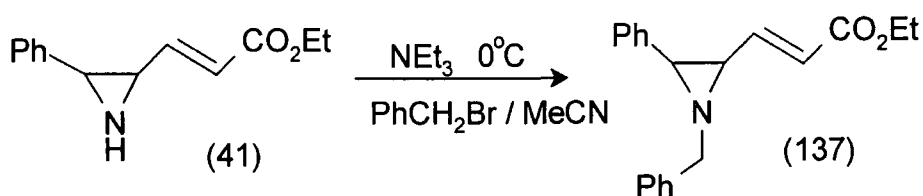
Scheme 144

Consequently, triethylamine was stirred with the aziridine in acetonitrile, and cooled before addition of benzyl bromide. After 24 hours the reaction contained starting material and some decomposed material.

^{1}H NMR of the decomposed material showed only aromatic, ethyl signals, and a doublet at $\delta = 0.9$. Why the aziridine is unreceptive to benzyl protection in this way is

unclear. Other methods exist for *N*-benzyl protection and remain to be fully explored, as does direct synthesis of protected aziridines from dienes or vinyl aldehydes. Given that Boc protection had been previously carried out and had not rearranged, we elected to pursue another *N*-protected aziridine. While an electron withdrawing group as a nitrogen protecting group was unlikely to favour the proposed rearrangement, we wished to ascertain if the instability of the aziridine was due to an electron donating protection, and given the relative instability of the free aziridine we chose to protect with benzoyl, Scheme 145. This would also enable us to further the work by our group, described in section 1.7.3.
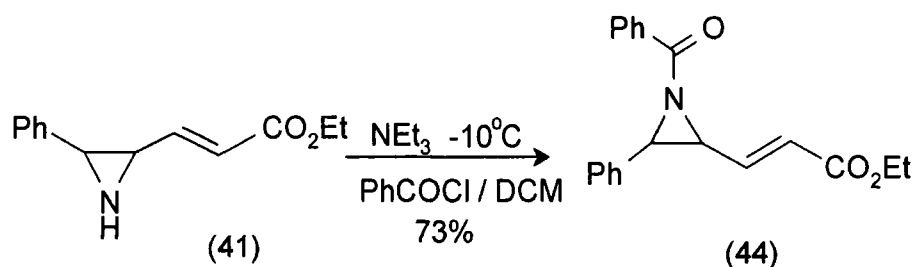
Scheme 145

Benzoyl protection was successfully carried out using triethylamine base for the reaction of benzoyl chloride with the free aziridine. Following workup, white crystals were obtained after flash chromatography, the reaction proceeding in 73% yield after purification. Characterisation of the product indicates that indeed the benzoyl aziridine (44) is the product: CHN microanalysis matches the calculated values, ^{1}H NMR gives benzoyl aromatic protons $\delta = 8.0$, aromatic protons, and the two vinyl signals. ($\delta = 6.4$, $\delta = 6.1$). the ethyl signals appear as expected ($\delta = 4.1$, 1.2), and the aziridine ring H's at $\delta = 3.4$, 3.8. The carbon NMR can be equally well assigned and the infra red shows C=O stretch at 1710cm^{-1}, C=C stretch at 1654cm^{-1}. The mass spectra (CI) shows the molecular ion + H$^+$, at 322, and assignable fragmentation. This compound had been previously reported in an undergraduate project but on comparison we discovered our data does not match that of this previous work.

The characterisations differ in the following respects, Table 12.

Data	This work (44)	Previous work[30]
^{1}H NMR (CDCl$_3$): Vinyl gp;	δ=6.44 (dd), δ=6.14 (d)	δ=7.05-7.16 (dd), δ=6.1 (dd)
Aziridine C2, C3 protons;	δ=3.8 (d), δ=3.4 (dd)	δ=5.3 (d), 4.83-4.88 (ddd)
^{13}C NMR: δ = / ppm.	176, 165, 143, 135, 133, 132, 130, 129, 128, 128, 126, 125, 60, 49, 47, 14.	166, 164, 146, 140, 132, 129, 128, 125, 123, 129, 128, 126, 122, 86, 60, 14.

Table 12

In order to confirm the correct structure a sample our compound (44) was subjected to X-Ray diffraction by Dr A. S. Batsanov, of Durham University Crystallographic Department. The crystal structure obtained, Figure 1, proves our compound was indeed aziridine (44), full details in Appendix A.
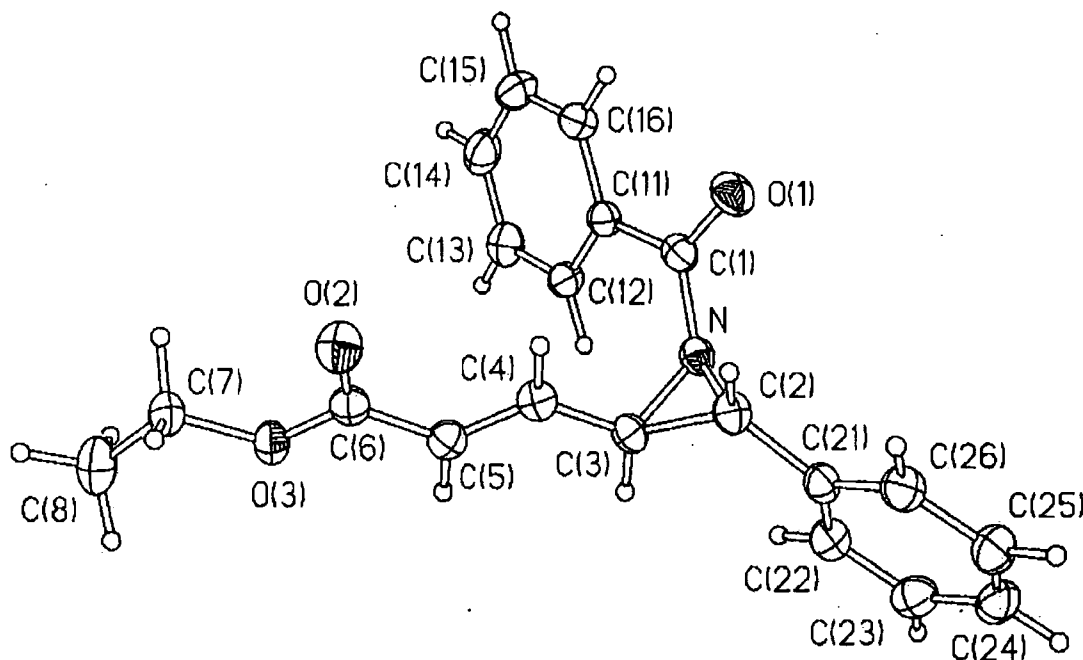
Figure 1

Close comparison of the spectra of the starting free aziridines indicated that they are identical. We have attempted to match the conditions previously used for the

protection by repeating the procedure with 10mol% DMAP, but obtained our previously described compound (44), in 70% yield. There was no evidence of the compound synthesised by the previous workers. This compound, with its limited analytical data presents a ^{1}H NMR spectra which is consistent with the expected rearrangement product.

Continuing our preparation of the rearrangement precursor we addressed the problems resulting in low yields in the ring closing step to generate the aziridine. It was postulated that the aziridine may be decomposing in the reaction mixture or on work up. We then sought an *in situ* protection of the aziridine in its *N*-benzoyl form, Scheme 146.
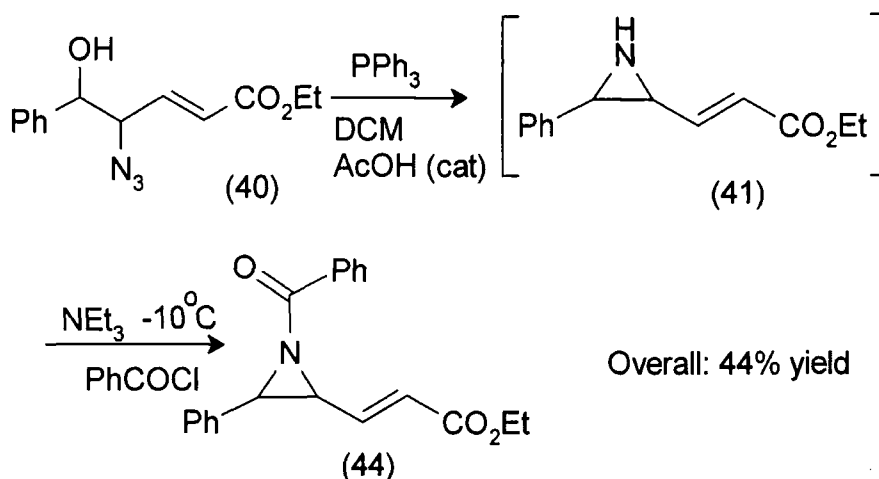
Scheme 146

Consequently PPh$_3$ was added to the azide alcohol (40) in DCM at 0°C and a drop of acetic acid added. When TLC indicated total loss of starting material, the mixture was re-cooled to 0°C at an excess of triethylamine added before dropwise addition of benzoyl chloride. After work up and purification, the benzoyl protected aziridine (44) was obtained and identified as the substance previously identified above (44). Overall yield was 44%, for the two step process. Given the combined yield of aziridine production followed by benzoyl protection would be 34%, this process represents a small efficiency saving but also a practical advantage.

5.4 Thermolysis of vinylaziridine

With an efficient and clean route to the benzoyl protected aziridine in hand we focused on the possibility for the rearrangement of this material, Scheme 147
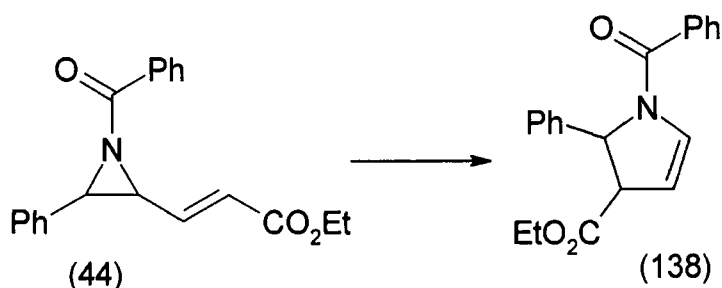
Scheme 147

.

In the first instance we examined Carius tube techniques which had proved most successful with the vinylepoxide rearrangement. The optimised conditions for the vinylepoxide were repeated for the related vinylaziridine, unfortunately without success. Usually a mixture of decomposed material or starting material was recovered. Both standard and "silylated" Carius tubes were utilised. Silylated tubes were made to decrease the acid nature of the glass at high temperatures and enable the substrate to be exposed to higher reaction temperatures with less influence from the glass on conditions, Table 13.

Time /hr	Temp./°C	Result	Silylated Tube?
6	130	SM & Decomp	No
6	180	Decomp & SM	Yes
10	180	Decomposed	Yes
22	180	Decomposed	No
16	200	Decomposed	No
10	150	Decomposed	No
6	200	Decomposed	No

Table 13.

A sample of N-benzoyl vinylaziridine (44) was heated at reflux in benzene over 96 hours, under argon. On workup, 33% of starting material was recovered. The remaining material was decomposition products.

Using 10mg of N-benzoyl vinylaziridine (44), in C_6D_6, in a sealed NMR tube, ^1H NMRs were taken at various intervals to monitor composition changes while refluxing the reaction at 80°C. After 4 hours, a small quantity of an unknown compound was observed. After 15 hours, the unknown compound (139) constituted 50% of the material present. After 28 hours, only decomposed material was present. A comparison of ^1H (200MHz, CDCl$_3$) for aziridine (44), and unknown compound (139) follows in Table 14.

(44) δ/ppm	(139) δ/ppm
8.05	8.15
7.3-6.9	7.3-6.9
6.65	6.80
5.95	6.15
3.89	3.89
3.45	3.60
3.10	3.00
0.89	0.89

Table 14

From the change in NMR shifts it is apparent that a "rearrangement" is taking place but it appears to us this is an isomerisation and quickly leads to decomposition. Noticeable are the changes in chemical shift for the vinyl protons and the aziridine ring protons. The changes are small and this indicates isomerisation of the aziridine ring or vinyl group. Attempts to isolate the material failed with chromatography recovering only 2mg of starting aziridine. Attempts to repeat the experiment on larger scale refluxing in benzene gave only decomposed material.

5.5 Summary of vinylaziridine studies

The vinylaziridine synthesis has been refined and, indeed, mis-characterisation of previous compounds uncovered. Our attempts to rearrange the *N*-benzoyl aziridine derivative failed with only one possible isomerisation product being seen in an NMR experiment. Attempts to isolate the compound / scale up this process failed. This is likely to be due to the electron withdrawing nature of the benzoyl group inhibiting the formation of the required ylide-type intermediate. It seems the vinylaziridine rearrangement requires an electron donating protecting group on the nitrogen, and future work must return to the *N*-benzyl protected compounds studied by Borel, for which a new synthesis of *N*-benzyl protected aziridines is required. Other protecting groups, such as tosyl remain unexplored.

Section C: Experimental

Chapter 6:   Experimental

6.1   Introduction

Infra red (IR) spectra were recorded on a Perkin Elmer FT-IR 1720X spectrophotometer, in a liquid film (NaCl plates), solution cell ($CHCl_3$), KBr disk, or on the above machine fitted with Graseby Specac Single Reflection Diamond ATR (10500 series) "Golden Gate" accessory, as specified in the text.

Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Gemini 200 (^{1}H at 199.975MHz, ^{13}C at 50.289MHz), Varian XL-200 (^{1}H at 200.057MHz), Bruker AMX-250 (^{1}H at 250.133MHz, ^{13}C at 62.896MHz), Varian VXR-400 (^{1}H at 399.968MHz, ^{13}C at 100.572MHz), Varian Oxford Unity 300 (^{1}H at 299.908MHz, ^{13}C at 75.412MHz) and Varian Oxford Mercury 200 (^{1}H at 199.975MHz, ^{13}C at 50.289MHz) spectrometers with deuterochloroform as solvent. Chemical shifts are recorded in ppm (δ units) relative to residual $CHCl_3$; ($\delta(^1H) = 7.26$, $\delta(^{13}C) = 77.0$), unless otherwise stated. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Coupling constants were recorded in Hz. All ^{13}C spectra were proton decoupled.

Low resolution mass spectra (EI and CI) were recorded on a VG Analytical 7070E organic mass spectrometer, or a Micromass Autospec mass spectrometer, and gas chromatography-mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 Series II GC, equipped with a 25m SE30 column, connected to a VG Mass Lab Trio 1000. Optical rotations were measured on an Optical Activity LTD AA-10 Automatic Polarimeter and are given as $[\alpha]_D$ in deg cm^2 g^{-1}. Melting points were determined using Gallenkamp melting point apparatus and are uncorrected.

Reactions were followed by gas chromatography (GC) using Perkin Elmer 8410 GC with a SA50 column or by thin-layer chromatography (tlc).   Flash column

chromatography was performed according to the method of Still *et al*[86] using 200-400 mesh silica.

Degassing of Carius tubes, sealed NMR tubes and stainless steel bombs was accomplished by freezing, evacuating, sealing, thawing. Three cycles of this process were completed before the solution was considered to be degassed.

Stainless steel high pressure bombs were the Parr series 4750 general purpose bombs.

All solvents were distilled prior to use. Petrol refers to petroleum spirit boiling in the 40-60°C range. Ether refers to diethyl ether. Solvents were distilled from the following reagents under a nitrogen (N_2) atmosphere: tetrahydrofuran and ether, (sodium benzophenone ketyl); benzene, hexane, dichloromethane, dimethylformamide (calcium hydride), chloroform (phosphorus pentoxide), methanol, ethanol (magnesium alkoxide), toluene (sodium) deuterochloroform (calcium hydride). Triphenyl phosphine (PPh_3) was recrystallized from hexane and dried under vacuum at 60°C, dimethylsulfate was distilled from calcium hydride, acetophenone distilled from calcium chloride. Trimethylsilyl trifluoromethanesulfonate was distilled under argon. All other reagents were reagent grade and used as supplied unless otherwise stated.

Commercially available reagents were used as received unless otherwise stated. Yields refer to isolated yields of products of greater than 95% purity as determined by ^1H + ^{13}C NMR spectroscopy or elemental analysis (Durham University Microanalytical Laboratory).

6.2 Experimental details

6.2.1 Epoxide precursors

3-Phenyloxirane-2-carboxaldehyde (32).
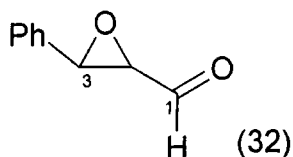
A solution of cinnamaldehyde (132g, 1mol) in methanol (400ml) was added dropwise over 60 minutes to a stirred solution of *tert*-butyl hydroperoxide (154ml, 108g in a 70% (w/v) aqueous solution, 1.2mol) in methanol (500ml) maintained at pH 10.5 by the addition of 1M sodium hydroxide (NaOH) (ca. 30ml), at 35-40°C. After stirring for 4 hours, a second portion of *tert*-butyl hydroperoxide (103ml, 72g in a 70% (w/v) aqueous solution, 0.8mol) was added. The pH was again maintained at 10.5 by addition of NaOH (20ml). After stirring for a further 48 hours, water (500ml) was added, and the reaction mixture extracted with DCM (3 x 200ml). The organic extracts were combined and dried (MgSO$_4$) and concentrated. Vacuum distillation, yielded the title compound (32) as a colourless oil (127.4g, 86%). (Epoxide isomer ratio by ^{1}H NMR *trans:cis* 6.5:1), Bp. 70-75°C, 0.5mbar (*lit.*[35] 66-68°C, 0.2mmHg). v_{max} (thin film), 2820, 1723 (C=O), 1459 cm^{-1}. *Trans*: δ_H (200MHz); 9.18 (1H, d, J=6 Hz, H-C=O), 7.5-7.2 (5H, m, Ar), 4.16 (1H, d, J=1.8Hz, C(3)H), 3.44 (1H, dd, J=6Hz, 1.8Hz, C(2)H). *Cis*: δ_H (200MHz); 9.09 (1H, d, J=6Hz, H-C=O), 7.5-7.2 (5H, m, Ar), 4.38 (1H, d, J=5Hz, C(3)H), 3.53 (1H, dd, J=6Hz, 5Hz, C(2)H). *Trans*: δ_C (50MHz); 199 (C=O), 131, 130, 130, 128, (Ar), 65 (C(3)), 59 (C(2)). *Cis*: δ_C (63MHz); 197 (C=O), 130, 129, 128, 126, (Ar), 63 (C(3)), 57 (C(2)). *m/z* (CI/NH$_3$); 149 (M+H$^+$ 100%), 119, 106, 91.

Ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33).

(33)
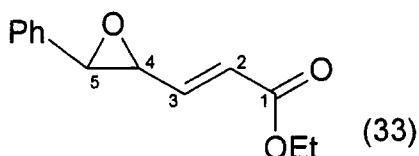
A solution of triethyl phosphonoacetate (98g, 0.44mol) in toluene (300ml) was added over 1 hour to a stirred suspension of NaH (13.6g, 0.55mol) in toluene (400ml) at -10°C after which the mixture was warmed to room temperature. The mixture was then cooled to -10°C and a solution of epoxy aldehyde (32) (50.0g, 0.338mol) in toluene (300ml) was added dropwise over 45 minutes. The reaction was warmed to room temperature after which water (500ml) was added. The organic layer was separated and combined with ether extracts (2 x 300ml) of the aqueous layer. The combined organic extracts were dried ($MgSO_4$) and concentrated. Vacuum distillation (86-95°C, 0.3mbar) gave the title compound (33) as a colourless oil, (58.2g, 79%). At this stage *cis* (33) and *trans* (33) epoxide isomers are separable by flash chromatography eluting with 12% ethyl acetate in petrol.

Cis-epoxide (33), δ_H (200MHz); 7.2-7.5 (5H, m, Ar), 6.46 (1H, dd, J=7Hz, 15Hz, C(3)H), 5.95 (1H, d, J=15Hz, C(2)H), 4.23 (2H, q, J=7Hz, CH_2CH_3), 4.32 (1H, d, J=5Hz, C(5)H), 3.83 (1H, dd, J=7Hz, 5Hz, C(4)H) 1.30 (3H, t, J=7Hz, CH_2CH_3).

Trans-epoxide (33), ν_{max} (thin film) 2983 (Ar), 1713 (C=O), 1655 (C=C), 1038, 1094 (C-O) cm^{-1}. Found; C, 71.23; H, 6.62; $C_{13}H_{14}O_3$ requires; C, 71.54; H, 6.46 %). δ_H (200MHz); 7.2-7.5 (5H, m, Ar), 6.81 (1H, dd, J=7Hz, 15Hz, C(3)H), 6.18 (1H, d, J=15Hz, C(2)H), 4.23 (2H, q, J=7Hz, CH_2CH_3), 3.83 (1H, d, J=1.5Hz, C(5)H), 3.47 (1H, dd, J=7Hz, 1.5Hz, C(4)H), 1.30 (3H, t, J=7Hz, CH_2CH_3). δ_C (50MHz); 160 (C(1)), 144 (C(3)), 139, 136, 129, 127, (Ar), 124 (C(2)), 60, 61, 62 (C(5), C(4), CH_2Me), 15 (CH_3). m/z (CI/NH_3) 236 (92%, M$^+$+NH_4), 219 (M$^+$+H, 79%), 203, 190, 173, 145, 116 (100%).

3-(3'-Phenyloxirin-2'-yl)propenoic acid (35).

(35)
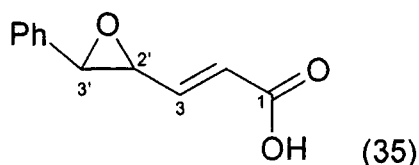
Epoxy ester (33) (4g, 18.3mmol) was added in THF:H_2O, (5:1) (50ml) to a stirred solution of lithium hydroxide, (0.785g, 18.7mmol) in THF:H_2O, (5:1) (100ml) at 0°C and allowed to warm to room temperature. After 20 hours stirring, the reaction mixture was diluted with sodium bicarbonate ($NaHCO_3$) (20ml) and the THF removed *in vacuo*. The resulting aqueous solution was washed with ether (30ml) before cooling to 0°C and gradually acidified to pH 3 with cold 2M HCl. The acidic solution was extracted with ether (2 x 30ml). The organic fractions were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid as a mixture of stereoisomers (3.3g, 95%). Recrystallization from ether/petrol yielded the pure *trans, trans* isomer as a white solid (35) (2.87g, 80%). Mp. = 86-88°C, ν_{max} (golden gate) 3430 (br, OH). 1687 (C=O), 1653, 1621 (C=C) cm^{-1}. Found; C, 69.22; H, 5.35; $C_{11}H_{10}O_3$ requires; C, 69.46; H, 5.30 %). δ_H (200MHz); 7.5-7.2 (5H, m, Ar), 6.93 (1H, dd, J=7Hz, 14 Hz, HC(3)), 6.20 (1H, d, 14Hz, C(2)H), 3.86 (1H, d, J=2Hz, C(3')H), 3.51 (1H, dd, J=2Hz, 7Hz, C(2')H). δ_C (50MHz); 171 (C(1)), 146 (C(3)), 135, 129, 126, 125 (Ar), 123 (C(2)), 61, 60 (C(2'), C(3')). *m/z* (CI/NH_3); 208 (M^++NH_4^+, 40%), 190 (M^+, 30%), 173, 147, 58, 44 (100%).

6.2.2 C2 Symmetric chiral auxiliary synthesis

Dimethyl pyrrolidine, asymmetric deprotonation.

Boc-pyrrolidine (50).

(50)
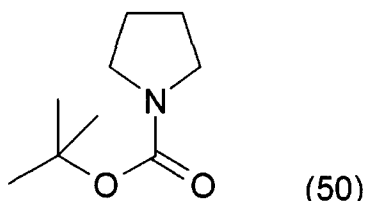
A solution of di-*tert*-butyl dicarbonate (27g, 0.124mol) in THF (150ml) was added dropwise over an hour to a stirred mixture of pyrrolidine (8.0g, 0.112mol) in THF (180ml) and sodium hydroxide (0.15M, 83ml, 0.124mol). After 1 hour, the reaction was extracted with ether and washed with water. The organic extract was dried (MgSO$_4$) and concentrated *in vacuo*. Vacuum distillation yielded the title amide (50) as a colourless liquid (17.65g, 92%). B.p. (44°C, 0.6mbar, *lit.*[87]), ν_{max} (thin film); 2974 (CH), 1690 (C=O), 1396, 1163, 1101 cm^{-1}. δ_H (200MHz); 3.35-3.15 (4H, br, ring CH$_2$), 1.9-1.7 (4H, br, N-CH$_2$), 1.4 (9H, s, C(CH$_3$)$_3$). *m/z* (EI); 171 (65%, M$^+$), 98, 57 (100%).

Boc-2-methylpyrrolidine (51).

(11)
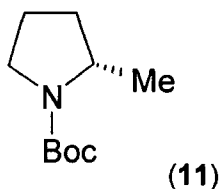
sec-Butyllithium (54ml, 1.3M in hexanes, 70mmol) was added to a stirred solution of freshly distilled (-)-sparteine (53) (16.2g, 69mmol) in diethyl ether (125ml) at -78°C. After 20 minutes this was added to a pre-cooled solution of Boc-pyrrolidine (50) (9.23g, 54mmol) in ether (80ml). After 6 hours dimethylsulfate (7.89g, 62.6mol) was added slowly and the mixture left to warm to room temperature overnight. Water

(100ml) was added and the reaction mixture extracted with ether (150ml x 3). The combined organic extracts were then washed with 5% H_3PO_4 (2 x 50ml) and water (100ml), dried (MgSO₄) and concentrated. Flash chromatography eluting with 6% ethyl acetate in petrol yielded the title compound (51) as a colourless liquid, (8.94g, 89%). $[\alpha]^{23}_D$ +30.1 (c.2.79 CHCl₃) (*lit.*[49] $[\alpha]^{23}_D$ +31.2 (c.2.76 CHCl₃)); v_{max} (thin film); 2966 (CH), 1686 (C=O), 1383, 1166, 1103 cm⁻¹. δ_H (200MHz); 3.85 (1H, br, CHN), 3.35 (2H, br, CH₂N), 2.0-1.7 (4H, br m, ring CH₂), 1.44 (9H, s, C(CH₃)₃), 1.16 (3H, br, CH₃); δ_C (50MHz); 154 (C=O), 79 (CMe₃), 53 (ring CH₂), 31 (NCH), 29 (C(CH₃)₃), 23(NCH₂), 20 (CH₃). *m/z* (CI/NH₃); 186 (M⁺+H, 15%), 170, 130 (100%), 86, 70, 57.

(*S,S*)-Boc-2,5-dimethylpyrrolidine (52).

(52)
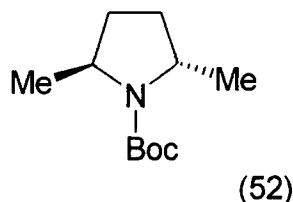
sec-Butyllithium (38ml, 1.3M in hexanes, 48mmol) was added to a stirred solution of (-)-sparteine (53) (11.3g, 48mmol) in dry diethyl ether (70ml) at -70°C. After 20 minutes this was added to a pre-cooled solution of Boc-2-methylpyrrolidine (51) (4.5g, 24.3mmol) in ether (30ml). After 11 hours dimethylsulfate (3.3g, 26mmol) was added slowly and the mixture left to warm to room temperature overnight. Water (50ml) was then added and the reaction mixture extracted with ethyl acetate (75ml x 3). The combined organic extracts were washed with 5% H_3PO_4 (2 x 25ml) and water (50ml), dried (MgSO₄) and concentrated. Flash chromatography with 1:15 ethyl acetate in petrol yielded the title compound (3.43g, 72%). $[\alpha]^{23}_D$ +44.7 (c.2.79 CHCl₃). v_{max} (thin film); 2974 (CH), 1690 (C=O), 1396, 1163, 1101 cm⁻¹. δ_H (200MHz); 3.8-4.1 (2H, m, CHN), 2.1 (4H, m, CH₂), 1.42 (9H, s, C(CH₃)₃), 1.12 (6H, br, CH₃); δ_C (50MHz); 154 (C=O), 79 (CMe₃), 53 (CH₂), 31 (NCH), 29 (C(CH₃)₃), 20 (CH₃). *m/z* (CI/NH₃); 186 (M⁺+H, 15%), 170, 130 (100%), 86, 70, 57.

<u>(*S,S*)-2,5-dimethylpyrrolidine (47).</u>

(52)
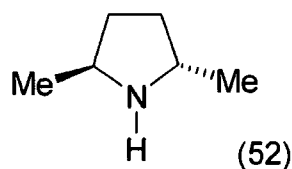
Trifluoroacetic acid (8ml), was added to a stirred solution of Boc-2,5-dimethylpyrrolidine (52) (0.495g, 5mmol) in DCM (50ml) and stirred for 6 hours. The solvent was removed from the reaction mixture and diluted with 10% sodium hydroxide (50ml) before the organic material was extracted with ether (3 x 30ml). The organic extracts were dried (MgSO$_4$) and concentrated. Vacuum transfer yielded the title amine (47) (351mg, 70%) as a volatile, colourless oil. v_{max} (CDCl$_3$ thin film); 3464, 3053, 1491, 1265 cm^{-1}. δ_H (200MHz); 3.55 (1H, q, J=7Hz, CHN), 3.4 (1H, q, J=7Hz, CHN), 2.2-1.9 (2H, m, CH$_2$) 1.45-1.3 (H, br, NH), 1.3 (6H, d, J=7Hz, CH$_3$). δ_C (50MHz); 54 (CH$_2$), 36 (NCH), 23 (CH$_3$). *m/z* (CI/NH$_3$); 100 (M$^+$+H, 100%), 84, 71.

2,5-Diphenylpyrrolidine

<u>1,2-Dibenzoylethene, (57).</u>

(57)
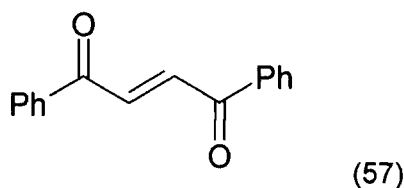
Fumaryl chloride (13.8g, 0.09mol) was added dropwise down a reflux condenser to a stirred suspension of aluminium trichloride (60g, 0.45mol) in benzene (150ml). On completion of the addition the mixture was heated under reflux for 30 minutes when it was poured onto ice water (100g). The layers were separated and the aqueous layer extracted with ether (100ml). The combined organic extracts were washed with NaHCO$_3$ solution, dried (MgSO$_4$) and concentrated *in vacuo* before recrystallization from hexane/ethyl acetate yielded the title diketone (57) as a yellow crystalline solid, (71%, 15.0g). Mp; (108-9°C, *lit.*[88] 110-111°C) v_{max} (golden gate); 3065, 1654, 1597,

1323, 1296, 1018 cm^{-1}. δ_H (300MHz); 8.1-8.0, (4H, m, o-Ar), 7.8-7.4, (6H, m, m,p-Ar), 7.2, (2H, s, CH). δ_C (75MHz); 192 (C=O), 137, 136, 131.3, 130.8, 130.1, (Ar, C=C). m/z (EI); 236 (M$^+$, 33%), 208, 131, 105 (100%), 77.

1,2-Dibenzoylethane, (58).

(58)
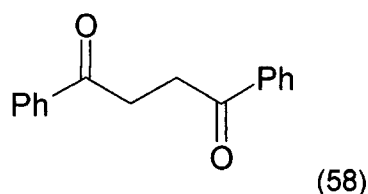
A boiling aqueous ethanolic solution of 1,2-dibenzoylethene (57), (5g, 21mmol, in 70ml) was added quickly to a stirred solution of sodium dithionite (Na$_2$S$_2$O$_4$) (6g, 34.5mmol) in boiling water (35ml). After stirring for 30 minutes, the mixture was diluted with cold water. The precipitate was collected, washed with water dried *in vacuo* and recrystallized from acetone/petrol (10:3) to yield the title diketone (58) as a white crystalline solid, (74%, 3.71g). Mp; (144-5°C, *lit.*[89] 142-145°C), ν_{max} (golden gate); 3049, 1676, 1445, 1223, 990 cm^{-1}. δ_H (200MHz); 8.1-8.0, (4H, o-Ar), 7.6-7.4, (6H, m, m,p-Ar), 3.47, (4H, s, CH$_2$); δ_C (75MHz); 200 (C=O), 135, 131, 130, 130 (Ar), 35 (CH$_2$). m/z (EI); 238 (21%), 133, 105 (100%), 77.

1-Phenyl-1-(trimethylsilyloxy)ethene (59).

(59)
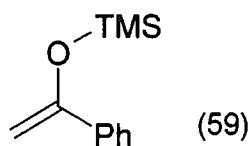
Acetophenone (50g, 0.41mol), was added to a stirred solution of triethylamine (216g, 2.14mol) and trimethylsilyl chloride (115ml, 1.07mol) in dry DMF (330ml) under argon. After heating under reflux for 60 hours the reaction was cooled and diluted with pentane (500ml), before being washed with cold sodium bicarbonate (3 x 500ml). The organic extracts were dried (MgSO$_4$) and solvent removed *in vacuo*. Vacuum

distillation of the resultant brown oil gave the title compound (59), as a colourless liquid (76g, 97%). Bp. (53-55°C, 0.8mbar, *lit.*[57] 89-91°C, 16mbar), ν_{max} (thin film); 2957, 2086, 1658, 1609, 1279, 1050 cm^{-1}. δ_H (300MHz); 7.4-7.3 (2H, m, Ar), 7.1-7.0 (3H, m, Ar), 4.65 (1H, d, J=1.6Hz, C=HCH), 4.16 (1H, d, J=1.6Hz, C=HCH), 0.03 (9H, s, (H$_3$C)$_3$Si). δ_C (75MHz); 156 (C=CH$_2$), 137.8, 128.5, 128.4, 125.6, 91 (C=CH$_2$) , 0 ((H$_3$C)$_3$Si).

1,2-Dibenzoylethane, method 2 (58).

(58)
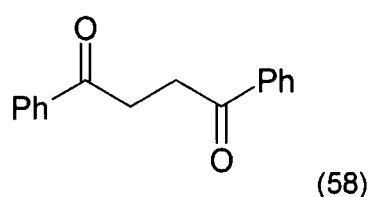
1-Phenyl-1-(trimethylsilyloxy)ethene (59) (3.26g, 0.017mol) in dry acetonitrile (10ml) was added dropwise to a solution of ammonium cerium(IV) nitrate (9.8g, 0.018mol), and potassium carbonate (7.4g, 0.054mol) in acetonitrile (30ml) under argon. The reaction was stirred for 1 hour before being poured into 75ml of water. The resulting mixture was extracted with DCM (4 x 200ml), and combined organic extracts dried (MgSO$_4$) and concentrated *in vacuo*. The resulting white crystalline solid was washed with petrol to yield the title product (58), (1.17g, 58%). Analytical data identical to that described above.

(*R,R*)-1,4-Diphenylbutan-1,4-diol (60).

(60)
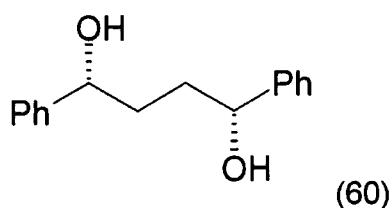
To a stirred solution of αα-diphenyl-2-pyrrolidine methanol (55) (2g, 8mmol) in THF (50ml) at room temperature, trimethyl borate (B(OMe)$_3$) (1.15ml, 10mmol) was added and the resultant solution stirred for 1 hour. Borane-dimethylsulfide complex (9.27ml, 98mmol) was added, a solution of the diketone 1,2-dibenzoylethane (58) (11g, 46.2mmol) in THF (100ml). After a further hour at room temperature, the resulting mixture was slowly quenched with 2N HCl (69ml). The aqueous layer was extracted with ether (3 x 100ml) and the combined organic extracts were washed with water, brine, dried (MgSO$_4$) and concentrated *in vacuo*. The resulting oil was purified by flash chromatography eluting with 35% ethyl acetate in petrol to give the title diol (60), as a white solid (10.7g, 96%). Mp (73-75°C, *lit.*[50] 74-75°C). $[\alpha]_D^{25}$ +58 (c=1.02 CHCl$_3$). (*lit.*[50] $[\alpha]_D^{25}$ -58.5 (c=1.01 CHCl$_3$) for (*S,S*) enantiomer. ν_{max} (thin film); 3339 (OH), 3025 (Ar), 1207(CH), 990 cm^{-1}, δ_H (300MHz); 7.3-7.1 (10H, m, Ph), 4.58 (2H, br, CHOH), 3.0 (2H, br, OH), 1.84-1.6 (4H, m, CH$_2$), δC (75MHz); 144.6, 128.1, 127.0, 125.6 (Ar), 74.3 (HCOH), 35.1 (CH$_2$); *m/z* (EI); 242 (M$^+$), 224, 118 (100%), 107, 79.

(*R,R*)-1,4-*Bis*(methanesulfonyloxy)-1,4-diphenylbutane (61).

(60)
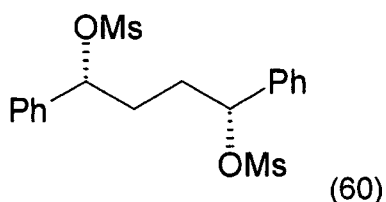
To a solution of methanesulfonyl chloride (400μl, 5.3mmol) in DCM (20ml) at -20°C was added a solution of (*R,R*)-1,4-diphenylbutan-1,4-diol (60), (500mg, 2.06mmol) and triethylamine (870μl, 6.2mmol) in DCM (20ml). The mixture was stirred for an hour at -20°C and then quenched with sat. NH$_4$Cl (2ml). The mixture was warmed to room temperature and solvent removed *in vacuo* to approximately 15ml. The solution was then diluted with ethyl acetate (80ml) and washed with water : brine : sat. NaHCO$_3$ (1:2:1) (4 x 20ml), and sat. NHCO$_3$ (2 x 20ml), before being dried (MgSO$_4$),

filtered through celite and concentrated *in vacuo* to approximately 8ml. The solution was then cooled to 0°C and set to stir and the crude dimesylate was precipitated out by dropwise addition of hexane (80ml). The resulting solid was recrystallized from ethyl acetate by addition of hexane at 0°C. The crystals were then recovered by filtration to yield the desired dimesylate (61) (680mg, 82%). This product had only moderate stability and was generally used directly in the next step: δ_H (200MHz, C_6D_6); 7.21-7.00 (10H, m, Ph), 5.74-5.70 (2H, m, CHOMs), 2.05-1.84 (4H, m, CH_2) 2.01 (6H, s, SO_2CH_3).

(S,S)-N-allyl-*trans*-2,5-diphenylpyrrolidine (62).

(62)
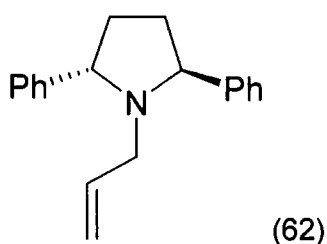
To a flask with cooled crystals (0°C) of (R,R)-1,4-*Bis*(methanesulfonyloxy)-1,4-diphenylbutane (61) (670mg, 1.68mmol) allylamine (25ml, 0.33mol) was added and stirred for 14 hours before allowing to warm to room temperature. The allylamine was then removed *in vacuo* and the residue dissolved in ether (70ml), and washed with sat. $NaHCO_3$ (2 x 25ml) and brine (25ml) and finally dried ($MgSO_4$). Concentration *in vacuo* gave the crude product as a yellow oil. Flash chromatography eluting with 3% ether/petrol the diastereomerically pure amine (62) as a colourless liquid (330mg, 75% yield). $[\alpha]_D$=-115 (c=1.12, $CHCl_3$) (*lit.*[50] $[\alpha]_D$=115.1 (c=1.40, $CHCl_3$), (R,R) enantiomer); CHN; Found, C, 86.38; H, 7.93; N, 5.57; $C_{19}H_{21}N$ requires; C, 86.65; H, 8.04; N, 5.32 %. ν_{max} (thin film); 3070, 2967, 2817, 1640, 1071, 916 cm^{-1}. δ_H (300MHz); 7.4-7.2 (10H, m, Ph), 5.7-5.55 (1H, m, $CH_2C\underline{H}=CH_2$), 4.92-4.87 (2H, m, CH=C$\underline{H}_2$), 4.32-4.30 (2H, m, CHPh), 2.95-2.68 (2H, m, NCH_2) 2.60-2.45 (2H, br, m,

CH$_2$CH$_2$), 2.01-1.90 (2H, br m, CH$_2$CH$_2$). δ$_C$ (75MHz); 144.6, 137.2, 128.5, 128.2,

127.1 (Ar, H<u>C</u>=CH$_2$), 115.9 (HC=<u>C</u>H$_2$), 65.9 (PhCHN), 50.2 (N<u>C</u>H$_2$CH=), 33.5

(CH$_2$CH$_2$). m/z (EI); 263 (M$^+$, 30%), 262, 186 (100%), 91.

(S,S)-Trans-2,5-diphenylpyrrolidine (63).

(63)
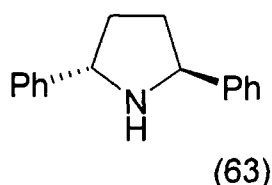
(S,S)-N-allyl-trans-2,5-diphenylpyrrolidine (62) (2.56g, 9.72mmol) and (Ph$_3$P)$_3$RhCl

(Wilkinson's catalyst, 44mg, 0.047mmol) was dissolved in 25ml of 84:16 w/w

acetonitrile/water mixture and placed in a 50ml 3 necked flask fitted with distillation

head and dropping funnel. The mixture was purged with nitrogen gas and heated to

boiling. The solvent level was maintained via the dropping funnel and reaction heated

for 5 hours. The reaction was then cooled to room temperature and diluted with 40ml

ether. The layers were separated and the organic layer washed with brine (2 x 20ml),

and combined aqueous washes back extracted with ether (10ml). The combined

organic extracts were dried (MgSO$_4$) and concentrated in vacuo. The resulting oil was

purified by flash chromatography eluting with 33% ethyl acetate in petrol to yield the

desired amine (63) (192mg, 89%) as a yellow oil which solidified overnight.

Mp; 43.0°C. [α]$_D$ = -108.2 (c=0.97, CHCl$_3$), (lit[50]. (R,R isomer) [α]$_D$ +104.5 (c=1.00,

CHCl$_3$). Found; C, 86.23; H, 7.63; N, 6.17; C$_{16}$H$_{17}$N requires; C, 86.05; H, 7.67; N,

6.27 %. ν$_{max}$ (thin film); 3360, 3055, 2962, 2867, 1598, 1489, 1450, 1402 cm^{-1}. . δ$_H$

(200MHz); 7.5-7.1 (10H, m, Ar), 4.5 (2H, t, J=6Hz PhCHN), 2.4-2.3 (2H, m, CH$_2$-CH$_2$),

2.3 (1H, br NH), 1.9-1.8 (2H, m, CH$_2$-CH$_2$). δ$_C$ (75MHz); 145.7, 128.2, 126.5, 126.1

(Ar), 62.1 (N<u>C</u>HPh), 35.3 (<u>C</u>H$_2$<u>C</u>H$_2$). m/z (EI); 223 (M$^+$, 31%), 222, 195 (100%).

Trimethyl((1-naphthylethenyl)oxy)silane (71).

(71)
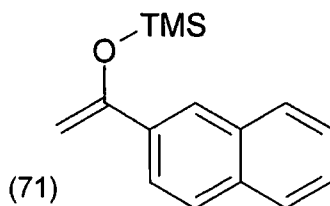
2-Acetonaphthone (12g, 71mmol) was treated to the method used in the synthesis of 1-phenyl-1-(trimethylsilyloxy)ethene (60) to give the title compound (71), as a colourless liquid (15.4g, 89%). Bp; (115°C, 0.6mbar). ν_{max} (thin film); 3059, 1627, 1468, 1361 1281, 1229, 1193 cm^{-1}. δ_H (200MHz), 7.8-7.1 (7H, m, Ar), 4.76 (1H, d, 1.5Hz, C=HC$\underline{H}$), 4.24 (1H, d, 1.5Hz C=HCH), 0.03 (9H, s, (H$_3$C)$_3$Si). δ_C (63MHz); 157, 135, 133, 129, 128, 127.5, 127.4, 126, 125, 124, 123 (Ar, COTMS), 91.8 (=CH$_2$), 0.0 (Si(CH$_3$)$_3$). m/z (EI); 242 (M$^+$, 34%), 241, 227, 127, 75 (100%).

1,4-Dinaphthylbutan-1,4-dione, (64).

(24)
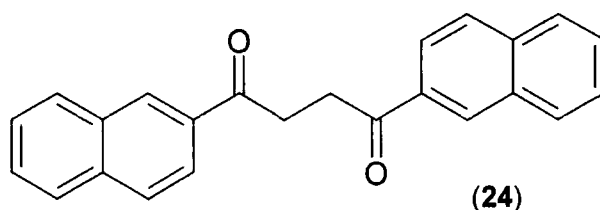
Trimethyl((1-naphthylethenyl)oxy)silane (71) (10g, 41mmol) was treated to the method used in the synthesis of 1,2-dibenzoylethane (58) to yield the title diketone (64) as a white crystalline solid, (2.8g, 40%). Mp; 214-216°C (lit.^{90} 213-215°C). Found; C, 84.68; H, 4.91; C$_{24}$H$_{18}$O$_2$ Requires; C, 85.18; H 5.36%. ν_{max} (golden gate); 3055, 1679, 1275, 1121 cm^{-1}. δ_H (300MHz); 8.6 (2H, s, Ar), 8.1-7.8 (8H, m, Ar), 7.6-7.3 (4H, m, Ar), 3.64 (4H, s, CH$_2$). δ_C (75MHz); 209 (C=O), 135, 133, 129, 128, 127.5, 127.4, 126, 125, 124, 123 (Ar), 36 (CH$_2$-CH$_2$); m/z (EI); 338 (M$^+$, 27%), 320, 183, 155 (100%, C$_{11}$H$_7$O), 127 (C$_{10}$H$_7$).

<u>Attempted synthesis of (R,R)-1,4-Dinaphthylbutan-1,4-diol (74).</u>

(25)
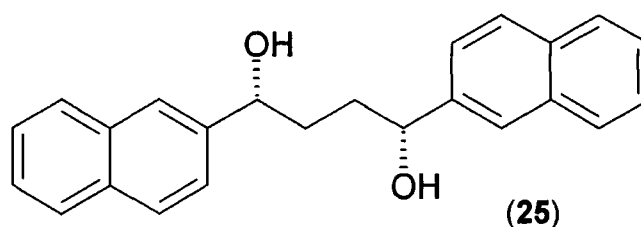
To a stirred solution of αα-diphenyl-2-pyrrolidine methanol (55) (138mg, 0.55mmol) in THF (7ml) at room temperature, the trimethyl borate (B(OMe)$_3$) (79μl, 0.68mmol) was added and stirred for 1 hour. After borane-dimethyl sulfide complex (636μl, 6.72mmol) was added, a solution of the 1,4-dinaphthylbutan-1,4-dione (64) (1.3g, 3.17mmol) in THF (15ml), was added over an hour. After 24 hours the resulting mixture was slowly quenched with 2N HCl (6ml). The aqueous layer was extracted with ether (3 x 10ml) before the combined organic extracts were washed with H$_2$O, brine, dried (MgSO$_4$) and concentrated *in vacuo.*   Starting material 1,4-dinaphthylbutan-1,4-dione (64) (0.9g) was isolated with no evidence of the desired diol (74).

<u>Attempted synthesis of (R,R)-1,4-Dinaphthylbutan-1,4-diol (74).</u>

To a stirred solution of 1,4-dinaphthylbutan-1,4-dione (64) (38mg, 0.112mmol) in MeOH (15ml) sodium borohydride (5mg, 0.123mmol) was added and the resulting mixture stirred for 5 hours under argon. The reaction was then heated at reflux for 14 hours. Ammonium chloride (aq) (20ml) was added and the solution extracted with ethyl acetate (3 x 30ml) the combined organic extracts were dried (MgSO$_4$) and

concentrated *in vacuo*. Starting material 1,4-dinaphthylbutan-1,4-dione (64) (19mg) was isolated with no evidence of the desired diol (74).

<u>(*R,R*)-Hexane-2,5-diol, (75).</u>

(75)
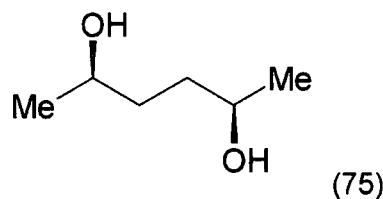
Hexan-2,5-dione (66) (3g, 26mmol) was treated using the previously described protocol for (*R,R*)-1,4-diphenylbutan-1,4-diol (60) to give hexanediol (66), as a colourless oil which solidified on standing (2.27g, 74%, 24% de). Mp; (48°C-51°C, *lit.*[47] 53.0-53.3°C) $[\alpha]_D^{25}$; -7 (c=11, $CHCl_3$), (*lit.*[47] +35.1 (c=9.5, $CHCl_3$ for (*S,S*)-hexan-2,5-diol.). ν_{max} (thin film); 3346 (OH), 3003 (CH), 1378,1307, 1052 cm^{-1}. δ_H (400MHz); 3.90-3.64 (2H, m, C<u>H</u>OH), 2.58 (2H, br, OH), 1.48 (4H, m, CH_2), 1.13 (6H, d, J=2Hz, CH_3). δ_C (75MHz); 67.9 (2C, HCOH), 35.0 (2C, CH_2), 23.5 (2C, CH_3). *Meso* (66), δ_C (75MHz); 68.4 (2C, HCOH), 36.0 (2C, CH_2), 23.8 (2C, CH_3).

<u>Trimethyl((1-*tert*-butylethenyl)oxy)silane (72).</u>

(72)
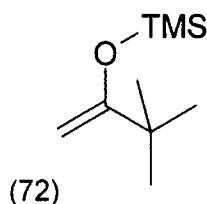
Pinacolone (70) (33.6ml, 0.336mol) was treated using the previously described protocol for 1-phenyl-1-(trimethylsilyloxy)ethene (59) to yield the title compound (72),

as a colourless liquid (37.6g, 65%). Bp; (60°C, 80mbar), v_{max} 2958, 1618, 1482, 1296, 1252, 1183 cm^{-1}. δ_H (300MHz); 4.08 (1H, d, 1.2Hz, C=HC$\underline{H}$), 3.92 (1H, d, 1.2Hz, C=$\underline{H}$CH), 1.04 (9H, s, C(CH$_3$)$_3$), (9H, s, (H$_3$C)$_3$Si). δ_C (63Hz); 167 (=COTMS), 86 (CH$_2$=), 36 ($\underline{C}$Me$_3$), 28 ((CH$_3$)$_3$), 0 ((SiCH$_3$)$_3$).

2,2,7,7-Tetramethyloctan-3,6-dione (65).
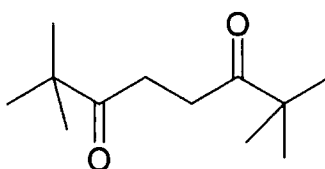
(65)

Methyl lithium (18ml, 1.6M in hexanes, 0.029mol) in dry DMF (50ml), was added to a stirred solution of trimethyl((1-*tert*-butyethenyl)oxy)silane (72) (5g, 0.029mol) at -78°C. After 15 minutes, copper (II) chloride (3.8g 0.029mol), in DMF (50ml) was added and the reaction stirred for 30 minutes before allowing the reaction to warm to room temperature. After 10 minutes at room temperature, water (100ml) was added followed by 5% H$_2$SO$_4$ (10ml. The reaction mixture was then extracted with petrol (2 x 100ml), and DCM (100ml). The combined organic extracts were dried and solvent removed. Purification by flash chromatography eluting with 20% ethyl acetate in petrol afforded the desired diketone (65) (1.7g, 30%) as a white solid. v_{max}; 2968, 2871, 1703, 1479, 1365, 1062 cm^{-1}. Found; C, 72.82; H, 11.02; C$_{12}$H$_{22}$O$_2$ requires; C, 72.68; H, 11.18 %). δ_H (300MHz); 2.7 (2H, s, CH$_2$), 1.12 (9H, s, CH$_3$). δ_C (63MHz); 215 (C=O), 44 ($\underline{C}$Me$_3$), 30 (CH$_2$), 27 (CH$_3$). *m/z* (EI); 198(M$^+$), 180 (100%), 113 (*t*-BuCOCH$_2$CH$_2$), 57 (*t*-Bu), 41.

(R,R)-2,2,7,7-Tetramethyloctan-3,6-diol (76).
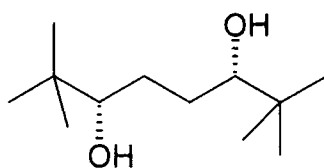
(76)

2,2,7,7-Tetramethyloctan-3,6-dione (65) (396mg, 0.2mmol) was treated to the previously described protocol for (R,R)-1,4-diphenylbutan-1,4-diol (60) to give diol (76), as white crystalline solid (230mg, 57%, 72% de), 14% *meso* compound (^{13}C NMR). M.p.; 142°C-143°C (*lit.* 160-165°C,[91] 178-183°C,[92] 155-156°C.[60]). $[\alpha]_D^{25}$; +37 (c=1 CH$_3$OH), (*lit.*[52] -34.3 (c=1, CH$_3$OH, (S,S) (*lit.*[60] -44.4 (c=0.94, CH$_3$OH, (S,S))). Found; C, 71.29; H, 13.01; C$_{12}$H$_{26}$O$_2$ requires; C, 71.23; H, 12.95). ν_{max} (solution); 3417 (OH), 2962, 2869, 1478,1383, 928 cm^{-1}, δ_H (300MHz); 3.20 (2H, d, J=10Hz, CHOH), 2.35 (2H, br, OH), 1.7-1.3 (4H, m, CH$_2$), 0.90 (18H, s, CH$_3$). δ_C (75MHz, CD$_3$OD); 81.4 (1C, (A) HCOH), 80.2 (1C, (B) HCOH), 36.0 (2C, (A,B) CMe$_3$), 30.4 (1C, (A) CH$_2$), 29.3 (1C, (B) CH$_2$), 26.4 (6C, (A,B), CH$_3$). m/z (CI); 203 (M$^+$+H), 185, 167, 127, 111, 97 (100%), 83.

(R,R)-1,5-Diphenylpentan-1,5-diol (79).
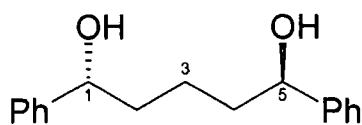
(79)

1,2-Dibenzoylpropane (67) (5g, 20mmol) was treated to the previously described protocol for (R,R)-1,4-diphenylbutan-1,4-diol (60) give the title diol (79), as a crystalline solid (4.6g, 91%). Mp; 101-102°C; $[\alpha]_D^{25}$ +20 (c=1.0, methanol), (*lit.*[52] -22.8 c=1.0, methanol). Found; C, 79.63; H, 7.94; C$_{17}$H$_{20}$O$_2$ requires C, 79.56; H,

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7.86%. ν_{max} (thin film); 3321 (OH), 2935 (Ar), 2855(CH), 1454, 1013 cm^{-1}. δ_H (400MHz); 7.3-7.1 (10H, m, Ph), 4.71-4.48 (2H, m, C$\underline{H}$OH), 2.1 (2H, br, OH), 1.84-1.6 (4H, m, C(2)H$_2$, (C(4)H$_2$), 1.54-1.28 (2H, m, C(3)H$_2$). δ_C (100MHz); 144.7, 128.4, 127.5, 125.8 (Ar), 74.4 (HCOH), 38.8 (C(2), C(4)), 22.2 (C(3)). m/z (CI/NH$_3$); 239 (M$^+$-OH), 221, 161, 117 (100%).

(R,R)-1,5-Bis(methanesulfonyloxy)-1,5-diphenylpentane (80).
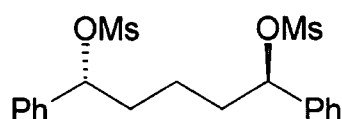
(80)

(R,R)-1,4-Diphenylpentan-1,4-diol (79), (3.5g, 13.6mmol) was treated to the previously described protocol for (R,R)-1,4-Bis(methanesulfonyloxy)-1,4-diphenylbutane (61) to yield the desired dimesylate (80) (3.30g, 76%). Limited analytical data due to instability of product: δ_H (300MHz); 7.42-7.2 (10H, m, Ph), 5.54-5.30 (2H, m, CHOMs), 2.02 (6H, s, SO$_2$CH$_3$), 1.81-1.67 (4H, m, CH$_2$) 1.44-1.32 (2H, m, CH$_2$).

(S,S)-N-allyl-trans-2,6-diphenylpiperidine (81).
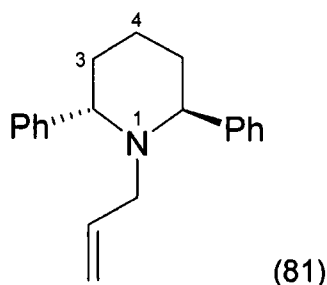
(81)

(R,R)-1,5-Bis(methanesulfonyloxy)-1,5-diphenylpentane (80) (3.30g, 10.4mmol), was treated to allylamine (50ml, 660mmol) as previously described for (S,S)-N-allyl-trans-2,5-diphenylpyrrolidine (62) to yield the amine (80) together with the cis isomer

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(R,S)(S,R)-*N*-allyl-*cis*-2,5-diphenylpiperidine (80) in an inseparable mixture as a colourless liquid (2.13g, 72% yield, de 89%). GC ratios, *cis*; 5.7% *trans*; 94.3%. $[\alpha]_D$=-80 (c=0.56, $CHCl_3$). Found; C, 86.45, H, 8.29, N, 4.94; $C_{20}H_{23}N$ requires; C, 86.59, H, 8.36, N, 5.05%. ν_{max} (thin film); 3059, 2932, 2862, 1640, 1600, 1492, 1448, 915 cm^{-1}. δ_H (400MHz); 7.4-7.1 (10H, m, Ph), 5.8-5.6 (1H, m, CH$_2$C$\underline{H}$=CH$_2$), 4.98 (1H, d, J=6Hz, CH=C$\underline{H}_2$), 4.94 (1H, s, CH=C$\underline{H}_2$), 4.10 (2H, dd, J=6.5Hz, 4.5Hz, CHPh), 3.05-2.80 (2H, m, NCH$_2$) 2.01-1.90 (2H, m, ring, CH$_2$CH$_2$) 1.8-1.6 (4H, m, ring CH$_2$). δ_C (100MHz) 144.3, 137.5, 128.2, 128.0, 126.3 (Ar, H$\underline{C}$=CH$_2$), 115.8 (HC=$\underline{C}$H$_2$), 58.6 (PhCHN), 50.9 (NCH$_2$), 27.7 (C(3)), 19.8 (C(4)). *m/z* (GCMS, EI) (*Cis*: RT 21.48min; 277 (M$^+$), 200 (100%), 144, 117, 91, 77). (*Trans*: RT 22.28min; 277 (M$^+$), 200 (100%), 144, 117, 104, 91, 77).

(*S,S*)-*Trans*-2,6-diphenylpiperidine (68).
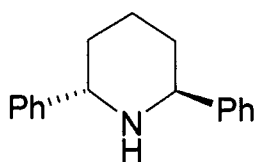
(68)

(*S,S*)-*N*-allyl-*trans*-2,6-diphenylpiperidine (81) (1g, 3.6mmol) was deprotected using Wilkinson's catalyst as described for (*S,S*)-2,5-diphenylpyrrolidine (63) to yield the desired amine (68) (642mg, 75%) as a yellow solid. Mp. 45-46 °C. $[\alpha]_D$ = -81.2 c=5, ethanol, (*lit.*[93] $[\alpha]_D$,=80.7 c=5, ethanol). Found; C, 85.82; H, 8.97; N, 6.04. $C_{17}H_{19}N$ requires; C, 86.03; H, 9.07; N, 5.90%. ν_{max} (golden gate); 3359, 3058, 2951, 2867, 1486, 1448, 1401 cm^{-1}. δ_H (300MHz); 7.3-7.1 (10H, m, Ar), 3.99 (2H, br, PhCHN), 2.2 (1H, br NH), 1.9-1.75 (4H, m, CH$_2$), 1.7-1.5 (2H, m, CH$_2$). δ_C (75MHz); 144.9, 128.1, 126.8, 126.3 (Ar), 59.4 (N$\underline{C}$HPh), 28.3 ($\underline{C}$(2,4)H$_2$), 18.7($\underline{C}$H$_2$). *m/z* (EI); 237 (M$^+$, 31%), 160, 181 (100%).

6.2.3 Coupling reactions

2,5-*trans*-Dimethylpyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (83).
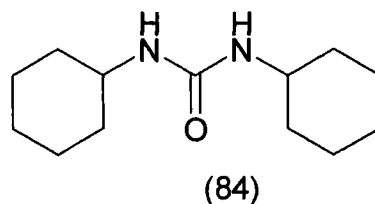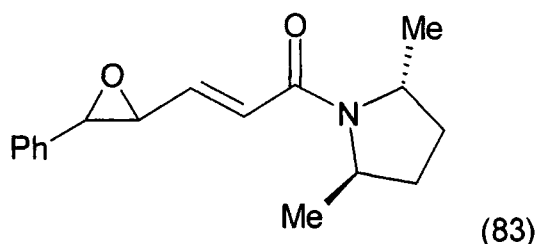
A solution of N,N'-dicyclohexylcarbodiimide (DCC) (228mg, 1.01mmol) and 4-dimethylaminopyridine (DMAP) (14mg, 0.11mmol) in DCM (5ml) was added by cannula to a stirred solution of 2,5-dimethylpyrrolidine (47) (100mg, 1.01mmol) in DCM (5ml) at room temperature under argon. To this a solution of 3-(3'-phenyloxirin-2'-yl)propenoic acid (35) (200mg, 1.05mmol) in DCM (10ml) was added and stirred for 24 hours. Water (20ml) was added and the organic extract washed with NaHCO$_3$ (30ml, saturated solution) and 1M HCl (30ml). The aqueous washes were back extracted with DCM and combined organic extracts dried (MgSO$_4$) and concentrated. Flash chromatography eluting with 25% ethyl acetate in petrol yielded a product that was co-polar and inseparable from the DCC urea product (84).

δ_H (200MHz); 7.5-7.2 (5H, m, Ar), 6.82 (1H, dd, J=6.5Hz, 15Hz, HC=CCO$_2$H), 6.55 (1H, d, 15Hz, C=CHCON), 4.2-4.0 (1H, m, CHMe), 3.82 (1H, d, J=1.8Hz, PhCH-O), 3.8-3.6 (1H, m, CHMe), 3.49 (1H, dd, J=1.8Hz, 6.5Hz, OCHC=C), 2.0-1.5 (10H, m, DCU), 1.5-1.1 (10H, m, DCU). δ_C (50MHz); 164 (C=O), 154 (C=O), 143 (C=C-CO), 136, 129, 126,126, (Ar), 125, 124 (C=C), 61, 60 (C-O-C), 56 (ring CH$_2$), 31(CHN), 49, 31, 29, 24, (cyclohexyl (CH / CH$_2$)), 26 (CH$_3$). m/z (Cl/NH$_3$); 291, 272 (M$^+$+H), 256, 229, 225 (M$^+$+H (83)), 173 (100%), 83.

<u>Pyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (84)</u>
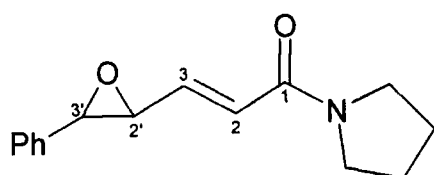
(84)

Trimethylacetyl chloride (66μl, 0.53mmol) was added in 2ml THF to a stirred solution of triethylamine (185μl, 1.33mmol, 2.5eq) and of 3-(3'-phenyloxirin-2'-yl)propenoic acid (35) (100mg, 0.53mmol) in 5ml THF at -20°C. After 2 hours LiCl (28mg, 0.6 mmol) and pyrrolidine (60μl, 0.6mmol) were added and the reaction stirred for 2 hours before allowing to return to room temperature and stir for 14 hours. The reaction mixture was diluted with $NaHCO_{3(aq)}$ (20ml) and extracted with ether (3 x 20ml). The organic extracts were dried ($MgSO_4$), solvent was removed *in vacuo* and purification by flash chromatography eluting with 40% ethyl acetate in petrol yielded the product (84) as a yellow solid (82mg, 64%).

v_{max} (golden gate); 2977, 2862, 1656, 1606, 1439, 1407, 1224 cm^{-1}. Found; C, 74.12; H, 6.98; N, 5.82; $C_{15}H_{17}NO_2$ requires; C, 74.05; H, 7.04; N, 5.76δ_H (200MHz); 7.38-7.25, (5H, m, (Ph)), 6.84, (1H, dd, J=15Hz, 6.5Hz, (C<u>H</u>=CHC=O)), 6.49, (1H, d, J=15Hz (=CHC=O)), 3.82, (1H, d, J= 6.3Hz, (PhCHO)), 3.54, (4H, t, J=6.8Hz, (CH_2-CH_2)), 3.50, (1H, s, (OC<u>H</u>CH=)), 2.0-1.9, (4H, m, (CH_2NCH_2)). δ_C (75MHz) 164 (C(1)), 140 (C(2)), 137 (Ar(q)), 129, 128, 126 (Ar), 124 (C(3)), 62, 61 (C(2'), C(3')), 47, 46 (NCH_2), 26, 25, (ring CH_2). *m/z* (CI/NH$_3$); 244 (H$^+$+M$^+$) (100%), 228, 156, 138.

2,5-*trans*-Dimethylpyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (83).

(83)
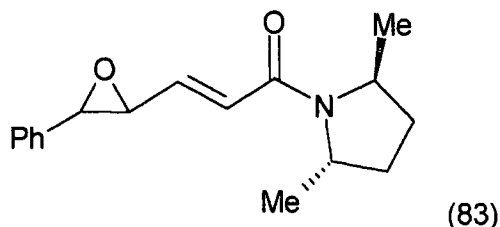
The above protocol was treated using 2,5-dimethylpyrrolidine (47), (66mg, 0.675mmol) to yield the product (83) as a yellow solid (89mg, 49%). ν_{max} (golden gate); 2989, 1662, 1608, 1434, 1204, 908 cm^{-1}. δ_H (300MHz); 7.5-7.2 (5H, m, Ar), 6.80 (1H, dd, J=6.5Hz, 15Hz, $\underline{H}$C=CCO$_2$H), 6.52 (1H, d, 15Hz, C=C$\underline{H}$CON), 4.12-3.97 (1H, m, CHMe), 3.81 (1H, d, J=1.6Hz, PhCH-O), 3.73-3.60 (1H, m, CHMe), 3.47 (1H, dd, J=1.6Hz, 6.5Hz, OCHC=C), 3.41-3.46 (2H, m, CHMe), 2.3-1.9 (2H, m, ring CH$_2$), 1.3 (6H, d, J=7Hz, CH$_3$). δ_C (50MHz); 163 (C=O), 142 ($\underline{C}$=C-CO), 136, 129, 126,126, (Ar), 125, 124 (C=C), 61, 60 (C-O-C), 56 (ring CH$_2$), 31(CHN), 26 (Me). *m/z* (Cl/NH$_3$); 291, 272 (M$^+$+H), 256, 229, 173 (100%), 98, 83.

2,5-*trans*-Diphenylpyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (85)

(85)
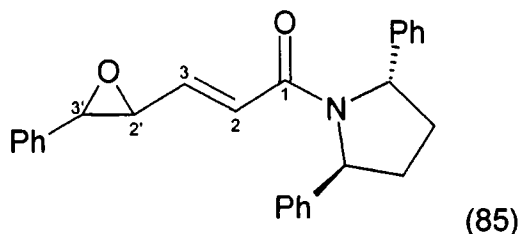
The above protocol was repeated using 2,5-*trans*-diphenylpyrrolidine (63), (250mg, 1.12mmol) to give the desired product (85) as a light brown solid (90mg, 55%). ν_{max} (golden gate); 3063, 3029, 1661, 1617, 1399 cm^{-1}. Found; C, 81.92; H, 6.23; N, 3.62;

$C_{27}H_{25}NO_2$ requires; C, 82.00; H, 6.37; N, 3.54 %. δ_H (300MHz); 7.5-7.0 (15H, m, (Ph)), 6.8-6.6 (1H, m, (C(3)H)), 6.4-6.2 (1H, m, (=C(2)H)), 5.4-5.7 (2H, m, NCHPh), 3.75, (1H, s, (PhCHO)), 3.3, (1H, d, (OC$\underline{H}$CH=)), 2.8-2.2, (2H, m, ring (CH$_2$)) 1.9-1.7 (2H, m, ring (CH$_2$)). δ_C (75MHz) 164 (C(1)), 143, 142, 141, 136, 129, 128, 127, 126, 125, 124 (C(2), C(3), (Ar), 62, 61 (C(2'), C(3'), 61 (NCH), 33 (ring CH$_2$). m/z (CI); 395 (M$^+$) (100%), 318, 241, 222, 173, 145, 119, 77.

Attempted synthesis of oxazolidone (91).

(91)   (90)
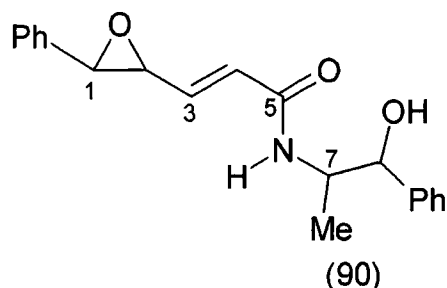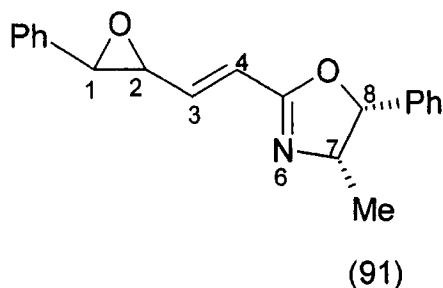
To a stirred solution of 3-(3'-Phenyloxirin-2'-yl)propenoic acid (35) (513mg, 2.7mmol), and 1-phenyl-2-amino-propanol (89) (503mg, 3mmol), in 15ml of acetonitrile / pyridine (1:1), carbon tetrachloride (2.08g, 13.5mmol) was added. The mixture was stirred at room temperature for 2 hours, and triphenyl phosphine (2.122g, 10.5mmol) added in acetonitrile / pyridine (1:1). After stirring for 2 hours, the mixture was concentrated to dryness and redissolved in water / ether. The aqueous portion was extracted with ether (2 x 50ml). The combined organic extracts were dried (MgSO$_4$) and flash chromatography eluting with 30% ethyl acetate in petrol yielded intermediate (90) as a white fibrous solid (641mg, 73%). Found; C, 73.81; H, 6.60; N, 4.29; $C_{20}H_{21}O_3N$ requires; C, 74.3; H, 6.50; N, 4.33; δ_H (300MHz); 7.4-7.2 (10H, m, Ar), 6.8 (1H, dd, J=6Hz, 14Hz, CH(3)), 6.15 (1H, d, J=14Hz, (CH(4)), 5.8, (H, d, J=8Hz, (CH(8)), 4.9 (1H, br, (NH), 4.5-4.3 (1H, m, (CH(7)), 3.8 (1H, d, J=2Hz, (CH(1)), 3.6 (1H, s, (OH), 3.45 (1H, dd, J=6Hz, 2Hz (CH(2)), 1.0 (3H, d, J=7Hz, Me). δ_C (50MHz); 166 (C(5)),

142, 141, 137, 130, 129.5, 129, 128, 127.5, 127, 126.5 (Ar, C(3), C(4)), 63 (C(8)), 62, 61, (C(1), C(2)), 52, (C(7), 15 (Me). m/z (EI+) 324 (M+H$^+$), 306, 216, 173, 110 (100%).

A solution of PPh$_3$ (2g, 7.6mmol) and CCl$_4$ (2g, 12mmol) in Acetonitrile/Pyridine, 1:1 (20ml) was added to a stirred solution of (90) (400mg, 1.3mmol) in acetonitrile/pyridine (20ml). After 90 minutes of stirring at room temperature the solvent was removed *in vacuo* before redissolving the mixture in ether and washing with water. The ether layer was concentrated *in vacuo*. The resulting mixture was subjected to flash chromatography, eluting in 15% ethyl acetate/petrol, to give unidentified decomposition products and starting material (90) (36%).

6.2.4 Rearrangements

Ethyl 2-phenyl-2,3-dihydrofuran-3-carboxylate (34), method 1.

(34)
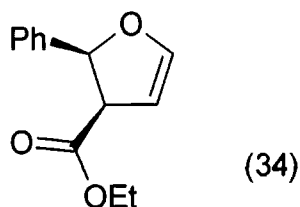
A solution of the freshly distilled ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33) (527mg, 2.4mmol) in toluene (20ml) was degassed and heated to 200°C in a sealed Carius tube (volume 50ml) for 18 hours. Evaporation of the solvent *in vacuo* followed by flash chromatography eluting with 10% ether in petrol yielded the title product as a colourless oil (447mg, 85%). ν_{max} (thin film); 2981 (Ph), 1729 (C=O), 1621 (C=C), 1454, 1142 cm^{-1}. δ_H (300MHz); 7.5-7.1 (5H, m, Ar), 6.72 (1H, d, J=4Hz, OCH=CH), 5.76 (1H, d, J=11Hz, PhCH), 5.06 (1H, dd, J=3Hz, 4Hz OCH=CH), 4.08 (1H, dd, J=11Hz, 3Hz CHCO$_2$), 3.6 (2H, q, J=7Hz, CH$_2$), 0.80 (3H, t, J=7Hz, CH$_3$). δ_C (75MHz);

172 (C=O), 149 (O$\underline{C}$=C), 138, 128, 127, 126 (Ar), 99 (OC=$\underline{C}$), 84 (PhCO), 61 (OCH$_2$), 53 ($\underline{C}$-CO$_2$Et), 14 (CH$_3$), m/z (CI/NH$_3$); 236 (M$^+$+NH$_4^+$), 219, 189, 145 (100%).

Attempted synthesis of Ethyl 2-phenyl-2,3-dihydrofuran-3-carboxylate (34), method 2.

Under a stream of N$_2$ a solution of ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33) (0.218g, 1mmol) in N-methyl pyrrolidine (NMP) (5ml) was refluxed at 202°C for 15 hours. The reaction was allowed to cool and experiment diluted with ether (10ml) and washed with water (10ml). The ether layer was concentrated and NMR revealed only decomposition products.

Ethyl 2-phenyl-2,3-dihydrofuran-3-carboxylate (34), method 3.

After degassing, a solution of ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33), (7g, 32.1mmol) in toluene (90ml) was heated in a stainless steel bomb (100ml) in an oil bath at 205°C at a self induced pressure of 30 bar for 8 hours. After cooling, the solution was concentrated and resulting light brown liquid purified by flash chromatography eluting with 10% ethyl acetate in petrol to yield the desired title furan (34) (5.1g, 71% yield) in an isomeric ratio of 9:1 cis : $trans$. Spectroscopic data identical to that described above.

Attempted synthesis of ethyl 2-phenyl-2,3-dihydrofuran-3-carboxylate (34), method 4.

In a 100ml conical flask capped with a narrow bore funnel, a solution of ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33), (0.218g, 1mmol) in 20ml toluene was heated in a conventional domestic microwave for 2 minutes on high power (700W) for ten repetitions, pausing 1 minute between each heating session to monitor by tlc. No change was seen by tlc, and after removal of solvent, NMR spectroscopy revealed no

isomerisation occurring with a spectra identical to that previously reported for ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33).

Attempted synthesis of ethyl 2-phenyl-2,3-dihydrofuran-3-carboxylate (34), method 5.

In a 30ml test-tube, a solution of ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33), (0.218g, 1mmol) in 6.5ml acetonitrile was subjected to ultrasonication for 90 minutes before solvent was removed *in vacuo* and analysis of resultant material showed it to be starting material (34), with spectroscopic data identical to that described above.

Pyrrolidine 2-phenyl-2,3-dihydrofuran-3-carboxylate (86),

(86)
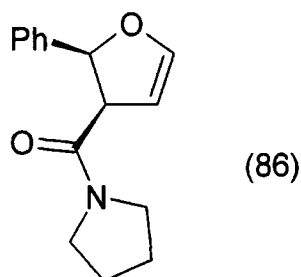
Pyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (84), (90mg) was dissolved in toluene (20ml) in a 120ml Carius tube, which was degassed and sealed. The tube was then heated at 180°C for 20 hours. After allowing the reaction to cool to room temperature the solvent was removed *in vacuo*. Purification by flash chromatography gave recovery of starting material (84), (40mg, 44%) and the title furan (86) with only evidence of the *cis* isomer, (9mg, 10%). v_{max} (solution); 2926, 2880, 1719, 1598, 1452, 1092 cm^{-1}. δ_H (300MHz); 7.3-7.1 (5H, m, Ar), 6.64 (1H, d, J=2.5Hz, OCH=), 5.59 (1H, d, J=11Hz, PhCH), 5.02 (1H, dd, J=2.5Hz, 2Hz, CH=CHO), 4.08 (1H, dd, J=2Hz, 11Hz, CHCO), 3.3-3.1 (2H, m, ring CH$_2$), 3.0 - 2.65 (2H, m, NCH$_2$), 1.5-1.3

(2H, m, ring CH₂). δ_C (300MHz); 171 (C=O), 138 (OC=C), 128, 128, 127, 126 (Ar), 99 (OC=C), 85 (PhC), 48 (CHC=O), 47 (NCH₂), 25 (CH₂CH₂).

Attempted Synthesis of Dimethylpyrrolidine 2-phenyl-2,3-dihydrofuran-3-carboxylate (87).
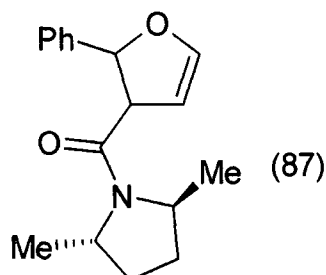
Using the protocol described above the reaction gave only decomposed material.

Attempted Synthesis of Diphenylpyrrolidine 2-phenyl-2,3-dihydrofuran-3-carboxylate (88).
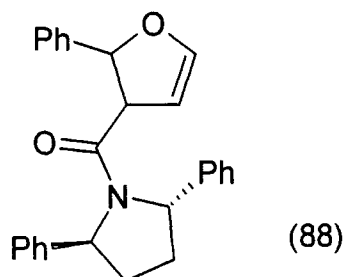
Using the protocol described above the reaction gave only decomposed material.

Attempted Synthesis of Diphenylpyrrolidine 2-phenyl-2,3-dihydrofuran-3-carboxylate (88).

Diphenylpyrrolidine 3-(3'-phenyloxirin-2'-yl)propenoate (85), (50mg) dissolved in toluene (35ml) and the solution degassed in a 100ml stainless steel bomb. The bomb was then heated at 180°C for 20 hours. After allowing the reaction to cool to room temperature the solvent was removed *in vacuo* to give only decomposed material.

From a 50mM solution of ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33), 3 dram vials were charged with 0.1mmol of the substrate in 2ml of solvent. To these 0.1mmol of Lewis acids were added in a nitrogen atmosphere. The experiments were shaken for 4 days on an orbital shaker, at 23°C. Samples were concentrated to dryness *in vacuo* in a Genie multiple rotary evaporator, then dissolved in chloroform (2ml) and NaHCO$_{3(aq)}$ (5% w/v, 2ml) and shaken overnight. The organic fraction was then separated using Jones's tubes and washed using NaHCO$_{3(aq)}$ (5% w/v, 2ml) by the same procedure. Analysis by TLC and NMR revealed only starting or decomposed material.

6.2.5 Application in target molecule synthesis

2-Phenyl-3-hydroxymethan-2,3-dihydrofuran (99), method 1.
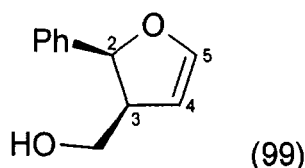
A solution of 2-phenyl-3-ethylmethanoate-2,3-dihydrofuran (34a) (400mg, 1.8mmol) in dry ether (5ml) was added dropwise to a stirred suspension of LiAlH$_4$ (160mg, 4.2mmol) in ether (15ml) at -30°C, under a stream of N$_2$ and allowed to slowly warm to 0°C. After 90 minutes water (160µl) was added followed by 3M NaOH (160µl) and water (480µl) to quench. The reaction was filtered through a celite plug and washed with ether. Evaporation of solvent gave a slightly yellow crude product which was purified by flash chromatography eluting with 20% ether in petrol yielding the desired furan alcohol (99) (299mg, 94%) as a colourless liquid. This product had only moderate stability and was generally used directly in the next step.

v_{max} (thin film); 3332 (OH), 2880, 1616 (C=C), 1139, 1024 cm^{-1}. δ_H (200MHz); 7.4-7.2 (5H, m, Ar), 6.57 (1H, d, J=2z, C(5)H), 5.58 (1H, d, J=9Hz, PhC(2)H), 4.97 (1H, m, C(4)H=), 3.35-3.05 (4H, m, O$\underline{H}$, C$\underline{H}_2$, C(3)$\underline{H}$). δ_C (50MHz); 147, 138, 129, 128, 127 (Ar, OC=), 102 ($\underline{C}$(4)=C), 85 (PhC(2)), 63 ($\underline{C}$(3)CH$_2$), 49 (CH$_2$OH).

3.2.6.3 Attempted synthesis of 2-Phenyl-3-trimethylsilyloxymethan-2,3-dihydrofuran (100).

(100)
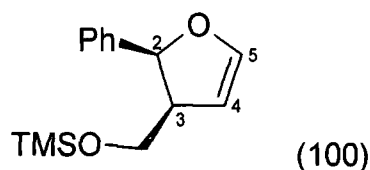
Trimethylsilyl chloride (TMSCl) (1ml, 7.9mmol) was added dropwise to a stirred solution of 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (700mg, 4mmol) and 4-dimethylaminopyridine (DMAP) (80mg, 0.6mmol) in DCM (30ml) at 0°C, under argon. The reaction was stirred for 3 hours and slowly warmed to room temperature, when the mixture was washed with sat. NaHCO$_3$ (aq) (20ml) and dried (MgSO$_4$). The solvent was removed *in vacuo* and residue analysed revealing only decomposed material.

Attempted synthesis of 2-phenyl-3-trimethylsilyloxymethan-2,3-dihydrofuran (100).

N,N'-*Bis*(trimethylsilyl)urea (168mg, 0.82mmol) was added to a stirred solution of 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (291mg, 1.65mmol) in DCM (5ml) at 20°C. The reaction was stirred for 3 hours after which tlc indicated complete consumption of starting material (99). Solvent was removed and resulting precipitate (urea side product) washed with ether (3 x 20ml). The organic filtrates were concentrated *in vacuo* and subsequent analysis revealed only decomposed material.

(102)
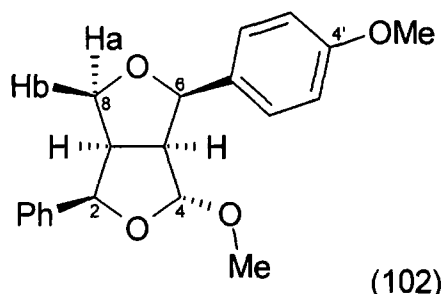
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (70μl, 0.39mmol) in DCM (10ml), was added under argon to a stirred solution of 4-methoxybenzaldehyde dimethyl acetal, (137μl, 0.7mmol) in DCM (10ml) at -20°C. After 20 minutes a solution of 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (60mg, 0.34mmol) in DCM (10ml) was added dropwise over 5 minutes. After stirring for 16 hours at -20°C, MeOH (1ml) was added. After a further 20 minutes NaHCO$_3$ (aq) (30ml) was added, the layers separated and the aqueous portion extracted with DCM (2 x 30ml). The combined organic layers were dried (MgSO$_4$), and solvent removed *in vacuo*. Purification by flash chromatography eluting with 6% ethyl acetate in petrol afforded the title lignan (102) (90mg, 81%) as a white solid. Mp. 65.1-65.8°C; Found; C, 73.68; H, 7.07; C$_{20}$H$_{22}$O$_4$ requires; C, 73.6; H, 6.79%. v_{max} (golden gate); 2880, 1580, 1320, 1065 cm^{-1}. δ_H (500MHz); 7.45-7.39 (4H, m, Ph), 7.35-7.30 (3H, m, Ph, Ar), 6.93 (2H, d, J=9Hz, Ar), 5.27 (1H, d, J=6.5Hz, C(2)H), 4.86 (1H, d, J=6.5Hz, C(6)H), 4.54 (1H, s, C(4)H), 3.82 (3H, s, C(4')OCH$_3$), 3.64 (1H, d, J=10Hz, C(8)-H$_b$), 3.47 (1H, dd, J=10Hz, 6Hz, C(8)-H$_a$), 3.17 (1H, m, C(1)H), 3.09 (3H, s, C(4)OCH$_3$), 3.05 (1H, m, C(5)H). δ_C (125MHz); 159, 138, 131, 128, 126, 127, 127, 114 (Ar), 105 (C(4)), 83 (C(6)), 82 (C(2)), 69 (C(8)), 56 (C(5)), 55 (Ar-OCH$_3$), 54 (C(1)), 48 (C(4)-OCH$_3$). *m/z* (EI), 326 (M$^+$ 30%), 192 (100%), 159, 135, 117, 84.

<u>4'-Methoxy-6-*exo*-(4'-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0] octane</u>
<u>(103) (Method B).</u>

(103)
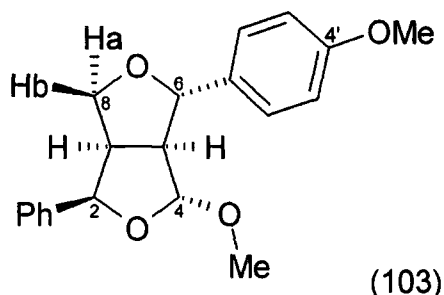
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (180μl, 0.98mmol) in DCM (10ml), was added under argon to a stirred solution of 4-methoxybenzaldehyde dimethyl acetal, (250μl, 1mmol) in DCM (25ml) at -20°C. After 20 minutes a solution of 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (150mg, 0.85mmol) in DCM (5ml) was added dropwise over 5 minutes. After stirring for 14 hours at -20°C, the reaction was allowed to return to ambient temperature. After one hour at room temperature MeOH (1ml) was added. After a further 20 minutes NaHCO$_3$ (aq) (50ml) was added, the layers separated and the aqueous portion extracted with DCM (2 x 50ml). The combined organic layers were dried (MgSO$_4$), and solvent removed *in vacuo*. Purification by flash chromatography eluting with 6% ethyl acetate in petrol afforded the title lignan (103) (190mg, 68%) as a white solid. Mp. 77-79°C; Found; C, 73.14; H, 6.68; C$_{20}$H$_{22}$O$_4$ requires; C, 73.6; H, 6.79%; v_{max} (golden gate); 3022, 1512, 1234, 1205 cm^{-1}. δ_H (500MHz); 7.3-7.2 (7H, m, Ar), 6.84 (2H, d, J=9Hz, Ar), 5.31 (1H, d, J=6Hz, C(2)H), 5.04 (1H, s, C(4)H), 4.51 (1H, s, C(6)H), 3.73 (3H, s, C(4')OCH$_3$), 3.67 (1H, d, J=9Hz, C(8)-H$_b$), 3.33 (3H, s, C(4)OCH$_3$), 3.32 (1H, m, C(1)H), 3.22 (1H, dd, J=9Hz, 6Hz, C(8)-H$_a$), 2.91 (1H, m, C(5)H). δ_C (125MHz); 159, 138, 132, 128, 127, 127, 125, 114 (Ar), 107 (C(4)), 85 (C(6)), 79 (C(2)), 69 (C(8)), 60 (C(5)), 55.3 (Ar-OCH$_3$), 54.7 (C(1)), 49 (C(4)-OCH$_3$). *m/z* (EI), 326 (M$^+$ 34%), 192, 159, 135, 91, 84 (100%).

<u>3,4-Methylenedioxybenzaldehyde dimethyl acetal (107).</u>

(107)
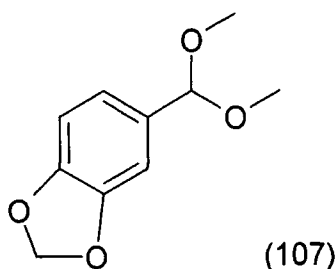
A solution of piperonal (500mg, 3.33mmol) in methanol (3ml) was added dropwise to a solution of trimethyl orthoformate (1ml, 9.12mmol) and $CeCl_3.7H_2O$ (1.25g, 3mmol) in methanol (7ml) at room temperature and stirred for 10 minutes. The reaction mixture was then poured onto 25ml $NaHCO_3$ and extracted with diethyl ether. The organic extracts were dried (Na_2SO_4) and solvent removed *in vacuo* to give the title product (107) as a yellow solid, (87%, 434mg). δ_H (300MHz); 6.94 (2H, m, Ar), 6.81 (1H, Ar), 5.96 (2H, s, CH_2) 5.29 (1H, s, CH), 3.32 (6H, s, CH_3).

<u>4-Bromobenzaldehyde dimethyl acetal (106).</u>

(106)
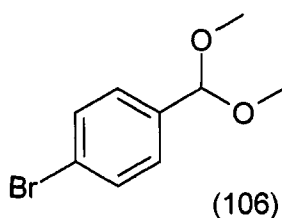
Trimethyl orthoformate (12ml, 77mmol) was added to a stirred solution of 4-bromobenzaldehyde (5.1g, 27mmol) and *p*-toluenesulfonic acid monohydrate ($TsOH.H_2O$), (0.5g, 2.6mmol) in methanol (60ml) before heating to reflux. After 24 hours the reaction was cooled and washed with $NaHCO_3$ (aq) before extracting with Et_2O (50ml) and DCM (50ml). The combined organic extracts were dried (Na_2SO_4), concentrated and liquid gave the required acetal (106) (6.1g, 96%). v_{max} 2991, 2940,

2829, 1592, 1485, 1351, 1205, 1101 cm^{-1}. δ_H (300MHz); 7.5- 7.3 (4H, m, Ar), 5.36 (1H, s, CH), 3.31 (6H, s, CH$_3$). δ_C (75Hz); 137, 132, 129 122 (Ar), 103 (CH), 53 (H$_3$CO). m/z (EI); 232 (M$^+$, 7.5%), 230 (M$^+$, 7.5%), 201 (92%), 199 (100%), 185, 183, 157, 155, 120, 92, 91, 89, 77, 76, 75, 74.

4-Methoxy-6-*endo*-phenyl-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (108).

(108)
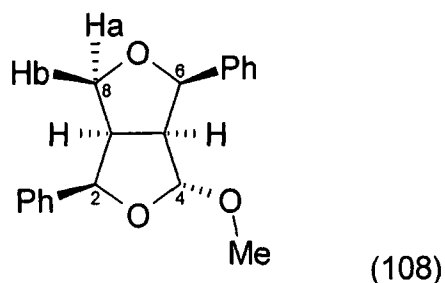
A stirred solution of benzaldehyde dimethyl acetal (104), (225µl, 1.5mmol) was treated to the previously described protocol, method A, and 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (220mg, 1.36mmol) to afford the title lignan (108) (260mg, 64%) as a white solid. Mp. 65.1-65.8°C; Found; C, 76.63; H, 6.63; C$_{20}$H$_{22}$O$_4$ requires; C, 77.00; H, 6.80%); ν_{max} (golden gate); 2897, 1568, 1274, 1049 cm^{-1}. δ_H (500MHz); 7.40-7.3 (10H, m, Ph), 5.36 (1H, d, J=6Hz, C(2)H), 4.94 (1H, d, J=6.5Hz, C(6)H), 4.51 (1H, s, C(4)H), 3.70 (1H, d, J=11Hz, C(8)-H$_b$), 3.49 (1H, dd, J=11Hz, 6Hz, C(8)-H$_a$), 3.19 (1H, m, C(1)H), 3.16 (1H, m, C(5)H), 3.14 (3H, s, C(4)OCH$_3$). δ_C (125MHz); 139, 138, 129, 128, 127, 127, 127, 126 (Ar), 105 (C(4)), 83 (C(6)), 82 (C(2)), 69 (C(8)), 56 (C(5)), 54 (C(1)), 48 (C(4)-OCH$_3$). m/z (EI), 296 (M$^+$ 8%), 265, 159, 134, 117, 84 (100%).

<u>4-Methoxy-6-*exo*-(3',4'-methylenedioxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]</u>
<u>octane (109).</u>
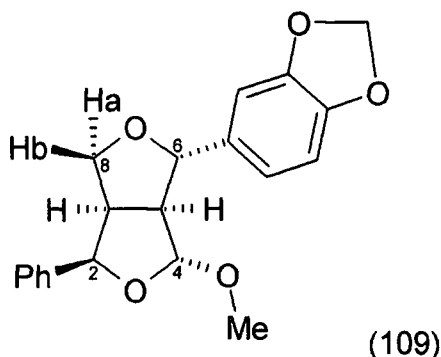
(109)

3,4-methylenedioxybenzaldehyde dimethyl acetal (107), (285mg, 1.45mmol) and 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (250mg, 1.42mmol) were treated to the protocol previously described, method B to give the title lignan (109) (180mg, 38%) as a yellow waxy solid. Found; C, 69.97; H, 6.12; $C_{20}H_{20}O_5$ requires; C, 70.57; H, 5.92%); v_{max} (golden gate); 2893, 1489, 1249, 1039 cm^{-1}. δ_H (500MHz); 7.20-7.15 (6H, m, Ar), 6.8 (1H, s, Ar) 6.6 (1H, d, J=5Hz, Ar), 6.4 (1H, s, C(4)H), 5.85 (2H, s, O-CH$_2$-O), 5.42 (1H, s, C(6)H), 3.92 (2H, d, J=5Hz, C(2)H), 3.42 (2H, m, C(8)-H$_{b+a}$), 3.1 (3H, s, C(4)OCH$_3$), 2.96 (1H, m, C(5)H), 2.4 (1H, m, C(1)H)). δ_C (125MHz); 147, 146, 140, 139, 128, 127.5, 127, 120, 108, 105 (Ar), 106 (C(4)), 101 (OCH$_2$O), 87 (C(6)), 86 (C(2)), 70 (C(8)), 57 (C(5)), 56 (C(4)-OCH$_3$), 54 (C(1)). *m/z* (EI), 340 (M$^+$ 7%), 190, 121 (100%), 91, 77.

<u>4-Methoxy-6-*endo*-(3',4'-methylenedioxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo</u>
<u>[3.3.0]octane (110).</u>
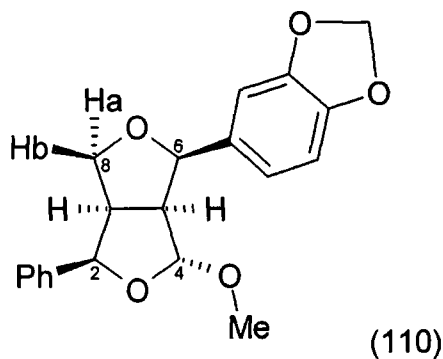
(110)

161

3,4-Methylenedioxybenzaldehyde dimethyl acetal (107), (285mg, 1.45mmol) and 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (250mg, 1.42mmol) were treated to the protocol previously described, method B, to afford the *endo, endo* isomer (109), (44mg, 9%), with spectroscopic data identical to that described above, and the title lignan (110) (132mg, 27%) as a yellow waxy solid. Found; C, 70.21; H, 6.14; $C_{20}H_{20}O_5$ requires; C, 70.57; H, 5.92%); v_{max} (golden gate); 2902, 1493, 1251, 949 cm⁻¹. δ_H (500MHz); 7.40-7.26 (6H, m, Ar), 6.8-6.65, (2H, m, Ar), 5.95 (2H, s, O-CH_2-O), 5.42 (1H, d, J=6Hz, C(2)H), 5.1 (1H, s, C(4)H), 4.48 (1H, d, J=7Hz, C(6)H), 3.70 (1H, m, C(8)-H_b), 3.40 (3H, s, C(4)OCH_3), 3.38 (1H, m, C(1)H), 3.30 (1H, m, C(8)-H_a), 2.90 (1H, dd, J=7Hz, 5Hz, C(5)H)). δ_C (125MHz); 148, 147, 138, 135, 128, 127, 126, 120, 108, 106 (Ar), 107 (C(4)), 101 (OCH_2O), 85 (C(6)), 79 (C(2)), 69 (C(8)), 61 (C(5)), 55 (C(4)-OCH_3), 49 (C(1)). *m/z* (EI), 340 (M⁺ 4%), 308, 295 (100%), 280, 202, 173, 121, 77.

4-Methoxy-6-*endo* –(4'-bromophenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0] octane (111).

(111)
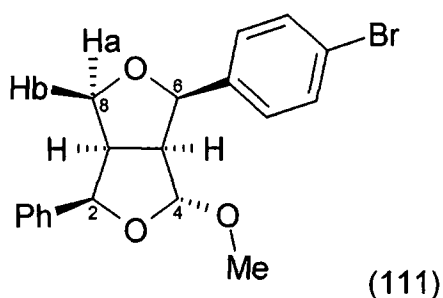
4-Bromobenzaldehyde dimethyl acetal (106), (337mg, 1.56mmol) and 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (250mg, 1.42mmol) were treated with the protocol previously described, method A to afford the title lignan (111) (165mg, 31%) as a yellow amorphous solid. Found; C, 60.39; H, 5.06; $C_{20}H_{20}O_5$ requires; C, 60.81; H, 5.10%); v_{max} (golden gate); 2931, 1487, 1452, 1266, 1069 cm⁻¹. δ_H (500MHz); 7.5-

7.1 (9H, m, Ar), 5.28 (1H, d, J=6Hz, C(2)H), 4.8 (1H, d, J=6Hz, C(6)H), 4.40 (1H, s, C(4)H), 3.60 (1H, d, J=9Hz, C(8)-H$_b$), 3.40 (1H, dd, J=5Hz, 9Hz, C(8)-H$_a$), 3.12 (1H, m, C(1)), 3.10 (3H, s, C(4)OCH$_3$), 3.05 (1H, m, C(5)H)). δ_C (125MHz); 138, 137, 132, 129, 128, 128, 127, 126, (Ar), 105 (C(4)), 82 (C(6)), 81 (C(2)), 69 (C(8)), 56 (C(5)), 54 (C(1)), 48 (C(4)-OCH$_3$). m/z (EI), 376 (23%), 374 (M$^+$, 24%), 345, 343, 269, 267, 134, 121, 84.

4-Methoxy-6-*endo*-methyl-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (112).

(112)
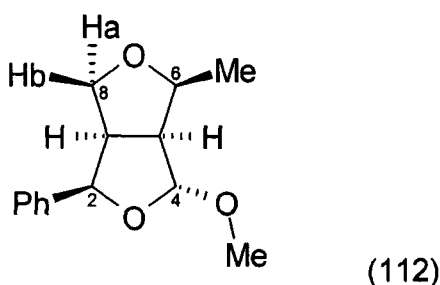
Ethanal dimethyl acetal (105), (146mg, 1.4mmol) and 2-phenyl-3-hydroxymethan-2,3-dihydrofuran (99) (250mg, 1.42mmol) were treated with the protocol previously described, method A to afford the title lignan (112) (100mg, 30%) as a white waxy solid, attempts to recrystallize (from ether/petrol and ethyl acetate/hexane) failed. Found; C, 71.69; H, 7.67; C$_{20}$H$_{20}$O$_5$ requires; C, 71.77; H, 7.74%); ν_{max} (golden gate); 2933, 1453, 1100, 1025 cm^{-1}. δ_H (500MHz); 7.4-7.1 (5H, m, Ar), 5.23 (1H, d, J=5Hz, C(2)H), 5.08 (1H, s, C(4)H), 3.82 (1H, m, C(6)H), 3.38 (1H, d, J=7Hz, C(8)-H$_b$), 3.32 (3H, s, C(4)OCH$_3$), 3.23, (1H, m, C(8)-H$_a$), 3.08 (1H, m, C(5)H), 2.88, (1H, m, C(1)H)), 1.35 (3H, d, 7Hz, CH$_3$). δ_C (125MHz); 137, 127, 126, 125 (Ar), 103 (C(4)), 80 (C(2)), 75, (C(6)), 67 (C(8)), 56 (C(1)), 53 (C(4)-OCH$_3$) 48 (C(5)), 15 (CH$_3$). m/z (EI), 234 (M$^+$, 11%), 203, 129, 121 (100%), 105, 91, 84, 77.

<u>2,6-*endo*-diphenyl-3,7-dioxabicyclo[3.3.0]octane (117).</u>
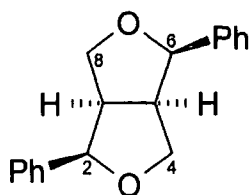
(117)

Boron trifluoride diethyl ether complex (BF$_3$.Et$_2$O), (200µl, 1.25mmol) was added to a stirred solution of triethylsilane (Et$_3$SiH) (1.5ml, 18mmol) and 4-methoxy-6-endo - phenyl-2-endo-phenyl-3,7-dioxabicyclo[3.3.0]octane (102) (110mg, 0.37mmol) in DCM (20ml) at 0°C. On addition of BF$_3$.OEt$_2$ the reaction mixture immediately turned dark green and after 30 minutes the reaction was warmed to room temperature and stirred for 30 hours before NaHCO$_3$ (aq) (20ml) was added. The organic layer was washed with NaHCO$_3$ (aq) (20ml) and the combined aqueous phases back extracted with DCM (20ml). The combined organic phases were dried (MgSO$_4$), and solvent removed *in vacuo*. The resulting residue was purified by flash chromatography eluting with 3% ethyl acetate in petrol to yield the desired symmetrical lignan (117) (60mg, 61%), which solidified on standing to a white solid and was recrystallized with ether/petrol. M.p. 73-74°C. Found; C, 80.92; H, 6.76; C$_{18}$H$_{18}$O$_2$ requires; C, 81.17; H, 6.81 %). ν_{max} (golden gate); 3002, 1524, 1241, 911 cm^{-1}. δ_H (300MHz); 7.45-7.32 (10H, m, Ph), 4.91 (2H, d, J=6Hz, C(6)H, C(2)H), 3.74 (2H, m, C(4)-H$_b$ C(8)-H$_b$), 3.59 (2H, m, C(4)-H$_a$ C(8)-H$_a$), 3.15 (2H, m, C(1)H), 3.12 (2H, m, C(5)H). δ_C (50MHz); 138, 128, 127, 126 (Ar), 84 (C(6), C(2)), 69 (C(4), C(8)), 54 (C(1), C(5)). *m/z* (EI); 266 (M$^+$, 45%), 189, 165, 117 (100%), 84.

<u>6-*endo*-(4'-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (118).</u>
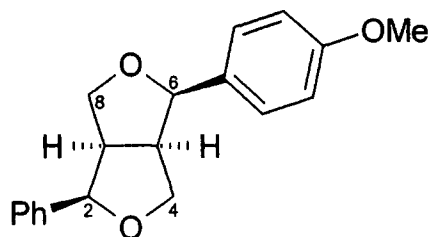
(118)

4-Methoxy-6-*endo* –(4'-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (102) (80mg, 0.25mmol) was treated with the protocol described above to yield the lignan (118) (50mg, 68%) which produced a white waxy solid on standing. Recystalization from ether/petrol failed to solidify the product. Found; C, 76.12, H, 6.85, $C_{19}H_{20}O_3$ requires; C, 77.00, H, 6.80); v_{max} (golden gate); 2959, 2858, 1612, 1514, 1247, 1067 cm^{-1}. δ_H (300MHz); 7.3-7.15 (7H, m, Ar) 6.82 (2H, d, J=8Hz, Ar), 4.85 (1H, d, J=4.5Hz, C(2)H), 4.35 (1H, d, J=4.5Hz), 4.02 (1H, d, J=8Hz, C(4)H$_b$), 3.85 (2H, m, C(4)H$_a$, C(8)H$_b$), 3.73 (3H, s, OCH$_3$), 3.45 (1H, m, C(8)H$_a$), 3.28 (1H, m, C(1)H), 2.88 (1H, m, C(5)H). δ_C (75MHz); 160, 138, 133, 128, 127, 127, 126, 125, 114 (Ar), 88 (C(6)), 82 (C(2)), 71 (C(8)), 70 (C(4)), 56 (C(4')-OCH$_3$), 55 (C(1)), 50 (C(5)). m/z (EI); 296 (M$^+$, 25%), 265, 159, 135 (100%), 117.

<u>6-*endo*-(4'-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (119).</u>
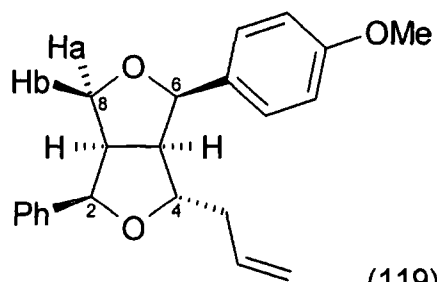
(119)

Boron trifluoride diethyl ether complex ($BF_3.Et_2O$), (250µl, 2.2mmol) was added to a stirred solution of allyltrimethylsilane (267µl, 3.3,mol) and 4-methoxy-6-*endo* –(4'-methoxyphenyl)-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (102) (55mg, 0.17mmol) in DCM (10ml) at 0°C. The reaction mixture went dark green and was stirred for 48 hours before warming to room temperature. $NaHCO_3$ (aq) (20ml) was added. The organic layer was washed with $NaHCO_3$ (aq) (20ml) and the combined aqueous phases back extracted with DCM (20ml). The combined organic phases were dried ($MgSO_4$), and solvent removed *in vacuo*. The resulting residue was purified by flash chromatography eluting with 3% ethyl acetate in petrol to yield the desired allyl substituted lignan (119) (32mg, 56%), which solidified on standing, attempts to recrystallize (petrol/ether, ethyl acetate/hexane) gave a yellow waxy solid. v_{max} (solution); 3015, 1721, 1612, 1513, 1249, 1215, 1030. cm^{-1}. Found; C, 78.62; H, 7.12; $C_{22}H_{24}O_3$ requires; C, 78.54; H, 7.19 %). δ_H (500MHz); 7.4-7.2 (7H, m, Ar), 6.85 (2H, m, Ar), 5.82 (1H, m, CH=), 5.27 (1H, d, J=7Hz, C(2)H), 5.19-5.11 (2H, m, =CH_2), 4.62 (1H, d, J=7Hz, C(6)H), 4.38 (1H, m, C(4)H), 3.82 (3H, s, CH_3), 3.79 (1H, m, C(8_b)H), 3.40 (1H, m, C(8_a)H), 3.38 (1H, m, C(1)H), 2.80 (1H, m, C(5)H), 2.46, 2.37 (2H, m, C(4)CH_2). δ_C (125MHz); 159, 139, 134, 128, 127, 127, 126, 114 (Ar), 133 (CH=), 118 (CH_2=), 87 (C(6)), 83 (C(4)), 80 (C(2)), 69 (C(8)), 59 (C(5)), 55 (CH_3), 50 (C(1)), 39 (C(4)$\underline{C}$H_2). *m/z* (EI); 336 (M^+, 5%) 295, 175, 159, 91 (100%).

Attempted synthesis of 4-Hydroxy-6-*endo* -phenyl-2-*endo*-phenyl-3,7-dioxabicyclo [3.3.0]octane (140).

(140)
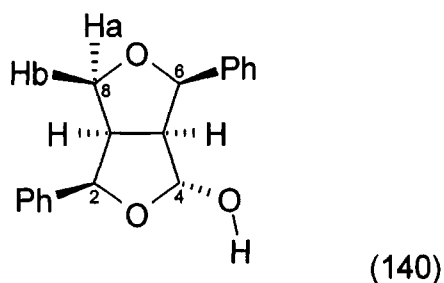
Hydrochloric acid (1M, 1ml) was added to a stirred solution of 4-Methoxy-6-*endo* -phenyl-2-*endo*-phenyl-3,7-dioxabicyclo[3.3.0]octane (108) (50mg, 1.69mmol) in 1:8 H_2O/THF (9ml) and stirred at ambient temperature for 36 hours. Careful addition of 25ml of sat. Na_2CO_3 (aq) and extraction with DCM (2 x 25ml) yielded only starting material (108), (41mg, 82% yield).

Synthesis of 2-Phenyl-3-carboxy-2,3-dihydrofuran (129).

(129)
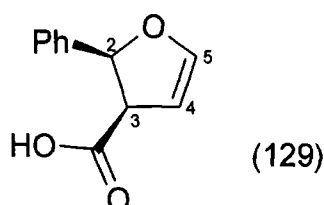
$LiOH.H_2O$ (218mg, 5.2mmol) in H_2O (7ml) was added dropwise to a solution of 2-phenyl-3-ethylmethanoate-2,3-dihydrofuran (34) (1g, 4.6mmol) in THF (33ml) and stirred for 12 hours at 0°C. Sat. Na_2CO_3 (aq) (40ml) was then added and THF removed *in vacuo*. The aqueous reaction mixture was washed with ether (2 x 20ml), before being gradually acidified with cold HCl (2M) to pH 4. The acidic solution was the extracted with ether, and dried ($MgSO_4$) before concentration *in vacuo*, to yield the desired carboxylic acid (129) as a yellow oil (610mg). Recrystallization with petrol from ether, gave a pale yellow crystalline solid (244mg, 35% yield). The solid decomposed on heating. v_{max} (golden gate); 3302 (br), 2981, 1721, 1603, 1259, 1002 cm^{-1}. δ_H (300MHz); 10.2 (1H, br, COOH), 7.4-7.35 (5H, m, Ar), 6.59 (1H, d, J=4Hz, OCH=), 5.85 (1H, d, J=11Hz, PhCH), 5.09 (1H, dd, J=4Hz, 3Hz, =C(4)H), 3.75 (1H, m, C(3)H). *m/z* (EI) 190 (M^+, 38%), 145 (100%), 113.

2-Phenyl-3-(1'-hydroxydimethyl)methan-2,3-dihydrofuran (122).
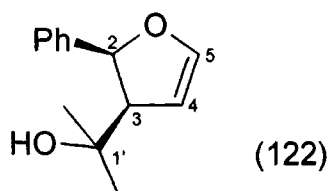
(122)

A solution of 2-phenyl-3-ethylmethanoate-2,3-dihydrofuran (34) (500mg, 2.3mmol) in ether (5ml), was added to a stirred solution of methylmagnesium bromide (1.68ml, 3M solution, 5.04mmol), in ether (5ml), at -15°C under argon. After 2 hours ammonium chloride (20ml) was added and the reaction allowed to warm to room temperature. The resulting oil was purified by flash chromatograph eluting with 15% ethyl acetate in petrol to yield the desired tertiary alcohol (122) (343mg, 73%) as a colourless oil. Limited analytical data due to unstable nature of tertiary alcohol. v_{max} (thin film); 3344, 1612, 1126, 1042 cm^{-1}. δ_H (300MHz); 7.45-7.1 (5H, m, Ar), 6.18 (1H, d, 6Hz, C(5)H), 5.58 (1H, d, 9Hz, C(2)H), 5.06 (1H, m, C(3)H), 3.4-3.6 (1H, m, C(4)H), 3.05 (1H, s, OH), 0.88, 0.85 (2H, s, s, (CH$_3$). δ_C (75MHz); 147 (C(5)), 137, 127, 126, 125 (Ar), 104 (C(4)), 84 (C(2)), 57 (C(3)), 53 (C(1')), 28, 27 (CH$_3$).

Attempted synthesis of 4-Methoxy-6-*endo*-(4'-methoxyphenyl)-2-*endo*-phenyl-8,8-dimethyl-3,7-dioxabicyclo[3.3.0] octane (123).

(123)
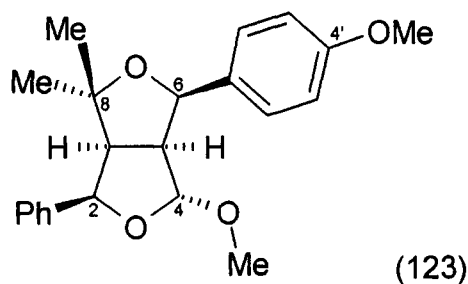
Trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1ml, 1.1mmol) in DCM (10ml), was added under argon to a stirred solution of 4-methoxybenzaldehyde dimethyl acetal, (1g, 5.9mmol) in DCM (60ml) at -20°C. After 20 minutes a solution of 2-phenyl-3-(1'-hydroxydimethyl)methan-2,3-dihydrofuran (122) (1.1mg, 5.4mmol) in DCM (30ml) was added dropwise over 5 minutes. After stirring for 16 hours at -20°C, MeOH (1ml) was added. After a further 20 minutes NaHCO₃ (aq) (30ml) was added, the layers separated and the aqueous portion extracted with DCM (2 x 30ml). The combined organic layers were dried (MgSO₄), and solvent removed *in vacuo*. Purification by flash chromatography eluting with 4% ethyl acetate in petrol afforded only decomposed material and 4-methoxybenzaldehyde.

Attempted Synthesis of 2-Phenyl-3-(1'-hydroxymethyl)methan-2,3-dihydrofuran (127).
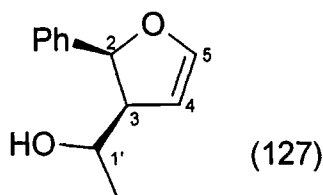
(127)

A solution of 2-phenyl-3-ethylmethanoate-2,3-dihydrofuran (34) (500mg, 2.3mmol) in ether (5ml), was added to a stirred solution of methylmagnesium bromide (0.84ml, 3M solution, 2.52mmol), in ether (5ml), at -15°C under argon. After 2 hours ammonium chloride (20ml) was added and the reaction allowed to warm to room temperature. The resulting oil was purified by flash chromatograph eluting with 15% ethyl acetate in petrol to yield the tertiary alcohol (127) (140mg, 28%) as a colourless oil. All spectroscopic data was identical to that described above.

Attempted Synthesis of 2-Phenyl-3-(1'-(1"-methyl-1"-methoxyamine)-methyl)methan-2,3-dihydrofuran (125).

(125)
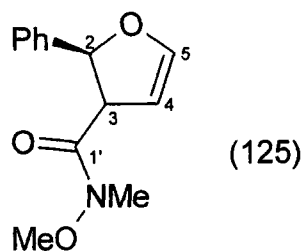
A solution of trimethylaluminium (2M, 1.5ml, 3mmol) in hexane was added to a stirred solution of *N,O*-dimethylhydroxylamine, (183mg, 3mmol) in DCM (10ml) at -15°C, under argon. After stirring for 20 minutes the reaction is allowed to warm slowly to room temperature over 45 minutes. This aluminium complex was then added by cannula to a stirred solution of 2-phenyl-3-ethylmethanoate-2,3-dihydrofuran (34) (460mg, 2.11mmol) in DCM, 10ml. After stirring for 2 hours, 5% HCl (aq) (20ml) was added, and reaction mixture extracted with DCM (2 x 30ml). The organic extracts were dried (MgSO₄), and concentrated *in vacuo*, yielding only decomposed material.

Attempted Synthesis of 2-Phenyl-3-(1'-(1"-methyl-1"-methoxyamine)-methyl)methan-2,3-dihydrofuran (125), method 2.

Trimethylacetyl chloride (250μl, 2mmol) was added in 7ml THF to a stirred solution of triethylamine (700μl, 5mmol) and 2-phenyl-3-carboxy-2,3-dihydrofuran (129), (372mg, 1.96mmol) in 25ml THF at -20°C. After 2 hours LiCl (107mg, 2.28mmol) and *N,O*-dimethylhydroxylamine (78mg, 1.81mmol) were added and the reaction stirred for 2 hours, before allowing to return to room temperature and then stirred for 24 hours. The reaction mixture was diluted with NaHCO₃(aq) (75ml) and extracted with ether (3 x 75ml), dried (MgSO₄) and solvent removed *in vacuo* producing only decomposed material.

6.2.6 Aziridine Precursor Synthesis

<u>(*R,S*) -Ethyl 4-azido-5-hydroxy-5-phenylpent-2-enoate, (40).</u>

(40)
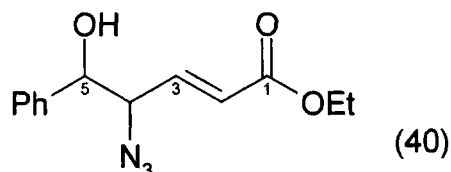
A solution of the Ethyl 3-(3'-phenyloxirin-2'-yl)propenoate (33), (10.12g, 0.046mol) in ethanol (100ml) was added dropwise, over 30 minutes to a stirred solution of sodium azide (9.21g, 0.14mol) and ammonium chloride (8.67g, 0.16mol) in ethanol (250ml) and water (50ml), at 35°C under argon. The reaction was then heated under reflux for 5 hours before being cooled and solvent removed. The organic material was eluted from the resultant residue with methanol, separating it from the precipitated inorganics. The methanol was removed *in vacuo* and purification of the resultant residue by flash chromatography eluting with 20% ethyl acetate in petrol, gave the title product (40) (10.08g 84%). v_{max} (thin film); 3440 (OH), 3060 (*N*-CH), 2981 (CH), 2495 (N=N), 2102 (C-N=N), 1717 (C=O), 1661 (C=C), 1494 cm^{-1}. δ_H (200MHz); 7.6-7.25 (5H, m, Ph), 7.0-6.8 (1H, dd, J=2Hz, 14Hz, CH=CHC=O), 6.08 (1H, d, J=14Hz, CHC=O), 4.83 (1H, d, J=6Hz, PhCHOH), 4.65 (1H, d, J=6Hz, PhCHOH), 4.48 (1H, td, J=6Hz, 2Hz, CHN$_3$), 4.18 (2H, q, J=8Hz, OCH$_2$CH$_3$), 1.28 (3H, t, J=8Hz, CH$_3$). *m/z* (CI/NH$_3$) 279 (M$^+$+NH$_3$, 30%), 234, 219, 203, 128, 106 (100%).

<u>(*2S,3R*)-Ethyl 3-(3'-phenylaziridin-2'yl)propenoate (41).</u>

(41)
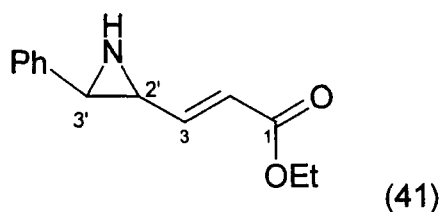
A solution of PPh$_3$ (427mg, 1.64mmol) and acetic acid (50μl) in DCM (4ml) was added under N$_2$ to a stirred solution of azide alcohol (40) (400mg, 1.52mmol) in DCM (1ml). The solution was stirred at room temperature for 3 hours. Water (30ml) was added and the mixture extracted with ether (2 x 20ml). The combined organic extracts were dried (MgSO$_4$) and concentrated and resulting product purified by flash chromatography eluting with 20% ethyl acetate in petrol to give the title compound (41) (153mg, 46%) as a yellow oil. ν$_{max}$ (thin film); 3310 (NH), 1703 (C=O), 1643 (C=C), 1495 cm^{-1}. δ$_H$ (300MHz); 7.45-7.2 (5H, m, Ph), 6.59 (1H, dd, J=9Hz, 15Hz, C(3)H), 6.08 (1H, d, J=15Hz, CH-C=O), 4.20 (2H, q, J=7Hz, CH$_2$CH$_3$), 3.10 (1H, d, J=2.5Hz, PhC(3')H), 2.63 (1H, d, J=2.5Hz, 9Hz, C(2')H). 1.6(1H, br, NH), 1.29 (3H, t, J=7Hz, CH$_3$). δ$_C$ (75MHz); 167 (C=O), 148 (C(2)), 139, 129, 128, 126 (Ar), 123 (C(3)), 61 (CH$_2$), 43 (C(2')), 42 (PhC(3')), 15 (CH$_3$). m/z (EI); 217 (M$^+$, 24%), 172, 144 (100%), 104.

(2S,3R)-Ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44).

(44)
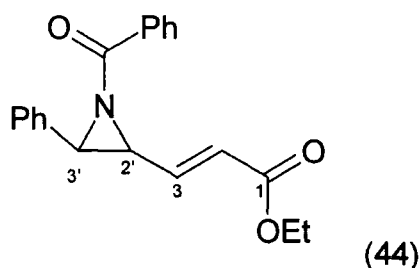
Triethylamine (64μl, 0.46mmol) was added to a stirred solution of aziridine (41) (50mg, 0.23mmol) in DCM (2ml) at -10°C. After 30 minutes benzoyl chloride (38mg, 2.7mmol) was added to the stirred reaction mixture which was then allowed to warm to room temperature. After stirring for a further 30 hours the reaction mixture was washed with water and the separated organic extracts dried (MgSO$_4$) and concentrated. Purification by flash chromatography eluting with 10% ethyl acetate in petrol gave the title amide (44) as a white crystalline solid (54mg, 73%). Mp. 117.7-

172

118.1°C. Found; C, 74.71; H, 5.96, N, 4.51; $C_{20}H_{19}NO_3$, requires; C, 74.7; H, 5.92; N, 4.36%). v_{max} (Golden gate); 1710 (C=O), 1654 (C=O), 1623 (C=C), 1447, 1297, 1257 cm^{-1}. δ_H (400MHz); 7.96 (2H, d, J=6.8Hz, o-Ar'), 7.3-7.6 (8H, m, Ar, Ar'), 6.44 (1H, dd, J=10Hz, 16Hz, C(3)), 6.14 (1H, d, J=16Hz C(2)), 4.13 (2H, q, J=7Hz, CH$_2$CH$_3$), 3.83 (1H, d, J=2.4Hz, PhC(3')H), 3.43 (1H, dd, J=10Hz, 2.4Hz, C(2')H), 1.23 (3H, t, J=7Hz, CH$_3$). δ_C (100MHz); 176 (PhC=O), 165 (C(1)), 143 (C(2)), 135, 133, 132, 130, 129, 128, 128, 126 (Ar), 125 C(3), 60 (PhC(3')H), 49 (C(2')), 47 (CH$_2$Me), 14 (CH$_3$). m/z (CI/NH$_3$); 322 (M$^+$+H, 33%), 276, 248, 216, 105 (100%). Crystallographic data in appendix A.

Attempted synthesis of Ethyl 3-(1'-benzyl-3'-phenylaziridin-2'-yl) propenoate (137).

(137)
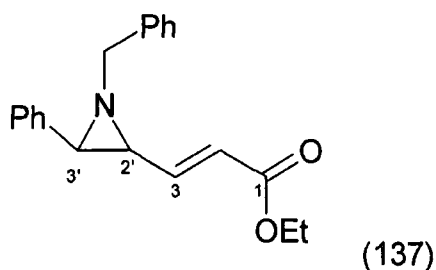
Triethylamine (56mg, 0.55mmol) was added to a stirred solution of the aziridine (41) (104mg, 0.48mmol) in acetonitrile (5ml) at 0°C under N$_2$. The solution was left to reach room temperature before being cooled again to 0°C when benzyl bromide in acetonitrile (5ml) was added dropwise. After 24 hours the mixture was dried (MgSO$_4$) in vacuo and purified by flash chromatography eluting with 20% ethyl acetate in petrol. This yielded 27mg of starting material and 65mg of unidentified decomposed material.

6.2.7 Vinylaziridine Rearrangements

Attempted synthesis of ethyl 1-benzoyl-2-phenyl-2,3-dihydropyrrole-3-carboxylate (138)

(138)
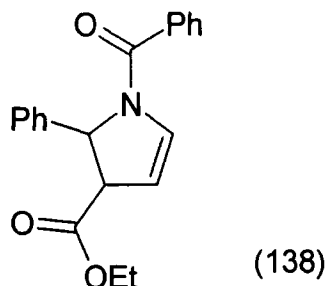
A solution of ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44) (81mg, 0.25mmol) in benzene (12ml) was refluxed for 96 hours. Tlc showed only starting material present. Removal of solvent *in vacuo* and purification by flash chromatography eluting with 20% ethyl acetate in petrol gave decomposed material and partial recovery of starting material (44) (27mg), spectroscopic data identical with that described above, section 3.2.2.5.

Attempted synthesis of ethyl 1-benzoyl-2-phenyl-2,3-dihydropyrrole-3-carboxylate (138)

A solution of ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44), (72mg, 0.22mmol) in toluene (12ml) was degassed and heated for 22hours in a sealed Carius tube at 180°C. Solvent was removed *in vacuo* and purification by flash chromatography eluting with 20% ethyl acetate in petrol yielded decomposition products.

Preparation of silylated Carius tubes.

A solution of 1:3 N,O-*bis*(trimethylsilyl)acetamide : Pyridine (BSA) was heated in a dry

Carius tube for 4hr at 65°C under argon. The treated tubes were washed with distilled

ether and stored in an oven at 150°C until needed.

Attempted synthesis of ethyl 1-benzoyl-2-phenyl-2,3-dihydropyrrole-3-carboxylate (138)

A solution of ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44), (75mg,

0.23mmol) in toluene (12ml) was degassed and heated for 10 hours in a sealed

silylated Carius tube at 180°C. Removal of solvent *in vacuo* yielded only decomposed

material.

NMR study of rearrangement to of ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44)

A solution of the title compound (9.8mg, 0.03mmol) in deuterated benzene (617mg)

was degassed and heated at 80°C in a sealed NMR tube monitored by NMR over

time, found to contain (44) and unknown compound (139).

4 Hours: δ_H (C_6D_6) 200MHz; 8.15 (0.5H, apparent dd, Ar), 8.05 (1.5H, apparent dd,

Ar), 7.3-6.9 (8H, Ar), 6.8 (0.25H, apparent dd, vinylic), 6.65 (0.75H, dd, J=9.5Hz,

16Hz), 6.15 (0.25H, d, J=16Hz, vinylic) 5.95 (0.75H, d, J=16Hz), 3.89 (2H, m,

OCH_2CH_3), 3.60 (0.25H, d, 5Hz), 3.45 (0.75H, d, J=2.5Hz), 3.1 (0.25H, apparent d),

3.0 (0.75H, dd, J=2.5Hz, 9.5Hz), 0.89 (3H, m, Me).

15 Hours: δ_H (C_6D_6) 200MHz; 8.15 (1H, apparent dd, Ar), 8.05 (1H, apparent dd, Ar,

SM), 7.3-6.9 (8H, Ar), 6.8 (0.5H, apparent dd, vinylic), 6.65 (0.5H, dd, J=9.5Hz, 16Hz),

6.15 (0.5H, d, J=16Hz, vinylic) 5.95 (0.5H, d, J=16Hz), 3.89 (2H, m, OCH_2CH_3), 3.60

(0.5H, d, 5Hz), 3.45 (0.5H, d, J=2.5Hz), 3.1 (0.5H, apparent d), 3.0 (0.5H, dd, J=2.5Hz, 9.5Hz), 0.89 (3H, m, Me).

28 Hours: Polymeric / decomposed material only.

Attempted synthesis of ethyl 1-benzoyl-2-phenyl-2,3-dihydropyrrole-3-carboxylate (138)

A solution of the ethyl 3-(1'-benzoyl-3'-phenylaziridin-2'-yl) propenoate (44), (50mg) was stirred with DMAP (4-dimethylamino pyridine) (40mg, 0.3mmol) in DCM (20ml) at room temperature for 36 hours. Analysis by TLC indicated only starting material (44) present. NEt$_3$ (2ml) was added to the solution and the reaction was heated under reflux for 24 hours then allowed to cool to room temperature before washing with water (10ml) and back extracted with DCM (10ml). The organic extracts were combined and concentrated *in vacuo* before purifying by flash chromatography eluting with 10% ethyl acetate in petrol to yield unidentified decomposition products.

Section D: Appendix A:
Crystallographic Data
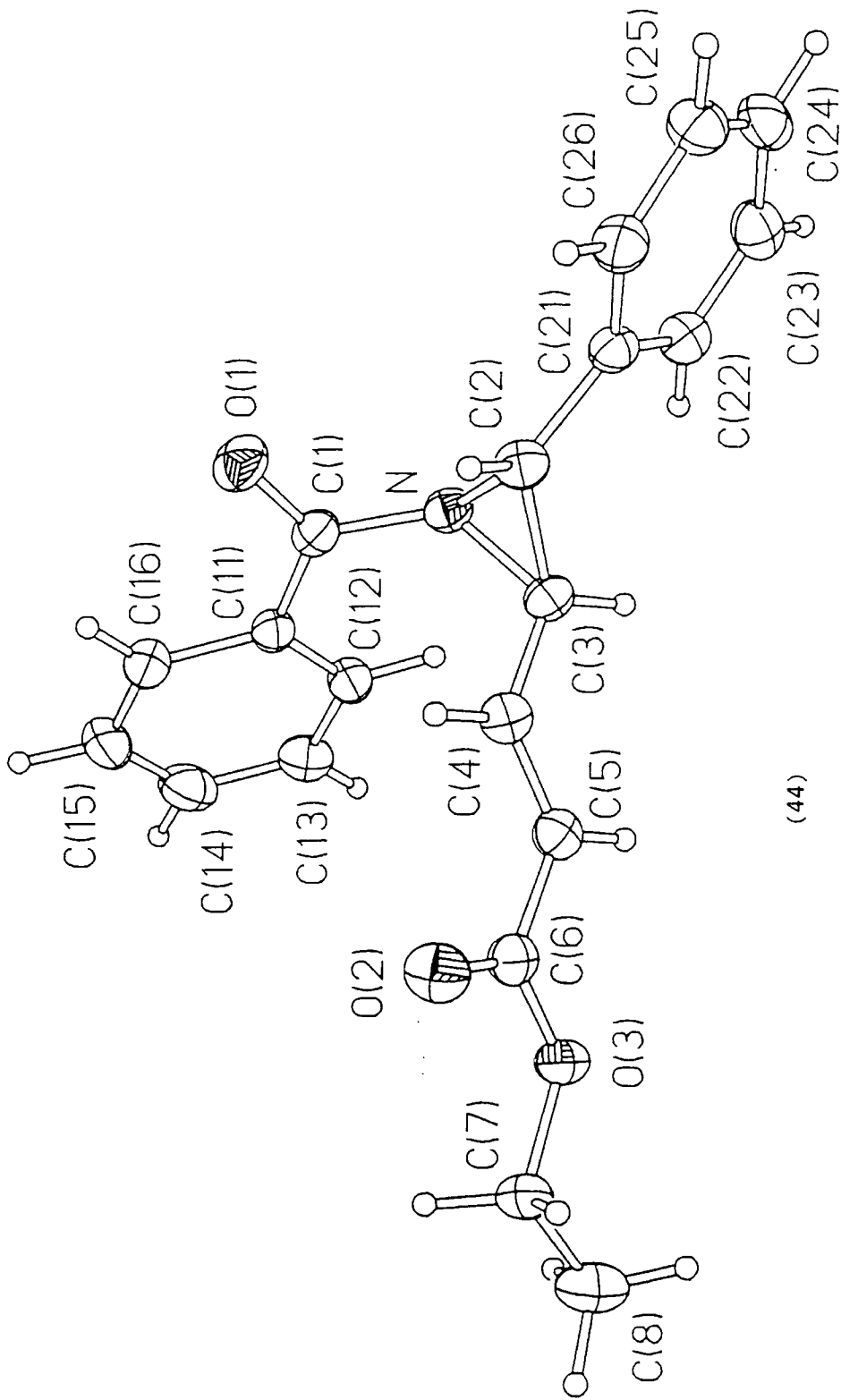
(44)

Table 15 Crystal data and structure refinement for (44)

Identification code	97srv189
Empirical formula	C20 H19 N O3
Formula weight	321.36
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 10.767(1) A alpha = 90 deg. b = 14.348(1) A beta = 93.52(1) deg c = 11.020(1) A gamma = 90 deg.
Volume	1699.2(3) A^3
Z	4
Density (calculated)	1.256 g/cm^3
Absorption coefficient	0.084 mm^-1
F(000)	680
Crystal size	0.4 x 0.3 x 0.2 mm
Theta range for data collection	1.89 to 27.49 deg.
Index ranges	-15<=h<=15, -19<=k<=17, -15<=l<=14
Reflections collected	18054
Independent reflections	3898 [R(int) = 0.0469]
Observed reflections, I>2sigma(I)	2856
Absorption correction	Semi-empirical from psi-scans
Max. and min. transmission	1.000 and 0.757
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3821 / 0 / 294
Goodness-of-fit on F^2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0421, wR2 = 0.0832
R indices (all data)	R1 = 0.0706, wR2 = 0.1003
Extinction coefficient	0.0096(8)
Largest diff. peak and hole	0.215 and -0.226 e.A^-3

Table 16   Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for (44)   U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	5981(1)	1950(1)	12(1)	36(1)
O(2)	3038(1)	5180(1)	1067(1)	36(1)
O(3)	2671(1)	5279(1)	3059(1)	31(1)
N	6584(1)	2656(1)	1818(1)	24(1)
C(1)	5747(1)	2147(1)	1058(1)	26(1)
C(2)	7330(1)	3413(1)	1345(1)	27(1)
C(3)	6361(1)	3612(1)	2254(1)	26(1)
C(4)	5212(1)	4098(1)	1833(1)	27(1)
C(5)	4491(1)	4539(1)	2580(1)	27(1)
C(6)	3348(1)	5030(1)	2124(1)	27(1)
C(7)	1506(2)	5765(1)	2736(2)	33(1)
C(8)	933(2)	5996(2)	3910(2)	43(1)
C(11)	4619(1)	1781(1)	1627(1)	26(1)
C(12)	4496(1)	1820(1)	2877(1)	28(1)
C(13)	3467(2)	1415(1)	3377(2)	36(1)
C(14)	2561(2)	972(1)	2633(2)	42(1)
C(15)	2670(2)	943(1)	1391(2)	44(1)
C(16)	3694(2)	1344(1)	882(2)	37(1)
C(21)	8694(1)	3405(1)	1685(1)	27(1)
C(22)	9175(2)	3150(1)	2843(1)	31(1)
C(23)	10454(2)	3089(1)	3095(2)	37(1)
C(24)	11264(2)	3280(1)	2190(2)	40(1)
C(25)	10794(2)	3555(1)	1054(2)	41(1)
C(26)	9518(2)	3620(1)	798(2)	35(1)

Table 17   Bond lengths [A] and angles [deg] for (44)

O(1)-C(1)	1.227(2)	O(2)-C(6)	1.211(2)
O(3)-C(6)	1.346(2)	O(3)-C(7)	1.460(2)
N-C(1)	1.398(2)	N-C(2)	1.465(2)
N-C(3)	1.478(2)	C(1)-C(11)	1.496(2)
C(2)-C(21)	1.493(2)	C(2)-C(3)	1.517(2)
C(2)-H(2)	0.99(2)	C(3)-C(4)	1.471(2)
C(3)-H(3)	0.97(2)	C(4)-C(5)	1.326(2)
C(4)-H(4)	0.96(2)	C(5)-C(6)	1.479(2)
C(5)-H(5)	0.98(2)	C(7)-C(8)	1.504(2)
C(7)-H(71)	0.99(2)	C(7)-H(72)	0.99(2)
C(8)-H(81)	0.99(2)	C(8)-H(82)	0.99(2)
C(8)-H(83)	1.01(2)	C(11)-C(12)	1.393(2)
C(11)-C(16)	1.399(2)	C(12)-C(13)	1.394(2)
C(12)-H(12)	0.96(2)	C(13)-C(14)	1.389(2)
C(13)-H(13)	0.98(2)	C(14)-C(15)	1.382(3)
C(14)-H(14)	1.00(2)	C(15)-C(16)	1.392(3)
C(15)-H(15)	0.98(2)	C(16)-H(16)	0.97(2)
C(21)-C(26)	1.395(2)	C(21)-C(22)	1.396(2)
C(22)-C(23)	1.391(2)	C(22)-H(22)	0.98(2)
C(23)-C(24)	1.391(2)	C(23)-H(23)	0.97(2)
C(24)-C(25)	1.379(3)	C(24)-H(24)	0.96(2)
C(25)-C(26)	1.389(2)	C(25)-H(25)	0.98(2)
C(26)-H(26)	0.97(2)		

Table 17 (cont.)

C(6)-O(3)-C(7)	115.90(12)	C(1)-N-C(2)	121.45(12)
C(1)-N-C(3)	124.68(11)	C(2)-N-C(3)	62.05(9)
O(1)-C(1)-N	121.40(14)	O(1)-C(1)-C(11)	122.11(13)
N-C(1)-C(11)	116.24(12)	N-C(2)-C(21)	117.26(12)
N-C(2)-C(3)	59.38(9)	C(21)-C(2)-C(3)	122.78(13)
N-C(2)-H(2)	114.6(9)	C(21)-C(2)-H(2)	116.8(9)
C(3)-C(2)-H(2)	113.5(9)	C(4)-C(3)-N	119.17(12)
C(4)-C(3)-C(2)	118.76(12)	N-C(3)-C(2)	58.56(9)
C(4)-C(3)-H(3)	117.0(9)	N-C(3)-H(3)	112.9(9)
C(2)-C(3)-H(3)	117.4(8)	C(5)-C(4)-C(3)	122.97(14)
C(5)-C(4)-H(4)	118.1(10)	C(3)-C(4)-H(4)	118.9(10)
C(4)-C(5)-C(6)	121.58(14)	C(4)-C(5)-H(5)	120.3(9)
C(6)-C(5)-H(5)	118.2(9)	O(2)-C(6)-O(3)	124.01(13)
O(2)-C(6)-C(5)	125.81(13)	O(3)-C(6)-C(5)	110.17(12)
O(3)-C(7)-C(8)	106.68(14)	O(3)-C(7)-H(71)	107.5(9)
C(8)-C(7)-H(71)	112.2(10)	O(3)-C(7)-H(72)	108.4(10)
C(8)-C(7)-H(72)	111.0(10)	H(71)-C(7)-H(72)	110.9(14)
C(7)-C(8)-H(81)	108.7(12)	C(7)-C(8)-H(82)	108.9(11)
H(81)-C(8)-H(82)	110(2)	C(7)-C(8)-H(83)	109.2(10)
H(81)-C(8)-H(83)	111(2)	H(82)-C(8)-H(83)	109(2)
C(12)-C(11)-C(16)	119.42(14)	C(12)-C(11)-C(1)	121.94(13)
C(16)-C(11)-C(1)	118.55(14)	C(11)-C(12)-C(13)	119.98(14)
C(11)-C(12)-H(12)	118.2(9)	C(13)-C(12)-H(12)	121.8(9)
C(14)-C(13)-C(12)	120.3(2)	C(14)-C(13)-H(13)	120.6(10)
C(12)-C(13)-H(13)	119.2(10)	C(15)-C(14)-C(13)	120.0(2)
C(15)-C(14)-H(14)	120.0(11)	C(13)-C(14)-H(14)	120.0(11)
C(14)-C(15)-C(16)	120.3(2)	C(14)-C(15)-H(15)	121.7(12)
C(16)-C(15)-H(15)	118.0(12)	C(15)-C(16)-C(11)	120.1(2)
C(15)-C(16)-H(16)	121.3(11)	C(11)-C(16)-H(16)	118.6(11)
C(26)-C(21)-C(22)	118.83(14)	C(26)-C(21)-C(2)	118.75(14)
C(22)-C(21)-C(2)	122.36(13)	C(23)-C(22)-C(21)	120.4(2)
C(23)-C(22)-H(22)	119.2(10)	C(21)-C(22)-H(22)	120.3(10)
C(22)-C(23)-C(24)	120.1(2)	C(22)-C(23)-H(23)	119.7(10)
C(24)-C(23)-H(23)	120.2(10)	C(25)-C(24)-C(23)	119.7(2)
C(25)-C(24)-H(24)	120.3(11)	C(23)-C(24)-H(24)	119.9(11)
C(24)-C(25)-C(26)	120.5(2)	C(24)-C(25)-H(25)	120.4(11)
C(26)-C(25)-H(25)	119.1(11)	C(25)-C(26)-C(21)	120.5(2)
C(25)-C(26)-H(26)	122.3(10)	C(21)-C(26)-H(26)	117.2(10)

Section E: Appendix B:

Lectures, Seminars, Colloquia

Appendix B

Lectures and Seminars from invited speakers 1996–99

<u>1996</u>

October 9   Professor G. Bowmaker, University Aukland, NZ
             *Coordination and Materials Chemistry of the Group 11 and Group 12
             Metals : Some Recent Vibrational and Solid State NMR Studies*

October 14   Professor A. R. Katritzky, University of Gainesville, Florida, USA*
             Recent Advances in Benzotriazole Mediated Synthetic Methodology

October 16   Professor Ojima, State University of New York at Stony Brook*
             Silylformylation and Silylcarbocyclisations in Organic Synthesis

October 22   Professor Lutz Gade, Univ. Wurzburg, Germany*
             *Organic transformations with Early-Late Heterobimetallics: Synergism
             and Selectivity*

October 22   Professor B. J. Tighe, University of Aston
             *Making Polymers for Biomedical Application - can we meet Nature's
             Challenge?*

October 23   Professor H. Ringsdorf, Johannes Gutenberg-Universitat, Mainz,
             Germany
             Function Based on Organisation

October 29   Professor D. M. Knight, University of Durham*
             The Purpose of Experiment - A Look at Davy and Faraday

October 30   Dr Phillip Mountford, Nottingham University*
             Recent Developments in Group IV Imido Chemistry

November 6   Dr Melinda Duer, Chemistry Department, Cambridge
             *Solid-state NMR Studies of Organic Solid to Liquid-crystalline Phase
             Transitions*

November 12 Professor R. J. Young, Manchester Materials Centre, UMIST
             New Materials - Fact or Fantasy?

November 13 Dr G. Resnati, Milan
             Perfluorinated Oxaziridines: Mild Yet Powerful Oxidising Agents

November 18 Professor G. A. Olah, University of Southern California, USA*
             Crossing Conventional Lines in my Chemistry of the Elements

November 19 Professor R. E. Grigg, University of Leeds*
             *Assembly of Complex Molecules by Palladium-Catalysed Queueing
             Processes*

November 20 Professor J. Earnshaw, Department of Physics, Belfast
Surface Light Scattering: Ripples and Relaxation

November 27 Dr Richard Templer, Imperial College, London*
Molecular Tubes and Sponges

December 3 Professor D. Phillips, Imperial College, London
"A Little Light Relief"

December 4 Professor K. Muller-Dethlefs, York University
Chemical Applications of Very High Resolution ZEKE Photoelectron Spectroscopy

December 11 Dr Chris Richards, Cardiff University
Stereochemical Games with Metallocenes

1997

January 15 Dr V. K. Aggarwal, University of Sheffield*
Sulfur Mediated Asymmetric Synthesis

January 16 Dr Sally Brooker, University of Otago, NZ
Macrocycles: Exciting yet Controlled Thiolate Coordination Chemistry

January 21 D. Rudge, Zeneca Pharmaceuticals*
High Speed Automation of Chemical Reactions

January 22 Dr Neil Cooley, BP Chemicals, Sunbury
Synthesis and Properties of Alternating Polyketones

January 29 Dr Julian Clarke, UMIST
What can we learn about polymers and biopolymers from computer-generated nanosecond movie-clips?

February 4 Dr A. J. Banister, University of Durham
From Runways to Non-metallic Metals - A New Chemistry Based on Sulphur

February 5 Dr A. Haynes, University of Sheffield
Mechanism in Homogeneous Catalytic Carbonylation

February 12 Dr Geert-Jan Boons, University of Birmingham*
New Developments in Carbohydrate Chemistry

February 18 Professor Sir James Black, Foundation/King's College London*
My Dialogues with Medicinal Chemists

February 19 Professor Brian Hayden, University of Southampton
The Dynamics of Dissociation at Surfaces and Fuel Cell Catalysts

February 25 Professor A. G. Sykes, University of Newcastle
The Synthesis, Structures and Properties of Blue Copper Proteins

February 26 Dr Tony Ryan, UMIST
Making Hairpins from Rings and Chains

March 4   Professor C. W. Rees, Imperial College*
Some Very Heterocyclic Chemistry

March 5   Dr J. Staunton FRS, Cambridge University*
Tinkering with biosynthesis: towards a new generation of antibiotics

March 11   Dr A. D. Taylor, ISIS Facility, Rutherford Appleton Laboratory
Expanding the Frontiers of Neutron Scattering

March 19   Dr Katharine Reid, University of Nottingham
Probing Dynamical Processes with Photoelectrons

October 8   Professor E Atkins, Department of Physics, University of Bristol
*Advances in the control of architecture for polyamides: from
nylons to genetically engineered silks to monodisperse oligoamides*

October 15 Dr R M Ormerod, Department of Chemistry, Keele University
Studying catalysts in action

October 21 Professor A F Johnson, IRC, Leeds
Reactive processing of polymers: science and technology

October 22 Professor R J Puddephatt, University of Western Ontario
Organoplatinum chemistry and catalysis

October 23 Professor M R Bryce, University of Durham, Inaugural Lecture.
*New Tetrathiafulvalene Derivatives in Molecular, Supramolecular and
Macromolecular Chemistry: controlling the electronic properties of
organic solids*

October 29 Professor R Peacock, University of Glasgow*
Probing chirality with circular dichroism

October 28 Professor A P de Silva, The Queen's University, Belfast
Luminescent signalling systems"

November 5 Dr M Hii, Oxford University*
Studies of the Heck reaction

November 11 Professor V Gibson, Imperial College, London*
Metallocene polymerisation

November 12 Dr J Frey, Department of Chemistry, Southampton University*
*Spectroscopy of liquid interfaces: from bio-organic chemistry to
atmospheric chemistry*

November 19 Dr G Morris, Department of Chemistry, Manchester Univ.*
*Pulsed field gradient NMR techniques: Good news for the Lazy
and DOSY*

November 20 Dr L Spiccia, Monash University, Melbourne, Australia
Polynuclear metal complexes

November 25 Dr R Withnall, University of Greenwich
Illuminated molecules and manuscripts

November 26 Professor R W Richards, University of Durham, Inaugural Lecture
A random walk in polymer science

December 2 Dr C J Ludman, University of Durham*
Explosions

December 3 Professor A P Davis, Department. of Chemistry, Trinity College Dublin*
Steroid-based frameworks for supramolecular chemistry

December 10 Sir G Higginson, former Professor of Engineering in Durham
and retired Vice-Chancellor of Southampton Univ.*
1981 and all that.

December 10 Professor M Page, University of Huddersfield*
The mechanism and inhibition of beta-lactamases

1998

January 14 Professor D Andrews, University of East Anglia
Energy transfer and optical harmonics in molecular systems

January 20 Professor J Brooke, University of Lancaster*
What's in a formula? Some chemical controversies of the 19th century

January 27 Professor R Jordan, Dept. of Chemistry, Univ. of Iowa, USA.
Cationic transition metal and main group metal alkyl complexes in olefin polymerisation

January 28 Dr S Rannard, Courtaulds Coatings (Coventry)
The synthesis of dendrimers using highly selective chemical reactions

February 3 Dr J Beacham, ICI Technology
The chemical industry in the 21st century

February 4 Professor P Fowler, Department of Chemistry, Exeter University
Classical and non-classical fullerenes

February 11 Professor J Murphy, Dept of Chemistry, Strathclyde University

February 17 Dr S Topham, ICI Chemicals and Polymers*
Perception of environmental risk; The River Tees, two different rivers

February 18   Professor G Hancock, Oxford University*
               Surprises in the photochemistry of tropospheric ozone

February 24   Professor R Ramage, University of Edinburgh*
               The synthesis and folding of proteins

February 25   Dr C Jones, Swansea University
               Low coordination arsenic and antimony chemistry

March 4   Professor T C B McLeish, IRC of Polymer Science Technology,
               Leeds University
               *The polymer physics of pyjama bottoms (or the novel rheological
               characterisation of long branching in entangled macromolecules)*

March 11   Professor M J Cook, Dept of Chemistry, UEA
               How to make phthalocyanine films and what to do with them.

March 17   Professor V Rotello, University of Massachusetts, Amherst
               *The interplay of recognition & redox processes – from flavoenzymes to
               devices*

March 18   Dr J Evans, Oxford University
               *Materials which contract on heating (from shrinking ceramics
               to bullet proof vests)*

October 7   Dr S Rimmer, Ctr Polymer, University of Lancaster
               New Polymer Colloids

October 9   Professor M F Hawthorne, Department Chemistry & Biochemistry,
               UCLA, USA

October 21   Professor P Unwin, Department of Chemistry, Warwick University
               Dynamic Electrochemistry: Small is Beautiful

October 23   Professor J C Scaiano, Department of Chemistry, University of
               Ottawa, Canada
               In Search of Hypervalent Free Radicals

October 26   Dr W Peirs, University of Calgary, Alberta, Canada
               *Reactions of the Highly Electrophilic Boranes $HB(C_6F_5)_2$ and $B(C_6F_5)_3$
               with Zirconium and Tantalum Based Metallocenes*

October 27   Professor A Unsworth, University of Durham*
               What's a joint like this doing in a nice girl like you?

October 28   Professor J P S Badyal, University of Durham
               Tailoring Solid Surfaces, Inaugural Lecture

November 4   Dr N Kaltscoyannis, Department of Chemistry, UCL, London
               Computational Adventures in d & f Element Chemistry

November 3   Dr C J Ludman, Chemistry Department, University of Durham*
               Bonfire night Lecture

November 10 Dr J S O Evans, Chemistry Department, University of Durham
Shrinking Materials

November 11 Dr M Wills, Department of Chemistry, University of Warwick*
New Methodology for the Asymmetric Transfer Hydrogen of Ketones

November 12 Professor S Loeb, University of Windsor, Ontario, Canada
From Macrocycles to Metallo-Supramolecular Chemistry

November 17 Dr J McFarlane*
Nothing but Sex and Sudden Death!

November 18 Dr R Cameron, Department of Materials Science & Metallurgy,
Cambridge University
Biodegradable Polymers

November 24 Dr B G Davis, Department of Chemistry, University of Durham*
Sugars and Enzymes

December 1 Professor N Billingham, University of Sussex
Plastics in the Environment - Boon or Bane

December 2 Dr M Jaspers, Department of Chemistry, University of Aberdeen*
*Bioactive Compounds Isolated from Marine Inverterates and
Cyanobacteria*

December 9 Dr M Smith Department. of Chemistry, Warwick University
*Multinuclear solid-state magnetic resonance studies of nanocrystalline
oxides and glasses*

1999

January 19 Dr J Mann, University of Reading
The Elusive Magic Bullet and Attempts to find it?

January 20 Dr A Jones, Department of Chemistry, University of Edinburgh
*Luminescence of Large Molecules: from Conducting Polymers to Coral
Reefs*

January 27 Professor K Wade, Department of Chemistry, University of Durham*
Foresight or Hindsight? Some Borane Lessons and Loose Ends

February 3 Dr C Schofield, University of Oxford*
Studies on the Stereoelectronics of Enzyme Catalysis

February 9 Professor D J Cole-Hamilton, St. Andrews University*
Chemistry and the Future of life on Earth

February 10   Dr C Bain, University of Oxford
              *Surfactant Adsorption and Marangoni Flow at Expanding Liquid
              Surfaces*

February 17   Dr B Horrocks, Department of Chemistry, Newcastle University
              *Microelectrode techniques for the Study of Enzymes and Nucleic Acids
              at Interfaces*

February 23   Dr C Viney, Heriot-Watt*
              Spiders, Slugs And Mutant Bugs

February 24   Dr. A-K Duhme, University of York
              *Bioinorganic Aspects of Molybdenum Transport in Nitrogen-Fixing
              Bacteria*

March 3   Professor B Gilbert, Department of Chemistry, University of York
              *Biomolecular Damage by Free Radicals: New Insights through ESR
              Spectroscopy*

March 9   Dr Michael Warhurst, Chemical Policy issues, Friends of the Earth*
              Is the Chemical Industry Sustainable?

March 10   Dr A Harrison, Department of Chemistry, The University of Edinburgh
              Designing model magnetic materials

March 17   Dr J Robertson, University of Oxford*
              *Recent Developments in the Synthesis of Heterocyclic Natural
              Products*

May 11   Dr John Sodeau, University of East Anglia*
              Ozone Holes and Ozone Hills

May 12   Dr Duncan Bruce, Exeter University
              *The Synthesis and Characterisation of Liquid-Crystalline Transition
              Metal Complexes*

* Those attended by the author.

First Year Induction Course

This course consists of a series of one hour lectures on services available in the department.

Safety Matters	Mr. D. Hunter
Electrical Appliances	Mr. B.T. Barker
Library Facilities	Mrs. M. Hird
Mass Spectrometry	Dr. M. Jones
NMR Spectroscopy	Dr. A.M. Kenwright
Glass-Blowing Techniques	Mr. R. Hart, & Mr. G. Haswell

Three courses, each of 8 hours tuition were also attended.

Molecular Modelling	Dr. C. W. Lehmann
Advanced Mass Spectrometry	Dr. M. Jones
Practical Nuclear Magnetic Resonance	Dr. A.M. Kenwright

Seminars, Colloquia, Presentations and Publications

December 1996   Postgraduate Symposium, Sunderland

December 1996   Modern Aspects of Stereochemistry, Sheffield

April   1997   Novel Organic Chemistry, 8th SCI Symposium, Aberdeen

May   1997   21st Century Heterocyclic Chemistry Symposium, Sunderland

July   1997   Synthesis in Organic Chemistry, St Catherines College, Oxford

December 1997   Modern Aspects of Stereochemistry, Sheffield

April   1998   1998 RSC National Congress, Durham[†]

June   1998   Graduate Colloquia, Durham

July   1998   ICOS-12, Venice[†]

December 1998   Modern Aspects of Stereochemistry, Sheffield

March   1999   Novel Organic Chemistry, 10th SCI Symposium, Glasgow

July   1999   Graduate Colloquia, Durham[‡]

July   1999   RPR Graduate Symposium, Dagenham Research Centre[‡]

[†] Poster presentation by author

[‡] Oral presentation by author

The following are relevant publications by the author:

"*Stereoselective Synthesis of 2,4-Disubstituted-3,7-dioxabicyclo[3.3.0]octanes*" Aldous, D.J., Dutton, W.M., Steel, P.G.; *Synlett* 1999, p474.

"*A Simple Enantioselective Preparation of 2,5-Diphenylpyrrolidine and Related Amines*" Aldous, D.J., Dutton, W.M., Steel, P.G.; *Tetrahedron: Asymmetry,* 2000, p2455.

Section F: References

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