SYNTHETIC APPROACHES TOWARDS THE BENZODIOXEPIN CORE OF THE STROBILURIN FAMILY

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by

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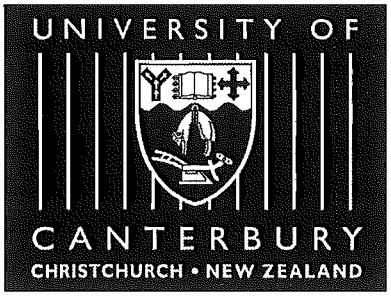

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"Difficulties embarrass, uncertainty perplexes, opposition retards, censure exasperates, or neglect depresses. We proceed because we have begun; we complete our design, that the labour already spent may not be in vain: but as expectation gradually dies away, the gay smile of alacrity disappears, we are compelled to implore severer powers, and trust the event to patience and constancy."

Samuel Johnson., *The Rambler*, Tuesday, 10 March, 1752

Chapter One

The History of the Strobilurin Family

1.1 Background on the strobilurin family

With the earth's population growing at a great rate, ways to increase the yields of plant matter from commercial horticulture are needed. A variety of methods have been investigated towards this end. Many of these methods have considerable associated risks. The genetic engineering of higher-yielding crops or the extensive use of fertilisers are two examples of this. One method which is often overlooked is the use of pesticides or fungicides to minimise the deleterious effects that plant pathogens have on crops. The fungal kingdom contains many members which are pathogenic to plants and as such, treatment of fungal infestations using commercial fungicides was a US$6 billion industry in 1996.[1]

One of the principal difficulties with the use of commercial fungicides is the development of wide-spread fungal resistance to their cytotoxic effects. The best method for countering this resistance is to develop new classes of fungicides with novel modes of action. Their judicious use would then offer a solution to the increasingly wide-spread problem of fungicidal resistance.[1] However, the development of an entirely novel class of fungicide is a rare event. Most new fungicides involve structural variation of previously used cytotoxins and therefore have limited use in the alleviation of fungal resistance.

In 1996, both BASF and Zeneca (now Astra-Zeneca) independently released fungicides which had an entirely novel mode of action. Azoxystrobin (BASF) and kresoxim methyl (Zeneca) inhibit fungal respiration on an enzymatic level. They were developed from a class of fungal-derived natural products known as the strobilurins. These are cytotoxic derivatives of β-methoxyacrylic acid and are characterised by the presence of an arene ring connected to a triene system, which terminates in a β-methoxymethacrylate unit as shown in **Figure 1.1**. The sales of azoxystrobin projected to peak at US$500 million dollars,[1] and as such the represent an important new class of commercial fungicide.

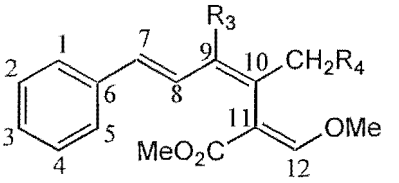
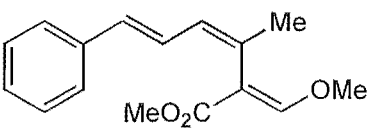


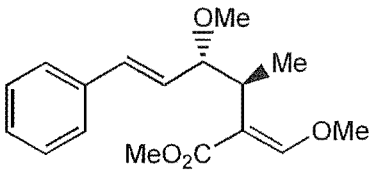
Figure 1.1 - A generalised structure of the strobilurin family. R_1, R_2, R_3, and R_4 indicate known points of substituent variation.

The history of the strobilurin family begins with the work of Steglich and Anke, who in 1976 initiated a program aiming at isolating antibiotic agents from the fungal class basidiomycetes. The basidiomycetes class had not previously been studied to any degree as they are difficult to culture, in contrast to other fungal classes.[2] The first publication from this collaboration detailed the isolation of strobilurin A (**1.1**) from the mycelium of the basidiomycetes *Strobiluris tenacellus*.[2] This compound possessed powerful antibiotic activity against a range of eukaryotic cells. Strobilurin A was found to have significant similarities to the antifungal antibiotic mucidin, whose biological activities and structural data were published by a Czech group in 1969,[3] and patented in 1970,[4] without any structure being proposed. The only discrepancy between the spectroscopic data of strobilurin A and those of mucidin was the optical activity reported for mucidin. This clearly ruled out a common identity with strobilurin A, as strobilurin A contains no stereochemical elements. Steglich and Anke made an attempt to establish the structure of Mucidin by re-isolating it from the basidiomycete *Oudemansiella mucida*.[5] This provided two materials - strobilurin A and the optically-active oudemansin A (**1.2**). Determining the stereochemistry of the triene system of strobilurin A also posed difficulties. In their original paper,[2] Steglich and Anke reported the stereochemistry as being (*E,E,E*) as shown. Initial synthetic work indicated that the triene stereochemistry was more likely to be (*E,Z,E*).[5] This proposal was eventually confirmed by a synthesis starting from materials of known stereochemical configuration (see **Section 1.4**).[6]



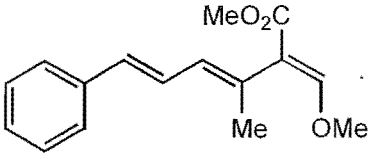
Strobilurin A

1.1



Oudemansin A

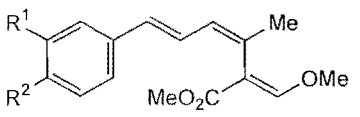
1.2



Proposed stucture for strobilurin A

After protracted study of the Czech patent literature, combined with direct spectroscopic comparison, it was determined that mucidin and strobilurin A were in fact the same compound. The optical activity attributed to mucidin was ascribed to a "printing error".[5]

After the isolation of strobilurin A, the groups of Steglich and Anke continued with their program of investigating the isolation of anti-fungal agents from basidiomycetes. In the following years, a wide range of strobilurins have been isolated by their group, as well as by other groups. An additional 13 strobilurins have been isolated to date, and these are shown in **Figure 1.2**.[7]



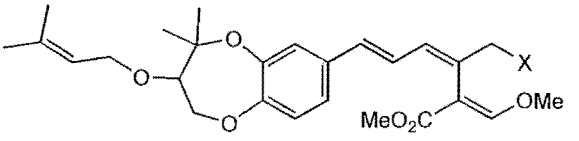
strobilurin B $R^1 = OCH_3$, R^2=Cl

strobilurin C $R^1 = OCH_2CH=C(CH_3)_2$, R_2=H

strobilurin F-1 R^1=OH, R^2=H

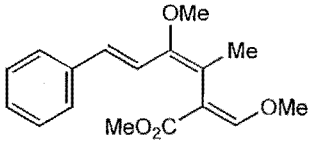
strobilurin F-2 R^1= H, $R_2=OCH_2CH=C(CH_3)_2$

strobilurin H R^1=H, $R^2=OCH_3$

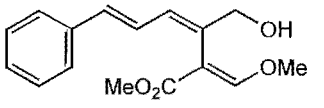


strobilurin D X=H

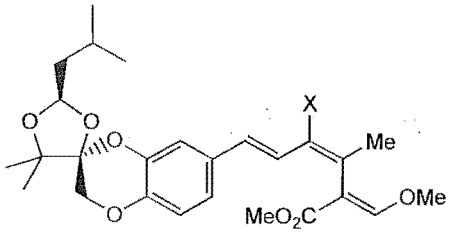
hydroxystrobilurin D X=OH



9-methoxystrobilurin A

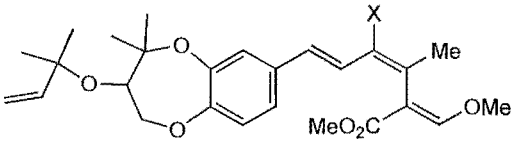


hydroxystrobilurin A



strobilurin E X=H

9-methoxystrobliurin E X=OMe



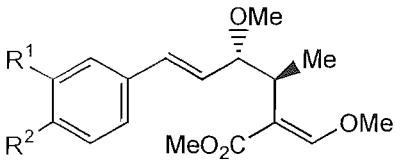
9-methoxystrobilurin K X=OMe

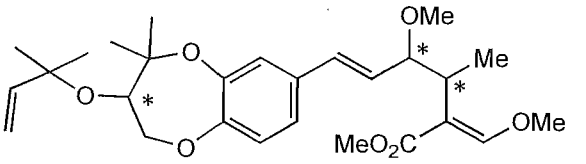
Strobilurin I X=H

Figure 1.2 The natural strobilurins

As can be seen, the common structural features of these compounds are an arene substituted with a triene with a β-methoxyacrylate system at its terminus. However, these compounds display considerable variation in the substituents present on the arene ring and to lesser degree, variation in functionality present on the triene system. The type of functionalisation on the arene ranges from the simple isopentenyl ethers of strobilurins F and C, to the dioxepin ring system of strobilurins D and K. The triene system shows comparatively little variation, with only carbons 9 (methyl ether), or 13 (hydroxyl group) varying in their substitution. The oudemansins are a closely related group of compounds which have been isolated from the same fungi as the strobilurins.[8] They display similar toxicity profiles, with the only structural difference being that the sp^2 carbons 9 and 10 in the strobilurins are now sp^3 centres in the oudemansins, with carbon-9 bearing a methoxy substituent. This similarity, combined

with their common occurrence suggests that the oudemansins share a common biosynthetic ancestry to the 9-methoxystrobilurins.[7]





Oudemansin A R^1= H, R^2=H

Oudemansin B R^1= OCH_3, R_2=Cl

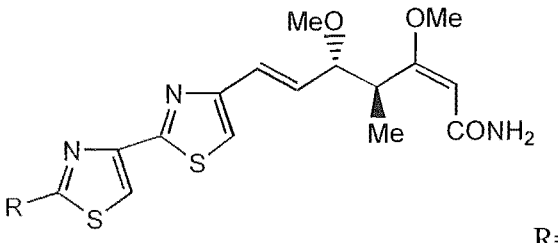
Oudemansin X R^1=H, R^2=OCH_3

Oudemansin L

1.2 Biological Activity of the Strobilurins

The fungi which produce the strobilurins have a world-wide distribution.[7] A variety of these fungi have been shown to produce sufficient quantities of the strobilurins to inhibit growth of other fungal species when cultivated in conditions mimicking the strobilurin-producing fungus' natural environment.[9] This suggests that the presence of the strobilurins confers a competitive advantage to their producers, by preventing other fungal species from growing on the same substrate.

Soon after the isolation of strobilurin A, Steglich and Anke's groups showed that its cytotoxicity was due to the inhibition of eukaryotic respiration.[10] Although protein, RNA and DNA synthesis were also inhibited, this was attributed to the resultant deficit in intracellular ATP.[5] The strobilurins and oudemansins were shown to inhibit the cytochrome bc_1 complex present in the inner mitochondrial membrane of fungi and other eukaryotes.[10,11] This enzyme complex catalyses the transfer of electrons from the lipid-soluble carrier ubiquinol to the water-soluble acceptor cytochrome c. Concomitant with this, protons are translocated across the mitochondrial membrane. This establishes the proton gradient which drives ATP generation.[5] The strobilurins share their inhibitory mode of action with the oudemansins and the myxothiazols, another class of fungal metabolite whose general form is shown in **Figure 1.3**.



1.3

R=Isoprene-derived system

Figure 1.3 - The general structure of the myxothiazol family, a class of respiratory inhibitor.

The strobilurins, the oudemansins and the myxothiazols are all derivatives of (*E*)-β-methoxyacrylic acid. This moiety is the "toxophore", that is the constituent which gives these metabolites their cytotoxic activity.[12] The (*E*)-β-methoxyacrylic acid moiety reversibly binds to the heme centre of the ubihydroquinone oxidation centre (Q_o) on cytochrome b.[11] Through a combination of genetic[13] and X-ray crystallographic studies,[11] it has been found that this binding results in a conformation restriction of the cytochrome bc complex. This slightly displaces ubiquinol from its binding site.[12] and prevents the transfer of electrons from cytochromes b and c_1. Hence, respiration is prevented.

Only (*E*)-β-methoxyacrylic acid-derivatives display any significant cytotoxicity, with the (*Z*) isomers not being cytotoxic.[14] Molecular orbital calculations have established that the minimum energy conformation for the natural (*E,Z,E*) triene has the planar phenylpentadienyl and β-methoxyacrylate groups positioned orthogonally to one another.[14,15] The synthetic (*all-E*) isomer adopts a radically different shape and cannot efficiently bind the cytochrome bc_1 centre. Calculations showed the oudemansins adopt a similar minimum energy conformation to that of the strobilurins, despite the flexibility imparted by the two sp^3 centres adjacent to the β-methoxyacrylate group.[15]

Obviously, the fungi which produce the strobilurins and other related respiratory-inhibitors have an inbuilt resistance to their cytotoxic effects. The mode of resistance has been shown to involve mutation of the ubiquinol binding site on the cytochrome b protein.[13] This mutation involves the substitution of a small amino acid (alanine) for a

larger amino (generally isoleucine) at position 127 of the binding envelope of the reduced ubiquinol moiety. The steric bulk at this position hinders the binding of the strobilurins and oudemansins, but not that of ubiquinol.[13] This mutation was found across a wide range of strobilurin- and oudemansin-producing fungi.

1.3 - The strobilurins as lead compounds for fungicide development[†]

Soon after Steglich and Anke's group first isolated strobilurin A,[2] it was tested at the National Cancer Institute for potential antitumour activity. While it displayed no acute toxicity in the tumour-bearing mice, it had only weak antitumour activity.[9] This ruled out its development as an anti-cancer agent. However, there are four main characteristics lead compounds for fungicide development must display :

- High fungal cytotoxicity
- Low toxicity to humans
- A novel mode of action
- A structurally-simple toxophore.

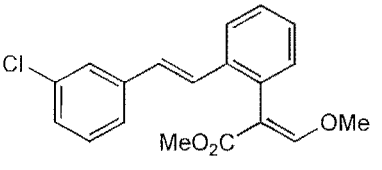
The strobilurins demonstrate all these characteristics and as such, they quickly drew the attention of agrochemical companies. The two main companies involved in the development of commercial fungicides based on the strobilurins are BASF and Zeneca (now Astra-Zeneca). In 1982 Zeneca obtained a sample of myxothiazol from Anke's group and trialed it in a standard greenhouse assay for fungicidal activity, where it performed admirably. However, when strobilurin A was trialed, it was essentially inactive against a range of fungi growing on whole plants in a greenhouse trial. This was in stark contrast to the high activity it displayed in a variety of *in vitro* assays. It was eventually determined its inactivity was due to a combination of photochemical degradation and loss through volatilisation.[13] In 1983 BASF entered

[†] Due to the commercial sensitivity associated with fungicide development, only one comprehensive review of the development of azoxystrobrin and kresoxim methyl has been published. The information in this section is sourced from Sauter, H.; Steglich, W.; Anke, T.; *Angew. Chem. Int. Ed.* **1999**, *38*, 1328-1349.

the field with trials of strobilurin A and encountered similar difficulties with a low activity against a range of fungi in greenhouse trials.

The extreme photolability of strobilurin A effectively ruled out its use as a fungicide. However, it was clear that the β-methoxyacrylate moiety imparted significant antifungal activity. Based on the efficacy of oudemansin in greenhouse trials it was clear that the β-methoxyacrylate moiety was not susceptible to photochemical cleavage. Thus, attention was focussed on creating analogues which retained the toxophore, while having greater photochemical stability.

Both the BASF and Zeneca groups quickly arrived at the stilbene structure **1.4**. The middle olefin in the triene system is locked by forming a ring. This proved to have higher activity in greenhouse tests, but was still subject to some photochemical breakdown.



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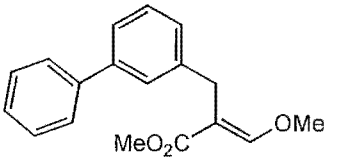

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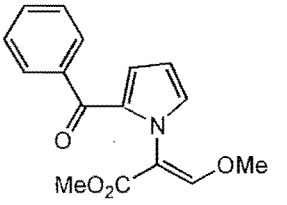
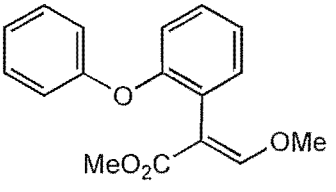


1.6

More stable variants of this core structure were prepared (**1.5** and **1.6**). These gave vast improvements in both greenhouse activity and photostability.

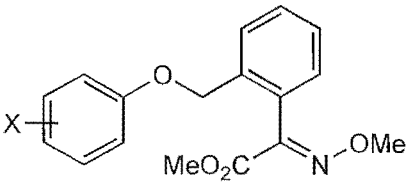


1.7

The key compound for the Zeneca team was the diphenyl ether **1.7**, which showed high photochemical stability, high activity in greenhouse trials and a broad range of antifungal activity. Additionally, it displayed systemic transport capabilities in plants,

which meant that it was readily solubilised and transported throughout the plants. This allowed more effective treatment at lower dosages. However, this was coupled with low level toxicity to some target plant species. Phenyl ether **1.7** formed the basis for a patent application filed by the Zeneca group in October 1984.[15] This covered a wide range of substituted arenes coupled to a β-methoxyacrylate group. This patent application preceded the earliest patents filed by BASF, by six months.[16a-d] These patents were broad enough to prevent further work by BASF on the β-methoxymethacrylates as a basis for fungicide development. Thus, the research group at Zeneca continued with the refinement of the carrier group for delivering the β-methoxymethacrylate group.

The BASF group was forced to find a way around the tight confines of Zeneca's patents. The only loophole in the patents was in the variation of the actual pharmacophore. Thus, they began a search for new target species which could adopt conformations isosteric to those of the β-methoxyacrylates. The β-methoxyacrylamide moiety seen in the myxothiazol class clearly demonstrates that variation in the substituents present on the toxophoric unit does not destroy activity. Another BASF group had previously conducted work in this area and found that oxime ethers of general type **1.8** and **1.9** showed considerable greenhouse activity. A patent was quickly filed.[17] The Zeneca team had also been working on oxime ether-type fungicides. Ironically, their patent application on this type of compound was filed only two days after that of the BASF team![18] An *in vitro* test was developed which measured the strength of docking between a cytotoxin and the cytochrome bc complex. This test showed that oxime ethers of general type **1.8** were around ten times more active than the isomeric class **1.9** in a wide range of *in vitro* tests. Such a result would be less clear in a greenhouse test, which contain more independent variables and often give less precise results.



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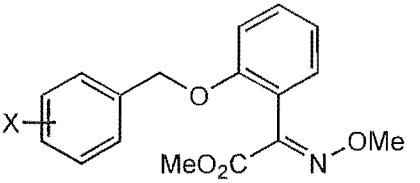
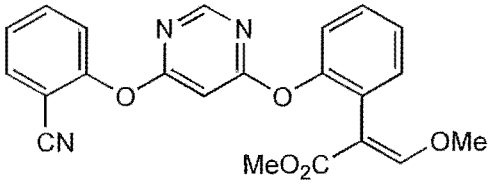


1.9

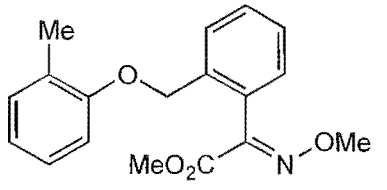
By early 1990, both the BASF and Zeneca teams had lead compounds which contained a viable toxophore and a general carrier structure. Both teams now turned their attention to the optimisation of the carrier portion. The Zeneca team focussed on the development of a carrier which allowed systemic transport of the fungicide, without any associated phytotoxicity. It was eventually found that a hetereoatom configuration like that in triaryl ether **1.10** optimised these two requirements.



1.10

Compound **1.10** showed an excellent cytotoxicity profile, systemic transport capabilities, and little associated phytotoxicity. It was named azoxystrobin and was first released onto the market in February 1996.

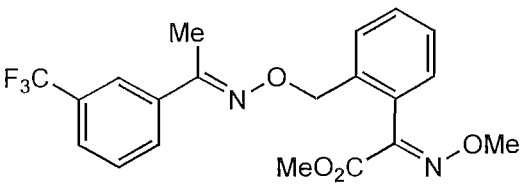
The BASF team had a somewhat shorter route to a commercially-viable fungicide. Aryl ether **1.11** gave an optimal balance of high fungicidal performance, combined with a cost-effective synthesis. Compound **1.11** was named kresoxim-methyl and was released onto the market in 1996, a few days before the release of azoxystrobin. Given the large number of strobilurin-producing fungi, it was clear that fungal species targeted by azoxystrobin or kresoxim methyl could, in time, develop resistance to their cytotoxic activities. To this end, both fungicides were sold as a mixture with other fungicides, to minimise the chance of mutations affording fungicidal resistance.



1.11

Two other companies have subsequently joined the race to develop commercial fungicides. Shinogi released the oxime-ether metominostrobin onto the Japanese market in 1998, primarily for the treatment of rice diseases.

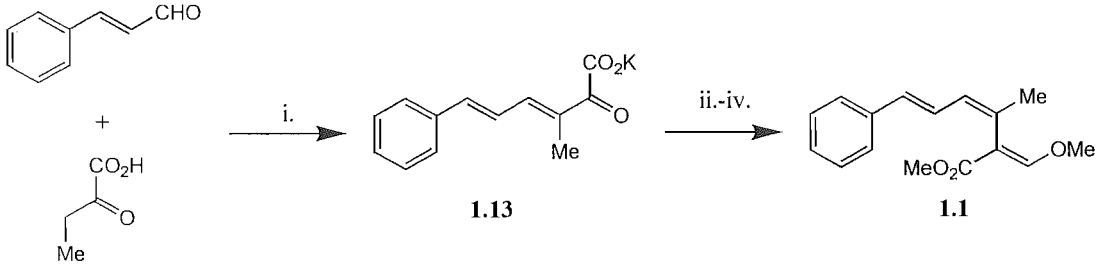
Novartis (formerly Ciba-Giegy) have developed the oxime ether trifloxystrobin (**1.12**), which is currently in the process of registration in the USA.



1.12

1.4 Previous synthetic work on the strobilurins

A large amount of synthetic chemistry has been undertaken with the aim of developing fungicides based around the strobilurin nucleus. However, comparatively little work has been performed on syntheses of members of the strobilurin family themselves. To date, total syntheses of strobilurins A, B, and E have been achieved. Most attention has focussed on strobilurin A due to its simplicity and role in fungicide development. The first synthesis was carried out by Steglich and Anke's group to try to confirm their proposed all-(*E*) stereochemical assignment for the triene system (see **Scheme 1.1**)[19,20] *E*-Cinnamaldehyde was coupled with the enolate of 2-ketobutyric acid to give diene **1.13**. This was converted to the methacrylate ester and the resultant trienoate subjected to photoisomerisation.

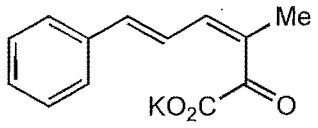


1.13 **1.1**

Reagents - i) KOH, ii) $SOCl_2$, MeOH, iii) Ph_3PCH_2OMe iv) *hv*

Scheme 1.1 - Steglich and Anke's synthesis of strobilurin A

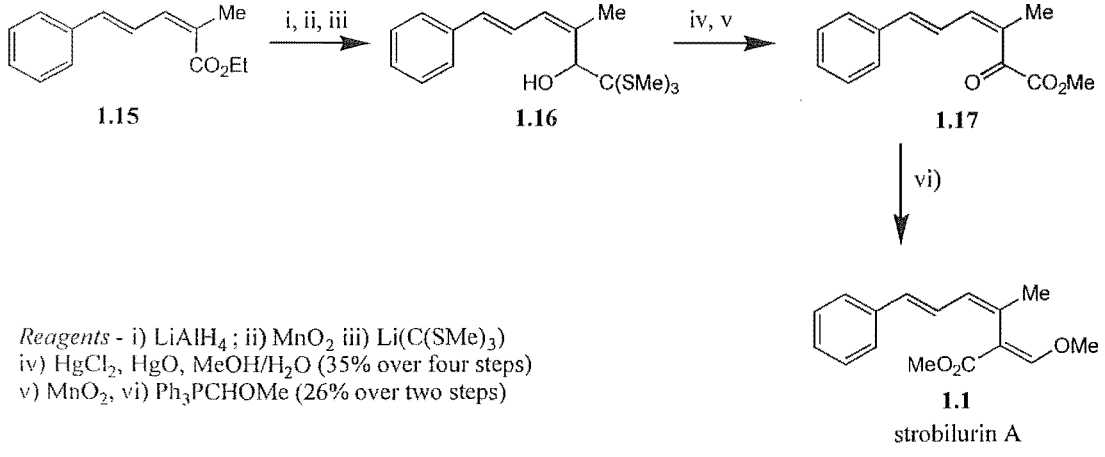
Originally, the authors thought that the initial alkylation had given diene **1.14** and that this species required isomerisation to form the desired all-(*E*) isomer.[19]



1.14

In fact, the alkylation had given diene **1.13**, which when subjected to photoisomerisation gave the (*E,Z,E*)-triene. The nmr data of which concurred with that of the natural product. These errors were subsequently corrected by the authors, when they republished the synthesis, with the correct stereochemical assignments.[20]

The first stereo-controlled synthesis of strobilurin A (**Scheme 1.2**) was carried out by the Zeneca group during their development of azoxystrobin.[14,15] The (*Z,E*)-dienoate **1.15** was chosen as the starting material. As all four possible isomers had been characterised, its configuration could be assigned with certainty. Dienoate **1.15** was converted to dienol **1.16**, *via* conversion to the aldehyde and addition of tris(thiomethyl)lithium. Methanolysis, to give the methyl ester, was followed by oxidation to the ketone **1.17**. Reaction of methoxymethyltriphenylphosphorane with ketone **1.17** gave strobilurin A (**1.1**). This was achieved in 9.2% overall yield from the dienoate **1.15**.



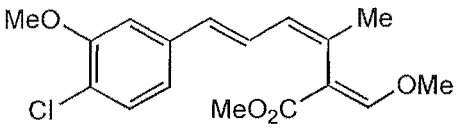
1.15 **1.16** **1.17**

1.1
strobilurin A

Reagents - i) $LiAlH_4$; ii) MnO_2 iii) $Li(C(SMe)_3)$
iv) $HgCl_2$, HgO, $MeOH/H_2O$ (35% over four steps)
v) MnO_2, vi) $Ph_3PCHOMe$ (26% over two steps)

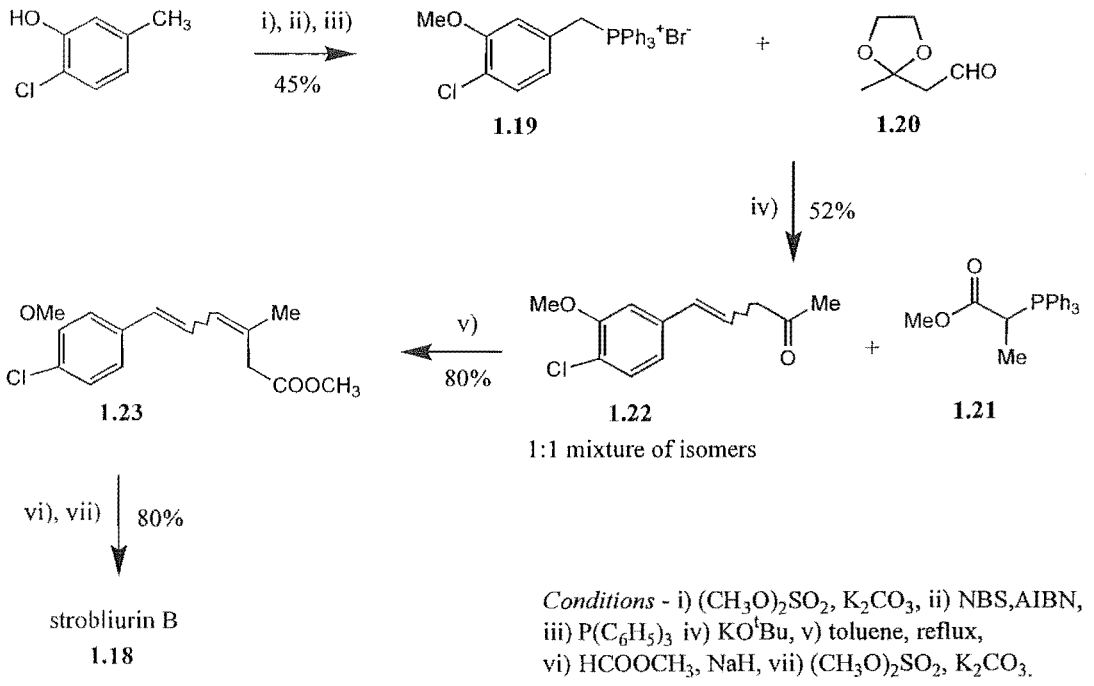
Scheme 1.2 - Clough *et al.*'s stereo-controlled synthesis of strobilurin A

Strobilurin B (**1.18**) was synthesised by Sutter working at Ciba-Giegy (now Novartis) as detailed in **Figure 1.19** .[21]



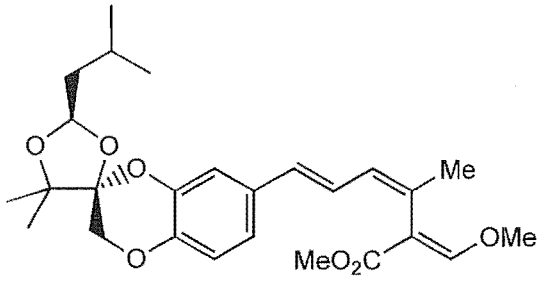
1.18
strobilurin B

The phosphonium salt **1.19** was formed *via* a sequence of alkylation, radical bromination and phosphine addition starting from 2-chloro-4-methylphenol. The chain was extended using Wittig chemistry. The reaction of phosphonium salt **1.19** with the acetal-protected butyraldehyde **1.20** gave a 1:1 mixture of the *E* and *Z* isomers of the alkene. This acetal was deprotected to give an isomeric mixture of ketone **1.22**. This ketone was subjected to another Wittig coupling with phosphorane **1.21** to give dienoate **1.23**. This was formylated at the α-position relative to the ester. Ester **1.23** was enolised, and the resultant enol *O*-methylated, to give the β-methoxymethacrylate moiety and thus, the complete triene system. As there is a 1:1 mixture formed in step iv), the overall yield of the desired (*E,Z,E*) isomer was only 4.5% ; in addition to an equal amount of the all-*E* isomer.



Scheme 1.3 - Sutter's synthesis of strobilurin B

The only other total synthesis of a strobilurin that has been completed is Steglich and Anke's synthesis of the structurally-complex strobilurin E (**1.24**).[22]

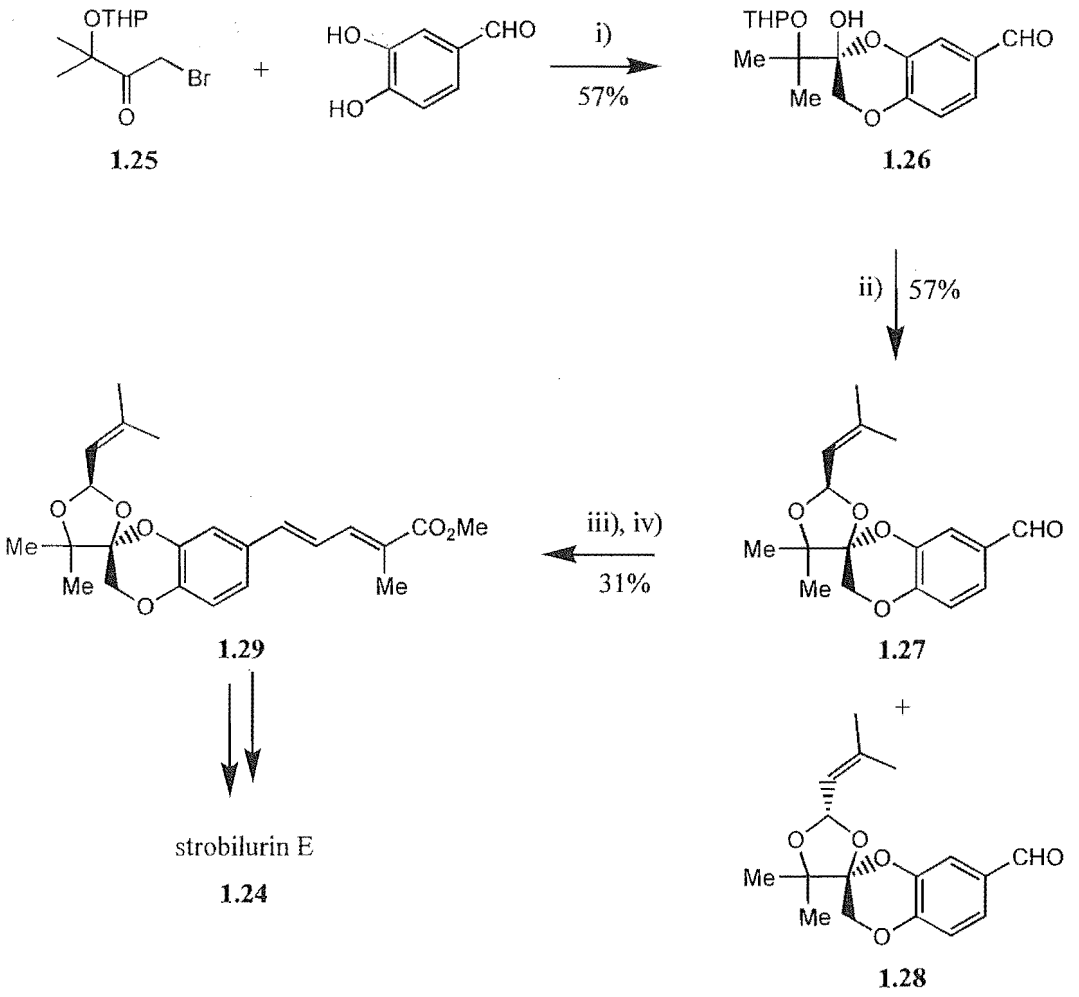


strobilurin E
1.24

The distinguishing structural feature of this strobilurin is the spiroacetal ring system adjoined to the arene ring. Clearly, a synthetic approach was required which avoided acidic conditions after the spiroacetal was formed. In Steglich and Anke's synthesis (shown in **Scheme 1.4**), the spiroacetal was constructed in two steps. 3,4-Dihydroxybenzaldehyde was alkylated, using bromoketone **1.25**, to give the desired six-membered ring hemiacetal **1.26**, with the appropriate regiochemistry. The tetrahydropyran protecting group was removed and the resultant diol reacted with 3-

methylbutenal under acid catalysis to give the desired spiroacetal **1.27** in 57% yield, along with 43% of the diastereomeric spiroacetal **1.28**.

Steglich and Anke's approach to the triene system centred around the use of Wittig-type homologations to extend the carbon skeleton. Non-stabilised phosphoranes were used so as to favour the formation of the *E*-olefin. The first olefinic unit was formed *via* the reaction of spiroacetal **1.27** with formylmethylenetriphenylphosphorane to give the desired enal in 36% yield. This enal was converted to dienoate **1.29** in 86% yield *via* another Wittig homologation. Finally, the β-methoxyacrylate was installed *via* a Wittig reaction of dienoate **1.29** with methoxytriphenylphosphorane to give the all-(*E*) stereoisomer. This material was then photoisomerised in 80% yield to give the correct (*E,Z,E*) stereochemistry.



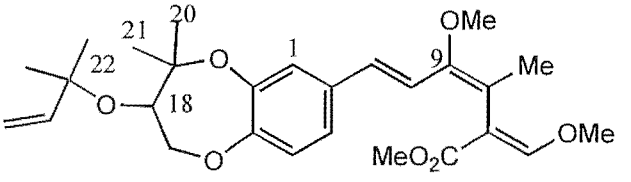
i) K_2CO_3, ii) 3-methylbutenal, cat. PPTS,
iii) $Ph_3PCHCHO$, iv) $Ph_3PCHOCH_3$

Scheme 1.4 - Key steps in Steglich and Anke's synthesis of strobilurin E

This synthesis highlights the difficulties associated with the use of the Wittig methodology for developing the triene system of the strobilurins. Although the (*E,E,E*)- triene system was able to be elaborated without disrupting the spiroacetal, the three Wittig reactions proceeded in a combined yield of only 11.1%. Principally, this is as a result of the low-yields of the desired *E* isomer during the Wittig reactions.

1.5 The structural revision of strobilurins K and D

Recent work at the University of Canterbury has centred around the isolation of biologically-active natural products from New Zealand terrestrial fungi.[23] In 1994 the basidiomycete *Favolaschia calocera* was investigated as part of an M.Sc thesis. It was found to contain a isoprenoid-derived cytotoxic product, which was named 9-methoxystrobilurin L and assigned structure **1.30**. There were two crucial pieces of evidence which supported this putative structure; an HMBC correlation seen from C-22 to H-18, and an nOe correlation from C-21 to C-22 to C-1 on the aromatic ring.

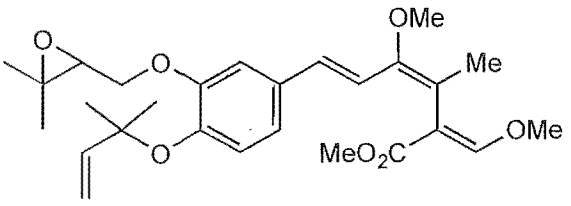


9-methoxy strobilurin L

1.30

Figure 1.4 - Nicholas *et al.*'s proposed structure for 9-methoxystrobilurin L

Concurrent with this work, Steglich's group. published an account detailing the isolation of 9-methoxystrobilurin K from an unidentified Ethiopian fungus of the *Favolaschia* genus.[24] HREIMS analysis, combined with extensive two-dimensional nmr analysis, led to 9-methoxystrobilurin K being assigned structure **1.31**.

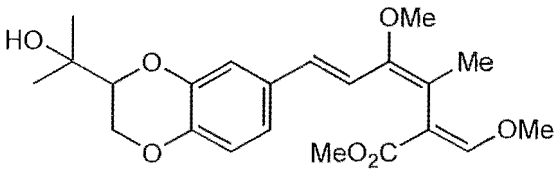


9-methoxystrobilurin K

1.31

Figure 1.5 Steglich *et* al's proposed structure for 9-methoxystrobilurin K.

In 1996 Wood *et al.* investigated Ethiopian fungus *Favolaschia pustulosa* and reported the new strobilurin 9-methoxystrobilurin L (**1.32**).[25]



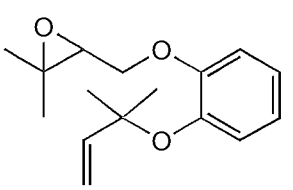
9-methoxy Strobilurin L

1.32

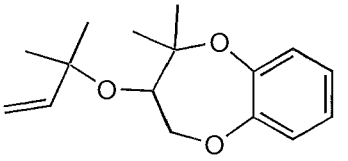
Figure 1.6 - Wood *et al.*'s proposed structure for 9-methoxystrobilurin L

The spectroscopic data for both of these compounds were found to be identical to those of the compound isolated by Nicholas *et al.* at the University of Canterbury. Clearly, two of the proposed structures were incorrect. Two-dimensional nmr studies carried out by Nicholas *et al.* allowed them to discount Wood proposed structure. When an HMBC experiment was performed upon their sample in $CDCl_3$, a correlation was seen from H18 to C22. This correlation effectively ruled out Wood proposed dioxane structure (**1.32**). Wood had performed their HMBC experiments in MeOD. When this was repeated by Nicholas *et al.*, the key correlation from H18 to C22 was not observed due to the presence of an overlapping T_1 noise ridge. This meant that either Nicholas's, or Steglich's proposed structure of 9-methoxystrobilurin K was the correct one.

In an thorough piece of follow-up work,[27] Nicholas *et al.* conclusively proved that their proposed benzodioxepin structure **1.30** was the correct structure of 9-methoxystrobilurin K, and that 9-methoxystrobilurin K and 9-methoxystrobilurin L were the same compound. This was achieved by preparing a model system of their proposed benzodioxepin structure (**1.33**) and a model of Steglich *et al.*'s proposed structure (**1.34**). The preparation of these model fragments will be discussed further in **Chapter 2.**



1.33

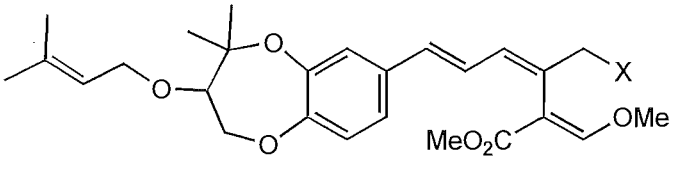


1.34

Figure 1.7 - Model fragments of the two possible structures of 9-methoxystrobilurin K

The ^{1}H and ^{13}C nmr data for fragment **1.33** were inconsistent with those published for the natural product. Principally, the epoxide carbons in **1.33** gave significantly different chemical shifts from those observed in the ^{13}C spectrum of the natural product. Contrastingly, fragment **1.34** gave ^{1}H and ^{13}C nmr data which were consistent with those observed in the natural product. This finding, combined with the previous nmr-based arguments, indicated that the correct structure for 9-methoxystrobilurin K was **1.30**.

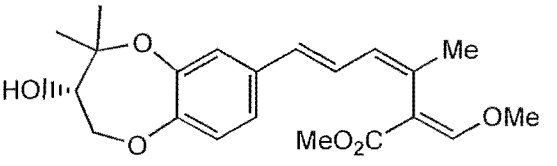
Nicholas *et al.* proposed that the structures of strobilurin D (**1.35**)[28] and hydroxystrobilurin D (**1.36**)[29] were also incorrect Both had previously been assigned the epoxyprenyl structure shown in **1.33**. Inspection of their ^{1}H and ^{13}C data suggested that the benzodioxepin ring system was present



strobilurin D X=H **1.35**

hydroxystrobilurin D X=OH **1.36**

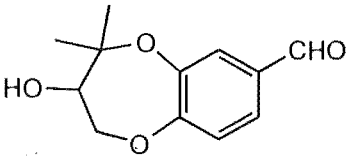
Concurrent with the work discussed in this thesis, Steglich and Anke's group published a paper detailing the isolation, structural assignment and stereochemistry of strobilurin I (**1.37**).[30]



strobilurin I

1.37

The triene system was degraded by ozonolysis to give the corresponding benzodioxepin carbaldehyde **1.41**. Stereoselective syntheses of both the R and S-enantiomers of this moiety allowed the confirmation of the stereochemistry of the natural product.



1.41

Cinnamate **1.38** was obtained from ethyl 3,4-dihydroxycinnimate *via* alkylation and epoxidation. The benzodioxepin was formed by a Lewis acid-catalysed cyclisation of cinnamic acid derivative **1.38**, which proceeded in 20% yield. Benzodioxepin **1.39** was oxidised to the corresponding benzodioxepinone **1.40** in 59% yield. This was subjected to a stereoselective reduction using Corey's oxazaborolidine methodology.[31] This technology allowed both enantiomers to be developed. Ozonolysis of the resultant alcohols gave the desired alcohols, (R)- and (S)-**1.41**. Derivatisation with (R)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetyl chloride (MTPA-Cl)[32] and analysis using Mosher's method[32] showed that the natural alcohol possessed the S stereochemistry.

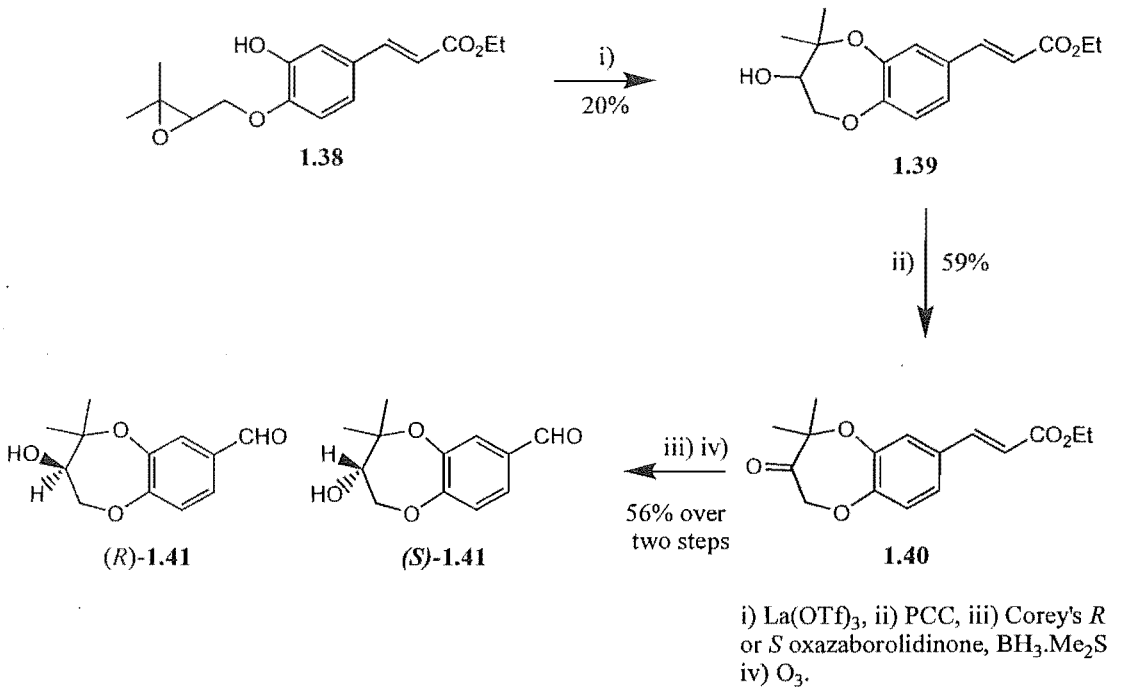
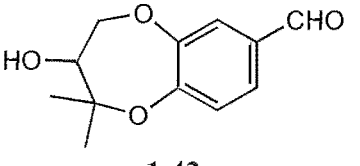


Figure 1.8 - Key steps in Steglich and Anke's stereo-controlled synthesis of the benzodioxepin core of strobilurin I.

In this paper, Steglich and Anke also confirmed the regiochemical arrangement of the *gem*-dimethyl groups present on the dioxepin ring. Nicholas *et al.* had based their assignment of the methyl groups' position on an nOe correlation, but there had been some conjecture as to the accuracy of the assignment.[26] The regioisomeric benzodioxepin **1.42** was prepared and GC-MS comparison showed this to be different to *rac*-**1.41**



1.42

Although it was not discussed by the authors, it is clear that alcohol **1.39** could serve as an effective model system for a synthesis of 9-methoxystrobilurin K. If the methyl cinnamic ester was employed as the starting material, Wittig-based methodology similar to that employed in the synthesis of strobilurin E could potentially lead to the complete 9-methoxytriene system.

1.6 Synthetic strategy

The syntheses in **Section 1.4** demonstrate that while the strobilurin triene system can be generated, the methods employed to date are not entirely satisfactory. Clearly, there are stereochemical issues with the Wittig-based methodology and although the correct stereochemistry of the natural product is attainable *via* photoisomerisation of the all (*E*)-stereochemistry, it would be aesthetically more pleasing if a controlled route to the (*E,Z,E*) triene could be established. Additionally, there have been no syntheses of the 9-methoxy- or 13-hydroxystrobilurins. Thus, methodology which allowed the construction of either of these fragments would be desirable. The 9-methoxystrobilurin sidechain poses the additional problem of the tetra-substituted double bond between carbons 9 and 10, this bears four unique substituents and as such presents considerable stereo- and regiochemical challenges in its construction.

The synthetic strategy for the preparation of 9-methoxystrobilurin K can be divided into two main parts - the synthesis of the functionalised 1,5-benzodioxepin ring adjoined to the arene ring and the synthesis of the triene system. The key disconnections in the retrosynthetic analysis and the associated target fragments are shown in **Figure 1.9**. Literature precedent exists for the generation of benzodioxepin ring systems *via* a Lewis acid-catalysed attack of a phenol on an epoxide, in this case epoxide **1.42**.[33,34] After cyclisation, and with appropriate protection of the alcohol moiety present on the benzodioxepin ring, the aryl aldehyde moiety could be elaborated to the aryl alkyne (fragment **1.43**) using the Corey-Fuchs homologation.[35]

Methoxypropyne (**1.44**) can be prepared from commercially available chloroacetaldehyde dimethoxy acetal *via* elimination, to give the alkynyl anion. Methylation of this species would then give methoxypropyne.[36] Fragment **1.45** (methyl-2-bromo-3-methoxypropenoate) has been prepared using a Stille coupling between methyl-*E*-2,3-dibromopropionate and tributytinmethoxide.[37]

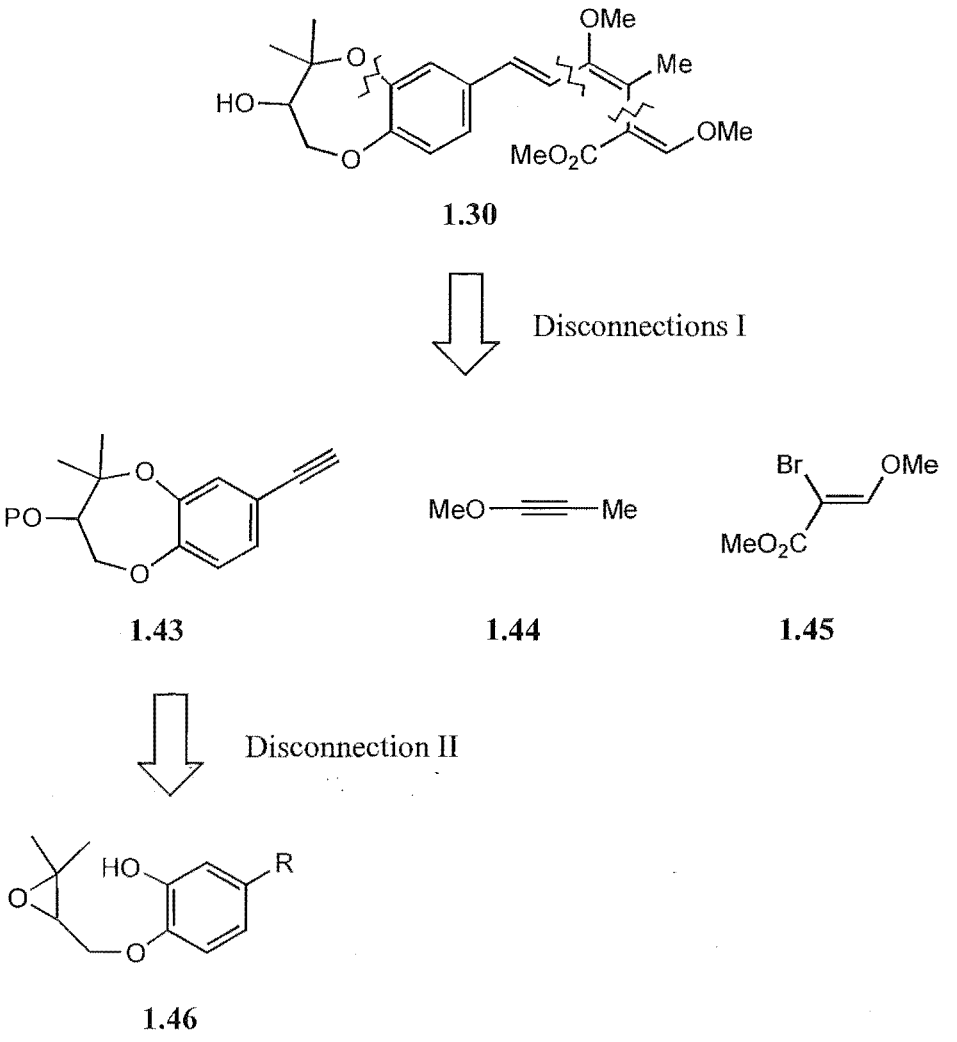
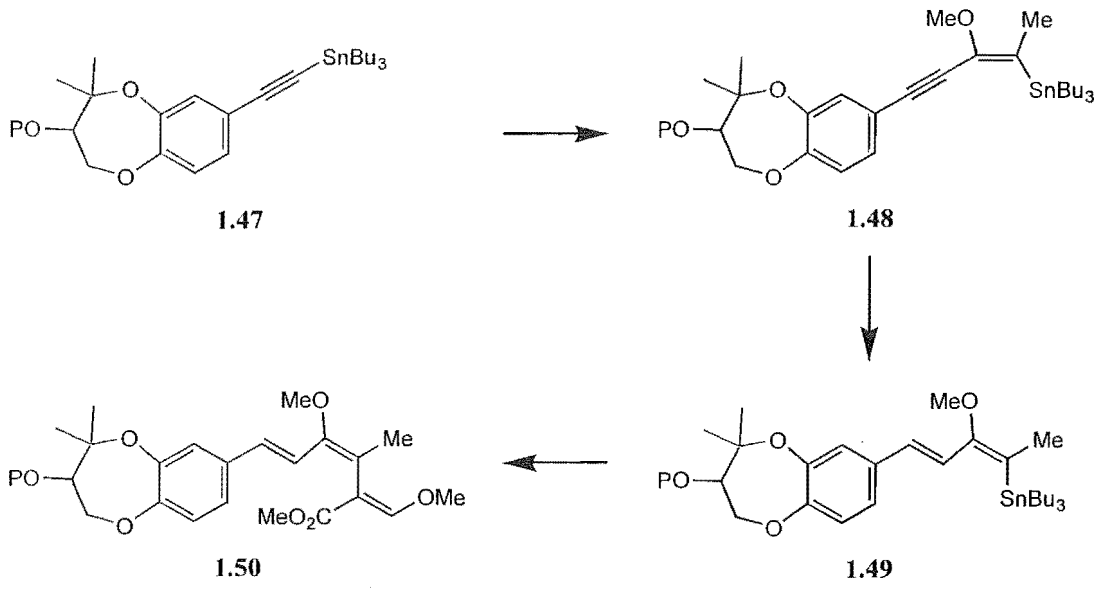


Figure 1.9 Disconnection of 9-methoxystrobilurin K

The strategy to be employed for coupling the fragments is shown below. It centres around carbostannylation of methoxypropyne with alkynyl stannane **1.47**. Shirakawa *et al.* have shown that Pd-catalysed aryl alkyne carbostannylation with alkoxypropynes proceeds in high yield to give an alkene with the alkoxy unit and the tributyltin groups on different carbons.[38] Thus, stannane **1.47** could be converted ether **1.48**. Reduction of the alkyne should give diene **1.49** and this could be coupled *via* a Stille-type coupling to methacrylate **1.45** to afford the protected version of 9-methoxystrobilurin K (**1.50**). Stannane **1.47** should be readily generated from the alkyne **1.43**



Scheme 1.5 - Coupling strategy to be employed for development of the 9-methoxystrobilurin side chain.

One of the strengths of this approach is that by changing the partner used for the carbostannylation the regiochemistry of the carbostannylation process can be reversed. Shirakawa *et al.* showed that methyl propiolate underwent carbostannylation in the opposite direction to that of alkoxypropynes.[38] An aryl alkynyl stannane should carbostannylate methyl propiolate to give an alkene with the ester moiety and the tributylstannane on the same carbons. Applying this to alkynyl stannane **1.47**, carbostannylation with methyl propiolate should give ester **1.51** (**Figure 1.10**). Reducing the ester to the alcohol and coupling with methacrylate **1.45** would afford the hydroxystrobilurin sidechain. This means that all known strobilurin side chains can be generated form the same alkynyl stannane. Routes to the triene system are under investigation by another student in the Morris research group.

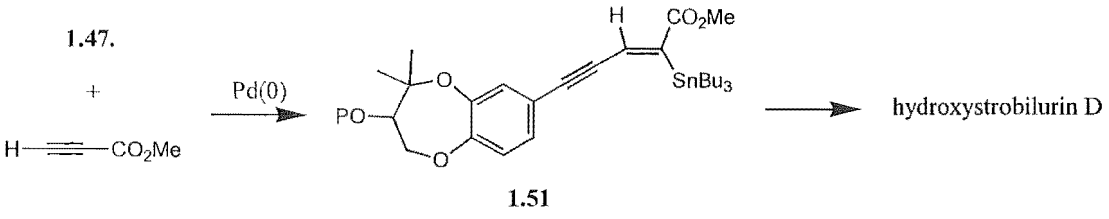


Figure 1.10 - The key coupling step in the preparation of the hydroxystrobilurin sidechain

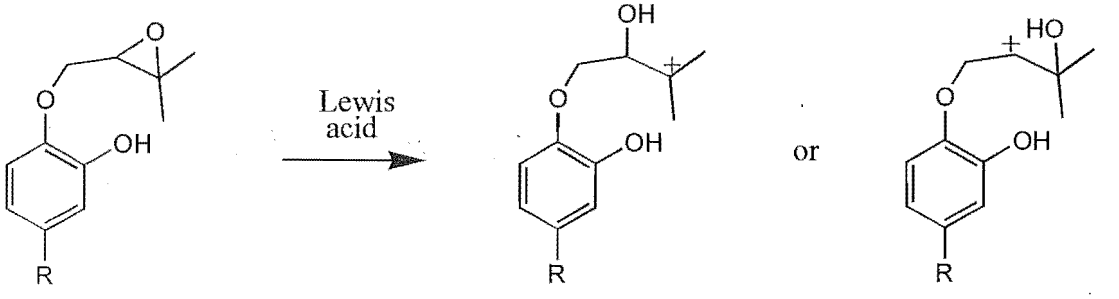
One of the major synthetic challenges posed by the strobilurin family is the preparation of the functionalised seven-membered benzodioxepin ring seen in strobilurins D, K and I. To the best of the author's knowledge there have only been two previous synthesis of this structural feature.[30,33,34] Both of these have involved a Lewis acid-catalysed epoxide opening as the key step for forming the dioxepin ring. The other two fragments required for this synthesis (**1.43** and **1.44**) can be prepared by literature methods. [36,37] However, alkyne **1.43** has not previously been prepared, and as such its synthesis offers the opportunity to test, and possibly extend, current synthetic methodology. This thesis deals with approaches to the construction of the benzodioxepin ring seen in some members of the strobilurin family. Coupled with this, is the chance to provide absolute confirmation of the proposed benzodioxepin structures of strobilurin D and hydroxystrobilurin D by achieving total syntheses of these materials.

Chapter Two

Lewis Acid-Mediated Benzodioxepin Formation

2.1 Introduction

Epoxides are a useful functionality for generating a wide range of oxygen-containing functionalities. Epoxides fragment when exposed to Lewis acids. Lewis acids lower electron-density on the oxygen atom and polarise the carbon-oxygen bond, making the carbon atom considerably more electrophilic. If the Lewis acid is strong enough, the carbon-oxygen bond can be polarised enough for it to cleave, thus giving a trigonal carbocation. Intramolecular nucleophilic attack by an oxygen atom on this pseudo-sp^2 centre can then result in the formation of an ether linkage. As discussed in Chapter 1 literature precedent exists for constructing benzodioxepin ring systems *via* a regioselective Lewis acid-catalysed opening of an epoxide of the general type **2.4**, in effect a 7-*exo*trig cyclisation.[39]



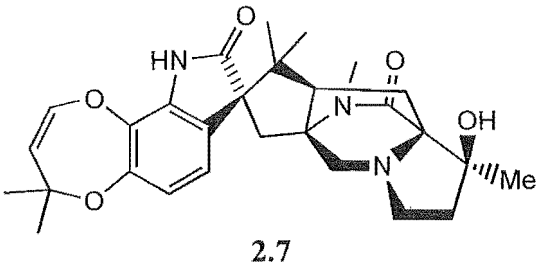
2.4 **2.5** **2.6**

Figure 2.2 - Products of ionisation of epoxide **2.4**

The Lewis acid can ionise the epoxide to give either the secondary, or tertiary carbocation. Ionisation to the more stabilised tertiary carbocation and attack by the phenol would result in the desired benzodioxepin.

2.2 - Paraherquamide B Studies

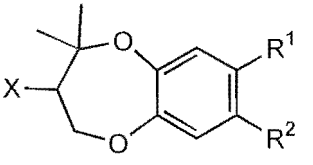
The first reported use of a Lewis acid-catalysed epoxide rearrangement for forming a functionalised benzodioxepin was by Williams and co-workers in their development of a synthetic route towards the mycotoxic mould metabolite, Paraherquamide B (**2.7**).[33,34]



2.7

This complex natural product contains a functionalised oxindole fused to a benzodioxepin system on its western side. This structural feature had not previously been synthesised.

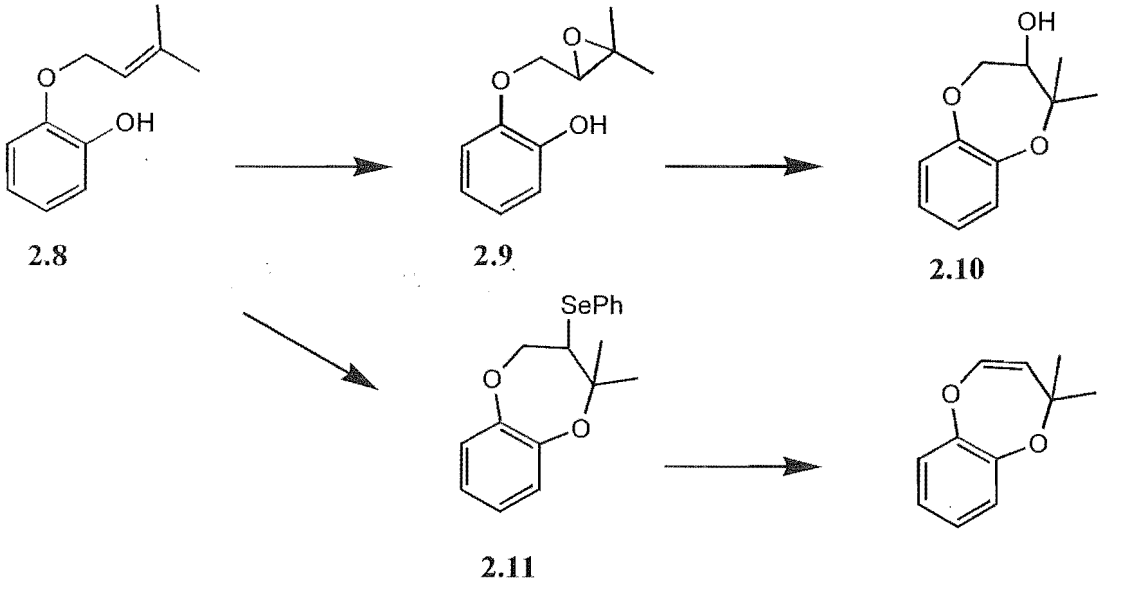
William decided to synthesise a precursor such as that shown below as it was reasoned that this compound could be easily converted to the desired alkene.



A range of simple model systems were studied to determine the most effective cyclisation strategy.[34] Attention was focussed on the key cyclisation reaction as it was expected that dehydration of the benzodioxepin would be relatively straight-forward. Two strategies were adopted for cyclising aryl alkene **2.8** as outlined in **Figure 2.5**. The first strategy involved a selenium-assisted carbocation formation. It was thought that the electrophilic selenium species would undergo addition to the alkene to yield the more stable tertiary carbocation, whereby intramolecular attack by the phenol would then give the benzodioxepin **2.11**. However, when **2.8** was reacted with (*N*-phenylseleno)phthalimide (*N*-PSP), the principal products arose from electrophilic aromatic substitution by the selenium species, with an overall yield of only 3% of the

desired selenobenzodioxepin **2.11**. Due to this low yield, this method was abandoned. Interestingly, other substrates reacted in an efficient manner under these conditions.

The alternative cyclisation strategy employed by Williams *et al.* involved a Lewis acid-catalysed epoxide rearrangement. Epoxide **2.9** was reacted with a stoichiometric amount of $SnCl_4$ to give the desired seven-membered ring **2.10** in 59% yield, This clearly showed that benzodioxepins could be constructed by this type of methodology.



2.8 **2.9** **2.10** **2.11**

Figure 2.3 - Williams *et al.*'s cyclisation strategies towards a functionalised benzodioxepin.

This work was repeated by Nicholas *et al.* to prepare the alcohol **2.10** so as to allow confirmation of their proposed structure of 9-methoxystrobilurin K (*see* **Section 1.5**). However, using the reported cyclisation conditions gave the benzodioxepin in less than 20% yield.[41] Despite extensive repetition with careful attention to Williams *et al.*'s experimental conditions, the benzodioxepin **2.10** could only be obtained in 23% yield.[26]

A range of other aryl systems were also studied to determine the effect of the substituents present on the arene upon the key cyclisation reaction. One model system that was investigated used the electron-poor arene *o*-nitrovanillin **2.12**. This was

demethylated and alkylated using K_2CO_3 and 4-bromo-3-methylbut-2-ene, ("prenyl bromide") as shown in **Figure 2.4**. The regiochemistry of the desired oxindole required alkylation at the 3-hydroxyl group. However, the 3-hydroxyl and 4-hydroxyl groups have very similar acidities. The electron-delocalising effects of the nitro group stabilise the 3-phenoxy ion, while the electron-delocalising effects of the aldehyde stabilise the 4-phenoxy ion. Thus, prenylation gave only a 20% yield of the desired 3-alkyl product (**2.14**), with the principal by-products being the 4-alkyl and 3,4-dialkyl products.

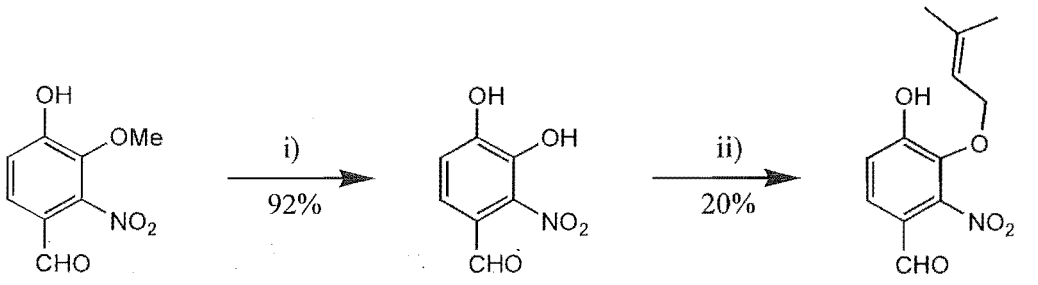
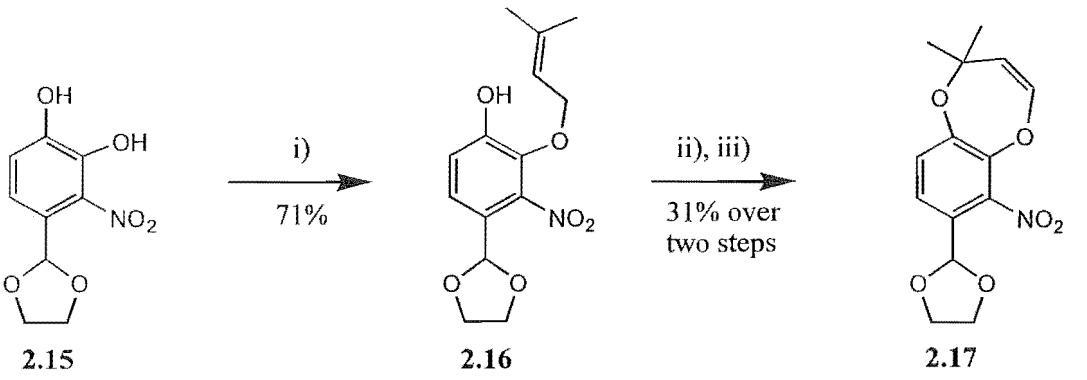


Figure 2.4 - Williams *et al.*'s initial approach to a model system for cyclisation studies .

Clearly, the substrate had to be altered so that there was a difference in the acidity of the two hydroxyl groups. Towards this end, the aldehyde was masked as the cyclic acetal **2.15**, which removed the ability of the aldehyde to stabilise the 4-phenoxy ion, and hence, decreased the acidity of the 4-hydroxyl group. With this change, the selective prenylation of **2.15** proceeded in 71% yield to give alkene **2.16**.

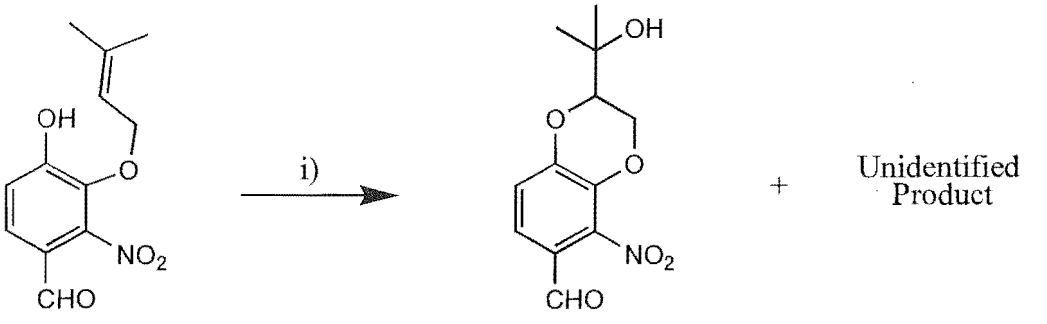
Two approaches were attempted for the key cyclisation of alkene **2.16**. The first involved a selenium-assisted cyclisation using (*N*-phenylseleno)phthalimide and acid catalysis. This gave the selenide, which was eliminated using treatment with *m*CPBA and heating to give benzodioxepin **2.17** in 42% yield over two steps.



2.15 **2.16** **2.17**

Conditions - i) prenyl bromide, K_2CO_3
ii) *N*-PSP, iii) mCPBA

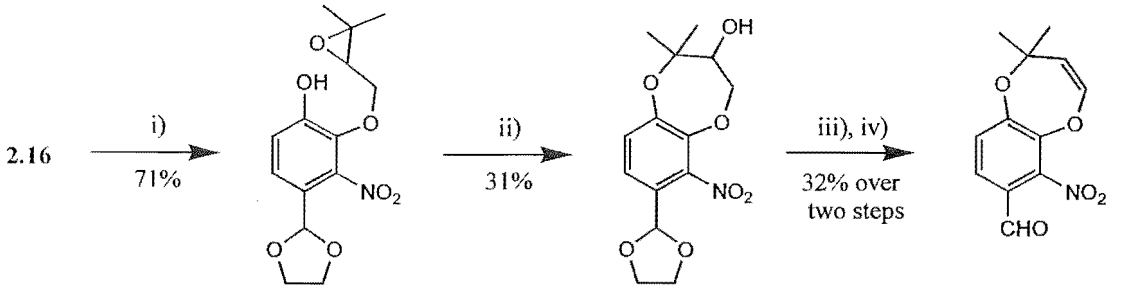
The other approach involved a $SnCl_4$-catalysed cyclisation like that used to construct the simple arene **2.10**. Epoxidation of acetal **2.16** using *m*CPBA proceeded quantitatively. However, when the same conditions were applied to the deprotected aldehyde **2.14**, two products were isolated; the tertiary alcohol dioxane **2.18** and an unidentified side-product.



2.14 **2.18**

Conditions:- i) mCPBA

Due to this side-reaction, the acetal-protected epoxide **2.19** was chosen as the cyclisation substrate. This was reacted with $SnCl_4$ to give the benzodioxepin **2.20** in modest yield (31%), which was deprotected (74%) and dehydrated (43%) to give the target benzodioxepin **2.21**.

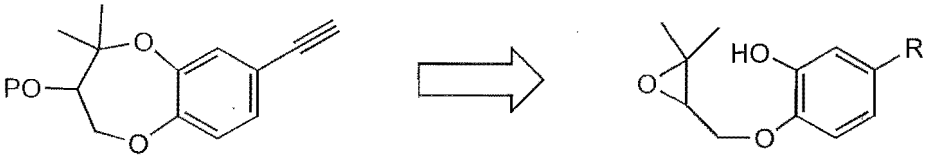


2.19 **2.20** **2.21**

Reagents:- i) mCPBA, ii) $SnCl_4$, iii) 5% HCl
iv) methyl triphenoxy phosphonium iodide

2.3 - Synthetic Strategy

The target of the work discussed in this thesis is the alkynyl benzodioxepin **1.43**. It is clear that dioxepins can be formed *via* Lewis acid-catalysed rearrangement of acyclic epoxides. To trial this strategy an epoxide such as **1.46** was required



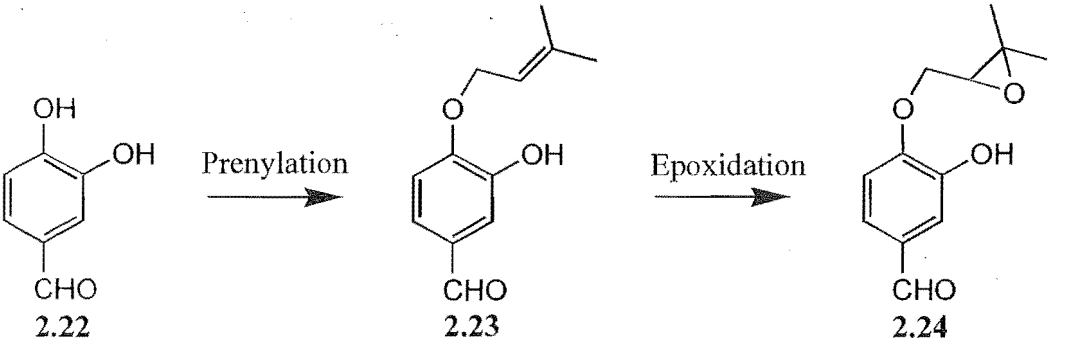
1.43 **1.46**

Our strategy calls for the introduction of the alkyne after the formation of the dioxepin. As such, the R group present in epoxide **1.46** had to be stable to the cyclisation conditions and allow for the introduction of the alkyne after the cyclisation.

The epoxide moiety in **1.46** can be prepared by epoxidation of the corresponding alkyl ether. One method for constructing aryl ethers is *via* the Williamson reaction of an alkyl halide with a phenoxide. In this case, the reaction of commercially available 4-bromo-2-methylbut-2-ene with the appropriate aryl alkoxide should afford the aryl ether.[30] The regiochemistry of the target strobilurin dictates that the 4-alkoxy species is the regioisomer required to form the desired benzodioxepin.

Commercially available 3,4-dihydroxybenzaldehyde (**2.22**) neatly solves both of these problems. As previously discussed (see **Section 1.6**), the presence of the aryl aldehyde is satisfactory for later introduction of the alkyne moiety using the Corey-Fuchs homologation.[35] Additionally, the desired 4-alkoxy species should be selectively generated due to the 4-hydroxyl group being considerably more acidic than the 3-hydroxyl group because of the electron-delocalising effects of the aldehyde. In this substrate, the 4-hydroxyl group has a pK_a of 7.2, while the 3-hydroxyl is noticeably less acidic (pK_a= 11.8), so reaction with one equivalent of base would allow for selective alkylation.

Based on this, the initial target for cyclisation studies was epoxide **2.24**. The strategy employed for its synthesis is shown below.



2.4 Synthesis of an aryl aldehyde-functionalised epoxide as a substrate for cyclisation studies

Synthesis of the aryl epoxide **2.24** began with the alkylation of commercially available 3,4-dihydroxybenzaldehyde, using the method of Dasenbrock and co-workers.[30] A solution of 3,4-dihydroxybenzaldehyde in DMF at 0^0C was treated with one equivalent of K_2CO_3 and excess prenyl bromide. Stirring at room temperature for 18 hours gave the desired alkene **2.23** in 74% yield. The ^{1}H nmr spectrum of this species was relatively simple as can be seen from **Figure 2.15**.

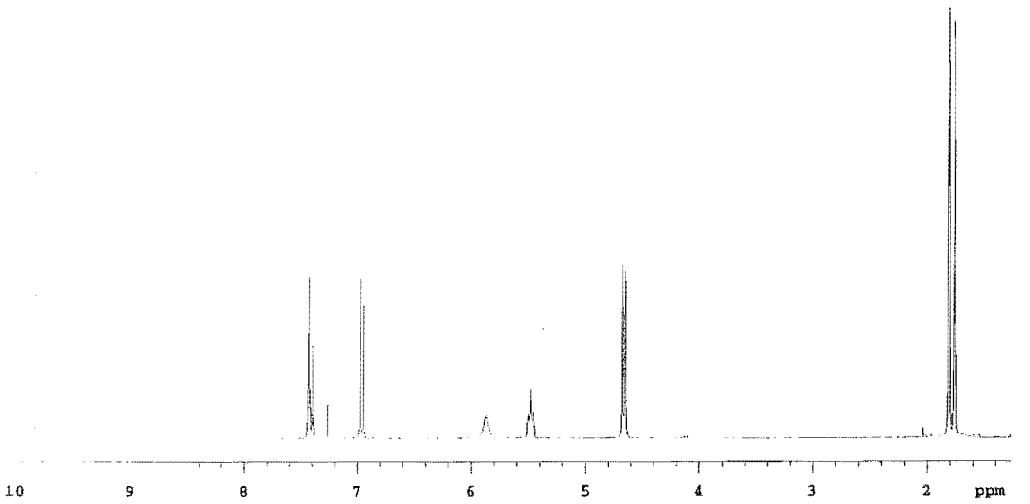
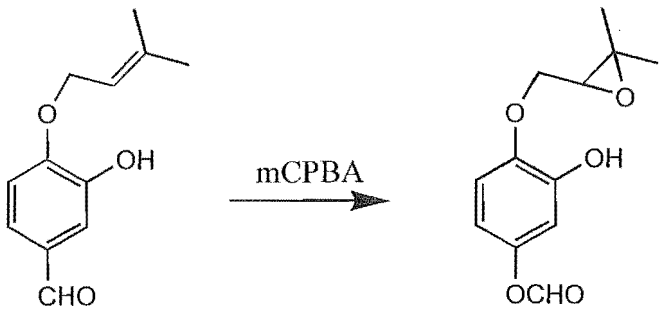


Figure 2.5 - 300MHz ^{1}H nmr spectrum of alkene 2.23

The triplet centred around 5.50 ppm corresponds to the alkenyl methine on the prenyl chain, while the doublet at 4.60 ppm corresponds to the prenyl methylene group. The two methyl moieties are present as two singlets at 1.80 and 1.75 ppm.

Initial attempts at converting alkene **2.23** to epoxide **2.24** involved reaction of the alkene **2.23** with one equivalent of *meta*-chloroperbenzoic acid in CH_2Cl_2 at room temperature for 16 hours.[26,27] A significant change in the ^{1}H nmr spectrum of the crude reaction material was the disappearance of the aldehyde signal at 9.80 ppm of the starting material. In its place was a new singlet at 8.20 ppm which integrated for one proton.. This suggested that a formate ester such as **2.25** had been formed by a Baeyer-Villiger oxygen insertion into the arene-aldehyde bond.[42] This is interesting in the light of Williams *et al.* observing a "mystery product" when attempting the buffered epoxidation of aryl aldehyde **2.14** using *m*CPBA.[34] It seems plausible that this was a formate ester. In addition to the formate ester, a small amount of the desired epoxide was present.



2.23 **2.25**

Reasons for the preferential Baeyer-Villiger oxidation can be gleaned by looking at a mechanism for the Baeyer-Villiger rearrangement.[42] Using benzaldehyde as a model, the mechanism is illustrated in **Figure 2.6**. It is thought that the first step in the reaction involves the ionisation of the carbonyl group to give a carbocation. This electrophilic centre undergoes peresterification with *m*CPBA. Migration of the phenyl group by nucleophilic attack on one of the peroxide oxygens, with concomitant loss of the free acid, gives a hemi-acetal. Loss of a proton yields the ester as the final product. It has been shown that the rate-determining step in the rearrangement is the migration step and this is concerted with peroxide cleavage.[42] Given that both Baeyer-Villiger oxidation product **2.25** and epoxide **2.24** were formed, it would seem that the migration step and epoxidation occur at similar rates.

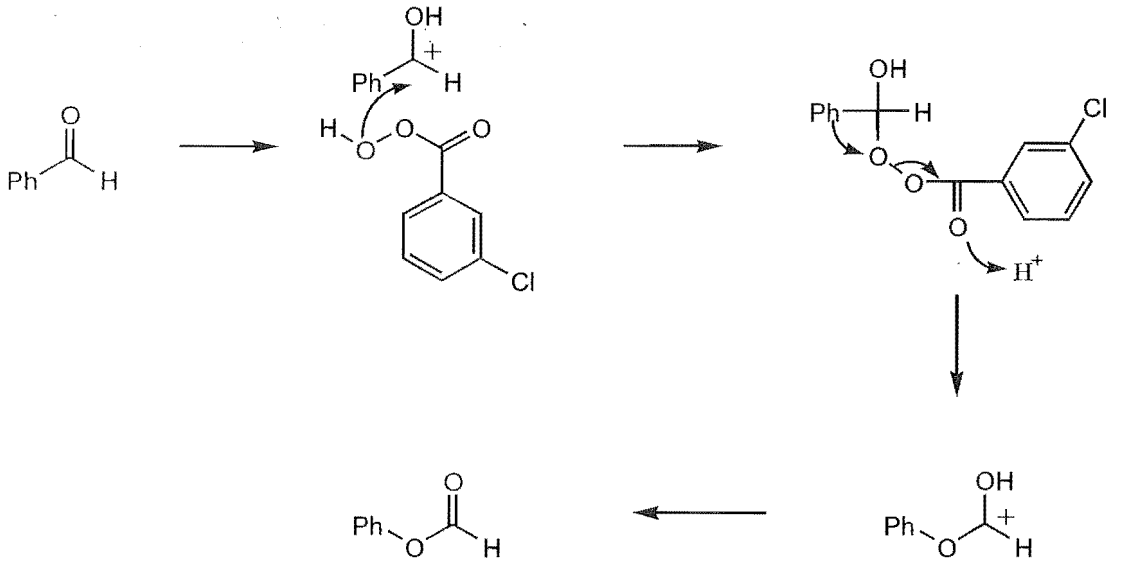
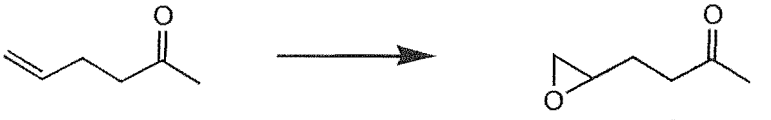


Figure 2.6 - A proposed mechanism for the Baeyer-Villiger oxidation of benzaldehyde.

The presence of the formate ester on the aryl ring was not satisfactory in terms of later synthetic manipulation and so a method was sought to achieve preferential epoxidation over Baeyer-Villiger rearrangement. As the Baeyer-Villiger oxidation is believed to proceed *via* an ionic intermediate, while epoxidation is thought to proceed by a one-step non-ionic mechanism[42] a less polar solvent should favour epoxidation,

since this Accordingly, epoxidation of **2.23** was attempted using *m*CPBA in benzene. This gave a mixture of formate ester **2.25** and the desired epoxide **2.24**, suggesting that *m*CPBA was too strong a Baeyer-Villiger oxidant to allow for selective epoxidation. Clearly, a different epoxidising agent was required. The ability of a peracid to perform Baeyer-Villiger oxidation is directly related to the strength of its conjugate base. With a weaker base, both peroxide oxygens have increased electron density and hence are less electrophilic. Making the peroxide oxygen less electrophilic should make nucleophilic attack by the migrating species on the peroxy oxygen considerably slower.

A review of the literature revealed that dimethyldioxirane is an effective epoxidising agent and a poor Baeyer-Villiger oxidant.[43,44] The chemoselectivity of dimethyldioxirane was illustrated by Curci *et al.* who reacted dimethyldioxirane with hex-1-en-5-one to give the epoxy ketone **2.26**, without any Baeyer-Villiger oxidation occurring. [44]



2.26

Dimethyldioxirane is formed by the reaction between potassium peroxomonosulfate and acetone. This reaction proceeds *via* a Baeyer-Villiger-like mechanism. The first step involves nucleophilic attack by the potassium peroxomonosulfate on the carbonyl carbon. Nucleophilic attack by the carbonyl oxygen with subsequent loss of potassium hydrogen sulfate yields the cyclic peroxide.[45]

Two methods exist for preparing dimethyldioxirane :

- *in situ* generation in a biphasic system,[44]
- isolation in an acetone solution.[46]

The *in situ* generation method has the advantage of being readily performed on a large scale. The difficulty with this method is the pH of the solution must be maintained between 7.5 and 8.0 to ensure optimum alkene conversion.[44]

Initial studies using dimethyldioxirane used the *in situ* generation method. Alkene **2.23** was reacted with acetone and Oxone® (potassium peroxomonosulfate) in a biphasic phosphate buffer/CH_2Cl_2 system held at 0°C, using 18-crown-6 as a phase-transfer catalyst.[44] An Oxone® solution was added dropwise over one hour to the biphasic solution. After 4 hours, only starting materials were recovered. Despite the presence of the phosphate buffer, the reaction could not be maintained at a pH of 8. When the Oxone® solution was added the pH dropped to around 6.5. A 2 M solution of KOH was used to readjust the pH, but even adding these two solutions together still gave a significant pH drop. At acidic pH, any dimethyldioxirane which does form will be destroyed by acid-catalysed cleavage of the peroxide bond. Similarly, at pH greater than 8 potassium peroxomonosulfate dismutation is favoured.[44] The authors note that a pH stat is used to control the pH during the addition of the oxone solution, however this type of device was unavailable and consequently, this method as abandoned.

The alternative method for forming dimethyldioxirane involves its preparation as a 0.1M solution in acetone.[46] Around 100 mL quantities of this solution were routinely prepared using the method of Adam *et al.*.[46] Solutions were stored in a freezer and due to the instability of dimethyldioxirane the solutions were used within a day. Reaction of alkene **2.23** with 1.5 equivalents of dimethyldioxirane for 2 hours gave the desired epoxide **2.24** in quantitative yield. The ^{1}H nmr spectrum of epoxide **2.24** is shown in **Figure 2.7**. The triplet at 5.50 ppm and the doublet at 4.60 ppm which were present in the ^{1}H nmr of the starting material had disappeared, indicating the loss of the double bond. The methylene protons were now split into two AB quartets centred around 4.40 and 4.10 ppm, thus indicating that epoxidation had occurred and that the methylene group was now adjacent to a stereocentre. Additionally, the methine proton had shifted upfield to 3.20 ppm, indicating that it was in a different chemical environment.

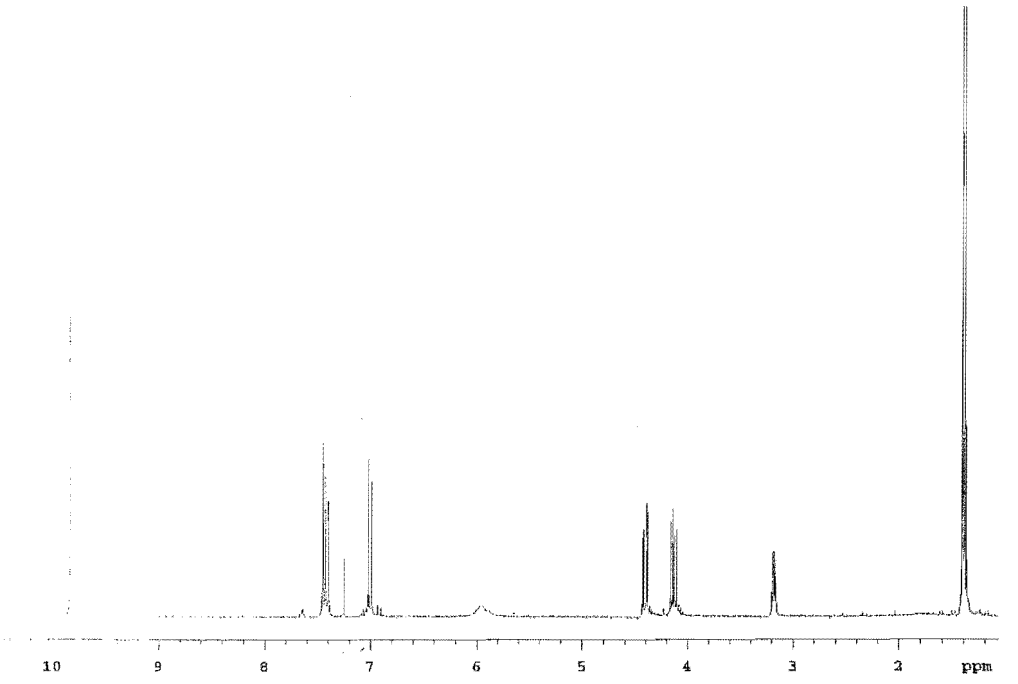


Figure 2.7 - 300MHz ^{1}H nmr spectrum of epoxide 2.24

2.5 Tin-(IV)-chloride mediated epoxide rearrangements

With a viable route to the desired epoxide established, attention was turned to the Lewis acid-mediated cyclisation reaction. Based on William's work, initial cyclisation trials involved the reaction of epoxide **2.24** with the strong Lewis acid $SnCl_4$.[47] The initial investigation repeated the exact conditions of Williams and co-workers, whereby one equivalent of freshly distilled $SnCl_4$ was added dropwise to an ice-cold solution of epoxide **2.24** in THF. Although the intramolecular cyclisation would most probably be faster than any intermolecular reactions, the reaction solutions were relatively dilute (0.07M) to help minimise intermolecular reactions. The starting material was consumed after 45 minutes, but examination of the ^{1}H nmr spectrum indicated only small amounts of the desired benzodioxepin had formed. Reaction temperature and the order of substrate addition have both been shown to influence $SnCl_4$'s behaviour as a Lewis acid.[48] Hence, the order of reagent addition, order of

substrate dissolution, and temperature were systematically varied as shown in **Table 2.1**.[†]

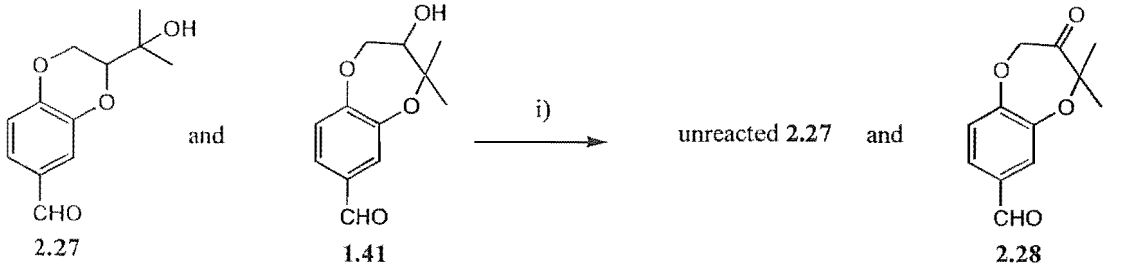
Conditions	Temperature	Time
$SnCl_4$ added to epoxide solution	0°C or 20°C or reflux	45 min
Epoxide solution added to $SnCl_4$ solution	0°C or 20°C	45 min
$SnCl_4$ solution added to epoxide solution	0°C or 20°C	45 min

Table 2.1 - $SnCl_4$-catalysed cyclisations

These variations had little effect upon the cyclisation. The reactions performed at 20°C gave slightly higher levels of benzodioxepin **1.41** than those performed at 0°C based on inspection of the ^1H nmr spectra. When the cyclisation was performed in refluxing THF, the reaction was substantially cleaner but the yield did not improve. This series of reactions demonstrate that the cyclisation conditions utilised by Williams *et al.*[33,34] were not effective for this substrate.

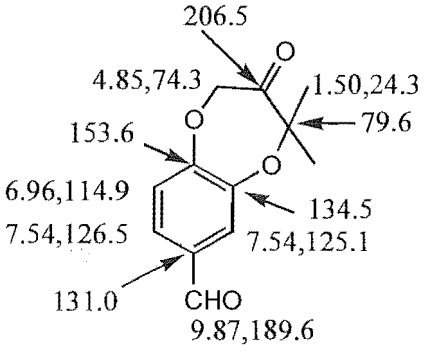
The benzodioxepin **1.41** could not be separated from the isomeric dioxane **2.27** by chromatography using normal or reverse-phase silica. Presumably, dioxane **2.27** forms when the epoxide ionises to give the secondary carbocation, with subsequent ring-closure giving **2.28**. Oxidation of a mixture of **1.41** and **2.27** using PCC gave the benzodioxepinone **2.28**. This was now readily separated by chromatography, but the ketone **2.28** was only isolated in a disappointing 7% yield.

[†] Unless otherwise stated, all yields quoted in this section were determined using integration of the relevant peaks in the ^1H nmr spectrum. Unless otherwise stated, all reactions involved one equivalent of the acid with one equivalent of epoxide **2.24** with the concentration at 0.07M in epoxide. A summary of all the acid-catalysed cyclisations can be found in Chapter 5

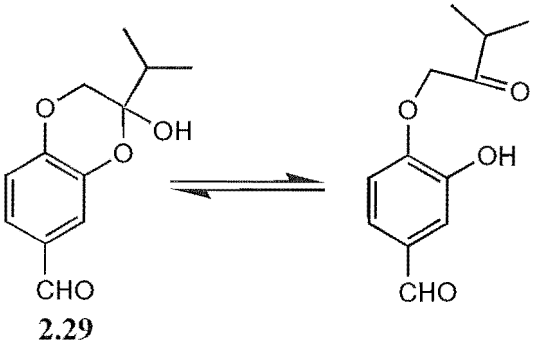


Conditions- i) PCC, CH_2Cl_2

Extensive two-dimensional nmr studies allowed full ^1H and ^{13}C assignment of dioxepinone **2.28** as shown below.



The major product from this series of reactions was identified as the six-membered ring hemiacetal **2.29**, which lay in equilibrium with a small amount of the corresponding ring-opened ketone.



The ^1H nmr spectrum of hemiacetal **2.29** is shown in **Figure 2.8**. The AB quartet centred around 4.20 and 4.00 ppm belongs to the methylene group and integrates for two protons. The splitting indicates the presence of the stereocentre on the adjacent carbon. The methine proton between the *gem*-dimethyl protons gives a distinctive

septuplet centred at 2.10 ppm. Although the hemiacetal is the major isomer, small amounts of the ring-opened ketone can also be seen. In this isomer the methylene group gives a singlet at 4.75 ppm, while the methine proton between the *gem*-dimethyl protons gives a singlet at 2.70 ppm.

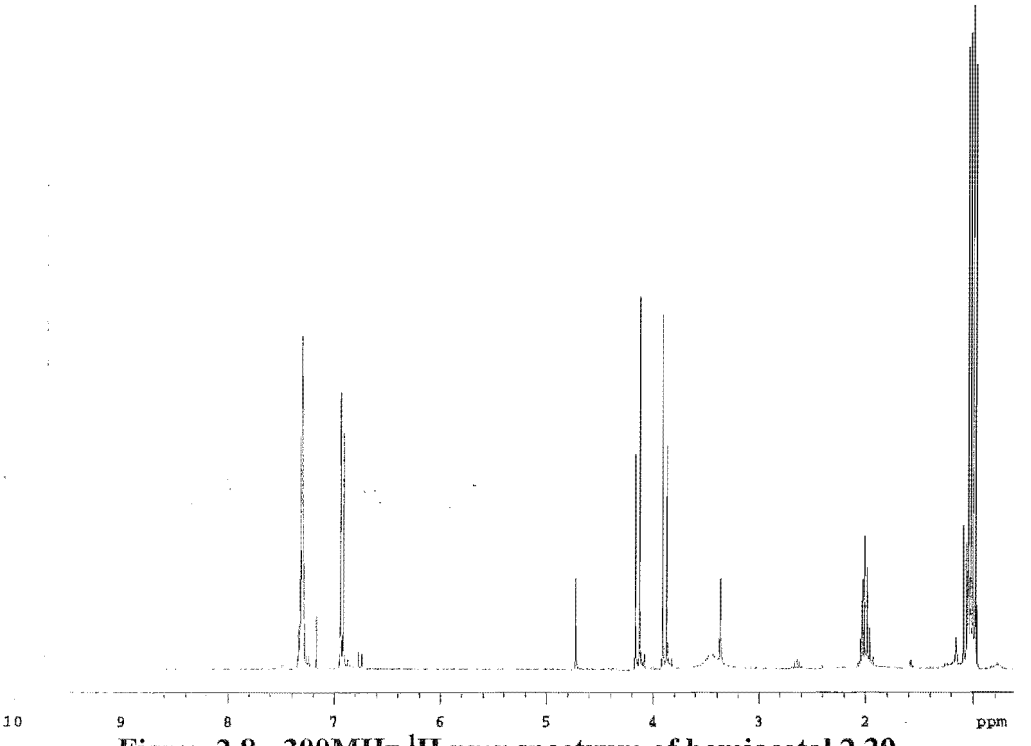


Figure 2.8 - 300MHz ^{1}H nmr spectrum of hemiacetal 2.29

Figure 2.9 details a proposed mechanism for the formation of hemiacetal **2.29**.[49] The first step in this reaction would be the coordination of the $SnCl_4$ to the epoxide oxygen. This oxycation could then cleave to give either a secondary or a tertiary carbocation. Clearly, the tertiary carbocation **2.31** would be the thermodynamically more favourable product. This was demonstrated by Williams *et al* forming the seven-membered benzodioxepin, rather than the six-membered dioxane. This carbocation can then undergo one of two reactions;

- nucleophilic attack by the phenol moiety to give the desired benzodioxepin
- a 1,2 hydride shift to give the secondary carbocation **2.32**.

Species **2.32** would only need to exist transiently as cleavage of the tin-oxygen bond would result in formation of the ketone isomer of hemiacetal **2.29**. Isomerisation would then lead to the formation of the more stable six-membered ring hemiacetal.

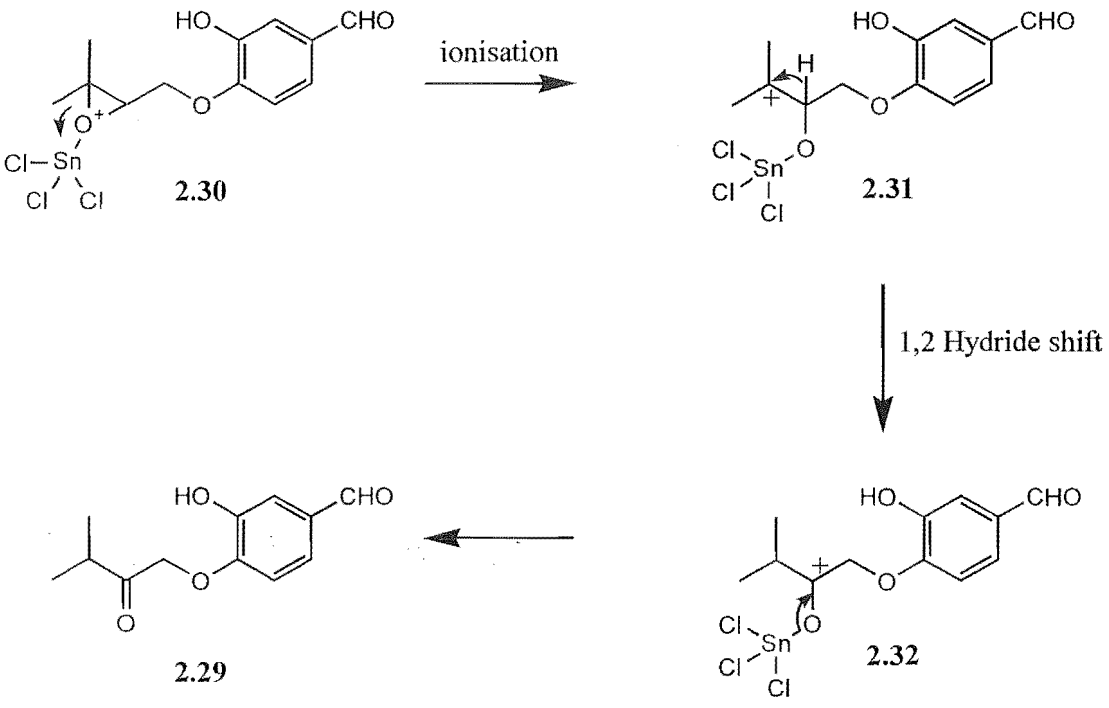


Figure 2.9 - A proposed mechanism accounting for the formation of hemiacetal **2.29**

Based on this mechanism, it would seem that epoxide **2.24** is ionising to give the desired tertiary carbocation, but the 1,2 hydride shift which results in the formation of hemiacetal **2.29**, is favoured over the desired intramolecular nucleophilic attack by the phenol. Obviously, the formation of the benzodioxepin requires the alkyl chain to adopt a conformation which places the carbocation centre close enough to the phenol to allow for nucleophilic attack. Despite the arene ring removing one degree of freedom from any possible conformation, the nucleophile and the electrophile are still separated by five atoms. In contrast, the 1,2 hydride shift isn't dependant on conformation. Its only requirement is for the carbocation and the relevant hydrogen atom to be in the same plane. The exact product of the cyclisation depends upon the relative rate of the alkyl chain attaining a conformation which allows for attack by the phenol, compared with the rate of the 1,2 hydride shift.

A mixture of two other side products was observed in the ^{1}H nmr spectrum. One of these compounds gave singlets at 5.15 and 5.00 ppm. The other compound, which was present in lesser quantities, gave signals at 6.00 and 5.85 ppm. This region is characteristic of olefinic protons, hence it was thought that these compounds were dehydration products. They could not be separated despite extensive chromatography. Given that these products were typically present in around 5% yield, their characterisation was not pursued any further.

2.6 - Investigation of other Lewis and Bronsted Acids

The above work demonstrates that Williams *et* al.'s cyclisation conditions do not provide a synthetically viable route to the desired benzodioxepin **1.41**. It was decided to investigate the effects of using other Lewis acids upon the cyclisation in the hope that the yield of the desired benzodioxepin would be increased.

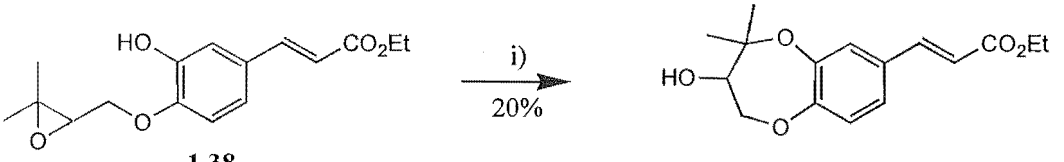
Boron trifluoride diethyl etherate is known for its ability to mediate epoxide rearrangements.[50] Treatment of epoxide **2.24** with one equivalent of $BF_3.OEt_2$ gave the hemi-acetal **2.29** as the major product, with a similar product distribution to that seen for the $SnCl_4$-catalysed cyclisations. Another strong Lewis acid, $AlCl_3$ gave an almost identical result.[51] The similarity of the ^{1}H nmr spectra of these reactions to those of the $SnCl_4$-catalysed cyclisations suggested that the use of these Lewis acids had very little effect upon the result of the cyclisation. This was in contrast to the reaction of $TiCl_4$[52] with epoxide **2.24** which gave dioxane **2.27** as the major product, along with low levels of the hemiacetal **2.29** and benzodioxepin **1.41**. Two equivalents of $TiCl_4$ gave an identical result. This result is somewhat inexplicable as it suggests that $TiCl_4$ induces epoxide cleavage to give the secondary carbocation to afford the dioxane. However, given the low levels of benzodioxepin this reaction was not pursued any further. These results indicate that the use of a strong Lewis acid to initiate cyclisation still results in the preferential formation of hemiacetal **2.29**.

A range of other Lewis acids were trialed as cyclisation catalysts. $LiClO_4$ is a mild Lewis acid, often used to catalyse epoxide rearrangement.[53] The reaction of one

equivalent of $LiClO_4$ with epoxide **2.24** in diethyl ether took 48 hours for complete consumption of starting material. Unfortunately, the major product was still the hemiacetal **2.29**.

Cyclisation was attempted using trimethylsilyl trifluoromethanesulfonate (TMS-OTf) in THF, but again hemiacetal **2.29** was still the major product. Using DMSO as the solvent slowed this reaction greatly, with completion only being reached after 24 hours, in contrast to the reaction in THF which took 30 minutes for complete consumption of starting material to occur. Disappointingly, hemiacetal **2.29** was the major product with only a low level of the benzodioxepin visible in the ^1H nmr spectrum.

As previously discussed, (see **Section 1.5**) Steglich and co-workers prepared the benzodioxepin system **1.39** during their confirmation of the absolute stereochemistry of strobilurin I.[30] This was formed by the lanthanum triflate-catalysed cyclisation of epoxide **1.38**. When they trialed William's conditions involving $SnCl_4$ in THF, they isolated the corresponding dioxane. Unfortunately, the use of Steglich's cyclisation conditions on epoxide **2.24** returned only starting material after 7 days

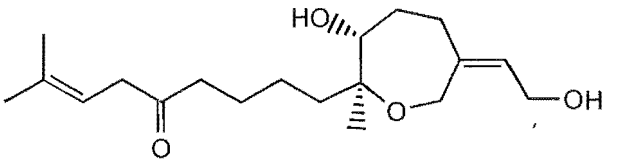


1.38 **1.39**

Conditions - i) $La(OTf)_3$, 7 days

This series of experiments showed that variation in the nature of the Lewis acid did not significantly increase the benzodioxepin formed during the cyclisation.

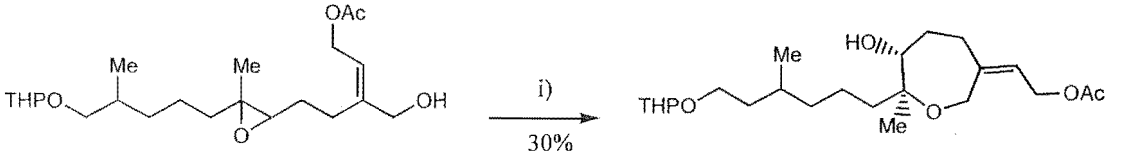
The next series of experiments involved investigations into the utility of Brönsted acids as cyclisation agents. This was prompted by work on the synthesis of the diterpenoid oxepane Zoapatanol (**2.33**).[54,55,56]



2.33

The main structural feature of this potent contragestational species is the oxepane ring. Although a variety of strategies were adopted to develop the other functionality present in the molecule, all the syntheses completed to date have used acid-catalysed cyclisation of epoxide substrates to form the oxepane.

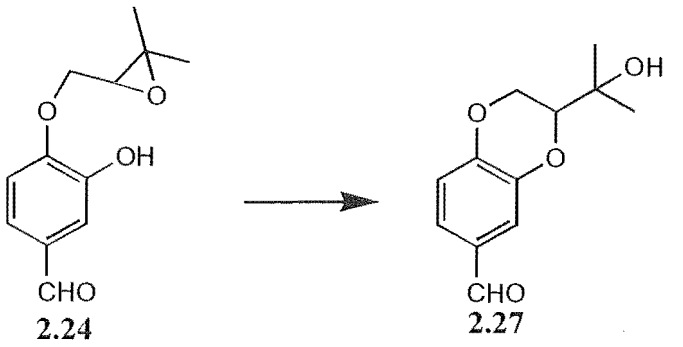
For instance, in the key step of their synthesis of Zoapatanol, Chen and Rowand cyclised epoxide **2.34** to oxepane **2.35** using 10 mol% trifluoroacetic acid.[54] This reaction proceeded in a disappointing 30% yield, with the major product being the corresponding pyran.



2.34 **2.35**

Conditions - i) 10 mol% trifluoroacetic acid, 30 minutes

Initial investigations into the effects of Brönsted acid-catalysis involved the use of Nicolaou's method for oxepane synthesis.[57] Epoxide **2.24** was exposed to 10 mol % *d*-camphor sulfonic acid in CH_2Cl_2. This reaction was considerably slower than the equivalent Lewis acid reactions, with the starting material only being consumed after 72 hours. The major product was identified as dioxane **2.27,** with only very low levels of the benzodioxepin being present.



Conditions :- 10 mol% trifluroacetic acid, 30 minutes.

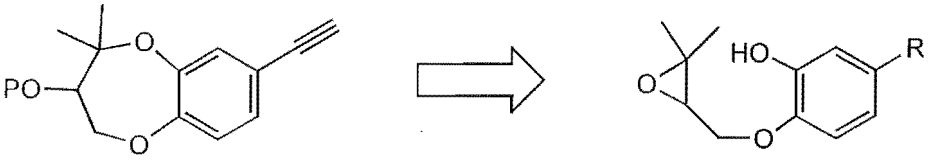
When a solution of epoxide **2.24** in CH_2Cl_2 was treated with 10 mol% trifluoroacetic acid in CH_2Cl_2, only starting material was recovered after 90 minutes. This was interesting in the light of Chen and Rowand's oxepane cyclisation being complete in 30 minutes. When the reaction was repeated using one equivalent of TFA the reaction was only 20% complete after 3 days. Eventually, it was found that the addition of 10 equivalents of TFA and stirring for 24 h gave complete consumption of starting material. However, this gave a very complex ^1H nmr spectrum with only a 15% yield of the benzodioxepin. It is unclear exactly why these cyclisations were so much slower than the oxepane cyclisations discussed previously.

Cyclisation using *para*-toluenesulfonic acid in CH_2Cl_2 was attempted. Whilst this reaction was considerably quicker than those involving the other Brönsted acids, it still gave only low levels of benzodioxepin **1.41**.

In summary, this series of experiments have shown that the $SnCl_4$/THF cyclisation conditions utilised by Williams for the construction of the non-functionalised benzodioxepin **2.10**, is still the best method for the synthesis of **1.41** from epoxide **2.24**. However, this yield was less than 20% and as such, a Lewis or Brönsted acid-mediated ring closure on substrate **2.24** is not a synthetically-viable route to the target benzodioxepin **1.41**.

2.7 Investigation of an aryl bromide-functionalised cyclisation substrate

Based on Williams' success with functionalised substrates, it was thought that changing the functionality present on the arene may allow the benzodioxepin cyclisation to proceed in better yield. As previously discussed, any functionality introduced onto the arene ring must allow later introduction of an alkyne (See **Section 1.7**), ideally in a single high-yielding reaction.



1.43 **1.46**

It was thought that a bromine group in the 4-position would satisfy this requirement in that an alkyne could later be introduced using Sonogashira chemistry.[58] Thus 4-bromocatechol is the material required to begin this sequence. However, there is unlikely to be an intrinsic difference in the reactivity of the two hydroxyl groups as was seen in the 3,4-dihydroxybenzaldehyde system and therefore there would be no selectivity for the alkylation of the 4-hydroxyl group. As previously mentioned, this is required for the formation of the correct regioisomer of the target benzodioxepin.

The observation of the propensity of aryl aldehydes to undergo Baeyer-Villiger oxidation lead us to the development of a synthesis that avoided these regioselectivity problems. The synthesis of the epoxide precursor is detailed in **Figure 2.10**.

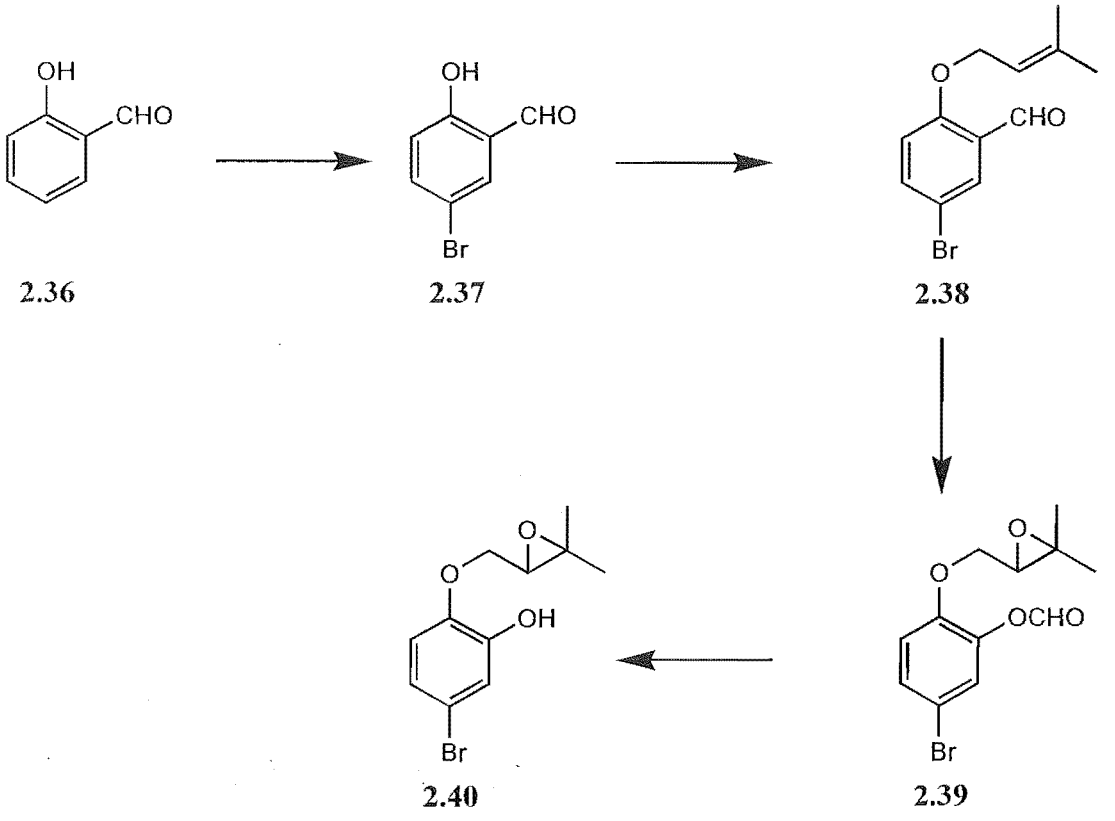
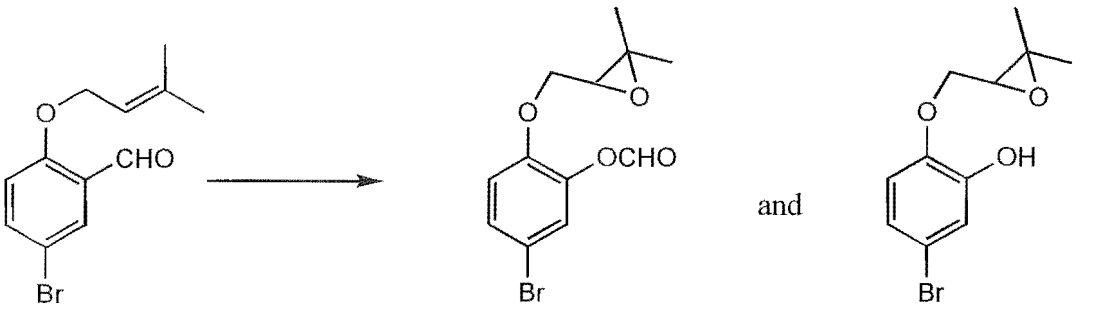


Figure 2.10 - Strategy for the development of cyclisation substrate

The construction of epoxide started with the bromination of salicylaldehyde.[59] A solution of one equivalent of bromine in $CHCl_3$ was added dropwise to a solution of salicylaldehyde in $CHCl_3$ at 30°C. The solution was refluxed for 2 hours to give the desired benzaldehyde **2.37** in 93% yield after dry column chromatography. Alkylation of **2.37** was carried out under identical conditions to those used previously.[30] Reaction of phenol **2.37** with 1.1 equivalents of K_2CO_3 and prenyl bromide in DMF for 16 hours gave the alkene **2.38** in 92% yield after flash chromatography.

The next step in the preparation of **2.40** involved the one-pot epoxidation and Baeyer-Villiger oxidation of alkene **2.38** to give formate ester **2.39**. Initial studies involved the reaction of benzaldehyde **2.38** with 2.05 eq of *m*CPBA in CH_2Cl_2 for 2 hours. This gave a 1:1 mixture of the desired epoxy formate ester **2.39** and the free phenol , with the ^1H nmr spectrum of the two products being very similar. The principal difference was the proton on the formate ester moiety of **2.39**, which was observed as a singlet at 8.20 ppm.



2.38 **2.39** **2.40**

Conditions - i) mCPBA, CH_2Cl_2, 2 hours

An attempt was made to hydrolyse the mixture to the phenol by exposure to one equivalent of LiOH in a 1:1 mixture of THF and methanol.[60] The solution was stirred for 30 minutes, to give a new product **2.41**. The ^{1}H nmr spectrum of this product was significantly different from that of the starting mixture. Both the formate ester and epoxide signals had disappeared and had been replaced with an AB quartet at 4.40 ppm and a multiplet between 3.85-4.00 ppm.

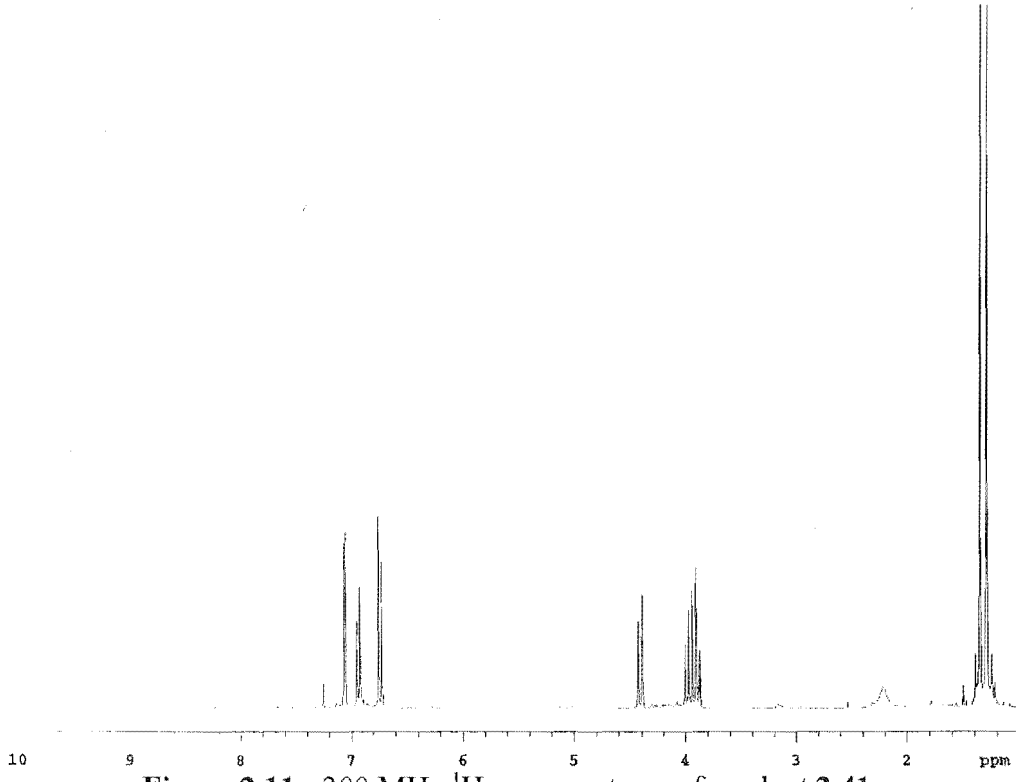
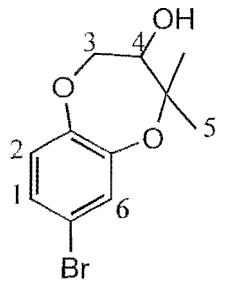
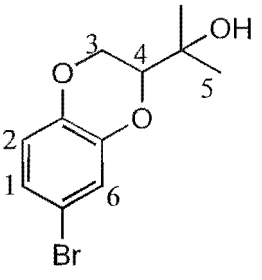


Figure 2.11 - 300 MHz ^{1}H nmr spectrum of product **2.41**.

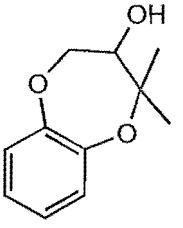
The ^{1}H nmr spectrum suggested that cyclisation had taken place to give either the target benzodioxepin (**A**), or the dioxane (**B**)



A



B



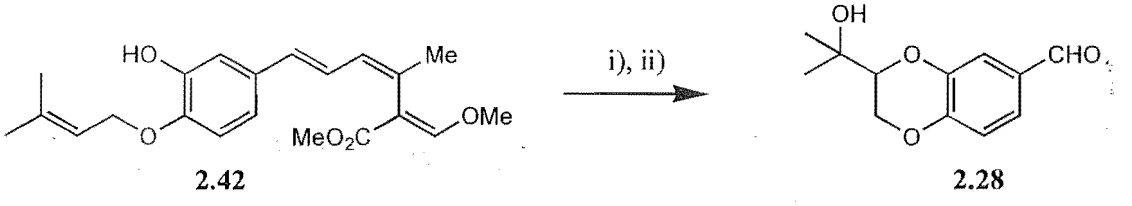
2.10

An authentic sample of the non-functionalised benzodioxepin ring system **2.10** was available. Comparison of the ^{1}H nmr spectrum for compound **2.41** with that of **2.10** showed different chemical shifts to those of **2.10**. Additionally, the new compound lacked a signal at around 3.80 ppm which corresponds to the methine in the non-functionalised parent system. A variety of two-dimensional NMR experiments were performed. HMBC analysis was inconclusive as the crucial correlation from C-6 to H-4 in the dioxane structure was not observed. Given this ambiguity, it was decided to dehalogenate **2.41** and compare its data with those of benzodioxepin **2.10**, thus offering more definitive proof of the compound's structure.

Initial experiments involved the addition of a slight excess of freshly titrated n-BuLi to a solution of **2.41** in THF at -78°C.[60] It was thought that metal-halogen exchange would occur, with subsequent quenching with methanol resulting in the formation of the dehalogenated parent system **2.10**. Disappointingly, this was not the case, with only starting material being isolated. A method developed by Corey and Suggs for dehalogenation using catalytic amounts of *in situ*-generated trialkyltin hydrides was next examined.[61] However, the conditions reported gave only starting material contaminated with a tributyltin species. Given that these dehalogenations were unsuccessful, an attempt was made to form the *para*-nitrobenzoyl ester of **2.41**. It was thought that this would make it more crystalline and additionally, the resultant ester would have an HMBC correlation which would allow confirmation of the proposed

structure. A solution of compound **2.41** was reacted with 1.1 equivalents of *para*-nitrobenzoyl chloride, 2.5 equivalents of triethylamine and a catalytic amount of 4-dimethylaminopyridine (DMAP). However, even after 18 hours at room temperature only a mixture of starting material and *para*-nitrobenzoic acid was isolated.

The identity of **2.41** was finally confirmed after extensive literature searching when a paper was found detailing the isolation and structural elucidation of Strobilurins F-2, G and H.[62] Strobilurin F-2 (**2.45**) was epoxidised using excess *m*CPBA and the resulting epoxide hydrolysed with Na_2CO_3. This gave dioxane **2.28**, which was oxidised to the corresponding benzoic acid.[62]



2.42 **2.28**

Conditions - i)mCPBA, ii) saturated Na_2CO_3.

Comparison of the spectral data of both **2.28** and **2.41** led us to the assignment of structure **B**. The dioxane was presumably generated by deprotonation of the phenol, and subsequent attack by the phenoxide ion on the epoxide. To avoid this reaction, a method for generating the formate ester or the phenol cleanly was vital.

The reaction was repeated using one equivalent of *m*CPBA to investigate the relative rate of Baeyer-Villiger oxidation versus the rate of formate ester hydrolysis. This gave a complex mixture of both epoxidised and non-epoxidised ester **2.39** and alcohol **2.40**.

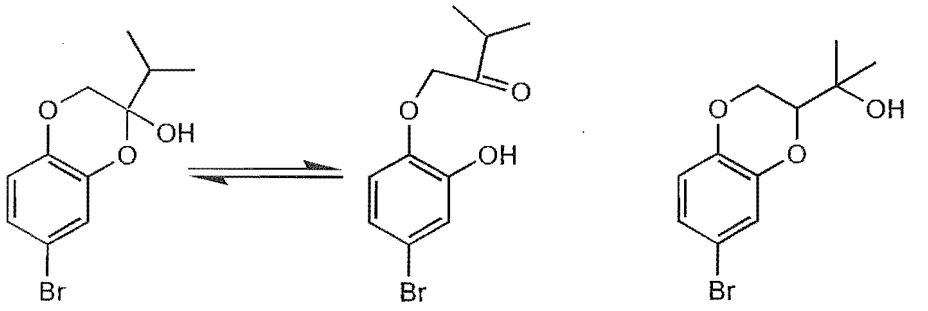
This indicated that the rates of epoxidation and Baeyer-Villiger insertion were comparable. The hydrolysis of formate ester was thought to be acid-catalysed and so attempts were made to buffer the epoxidation, such that the *meta*-chlorobenzoic acid (*m*CBA) formed during the reaction was removed. This buffer had to be sufficiently basic to remove *m*CBA, but not so basic as to induce cyclisation to the dioxane. The *m*CPBA that was used in these reactions was purchased as a 70/30 mixture of

*m*CPBA/*m*CBA. This is significantly safer than pure *m*CPBA, which is both difficult to produce and shock-sensitive. Pure *m*CPBA can be obtained by stirring the mixture of acid and peracid in a pH=7.4 phosphate buffer.[63] This separation method is based on mCBA being more acidic then *m*CPBA. Given that the epoxidation/Baeyer-Villiger rearrangement results in the formation of *m*CBA, this would seem an adequate method for buffering the reaction. The reaction was attempted using 2.3 eq of buffer to alkene **2.38**, but phenol **2.40** was still observed in the ^{1}H nmr spectrum.

After extensive experimentation, it was found that the presence of a 0.1 M $Na_2H_2PO_4$ solution gave the formate ester in good yield. Initial attempts at hydrolysis of the ester employed the method of van Reben.[64] This procedure for the hydrolysis of aryl formate esters involves the reaction of twenty equivalents of potassium hydrogen carbonate with formate ester in a 0.01M solution of 2 parts methanol/1 part water. Treatment of **2.39** for 20 minutes gave quantitative return of dioxane **2.43**, thus indicating that these conditions are too vigorous to allow for the desired transformation. The reaction was repeated using 0.1 equivalents of potassium hydrogen carbonate. The major product was the desired phenol **2.40** with a small amount of the dioxane **2.43**. After a considerable amount of experimentation, it was discovered that refluxing the formate ester in methanol for 16 hours gave only the desired phenol **2.40**.[65] Sufficient quantities of phenol **2.40** were now available to trial the Lewis acid-catalysed cyclisations. Cyclisations were also attempted on the formate ester as it was thought that a Lewis acid might cleave the formate ester *in situ* and cyclise the resultant phenol in one process.

Disappointingly, both of the aryl halide substrates gave poor yields of the target benzodioxepin in almost the same yields as those observed for cyclisation of aryl epoxide **2.24**. The major product for all these reactions was hemiacetal **2.44**, in equilibrium with its keto tautomer. Interestingly, cyclisations of formate ester gave approximately a 1:1 mixture of the hemiacetal to the ketone, as compared with a 95:5 mixture for cyclisations of phenol **2.40**. Once again, the target benzodioxepin could not be separated from dioxane **2.43** by flash chromatography and thus an accurate

yield could not be obtained. However, it was clear that the yields were comparable to those for the cyclisations in **Section 2.5**.



2.44 **2.43**

While only a few Lewis acid catalysts were trialed for the cyclisation of epoxide **2.40**, it was clear that from the previously observed behaviour of epoxide **2.24**, the yield of the desired benzodioxepin would not increase significantly and as such, this was not a synthetically-viable route to the target benzodioxepin **2.42**.

2.8 Summary

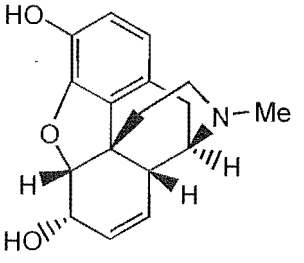
In summary, approaches towards a functionalised benzodioxepin ring system using a Lewis acid-mediated cyclisation were unsuccessful. The formation of a six membered ring hemi-acetal occurred preferentially to the desired benzodioxepin cyclisation regardless of whether there is an aldehyde or bromide substituent present on the aryl ring system. This observation means this approach is not synthetically-viable for use in a total synthesis.

Chapter Three

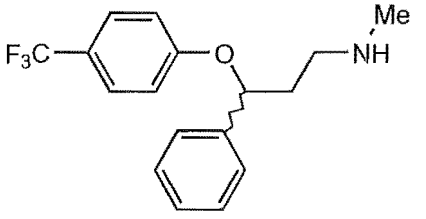
Palladium-Catalysed Aryl Ether Formation

3.1 Introduction

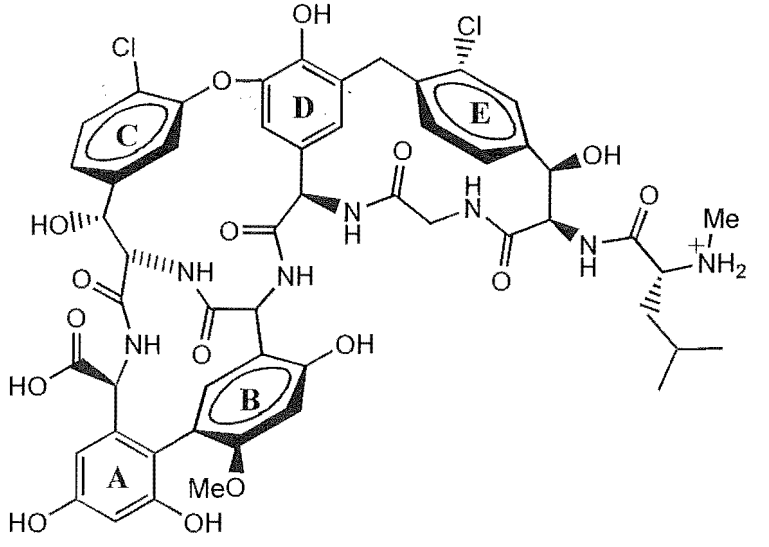
Aryl ethers are a common structural motif found in a wide variety of pharmacologically-important natural products and drugs. These include compounds such as the opiate analgesic morphine (**3.1**), the anti-depressant Prozac® (**3.2**) and the antibiotic Vancomycin aglycone (**3.3**).



3.1



3.2



3.3

Figure 3.1 The aryl ether-containing pharmaceuticals morphine, Prozac® and Vancomycin aglycone

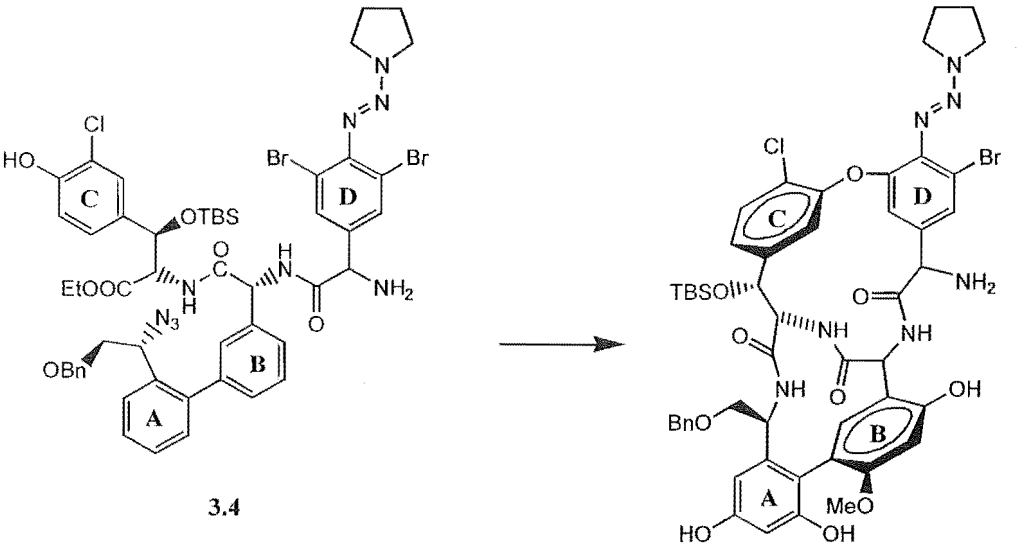
Despite the structural simplicity of aryl ethers, their synthesis is often difficult. They are traditionally prepared by direct nucleophilic substitution by a hydroxyl group on a functionalised arene (referred to as S_NAr-chemistry). Such a reaction involves the attack of an oxygen atom upon an electron-rich arene ring. The cloud of π-electrons which surround the arene ring make it a very poor electrophile. The presence of strong electron-withdrawing groups can increase the electrophilicity of the arene, thus

making attack more favourable.[66] Alternatively, the use of high temperatures and a highly polar solvent can allow this reaction to proceed. These conditions are intolerant to a wide range of functional groups, with the high temperatures and polar solvents facilitating a wide range of side reactions. As such, these couplings have limited use for intramolecular reactions.[66]

The difficulties associated with preparing aryl ethers were recently exemplified during two total syntheses of the Vancomycin aglycone (**3.3**) by the groups of Evans[67] and Nicolaou.[68]

Vancomycin is a complex antibiotic used in the treatment of the highly-pathogenic bacterium methicillin-resistant *Staphylococcus aureus* (MRSA).[69] Vancomycin is a heptapeptide containing three fused macrocyclic rings, each of which has associated atropisomerism due to the hindered rotation of each of the cyclic peptide subunits. This atropisomerism, in addition to the several unnatural amino acids present in the carbon skeleton, makes Vancomycin a challenging target for total synthesis. Although Vancomycin only contains biaryl ethers, some of the problems encountered its synthesis are illustrative of the difficulties in forming aryl ethers using traditional methodology.

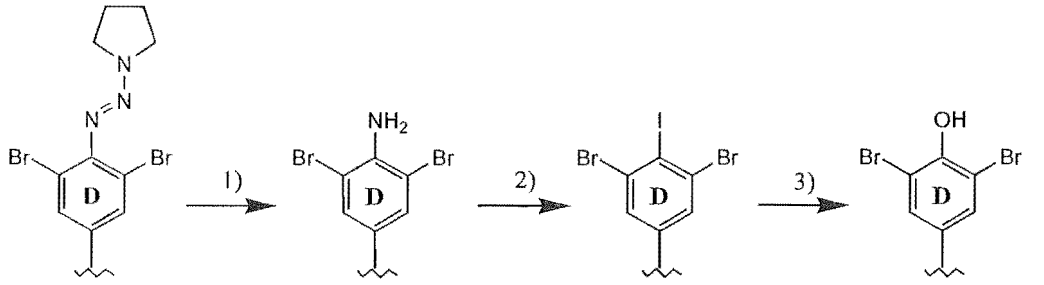
Vancomycin contains two biaryl ether linkages, centred around arene ring **D** as shown in **Figure 3.1**. This arene ring also lies at the head of two of the macrocyclic rings contained in Vancomycin. Construction of this structural motif was one of the weaknesses in Nicolaou synthesis.[68] In this synthesis, the C-*O*-**D** ring macrocyclic system was the first to be constructed as the Ullman coupling conditions required would be too harsh for functionality which was to be introduced later in the synthesis. Nicolaou coupled the two arenes using chemistry that his group had previously developed.[70] This involved the installation of a triazene functionality *ortho* to the coupling site. This acted as an "electron-sink" for nucleophilic attack on the aryl ring, thus allowing the coupling of substrate **3.4** to proceed in 60% yield, albeit as a 1:1 mixture of the desired and undesired atropoisomer, (see **Figure 3.2**)



Cyclisation Conditions - 3 eq. $CuBr.SMe_2$, 3 eq. K_2CO_3, 3 eq. pyridine, MeCN, 20 min.

Figure 3.2 - Nicolaou *et al.*'s triazene-based cyclisation substrate.

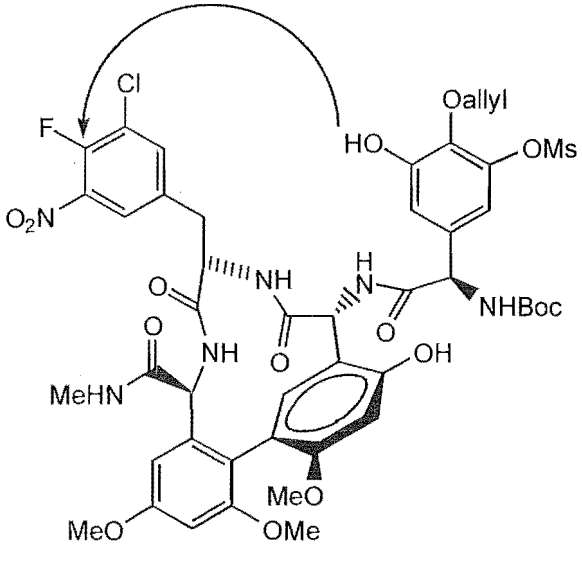
In addition to the poor yield, another difficulty associated with this method of forming the aryl ethers in Vancomycin is the later requirement for the triazene to be converted to an alcohol. This was carried out late in the synthesis by a cumbersome series of reactions as shown in **Figure 3.3.** The triazene was reduced to the corresponding amine using Raney Nickel (85% yield), which was diazotised using HBF_4 and isoamylnitrite. The diazonium salt generated was reacted with KI solution and the resultant iodide was converted to the corresponding boronate, which in turn was converted to the phenol using basic H_2O_2. These transformations, combined with deprotection elsewhere in the molecule, occurred in 50% yield from the amine. This illustrates the principal weakness of the triazene-based methodology. While the biaryl ether itself may form in acceptable yield, the triazene's later conversion to the required arene functionality often results in a considerable lengthening of the synthesis.



Reagents:- 1) Raney Ni (85%),
2) HBF_4 iso-amyl nitrite, then aqueous KI,
3) $B(OMe)_3$, $NaOH/H_2O_2$

Figure 3.3 - Nicolaou *et al.*'s alcohol formation strategy

A milder method for constructing the requisite aryl ether would allow the preparation of an appropriate stereochemical template, upon which the **C-*O*-D** ring system could be constructed, thus affording better stereoselectivity. Additionally, if the cyclisation conditions are mild enough, more sensitive functionalities can be introduced prior to cyclisation. This sort of approach was seen in Evans' synthesis. Both biaryl ether ring systems were constructed *via* a Na_2CO_3-catalysed S_NAr reaction performed at room temperature, as illustrated in **Figure 3.4**. In this approach, the **AB** ring system was constructed first and the **C-*O*-D** macrocycle was later built onto this system. The substrate for these cyclisations was a fluoride-substituted aryl ring (**C** or **E**) to which phenol **D** was annealed.



Conditions - Na_2CO_3, DMSO, 1.5h

Figure 3.4 - Evans *et al*'s biaryl ether cyclisation substrate

Cyclisation of this precursor occurred in 78% yield with a 5:1 isomeric ratio in favour of the desired atropoisomer. This method employed relatively mild conditions and did not have any effect on the sensitive functionalities and stereochemistry present elsewhere in the molecule. However, it has limited generality for preparing aryl ethers as the introduction of fluorine atoms onto arene rings *via* electrophilic aromatic substitution is difficult, due to such a reaction requiring the generation of a high energy F^+ cation. Indeed, in Evans *et al.*'s substrate, the fluorine atom was present in the commercially available starting material 4-fluorobenzaldehyde.

Although the above discussion deals with the preparation of biaryl ethers, it exemplifies the difficulties associated with the preparation of aryl ethers. An alternative method which is available for forming aryl ethers by a Williamson-type etherification.[71] This requires the direct introduction of an alcohol on to the arene and subsequent reaction with the desired alkyl halide. One approach to such a transformation involves bromination of the arene and subsequent direct displacement of the bromide using ^-OH. This typically requires activating groups on the arene and/or extremely high temperatures, which often result in low yields of the desired phenol.[72] An alternative method for the formation of aryl alcohols, shown in **Figure 3.5**, starts with the conversion of the bromoarene to the corresponding aniline derivative. With activated arenes this can be achieved by direct treatment with either ammonia, a primary amine or a secondary amine. Contrastingly, non-activated arenes require treatment with the sodium salt of the desired amine. These reactions are more facile when using the primary or secondary amine. Once formed, the imine can be deprotected to give the free amine. The amine can be diazotised using nitrous acid. The diazonium salt which is formed is an excellent leaving group and thus allows for direct displacement using ^-OH. When diazonium salts are made, they typically contain a small amount of water. Direct displacement by water is very slow at the temperatures employed for diazonium salt preparation (0-5^{0}C). However, if the reaction mixture is boiled, any excess nitrous acid is destroyed and nucleophilic substitution by water can occur on the arene. Alternatively, the addition of Cu_2O to a

dilute solution of the diazonium salt, with a large excess of $Cu(NO_3)_2$, allows the reaction to proceed at room temperature.

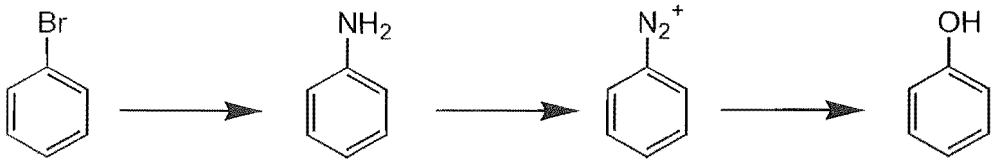
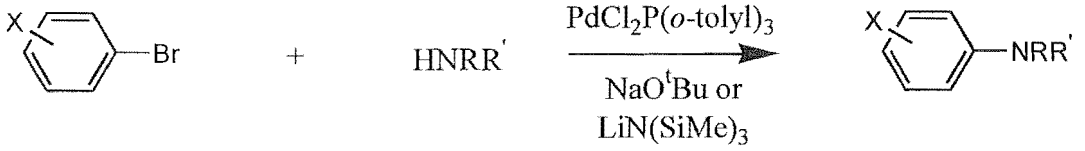


Figure 3.5 - Functional group interconversions leading to a free phenol from an aryl bromide.

While this sort of procedure allows for the introduction of a hydroxyl group onto an arene, it is lengthy and often requires protection of functionalities present elsewhere in the molecule. Adopting such a strategy adds at least four steps to a synthetic sequence to achieve effectively only one functional group conversion.

3.2 Pd-catalysed aryl ether formation

It is clear that no general method exists for the direct introduction of a hydroxyl group onto an arene, or for forming aryl ethers by S_NAr-type chemistry. The methodology discussed above can lead to their formation, but milder, general routes have not existed until recently. Methods for achieving these types of transformations were developed by the groups of Buchwald and Hartwig.[77] Both groups had been seeking improved catalytic methods for forming aryl amines utilising the palladium-catalysed reaction of aryl halides with alkyl amines. Early work towards this end had involved the Pd-catalysed reaction of dialkyl tin amides with electron-neutral aryl halides.[73] While this methodology provided good yields, it was substrate-specific. Additionally, difficulties in preparing air-sensitive tin amides and their considerable toxicity made this method far from ideal.[73] Guram and Buchwald improved upon this methodology by using tin amides prepared *in situ* and this allowed a variety of aryl halides to be used. However, good yields (>80%) were only attained when using tin amides derived from secondary amines. In 1995, Hartwig[75] and Buchwald[76] concurrently published papers outlining methods for the tin-free amination of aryl halides. These reactions worked in both inter- and intra-molecular cases.



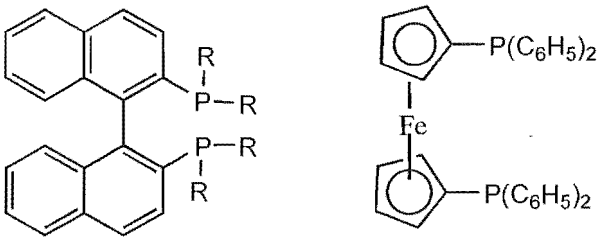
X=*o*-, *m*-, or *p*-alkyl, phenacyl, amino, alkoxy species
R, R'=Alkyl
Temperature= 80°-100°C
Solvent = toluene

Figure 3.6 - Buchwald's tin-free amination studies

An obvious extension of this amination work was to apply it to the formation of aryl ethers. Hartwig noted that reductive eliminations are faster with the more nucleophilic amines and thiolates. Given that alkoxides are less nucleophilic than either amines or thiolates,[77] it was thought that the formation of aryl ethers by a Pd-mediated method would be difficult to accomplish. However, it was also noted that reductive eliminations from Pd were faster when the Pd was bound to electron-poor arenes. This suggested that if aryl etherification were to occur, it would be likely to display some degree of substrate specificity. In their seminal 1996 paper, Buchwald *et al.*[78] detailed the development of methods for Pd-catalysed intramolecular aryl ether formation. They showed that 3-5 mol % $Pd(OAc)_2$ was capable of catalysing aryl ether formation under two sets of conditions:-

1) 5 mol % $Pd(OAc)_2$, 6 mol % Tol-BINAP (**5**), 1.2 equivalents of K_2CO_3 in toluene at 100°C.
2) 3 mol % $Pd(OAc)_2$, 3.6 mol % DPPF (**6**), 1.2 equivalents of NaO^tBu in toluene at 80°C.

Substrates reacted under the first set of conditions typically took around 24 hours for complete consumption of starting material to occur. The second set of conditions resulted in more rapid substrate consumption (1-6 hours), but gave more side-products. A variety of ligands were trialed, with the chelating bis(phosphine) ligands Tol-BINAP (**3.5**) and diphenylphosphinoferrocene (DPPF / **3.6**) shown to be the most effective.[78]



R= *p*-tolyl

3.5 **3.6**

Figure 3.7 - The ligands used for Buchwald's Pd-catalysed, intramolecular aryl ether cyclisations.

These conditions allow the cyclisation of five-, six- and seven-membered rings as illustrated in **Figure 3.8**

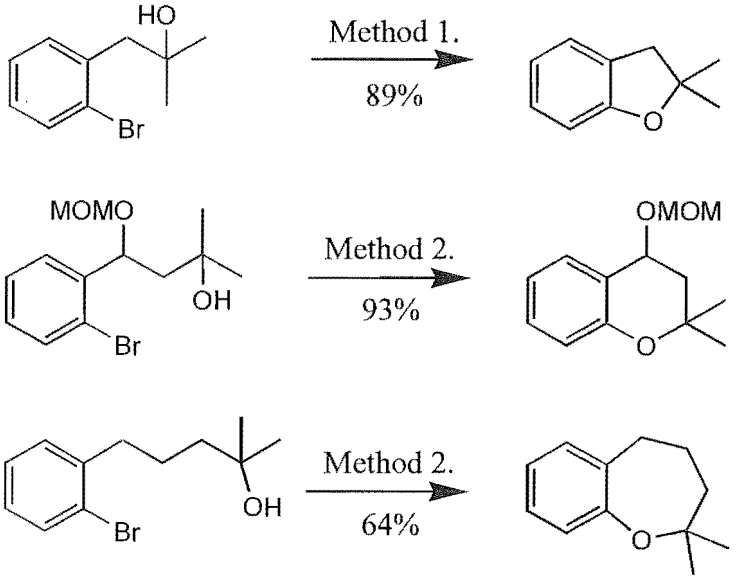


Figure 3.8 - Examples of Buchwald *et al.*'s Pd-catalysed aryl ether cyclisations

A number of functional groups were shown to be compatible with these cyclisation conditions, including acetals, silyl ethers and amides. The cyclisation conditions were found to favour tertiary alcohols. Reactions involving secondary alcohols required two equivalents of base relative to substrate and two equivalents of ligand relative to palladium in order to affect cyclisation. If this stoichiometry was lowered, secondary

alcohols were oxidised to the corresponding ketone. The mechanism for aryl ether formation by this method is thought to be analogous to that proposed for the Pd-catalysed amination reaction (as shown in **Figure 3.9**).[79] Some validation of this putative mechanism was provided when intermediate **3.7** bearing a DPPF ligand was isolated and characterised.[79] This complex was found to be both chemically and kinetically competent as a catalyst for the formation of 2,2-dimethylchroman (**3.8**).

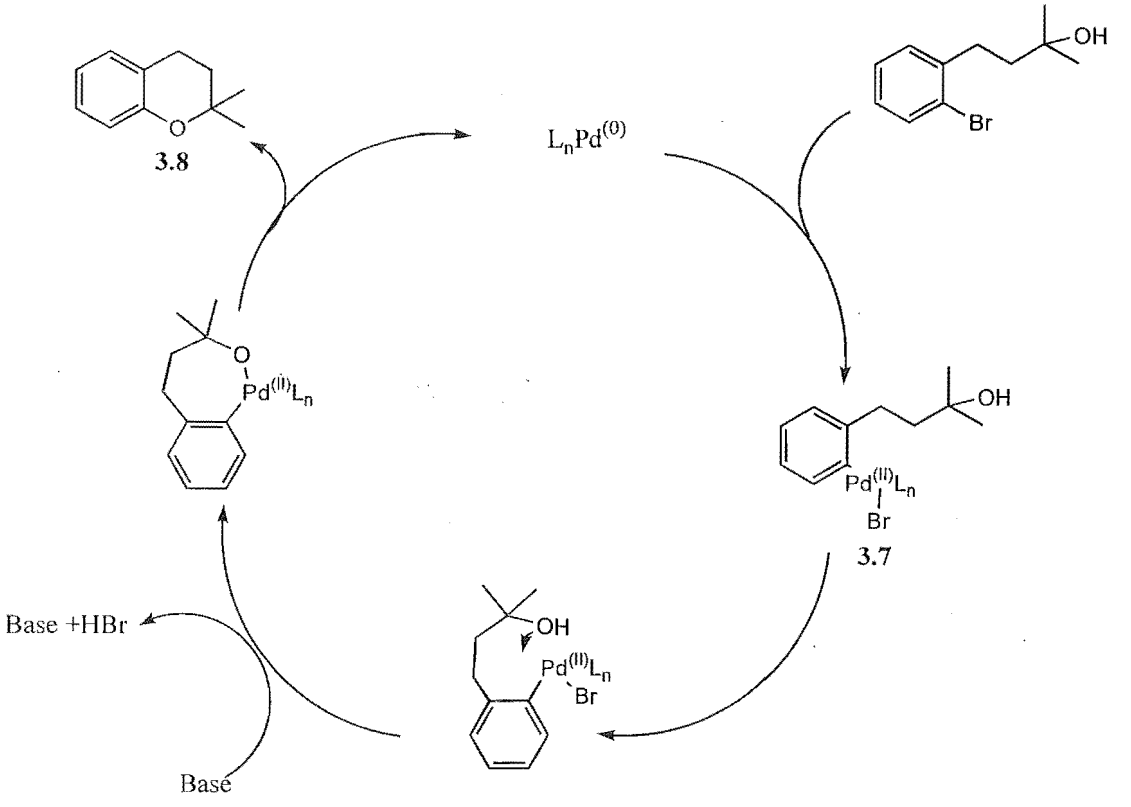


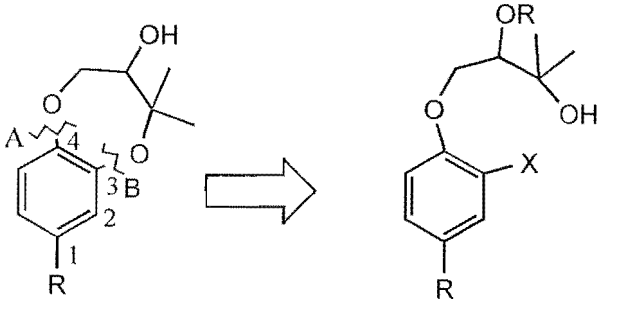
Figure 3.9 - A proposed catalytic cycle for Pd-catalysed aryl ether formation.

In a further extension of this work, Hartwig and Mann developed methods for the Pd-catalysed, intermolecular formation of aryl alcohols from aryl halides.[80] These methods centred around the reaction of the appropriate aryl halide with a $Pd(OAc)_2$/DPPF catalyst system, using NaO^tBu as the oxygen source. The resultant aryl ether could be deprotected *in situ* using acid to yield the free phenol in one step from the aryl halide. This chemistry was limited to electron-poor arenes, with electron-neutral and electron-rich arenes not undergoing reaction. This work was later

extended by Hartwig and Mann,[81] who showed that a $Ni(COD)_2$/DPPF catalyst system provides improved yields as compared with the $Pd(OAc)_2$/DPPF system.

3.3 Development of a substrate for Pd-catalysed aryl ether formation

From the work discussed above, it is clear that aryl ethers can be formed *via* Pd-catalysed intra-molecular *ipso*-attack of a hydroxyl group on an aryl halide.[78] It was thought that these methods could be applied to the problem of benzodioxepin formation, potentially allowing access to this family of oxygen heterocycles, and thus the desired members of the Strobilurin family. This would offer an opportunity to test, and possibly extend, the Pd-catalysed aryl ether formations discussed above. Aryl dioxepin **3.9** can be disconnected at either of the two arene-oxygen bonds. However, in light of Buchwald's observations that these type of cyclisations are more favourable with tertiary alcohol substrates, the obvious disconnection a



3.9 **3.10**

Figure 3.10 - The key disconnection for dioxepin cyclisation *via* Pd-catalysed aryl ether formation.

Therefore, the synthesis of alcohol **3.10** needed to be developed to allow investigation of these cyclisations. A plan for its preparation is detailed in **Figure 3.11**.

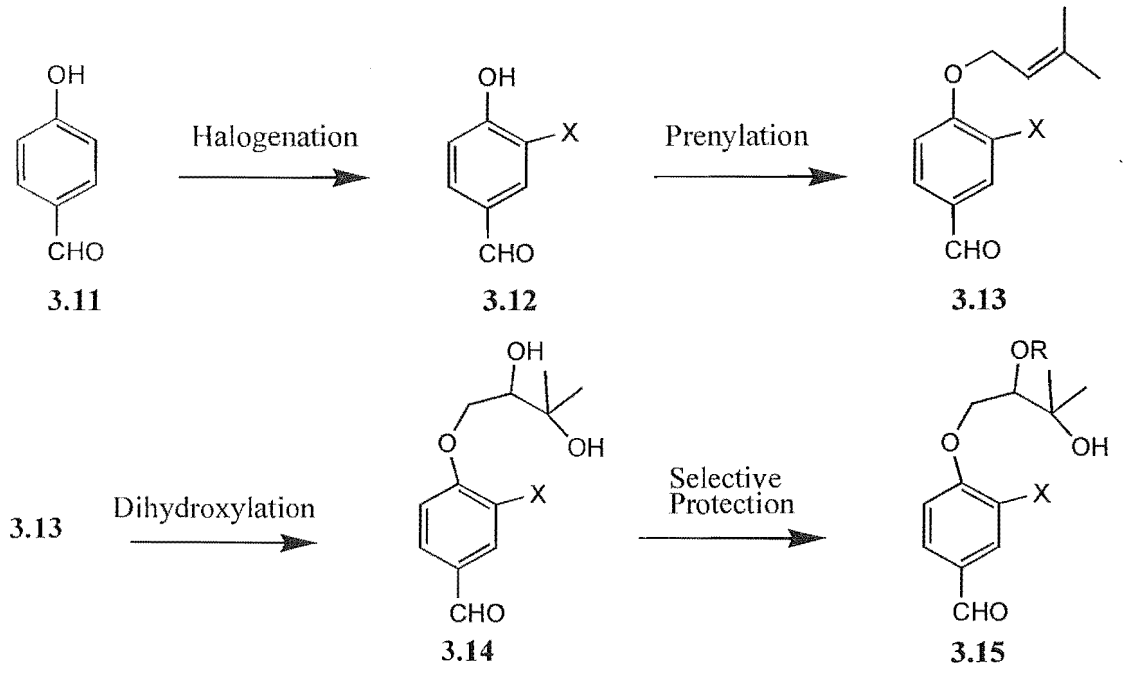
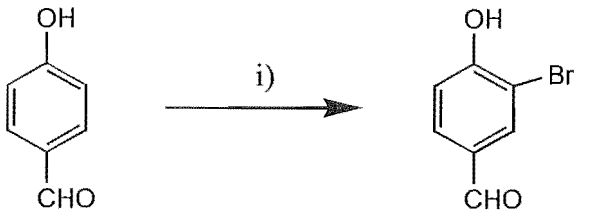


Figure 3.11 - General synthetic scheme for the development of aryl dioxepin cyclisation substrate.

It was envisaged that commercially-available 4-hydroxybenzaldehyde would be an appropriate starting material as the strong activating effects of the hydroxyl functionality would allow the introduction of a halogen at the 3-position with respect to the aldehyde. Literature methods exist for introducing a bromide[82] or an iodide[83] into this position. Both bromides and iodides have been shown to be amenable to Buchwald's cyclisation conditions.[78] The appropriate four carbon chain should be readily introduced by alkylation of the hydroxyl group to give the prenyl ether **3.13**. This could be achieved by utilising similar chemistry to that employed in the syntheses of the epoxide substrates discussed in Chapter 2. This alkene can be elaborated to give diol **3.14** by the use of standard dihydroxylation methods. This would generate a substrate with the required oxygenation pattern. Diol **3.14** could potentially be cyclised using Buchwald's conditions, in that it has the requisite halogen and tertiary alcohol groups. However, it was anticipated that the secondary alcohol may require protection as in **3.15**, so as to prevent its oxidation to the ketone.

Initial studies towards the preparation of alcohol **3.15** involved the selective bromination of the 3-position of 4-hydroxybenzaldehyde to give aryl bromide **3.16**.[82]



3.11 **3.16**

Conditions i) Br_2, $CHCl_3$

This was carried out *via* the addition of a bromine solution in $CHCl_3$ to a solution of 4-hydroxybenzaldehyde in $CHCl_3$ at 40°C. Heating for one hour gave the desired 3-bromo-4-hydroxybenzaldehyde in 85% yield after flash chromatography. The purification of the crude reaction product was readily achievable by flash chromatography on a scale of around one gram. However, on larger scale reactions, the reaction product was not sufficiently soluble to allow effective chromatography. Due to this problem, when large scale reactions were conducted the monobromide-dibromide mixture was directly converted to the corresponding prenyl ethers. The alkyl derivatives were substantially more soluble and were easily separated by flash chromatography.

Another obvious choice for a cyclisation substrate would be an iodo-functionalised phenol such as **3.12** (X=I). This is because palladium-species undergo oxidative addition to a carbon-iodide bond more readily than to the analogous carbon-bromide bond.[84] Buchwald *et al.* found that aryl bromides were suitable substrates for the aryl etherification.[78] Only one example of an aryl iodide was used in their study and interestingly, this gave a lower yield than the corresponding aryl bromide (see **Figure 3.12**). Additionally, the cyclisation of the iodinated-substrate was substantially slower than the corresponding bromide.

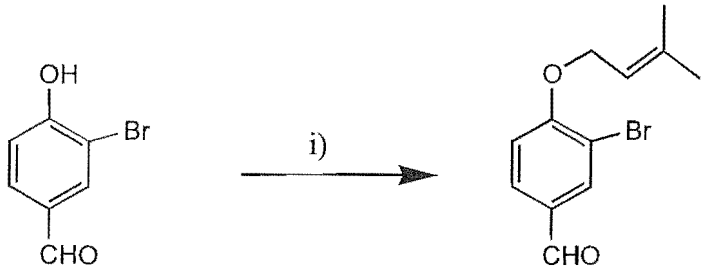
Conditions - 5 mol% $Pd(OAc)_2$, 6 mol % Tol-BINAP, 1.2 equiv of K_2CO_3, toluene at 100°C

X= Br Yield =89%

X=I Yield=60%

Figure 3.12 - Buchwald *et al.*'s investigation of the effects of changing aryl halides on cyclisations.

Accordingly, it was decided to focus on the use of the bromo-functionalised substrate **3.16**. The formation of prenyl ether **3.17** involved the same alkylation chemistry as utilised previously (see Chapter 2).[30] Monobromide **3.16** was alkylated under standard conditions using a slight excess of prenyl bromide and K_2CO_3 in DMF to give the desired alkene **3.17** in 93% yield. The splitting pattern in the ^1H nmr spectrum was analogous to that observed for 3-hydroxy-4-(2-methyl-but-2-en-1-yloxy)benzaldehyde (see Chapter 2). The chemical shifts of this were also almost identical to those recorded for that material.



3.16 **3.17**

Conditions i) K_2CO_3, prenyl bromide

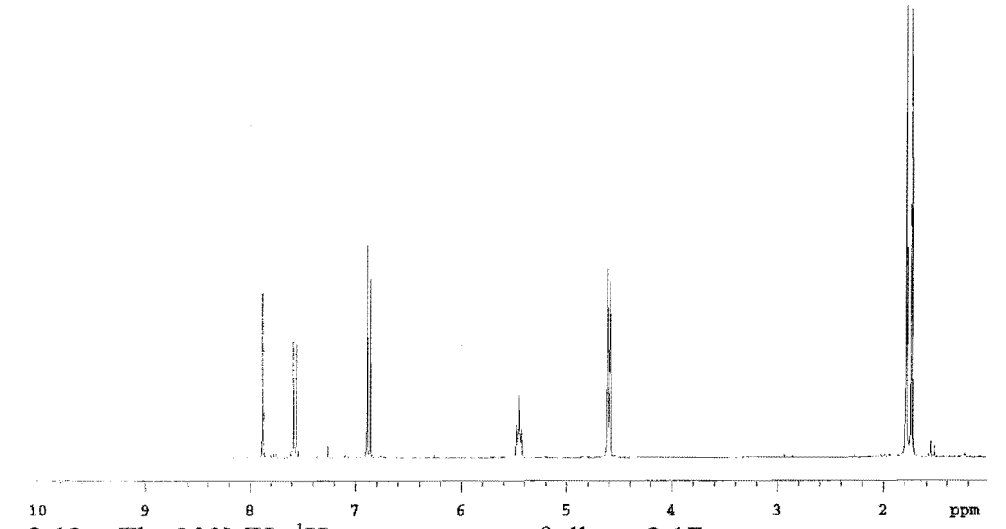
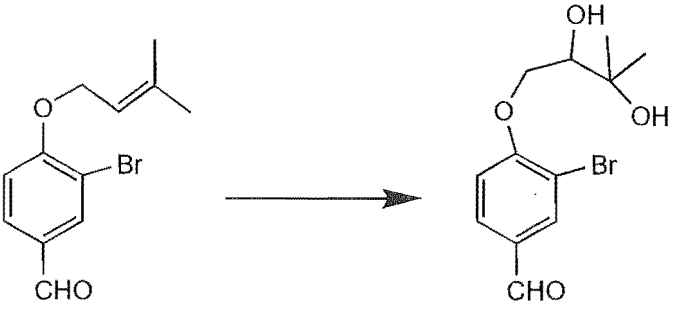


Figure 3.13. - The 300MHz ^{1}H nmr spectrum of alkene **3.17**

The next step in the preparation of substrate **3.15** was the dihydroxylation of alkene **3.17** to form diol **3.18**. Alkyl diols can be prepared from the corresponding alkenes *via* the use of stoichiometric amounts of osmium tetroxide. However, osmium tetroxide is both expensive and highly toxic.[85] A method employing only catalytic amounts of osmium tetroxide (1 mol %) was developed by Van Rheenen *et al.* using *N*-methylmorpholine-*N*-oxide (NMO) as the stoichiometric co-oxidant.[85] The reactions are carried out in a mixed solvent system of 25 parts water, 10 parts acetone and 2 parts *tert*-butanol. This solution is the key part of the catalytic method, in that it allows all three reagents to be dissolved in a relatively homogeneous solution. While the actual oxidations are slow, typically overnight, they are generally free of side products and result in high yields of the diol.



3.17 **3.18**

The method for working up these dihydroxylation reactions involves the reduction of the osmate species present in solution to osmium metal *via* the addition of sodium sulfite. The osmium metal can then be safely removed by adsorption on magnesium silicate.[85]

Using the dihydroxylation conditions of Van Rheenan *et al.* gave the desired diol as a gum. This required azeotroping with hexane and ether to remove the remaining solvent, to give diol **3.18** as a brown solid in 87% yield, which was used without further purification.

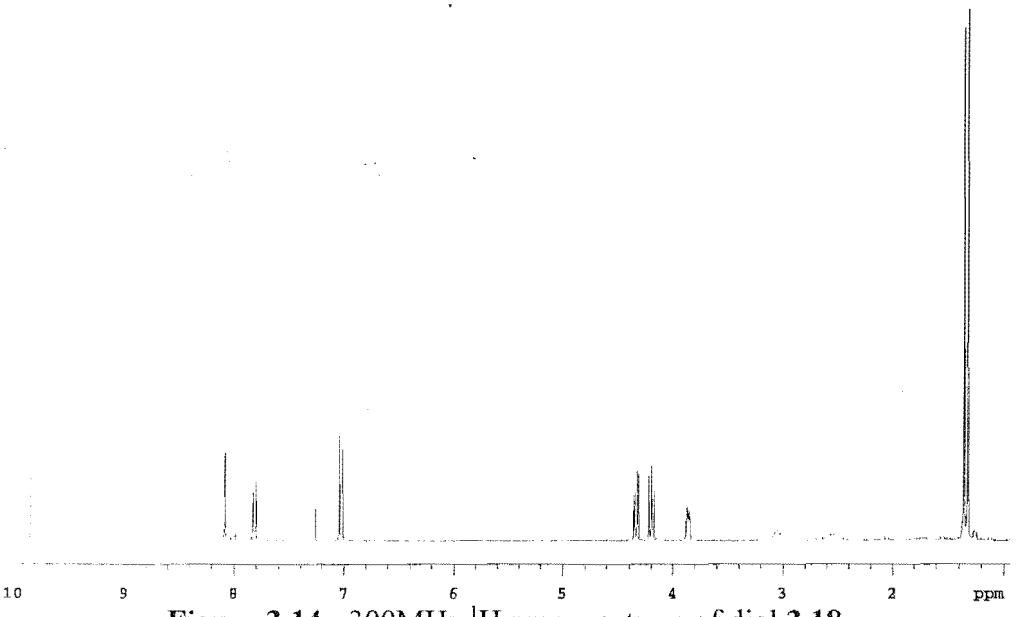


Figure 3.14 - 300MHz ^{1}H nmr spectrum of diol **3.18**

As can be seen in **Figure 3.14**, three new sets of signals have been generated in the ^{1}H nmr spectrum, centred around 4.30 ppm, 4.20 ppm and 3.80 ppm. respectively The two higher field signals correspond to the methylene present on the alkyl chain. They are present as an AB quartet, with a considerable amount of associated fine-structure, indicating their coupling is not-first order. Presumably, the fine structure is a result of the newly-created stereocentre which is now present on the adjacent carbon. The multiplet at 3.80 ppm obviously corresponds to the methine which is now a stereocentre. Unsurprisingly, given the absence of the olefinic system, the methyl protons had also shifted upfield substantially and were now centred around 1.30 ppm,

as compared with being around 1.80 ppm in the starting alkene. Reaction yields were consistent as the reaction scale was increased, with the reaction being successfully performed on five grams of alkene **3.17** With this route established, sufficient material was available to trial the Pd-catalysed cyclisations.

3.4 Cyclisation Trials

The crucial aryl halide and tertiary alcohol moieties required for arene coupling are present in diol **3.18**. The only dilemma remaining was the presence of the secondary alcohol – should it be protected? Buchwald *et al.* noted that secondary alcohols are oxidised under their Pd-catalysed cyclisation conditions unless an excess of both base and catalyst was used. However, none of the substrates investigated by Buchwald *et al.* contained both a tertiary alcohol and a secondary alcohol. From Buchwald's results it was felt that it might be possible that the tertiary alcohol would cyclise preferentially to the secondary alcohol oxidising.

When the cyclisation was attempted on diol **3.18** using $Pd(OAc)_2$/Tol-BINAP/ K_2CO_3 at 100 ^{0}C for 48 h, a mixture of starting material and a less polar compound was isolated. This new compound was identified as ketone **3.19** upon inspection of the comparatively simple ^{1}H nmr spectrum shown in **Figure 3.15**. The aromatic protons did not change significantly. The alkyl methylene gave a singlet at 5.20 ppm and the two methyl groups a singlet at 1.50 ppm.

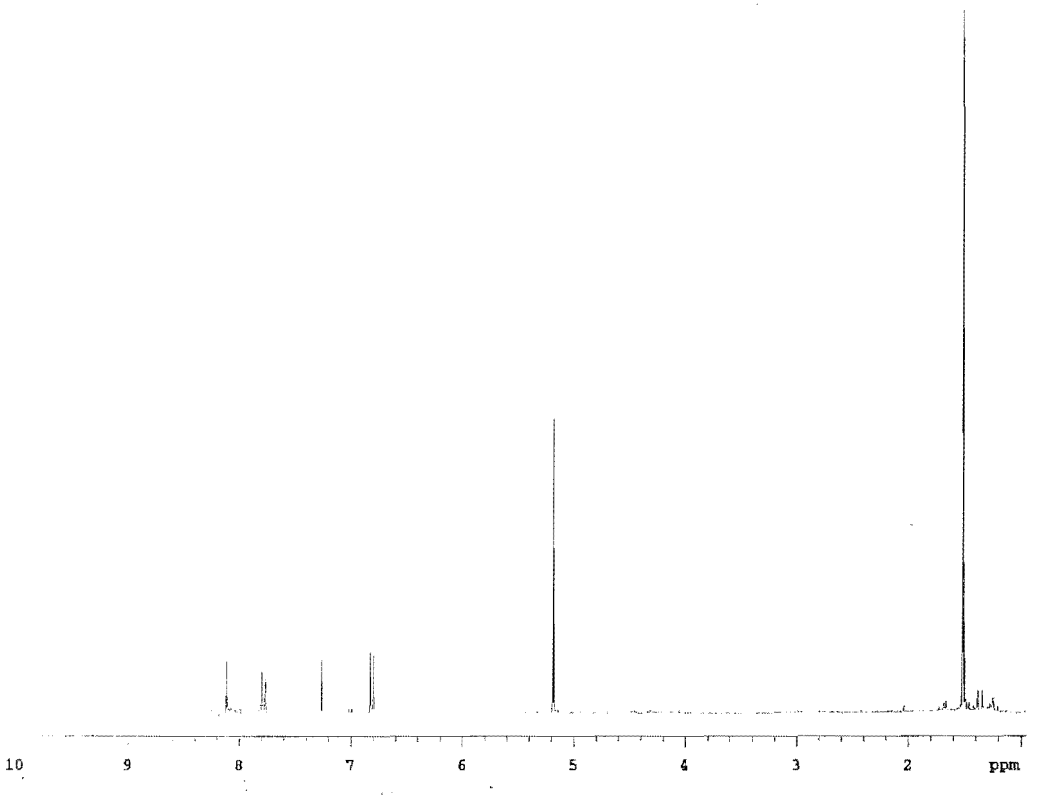
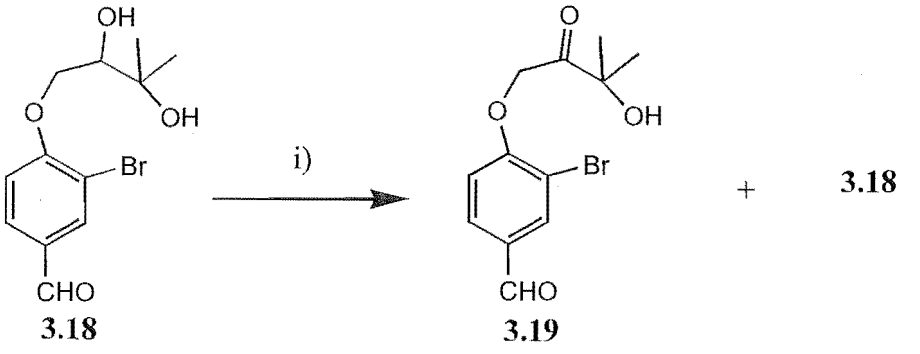


Figure 3.15 - ^{1}H nmr spectrum of the ketone **3.19.**



i) $Pd(OAc)_2$, K_2CO_3, Tol-BINAP, Toluene, 100°C

Figure 3.16 - Attempted cyclisation of diol **3.18** using Buchwald's conditions

Clearly, the secondary alcohol was oxidised in preference to the cyclisation and because of this, the secondary alcohol would require some form of protection before cyclisation could take place.

The principal requirement of such a protecting group was stability to basic conditions. The presence of either K_2CO_3 or NaO^{t}Bu was shown to be an essential requirement for the Pd-catalysed aryl ether cyclisations[78] and as such, the protecting group had to be stable to these conditions.

Accordingly, benzyl and silyl ether protecting groups were the first to be investigated. It was expected that selective protection of the secondary alcohol would be less sterically-hindered than the tertiary alcohol with its associated *gem*-dimethyl groups. Benzyl ethers are generally formed *via* the reaction of a benzyl halide with the appropriate alkoxy anion, while their cleavage is achieved using hydrogenation on a metal catalyst.[87]

Treatment of a solution of diol **3.18** in THF at 0 °C with one equivalent of sodium hydride, followed by the addition of one equivalent of benzyl bromide gave a complicated mixture of products. Flash chromatography allowed the isolation of the two regioisomeric benzyl ethers **3.20** and **3.21**. The ^{1}H nmr spectra of **3.20** and **3.21** are shown in **Figures 3.17** and **3.18** respectively

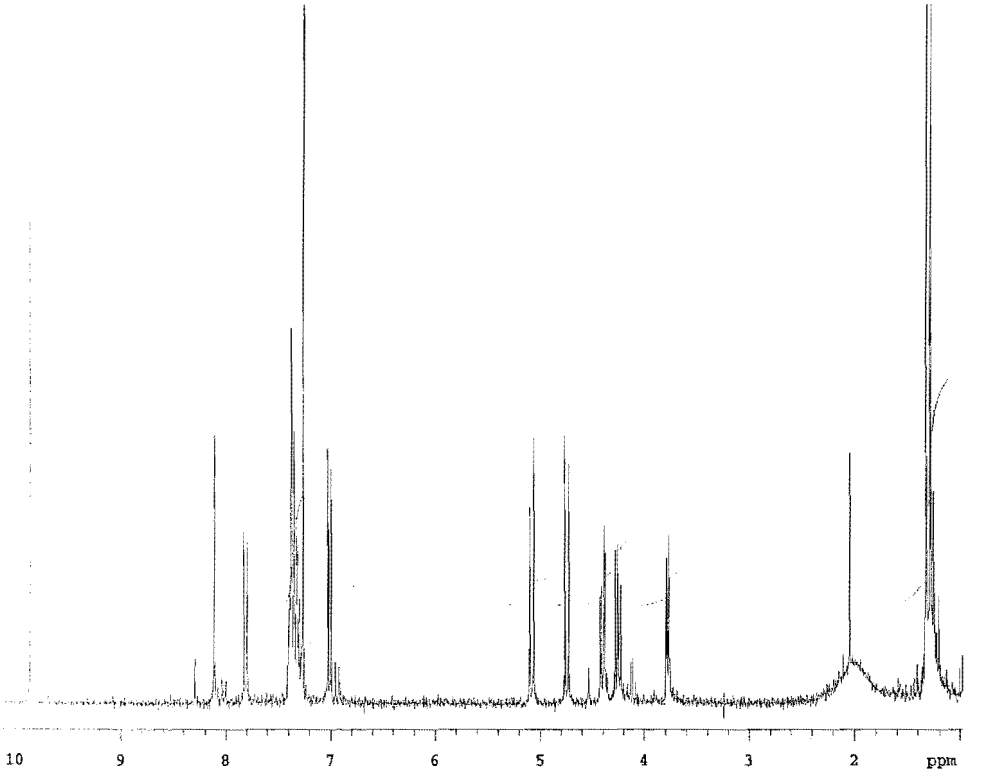


Figure 3.18 - 300 MHz ^{1}H nmr of secondary-protected benzyl ether **3.20**

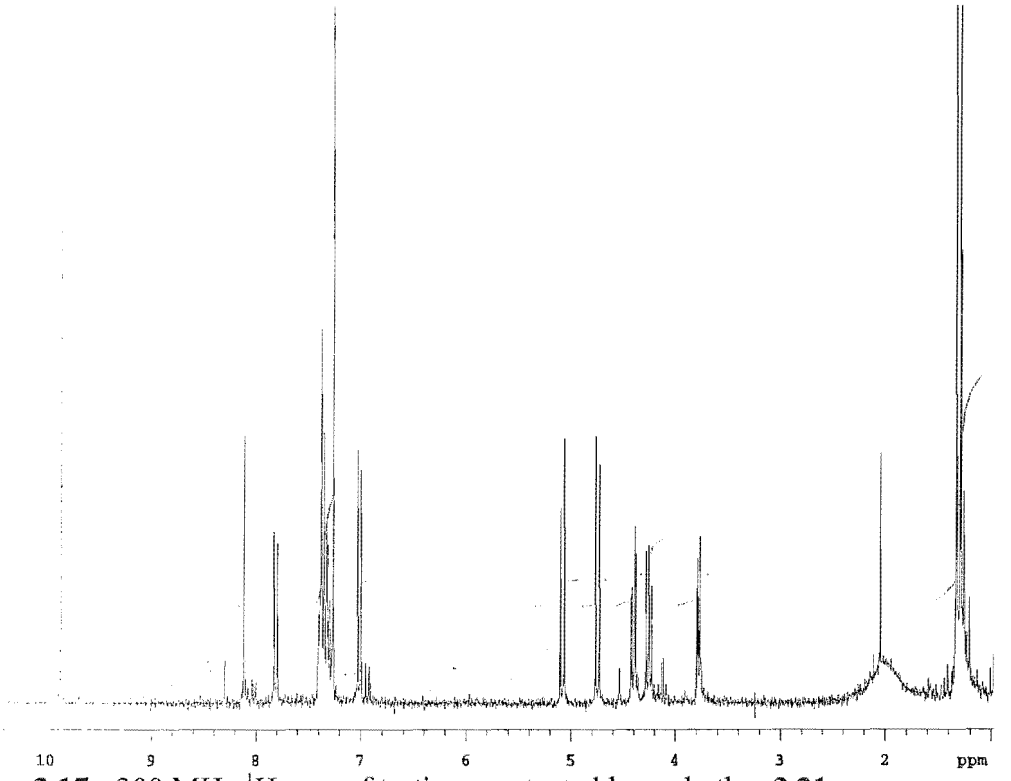


Figure 3.17 - 300 MHz ^{1}H nmr of tertiary-protected benzyl ether **3.21**

Compound **3.20** was identified as the desired secondary-protected alcohol by the appearance of an AB quartet centred around 5.10 and 4.75 ppm in the ^{1}H nmr spectrum. This was attributed to the benzyl methylene group being close to a stereocentre. Contrastingly, the benzyl group in **3.21** gave only a singlet at 4.55 ppm. Full ^{1}H and ^{13}C nmr assignments were achieved by two-dimensional nmr experiments as shown in **Figure 3.19**. The regioisomeric connectivity of the benzyl ether products was confirmed by HMBC correlation experiments. The crucial correlations which allowed the confirmation of the regioisomerism of the ethers are shown in **Figure 3.19**. The key correlation in the secondary ether was from the diastereotopic benzyl methylene group across the ether bond to the methine stereocentre. In the case of the tertiary ether structure, this would be an unlikely four bond correlation. Compound **3.21** gave a three bond correlation from the quaternary carbon attached to the *gem*-dimethyl groups across to the benzyl methylene, thus confirming that it was the tertiary ether.

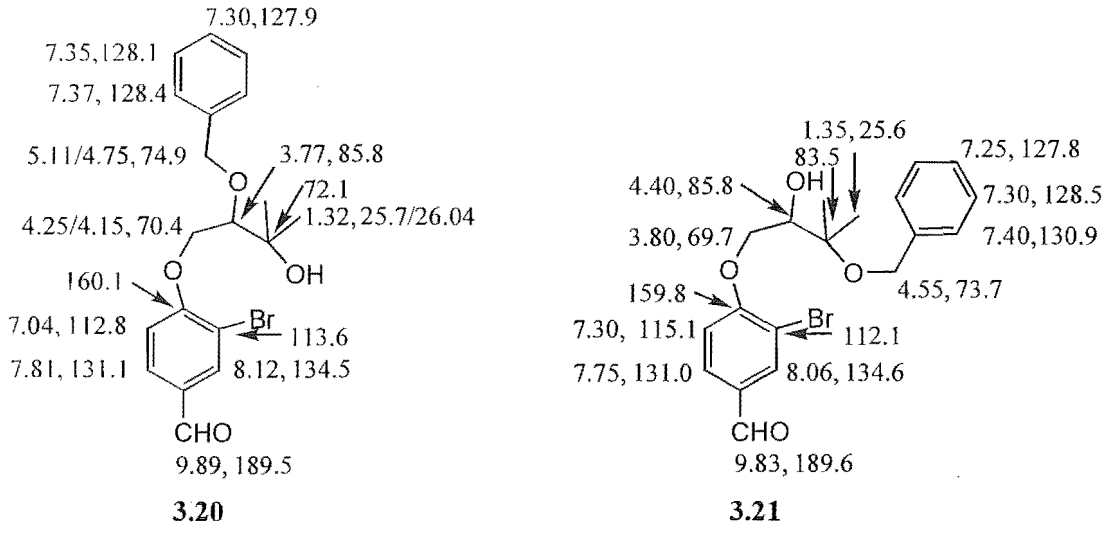


Figure 3.19 - ^{1}H and ^{13}C data for benzyl ethers **3.20** and **3.21** based on HMBC/HSQC-experiments. (All data are in the form δ_H,δ_C.)

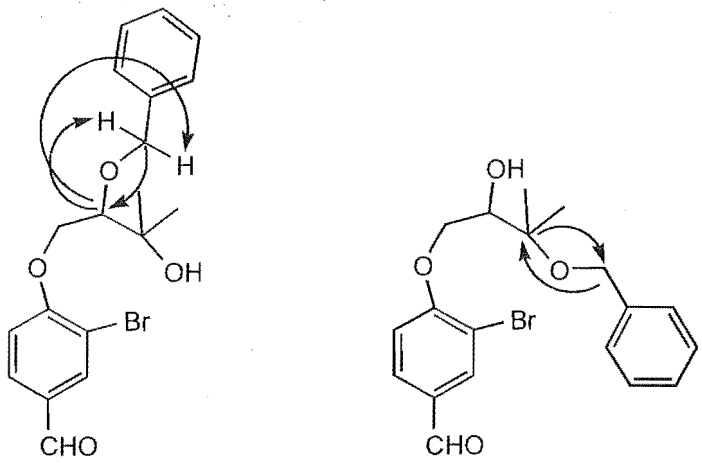


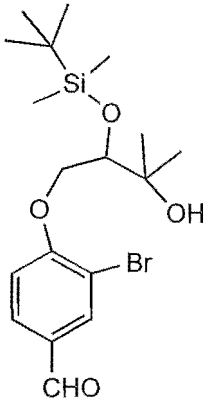
Figure 3.20 - The key HMBC correlations which allowed determination of the regiochemistry of the benzyl products

Although the initial benzylation allowed full identification of both **3.20** and **3.21**, they were isolated in low yield (9% and 5% respectively). Despite much experimentation, the yield of the desired ether **3.20** could not be increased.

The most commonly used silyl protecting group is the *tert*-butyldimethylsilyl (TBDMS) group.[87] Mild methods for its introduction were developed by Corey and Venkateswarlu.[88] These involve the use of TBDMSCl, with imidazole as the base and

DMF as the solvent. Previous methodologies for formation of TBDMS ethers had involved the use of excess chlorosilane and excess dry pyridine at elevated temperatures.[89] In addition to developing these mild formation methods, Corey and Venkateswarlu showed that silyl ethers could be readily cleaved to give the free alcohol by using excess tetra-*N*-butylammonium fluoride (TBAF).[88] Alternatively, TBDMS ethers may be cleaved using mild acid treatment (2:1 acetic acid/water at 25 °C). Buchwald *et al.* showed that TBDMS ether linkages were stable to the Pd-catalysed cyclisation conditions employed and thus, the synthesis of TBDMS ethers of diol **3.18** was investigated.

The secondary alcohol in **3.18** was also protected as the *tert*-butyldimethyl silyl ether. The standard conditions for this protection involve reacting the substrate alcohol with excess TBDMSCl and imidazole in a concentrated DMF solution.[88] When this was attempted on diol **3.18**, no reaction was observed after 24 hours. 4-dimethylaminopyridine (DMAP) has been shown to increase the rate of TBDMS ether formation reactions.[90] The silylation was attempted using 1.5 equivalents of imidazole, 0.2 equivalents of DMAP and one equivalent of TBDMSCl in a DMF solution. After the suspension was stirred for 36 hours the silyl ether **3.22** was obtained in 38% yield after flash chromatography. The remainder of the mixture was starting material, which would seem to indicate that the reaction occurs slowly, presumably because the bulky TBDMS group is slow to react with the hindered alcohol moiety.



3.22

Figure 3.21 - The desired TBDMS ether

Two sets of changes were observable in the ^{1}H nmr spectrum of tertiary alcohol **3.22** relative to that of the starting material; the appearance of signals corresponding to the methyl and *tert*-butyl groups of the TBDMS moiety and the multiplet of the methine stereocentre shifting downfield 0.10 ppm. While it was assumed that the desired secondary ether had been formed, this could not be confirmed by nmr methods as any useful C-H bond correlations would be over four bonds, including one Si-O bond. This is beyond the scope of a normal HMBC experiment. A solution to this problem was found *via* the use of single-crystal x-ray crystallography. Happily, this confirmed that **3.22** was the desired secondary protected silyl ether.

An attempted silylation using the more reactive *tert*-butyldimethylsilyl triflate gave a complex mixture of silylated and non-silylated products. Although the silylation using TBDMSCl was far from ideal, enough material was available to trial Buchwald's cyclisation conditions using this substrate.

Protecting group	Conditions	Yield of desired material
Benzyl	1eq BnBr, 1 eq. KO^{t}Bu, THF, 25°C, 16 hours.	9%
Tert-butyl dimethyl silyl (TBDMS)	1.2 eq. TBDMSCl, 1.5 eq. Imidazole, DMF, 25°C, 36 hours.	38%

Table 3.1 - Preparation of the benzyl and TBDMS-protected cyclisation substrates.

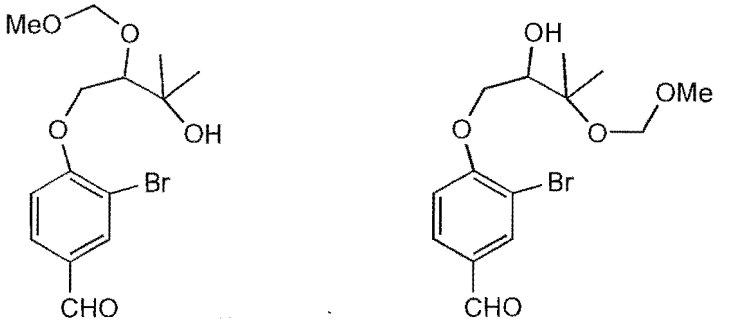
With the two tertiary aryl alcohols readily available by the above routes, it was possible to trial Buchwald *et al.*'s cyclisation conditions. These cyclisations were attempted on the same scale as that employed by Buchwald *et al.*, namely 0.3 mmol. Given that the bases involved were highly sensitive to small amounts of water, particularly sodium *tert*-butoxide, all manipulations were performed in a glove box. Disappointingly, even with extended heating, neither of the substrates gave any reaction upon exposure to either set of Buchwald *et al.*'s cyclisation conditions.[78]

The principal difference between the substrates and those successfully employed by Buchwald is the presence of the adjacent benzyl or silyl ether. While none of Buchwald's substrates were aryl aldehydes, it has been shown that these type of cyclisations occur more rapidly with electron-poor arenes.[77] However, both benzyl and TBDMS groups provide substantial steric bulk near the tertiary alcohol. Given the size of these groups, it seemed plausible that their steric bulk is in some way slowing the palladium-catalysed reaction

Since the benzyl and TBDMS ethers failed to cyclise, it was decided to trial a less sterically demanding protecting group. If it was the steric bulk of the benzyl and TBDMS groups that was preventing reaction, a smaller protecting group should allow the cyclisation to proceed. It was decided to protect the hydroxyl group as the methoxymethyl acetal (MOM). This was one of the protecting groups shown to be stable to Buchwald *et al.*'s cyclisation conditions. Like most acetals, MOM-protected alcohols are stable to base, an obvious requirement for any protecting group used in this synthesis (*vide infra*). One drawback of the use of MOM ethers is the comparatively harsh conditions required for their deprotection, which usually involves strong Lewis or Bronsted acid-catalysed cleavage. The earlier work on acid-catalysed epoxide opening showed that the target dioxepin ring was stable to a range of Lewis and Bronsted acids, so the MOM group should be removed after cyclisation.

Initial studies investigating the protection of the diol **3.18** as the MOM ether involved the reaction of a solution of diol **3.18** in CH_2Cl_2 with 1.1 equivalents of methoxymethyl chloride (MOMCl) and 1.4 equivalents of Hunig's base. These conditions resulted in incomplete reaction after 24 hours. The addition of an extra 0.5 equivalents of MOMCl and 0.6 equivalents of Hunig's base, and a further 12 hours of reaction allowed complete consumption of starting material and the generation of two products. Chromatography of the reaction mixture allowed separation of the two products to give the desired secondary-protected alcohol **3.23** in 38% yield and the regioisomeric alcohol **3.24** in 30% yield. The ^1H nmr spectra of these two products were very similar to those encountered with the corresponding benzyl ethers. Alcohol

3.23 gave an AB quartet centred at 5.00 and 4.80 ppm, which were assigned to the diastereotopic methylene of the MOM group. The only other addition to the spectrum was a singlet at 3.50 ppm, which corresponds to the methoxy ether present in the MOM group. Contrastingly, the ^{1}H nmr spectrum of **3.24** gave two new singlets, one at 4.80 ppm assigned to the methylene of the MOM group and the other at 3.40 ppm assigned to the methoxy group. The regioisomerism of the alkylation was determined based on these splitting patterns.

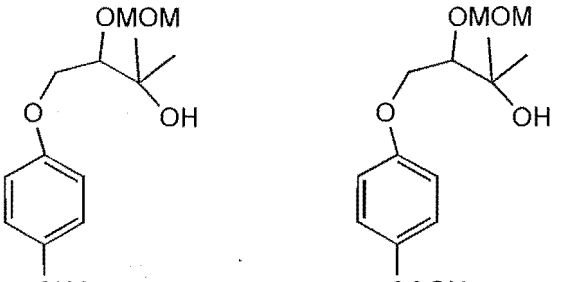


3.23 **3.24**

Figure 3.22 – The two MOM ethers isolated from the MOM-protection trials

Although once again the yield of **3.23** was far from ideal, sufficient material was available to trial the cyclisation reactions. The first cyclisation method to be trialed involved the K_2CO_3/$Pd(OAc)_2$/Tol-BINAP system, but heating alcohol **3.23** with this catalyst system for 48 hours gave no reaction. However, use of the NaO^{t}Bu/$Pd(OAc)_2$/DPPF system did give some reaction. The catalyst system was removed by filtering the reaction mixture through a silica plug. This method was not ideal for working up this particular reaction as material was lost, presumably due to adsorption onto silica. Even with extensive washing with methanol, mass balance was not attained. However, the product mixture showed the presence of two main products. One was identified as the dehalogenated arene **3.25** (14%). The ^{1}H nmr spectrum of the product gave only two signals in the aromatic region, a doublet at 7.80 ppm and a doublet at 7.00 ppm, both of which integrated for two protons. Electron Impact Mass Spectroscopy (EIMS) confirmed that the material had been dehalogenated. This suggested that the Pd catalyst had undergone oxidative addition to the aryl-bromide bond, but the reaction had not proceeded further. Hydrolysis of

the Pd-Br species either *in situ* or during workup would then allow for the formation of **3.25**. The other product of the reaction could not be purified and accordingly, was not conclusively identified. Again, its ^{1}H nmr spectrum gave two doublets in the aromatic region, at 7.90 ppm and 6.95 ppm. However, the main change was the disappearance of the aldehyde signal, which had been at 9.90 ppm in the starting material. It was thought that the aldehyde may have been oxidised to give a carboxylic acid. The increased polarity of the compound relative to **3.25** and **3.23** concurred with this proposal.

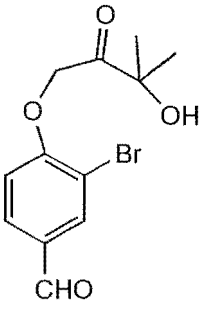


3.25 **3.26**

Figure 3.23 - Two of the products of the MOM-protected ether cyclisations.

The removal of the bromide in these two products was a reassuring result, in that it confirmed that the Pd-catalyst can undergo oxidative addition to the arene-bromide bond. This indicated that the presence of the aldehyde on the arene did not impede the oxidative addition. However, the reaction did not proceed further. It was assumed that the tertiary alcohol was not chelating to the Pd-catalyst and thus, cyclisation could not occur.

At this point, the protection strategy for the secondary hydroxyl group was re-evaluated. It was clear that even a relatively small protecting group such as a MOM ether prevented the key cyclisation from occurring. However, the secondary hydroxyl group must be included as it is part of the natural product. When it was exposed to the cyclisation conditions, it was oxidised to the corresponding ketone. These results provoked the thought that the conversion of the hydroxyl group to the ketone as in **3.19** might be a way to reduce the steric bulk adjacent to the tertiary alcohol.



3.19

Figure 3.24 - Keto-protected cyclisation substrate **3.19**

The catalytic tetrapropylammonium perruthenate (TPAP) system developed by Ley and co-workers was investigated for the conversion of diol **3.18** to ketone **3.19**.[93] Catalytic TPAP oxidations are normally carried out in CH_2Cl_2 and require 5 mol% TPAP, with NMO as the stoichiometric co-oxidant. The great strength of the TPAP methodology is its requirement for only a catalytic amount of the oxidant, as compared with other mild oxidation protocols such as the Dess-Martin periodinane,[94] or the Swern oxidation.[95] TPAP also avoids the harsh conditions and difficult work-up associated with chromium-based oxidants such as pyridinumchlorochromate (PCC).[96] Ley's standard method for oxidation involved 0.05 equivalents of TPAP being added to a suspension of 1.5 equivalents of NMO, diol **3.18** and powdered molecular sieves in CH_2Cl_2. Stirring for two hours and filtering through a silica plug eluting with ethyl acetate gave a mixture of approximately 75% starting diol and 25% of the desired ketone **3.19**. When the reaction was repeated and left to stir for 12 hours, only 30 % conversion was obtained. It has been found that some TPAP oxidations fail to go to completion when performed in CH_2Cl_2.[93] The addition of 10% acetonitrile is reported improve this conversion rate. [93] It is thought that acetonitrile has this effect by increasing the number of TPAP turnovers. The acetonitrile has to be removed before filtering through silica as it can co-elute residual TPAP.[93] When this method was trialed, an improved but still disappointing 40% yield was obtained after two hours at room temperature. As a method of last resort the reaction was attempted using acetonitrile as the solvent. This also gave a 40% yield of the desired ketone. It has been shown that TPAP displays some sensitivity to steric hindrance around a target hydroxyl group and that this is particularly a problem with sterically-congested secondary alcohols.[93] Given the slow speed of the TBDMS ether formation and the

resistance to complete conversion to TPAP oxidation, it would seem plausible that the secondary alcohol exists in a relatively hindered conformation, thus denying these regents ready access to the hydroxyl group. At this point two options were available; either find a more effective oxidising agent, or use TPAP and accept a 40% conversion. It was decided to continue using TPAP as it allowed for relatively quick reactions, easy separation, and the starting material could be easily recovered. It was found that the yields for this oxidation stayed constant with larger scale reactions, thus allowing access to sufficient material to trial the cyclisation.

When the cyclisation of ketone **3.19** was attempted using the NaO^{t}Bu/DPPF/Pd(OAc)$_2$ system, destruction of the substrate resulted after heating for 8 h. Mass balance was not attained, even with extensive washing of the silica plug. The reaction mixture was only slightly soluble in $CHCl_3$, with only aromatic protons being visible in the ^{1}H spectrum. Although the exact reason for substrate destruction was not elucidated, a potential explanation can be seen in the structure of ketone **3.19**. The alkyl chain has a methylene group on the carbon α to the ketone. Obviously, these protons have a relatively high acidity due to the ketone's ability to delocalise a negative charge at this position by formation of the corresponding enolate. Thus, upon exposure to the strong base NaO^{t}Bu, deprotonation to give **3.30** could occur competitively with the cyclisation. In aqueous solution the *t*-butoxide anion has a pK_b of 16 whereas the protons on a carbon α to a carbonyl have a pK_a of around 20, suggesting that the deprotonation would not occur. However, changing the solvent to toluene is likely to have a significant effect upon these values.

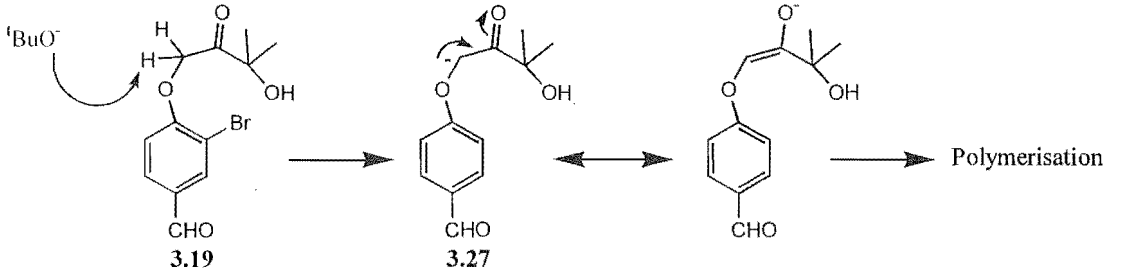
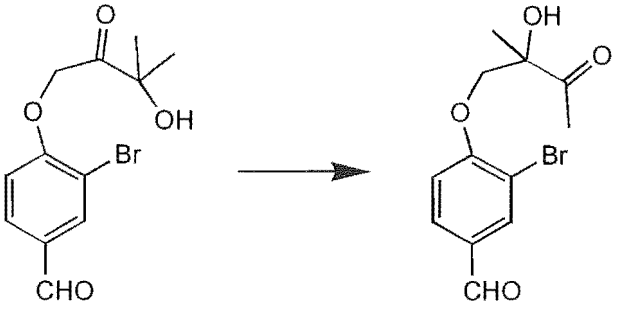


Figure 3.25 - A potential mechanism for destruction of ketone **3.19** when exposed to the NaO^{t}Bu/DPPF/Pd(OAc)$_2$-based cyclisation conditions

If deprotonation were to take place, the resulting carbanion could undergo intermolecular aldol reactions with the aldehyde, to afford polymeric material.

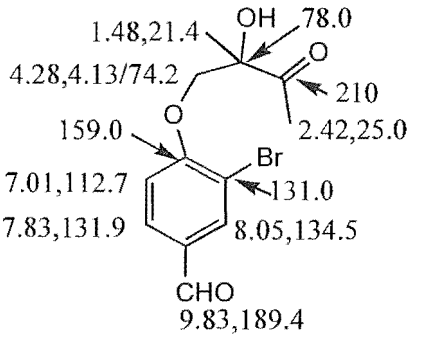
When ketone **3.19** was exposed to the alternative K_2CO_3/Tol-BINAP/$Pd(OAc)_2$ cyclisation conditions, it gave a most interesting result. Heating for 24 hours afforded a mixture of two products in the ratio of 5.5:1. Chromatography of the mixture allowed their separation. The minor product of this reaction (7% yield) was found to be the dioxepinone **2.29**. The data for this compound were found to be identical to those recorded previously (see **Section 2.5**). Although this was an very low yield, the result was met with a degree of jubilation as it proved that functionalised benzodioxepin rings could be constructed by a Pd-mediated aryl ether forming reaction.

The major product was isolated in 39% yield and had a ^1H nmr spectrum that was initially surprising. Little change was observed in the aromatic protons. However, the methylene signal at 5.20 ppm had disappeared and an AB-type system had developed at 4.30 and 4.10 ppm, similar to that seen in the secondary alcohol and secondary ether substrates (*vide infra*). This seemed to indicate that a stereocentre had been formed in the molecule. Additionally, a singlet which integrated for three protons was seen at 2.40 ppm. Extensive two-dimensional nmr experiments lead to the conclusion that the product was α-ketol **3.28**.[97]



3.19 **3.28**

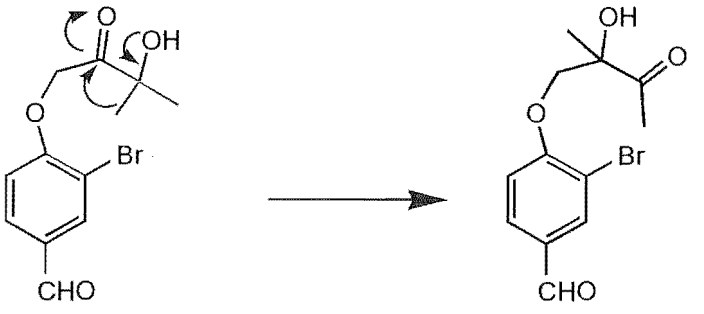
Figure 3.26 - Ketol **3.28**, the major product of the Pd-catalysed cyclisation attempts on ketone **3.19**. *Conditions* – i) 0.05 eq Pd(OAc)2, 0.06 eq Tol-BINAP, 1.2 eq K_2CO_3, Toluene, 100°C, 24 hours.



3.28

Figure 3.27 - $^{1}H/^{13}C$-based nmr assignments for α-ketol **3.28** based on HMBC/HSQC experiments (All data are in the form δ_H,δ_C.)

Presumably, this compound results from a methyl group shifting in a 1,2 fashion to give the observed α-ketol. It is reported that base is required to catalyse this rearrangement, presumably by deprotonating the alcohol.



3.19 **3.28**

However, it seemed unlikely that a base as weak as K_2CO_3 could affect deprotonation of the hydroxy group in ketone **3.19**. Thus, it was postulated that the Pd species may be acting as a catalyst for the reaction. By chelating the two oxygen atoms, it could aid methyl transfer by evenly distributing any charge-buildup during the reaction. To test this hypothesis, the reaction was repeated in the absence of both $Pd(OAc)_2$ and the Tol-BINAP ligand. Heating with potassium carbonate at 100 °C for 22 hours in toluene returned only ketone **3.19**. This offers some validity to the proposal that the α-ketol rearrangement is catalysed by the Pd-species present under the cyclisation conditions. This is an encouraging result in that it suggests that by altering the nature

of the Pd species which is present *in situ*, the α-ketol rearrangement might be suppressed and thus, allow for the dioxepin to form preferentially.

3.5 Summary

A low-yielding synthesis of dioxepinone **2.29** by a Pd-catalysed aryl ether formation has been described. Investigations of this Pd-catalysed reaction have indicated that the presence of the bulky benzyl and TBDMS protecting groups prevent the key cyclisation reaction from occurring. It has been shown that aryl bromides are capable substrates for the oxidative addition of a Pd species under these conditions.

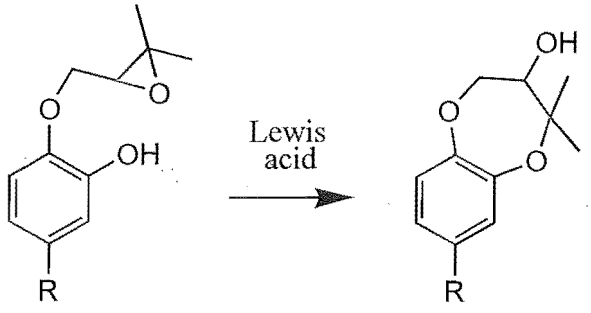
The smaller MOM protecting group allows the initial Pd oxidative addition into the arene-bromide bond to occur, but the reaction does not proceed further.
Converting the hydroxyl group into the ketone allows the cyclisation to occur, albeit in 7% yield. Unfortunately, this substrate preferentially undergoes a rearrangement to give an α-ketol. It would appear that this rearrangement is Pd-mediated. A clearer understanding of the mechanism of this reaction will require further investigation before the yield of the dioxepinone **2.29** can be increased.

Chapter Four

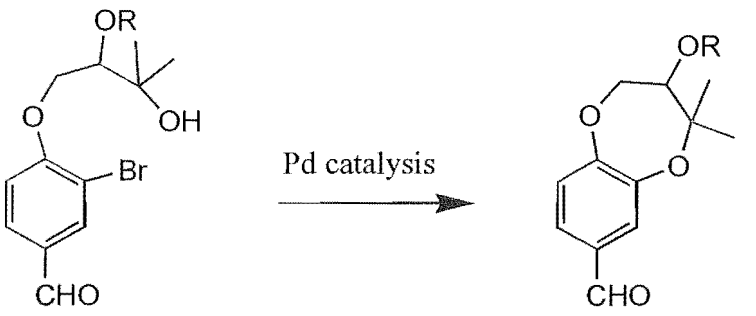
Summary and Future Potential of these Studies

4.1 Summary and Future Potential of these Studies

The two synthetic approaches discussed in this thesis have resulted in two low-yielding syntheses of the benzodioxepin ring system found in members of the strobilurin family. The yield of the Lewis acid-catalysed epoxide opening, previously used by Williams *et al.*,[33,34] Nicholas *et al.*[26,27] and Hellwig *et al.*[30] to form the benzodioxepin system, displays a considerable degree of substrate dependence. As such, its use to construct the benzodioxepin core of 9-methoxystrobilurin K as part of a total synthesis is not viable.



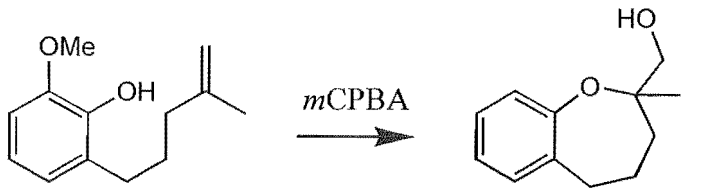
The Pd-mediated aryl ether formation offers more hope for the development of an efficient synthesis of the target benzodioxepin system. These cyclisations display sensitivity to steric bulk adjacent to the nucleophile tertiary hydroxyl group and as such, the use of the large benzyl and TBDMS protecting groups prevent the reaction from occurring. The use of the smaller MOM protecting group allows the Pd species to undergo oxidative addition to the arene-bromide bond, however the reaction does not proceed further. The keto-protected substrate undergoes cyclisation, but an α-ketol rearrangement occurs preferentially. This rearrangement appears to be Pd-assisted and as such, varying the nature of the ligands chelated to the Pd may allow for the selection of the cyclisation reaction over the α-ketol rearrangement.



Near the end of the work discussed in this thesis, an account was published of the development of an extremely active Pd catalyst system for forming *tert*-butyl ethers from aryl halides.[98] It was found that a mixture of 2 mol % $Pd(OAc)_2$ and 6 mol % $P(^tBu)_3$ allowed the formation of *tert*-butyl ethers when reacted with a range of aryl halides and 1.2 equivalents of NaO^tBu. In an interesting extension to the work of Buchwald discussed in **Chapter 3**,[78] this reductive elimination occurred with both electron-rich and electron-poor arenes. This catalyst system would seem to offer a alternative to Buchwald's Tol-BINAP- and DPPF-based systems. The use of a less crowded phosphine to chelate the Pd could alleviate the problems encountered with the more bulky DPPF and Tol-BINAP ligands.

Hartwig and Mann's work on the use of $Ni(COD)_2$/DPPF as a catalyst for the formation of protected phenols[81] also offers some hope for forming the target benzodioxepin by an approach involving reductive elimination. Although this method and the $Pd(OAc)_2/P^tBu$ catalyst system were developed for forming protected phenols, their use could be potentially be extended to allow intramolecular cyclisations. These catalyst systems offer additional hope for affecting the benzodioxepin cyclisation, rather than the α-ketol rearrangement. The unavailability of these catalysts prevented the investigation of their use during the course of the work discussed in this thesis.

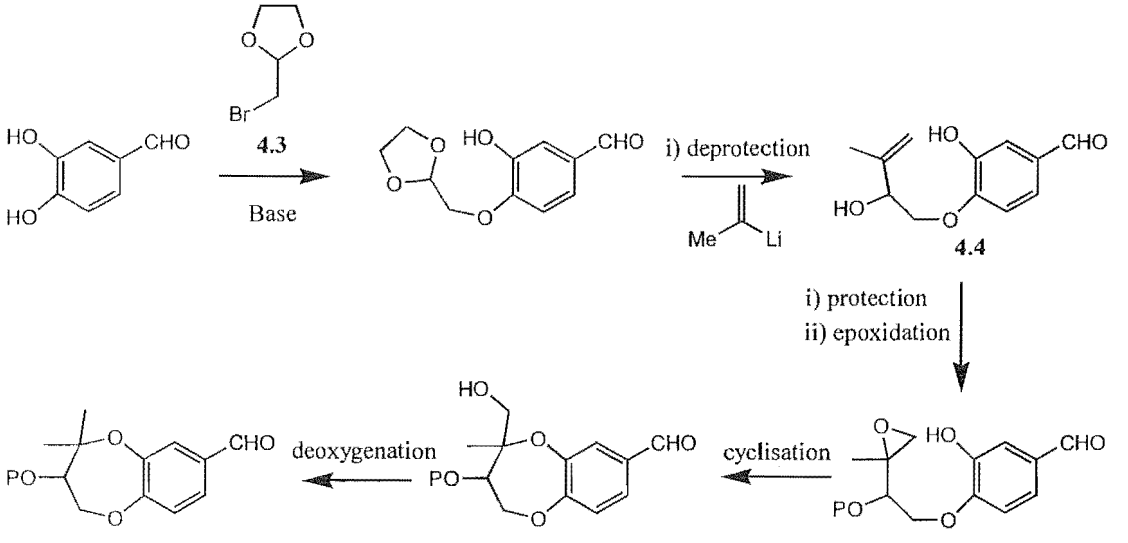
An alternative strategy for preparing the benzodioxepin species draws on the work of Bravo *et al.*[98] who investigated the relative rates of formation of a variety of medium-sized rings by acid-catalysed epoxide rearrangement, such as that detailed in **Scheme 4.1** by a favoured 7-*exo*-trig cyclisation. Treatment of olefin **4.2** with *m*CPBA gave the corresponding benxooxepin in 70% yield.



4.2

Scheme 4.1 – Bravo's epoxide rearrangement approach to the formation of benzooxepins.

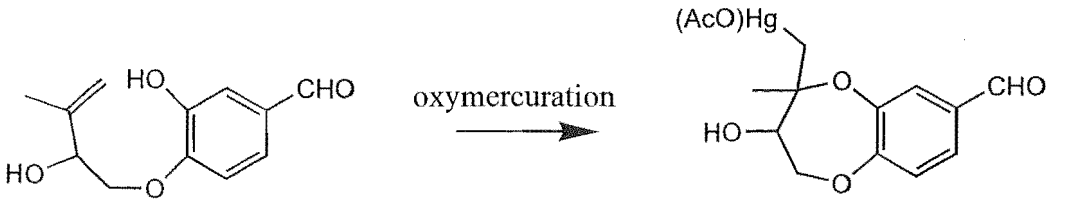
To trial such an approach, an olefin such as **4.4** would be required. This could be prepared by reaction of 3,4-dihydroxybenzaldehyde with bromo acetal **4.3** as shown.. Deprotection of the acetal and reaction with 2-propenyl lithium should give **4.4**. It would be hoped that he allylic alcohol and the phenol will have differing reactivity, allowing selective protection of the allylic alcohol. Epoxidation of the alkene, followed by cyclisation should afford the hydroxymethyl dioxepin. Deoxygenation of the resultant alcohol should afford the desired benzodioxepin.



Obviously such an approach would still be open to undesired epoxide rearrangements such as those discussed in **Chapter 2.**

An alternative strategy for the cyclisation of olefin **4.4**, would be to use an oxymercuration approach.[100] Electrophilic addition of mercuric acetate or mercuric

trifluoroacetate to olefin **4.4** should result in the formation of the mercurate **4.5** based on the addition occurring to give the more stable tertiary carbocation, with subsequent attack by the phenol resulting in benzodioxepin ring formation.



4.4 **4.5**

Reduction of mercurate **4.5** with sodium borohydride should replace the mercurate group with a proton, while the aldehyde would also be reduce, it can be oxidised selectively using MnO_2 as detailed by Steglich [30] to afford the desired benzodioxepin.

Chapter Five

Experimental

5.1 General Methods

Spectroscopic Considerations

Proton-detected NMR spectra were obtained on either a Varian Unity 300 spectrophotometer or a Varian XL300 spectrophotometer, both operating at 300 MHz. Carbon-detected NMR spectra were obtained on an XL300 spectrophotometer operating at 75 MHz. All spectra were obtained at 23 °C. The reverse-detected HSQC and HMBC experiments were obtained on the Unity 300 spectrophotometer operating at 300 MHz. At various stages this instrument was fitted with a Pulsed Field Gradient MLD driver with a 5mm Indirect Detection Probe. Chemical shifts in this thesis are recorded in parts per million (ppm) on the δ scale. All NMR spectra were recorded in $CDCl_3$, referenced to $CHCl_3$ at δ_H 7.26 and δ_C 77.01. ^{13}C nmr spectra were typically obtained with a delay (D_1) of 1s. HMQC experiments were run with a D_1 of 1.0s and $^1J_{CH}$ = 140 Hz. HMBC experiments were run with a D_1 of 0.3 s, $^1J_{CH}$ = 140 Hz and $^2J_{CH}$ = 8.3 Hz.

Mass Spectrometry was performed on a Kratos MS80 Mass Spectrometer operating at 4 kV.

IR spectra were obtained using a Shimadzu 8201PC Series FTIR interfaced to an Intel 486 PC running Shimadzu's HyperIR software. Spectra were run either neat on a KBr disk, or in $CHCl_3$ solution.

Reagents, Solvents and Experimental Considerations

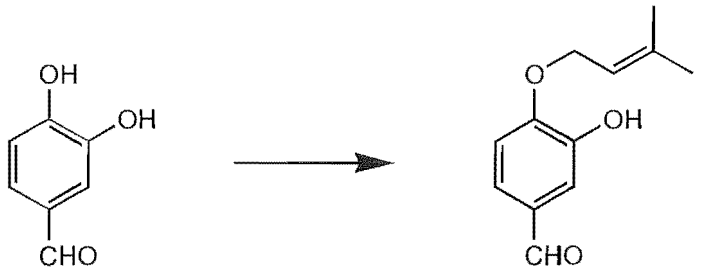
All reactions were performed in either oven- or flame-dried glassware under a nitrogen or argon atmosphere. Analytical thin-layer chromatography (TLC) was conducted on aluminium-backed Merck Kieselgel $KG60F_{254}$ silica plates. Visualisation was by short-wave ultraviolet light and subsequent staining with either anisaldehyde, $KMnO_4$, or 2,4-dinitrophenylhydrazine solutions. Flash chromatography was performed on Merck Silica 60 follow the guidelines of Still and co-workers.[102] Solvents were purified by well-established procedures.[103] Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl

immediately prior to use. Toluene and CH_2Cl_2 were distilled from CaH_2 prior to use. *N,N*-Dimethylformamide (DMF) was dried by standing over freshly-activated 4 Å molecular sieves for two periods of 24 hours, before finally being stored under Ar over fresh 4 Å molecular sieves. This was degassed under high vacuum for 2 minutes immediately prior to use.

Unless otherwise stated, all organic fractions were dried over Na_2SO_4 and filtered before solvent evaporation *in vacuo*.

5.2 Experiments described in Chapter 2

3-Hydroxy-4-(3-methyl-but-2-en-1-yloxy)benzaldehyde 2.25



2.22 **2.23**

3,4-Dihydroxybenzaldehyde **2.22** (1.025 g, 7.42 mmol) was dissolved in DMF (37 mL) and cooled to 0 °C. After 10 min K_2CO_3 (1.026 g, 7.42 mmol) was added via solid addition tube with vigorous stirring. 4-Bromo-2-methyl-buten-2-ene (940 µL, 8.16 mmol) was added dropwise over five min and the solution left to warm to RT. After 18 hours the reaction was quenched by the addition of 1M HCl solution (25 mL) and the resultant solution extracted with ethyl acetate (3 x 50 mL). The combined organic phases were washed with H_2O (2 x 100 mL) and brine (1 x 100 mL). The solvent was removed *in vacuo* to yield the crude product as a brown solid (1.560 g). Flash chromatography on silica using 25% ethyl acetate - petroleum ether as eluant, gave the title compound **2.25** as pale yellow crystals (1.126 g, 74%).

^1H NMR ($CDCl_3$) δ 9.83 (s , 1H, ArC**H**O), 7.39 - 7.43 (m, 2H, Ar**H**), 6.94 - 6.97 (d, J_{HH} = 8.3 Hz, 1H, Ar**H**), 4.67 (t, J_{HH} = 6.8Hz, 1H, $CH_2C\mathbf{H}C(CH_3)_2$), 1.80 (s, 3H, $CH_2CHC(C\mathbf{H}_3)_2$), 1.76 (s, 3H, $CH_2CHC(C\mathbf{H}_3)_2$).

^{13}C NMR ($CDCl_3$) δ 191.05 ,151.21, 146.32, 139.76, 130.34, 124.42, 118.27, 114.00, 111.17, 65.88 , 25.69 , 18.18 .

HREIMS calc. for $C_{12}H_{14}O_3$: 206.0943; found 206.0940.

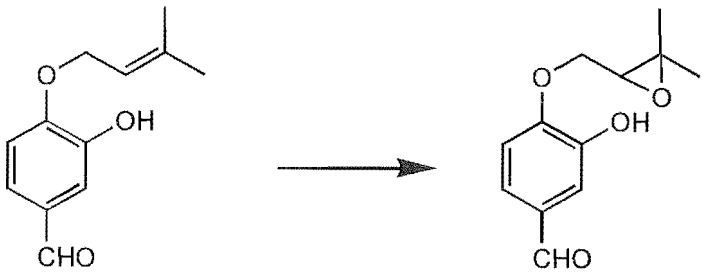
FTIR (cm^{-1}, $CHCl_3$) 2855, 1668.

m.p. = 68-69°C (recrystallised from ethyl acetate - hexane to give lemon plates).

Preparation of Dimethyldioxirane solution [46]

A 3L, three-necked flask was fitted with a solid-addition funnel, a mechanical stirrer and a distillation tube. To the other end of the distillation tube was fitted a 250mL two-necked collection flask connected to a vacuum source. The 3L reaction flask was charged with acetone (144 mL, 1.96 mmol), distilled water (190.5 g, 10.58 mol) and sodium bicarbonate (43.5 g, 0.52 mol). The resulting white suspension was stirred vigourously for 5 min and the reaction flask cooled to 4 °C via an ice-bath. The collection flask was cooled to -78 °C using an acetone/dry-ice bath. Oxone® (90 g, 0.146 mmol) was added in one portion to the stirred sodium bicarbonate suspension and the solid-addition funnel was replaced with a thermometer. After 15 min of vigourous stirring, a vacuum was applied (70-90 mmHg) and the reaction flask was warmed to 30 °C via a warm water bath. The reaction flask was maintained at 30 °C for 90 min at which time the vacuum was removed and the system flushed with argon. The pungent yellow solution in the collection flask was dried, filtered with activated 4 Å sieves (5 g) and decanted into a flask containing fresh 4 Å sieves. The flask was flushed with argon and kept at -18 °C. Immediately prior to use the dimethyldioxirane was titrated by the method of Adam *et al.*[46]

3-Hydroxy-4-(2,3-epoxy-3-methylbut-2-en-1-yloxy)-benzaldehyde 2.24 [46]



2.23 **2.24**

The alkene **2.25** (800 mg, 3.88 mmol), was cooled to -30 °C using a liquid N_2/ bromobenzene slush bath. A solution of dimethyldioxirane in acetone (0.092M, 63.5 mL, 5.83 mmol) was added via pipette under a rapid flow of argon. The golden yellow solution was allowed to warm to 25 °C over 20 h and the acetone was removed *in vacuo*. The resulting yellow emulsion was diluted with ethyl acetate (50 mL) and this solution was washed with brine (1 x 50 mL). The solvent was removed *in vacuo* to give the title compound **2.24** as a golden gum (864 mg, 100%).

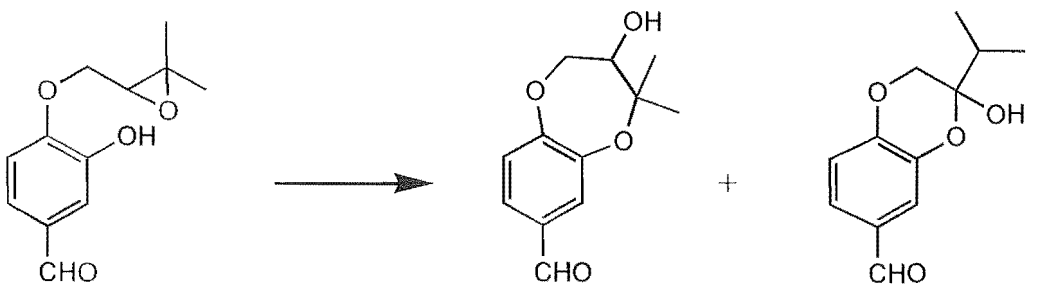
^1H NMR ($CDCl_3$) δ 9.84 (s, 1H, ArC**H**O), 9.45 - 9.39 (m, 2H, Ar**H**), 7.00 (d, J_{HH} = 8.4Hz, 1H, Ar**H**), 4.39 (dd, J_{HH} = 7.4, 3.9 Hz, 1H, OC**H**$_2$HCOC(CH$_3$)$_2$), 4.13 (dd, J_{HH} = 6.3, 4.4 Hz, 1H, OC**H**$_2$HCOC(CH$_3$)$_2$) 3.17 (dd, J_{HH} = 3.9 Hz, 2.4 Hz 1H, OCH$_2$**H**COC(CH$_3$)$_2$), 1.41 (s, 3H, OCH$_2$HCOC(C**H**$_3$)$_2$), 1.38 (s, 3H, OCH$_2$HCOC(C**H**$_3$)$_2$).

^{13}C NMR ($CDCl_3$) 191.2, 151.1, 146.4, 130.9, 124.4, 114.7, 111.6, 68.4, 60.9, 58.7, 24.5, 19.0.

HREIMS Calc. for $C_{12}H_{14}O_4$: 222.0892; found: 222.0901.

FTIR (cm^{-1}, $CHCl_3$) 2978, 1682.

$SnCl_4$-mediated cyclisation of epoxide 2.24



2.24 **1.41** **2.29**

Tin (IV) chloride (76 μL, 0.65 mmol) was added dropwise to a golden-yellow solution of epoxide **2.24** (145 mg, 0.65 mmol) in THF (9.3 mL). The reaction was stirred for 30 min and quenched by the addition of aqueous saturated sodium bicarbonate solution (50 mL). The cloudy solution was extracted with ether (3 x 50mL). The combined organic phases were washed with water (2 x 50mL) and brine (1 x 50ml). The solvent was removed *in vacuo* to give the crude product (183 mg). Purification by flash chromatography on silica using 30 % ethyl acetate - petroleum ether as the eluant, gave:-

(i)Hemi-acetal **2.29** (65 mg, 45%)

^1H NMR ($CDCl_3$) δ 9.81 (s, 1H, ArC**H**O), 7.45-7.40 (m, 2H, Ar**H**), 7.04 (d, J_{HH} = 8.8 Hz, 1H, Ar**H**), 4.25 (d, J = 11.3 Hz, 1H, OC**H**$_2$HCOC(CH_3)$_2$), 3.98 (d, J_{HH} = 11.3 Hz, 1H, ArOC**H**$_2$), 3.25 (br s, 1H, O**H**), 2.10 (sept, J_{HH} = 6.8Hz, 1H, H_3CC**H**CH_3), 1.13 (d, J_{HH} = 6.8Hz, 3H, CH_3HCC**H**$_3$), 1.09 (d, J_{HH} = 7.3 Hz, 3H, C**H**$_3$HCCH_3).

^{13}C NMR ($CDCl_3$) δ 190.9, 148.2, 142.0, 131.0, 124.4, 123.7, 118.7, 117.3, 116.3, 113.8, 96.1, 67.9, 34.4, 16.4, 15.5.

HREIMS Calc. for $C_{12}H_{14}O_4$: 222.0892 ; found : 222.0892.

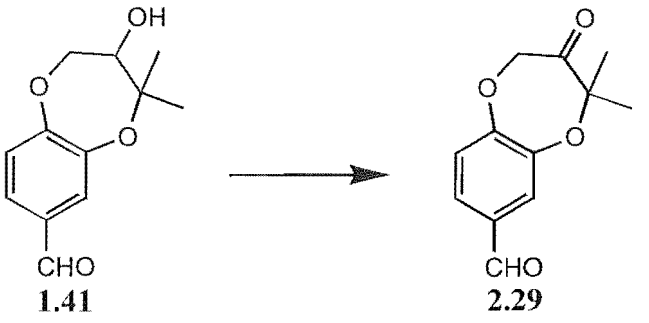
FTIR (cm^{-1}, $CHCl_3$) 3427, 1682.

Selected ^{1}H nmr data on the ring-opened ketone form

^1H NMR ($CDCl_3$) δ 9.83 (s, 1H, ArC**H**O), 6.87 (d, J = 7.8 Hz, 1H, Ar**H**), 4.83 (s, 1H, ArOC**H**$_2$CO), 2.73 (sept, 1H, H_3CC**H**CH_3).

(ii) A mixture of more polar products was also isolated (38 mg) and this contained the desired benzodioxepin and the six-membered ring tertiary alcohol. This mixture was subjected to PCC oxidation as described by Steglich[30] to allow separation.

4,4-dimethyl-3-oxo-3,4-dihydro-*2H*-benzo-[b]-[1,4]-dioxepin-7-carbaldehyde 2.29



To a stirred suspension of PCC (44 mg, 0.22 mmol) in CH_2Cl_2 (0.35 mL), was added a solution of the above mixture (30 mg, 0.14 mmol) in CH_2Cl_2 (0.57 mL). After 24 h, the black suspension was washed with ether (3 x 5 mL). The yellow washings were concentrated and purified by flash chromatography on silica using 25% ethyl acetate - petroleum ether as the eluant, to give the benzodioxepin **2.29** (9 mg, 7% over two steps).

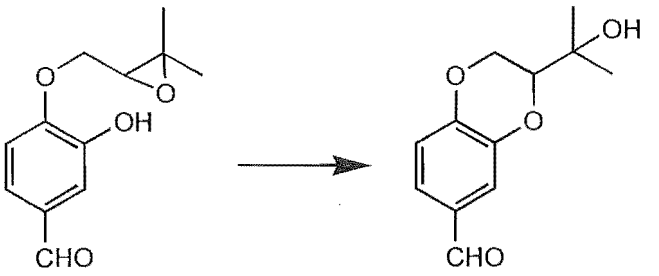
^1H NMR ($CDCl_3$) δ 9.87 (s, 1H, ArC**H**O), 7.54 (m, 2H, Ar**H**), 7.06 (d, J_{HH} = 8.8 Hz, 1H, Ar**H**), 4.85 (s, 2H, ArOC**H**$_2$), 1.50 (s, 6H, COC(C**H**$_3$)$_2$.

^{13}C NMR ($CDCl_3$) δ 206.5, 189.6, 153.6, 134.5, 126.5, 125.1, 114.9, 79.6, 74.2, 24.3.

HREIMS Calc. for $C_{12}H_{12}O_4$: 220.0736 ; found : 220.0732.

FTIR (cm^{-1}, $CHCl_3$) 1693, 1604.7.

3-Formyl-4-[(2-hydroxy-2-methyl)]-ethyl)-2H-1,5-benzodioxane 2.28 [60]



2.24 **2.28**

LiOH (6.2 mg , 0.299 mmol) was added via a solid addition tube to a solution of epoxide **2.24** (53 mg , 0.239 mmol) in methanol (0.65 mL) and THF (0.65 mL). The resulting green solution was stirred for 30 min and quenched by acidification of the solution using 5% HCl aqueous solution. The solution was diluted with water (20 mL) and extracted using CH_2Cl_2 (3 x 40 mL). The organic extracts were washed with water (2 x 100 mL) and brine (1 x 75 mL). Removal of the solvent gave the title compound **2.28** as a brown gum (53 mg, 100%)

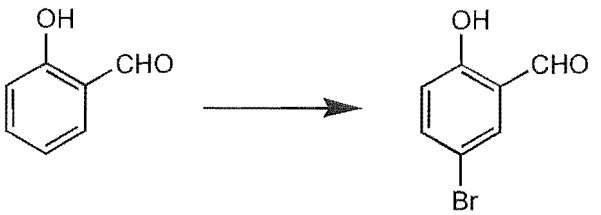
^1H ($CDCl_3$) δ 9.81 (s, 1H, ArC**H**O), 7.39-7.45 (m, 2H, Ar**H**), 6.99(d, J_{HH} = 8.3 Hz, 1H, Ar**H**), 4.51(dd, J_{HH} = 9.7Hz, 2.0Hz, 1H, ArOC**H**$_2$), 3.91-4.09 (m,1H, ArOCH$_2$C**H**), 1.39 (s, 1H, H$_3$CCOHC**H**$_3$), 1.33 (s, 1H, **H**$_3$CCOHCH$_3$).

^{13}C NMR ($CDCl_3$) δ 190.7, 148.8, 143.9, 130.5, 124.4, 118.1, 117.4,78.6, 70.5, 65.2, 25.7, 8, 25.3.

HREIMS Calc. for $C_{12}H_{14}O_4$: 222.0892; found 222.0897.

FTIR (cm^{-1}, KBr disk) 3440.8, 1585.8.

2-Hydroxy-5-bromo-benzaldehyde 2.37 [59]



2.36 **2.37**

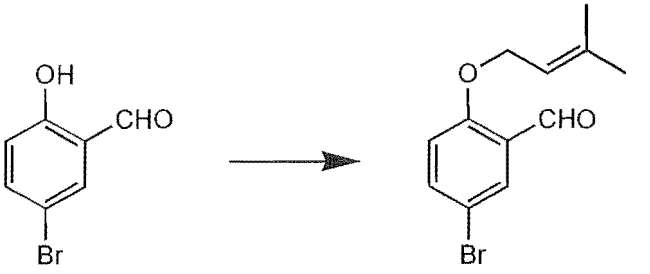
A solution of 2-hydroxybenzaldehyde (1.743 g, 14.3 mmol) in $CHCl_3$ (2.30 mL) was heated to 30 °C and a solution of Br_2 (740 μL, 14.3 mmol) in $CHCl_3$ (2.30 mL) was added dropwise over 20 min. The solution was heated at reflux for 2 h and upon cooling to RT gave a cream solid (2.750 g). Purification using dry column chromatography with 25% ethyl acetate - petroleum ether as eluant gave the title compound **2.38** as a cream solid (2.67 g, 93%).

^1H NMR ($CDCl_3$) δ 10.93 (s, 1H, ArO**H**), 9.84 (s, 1H, ArC**H**O), 7.67 (d, J_{HH} = 2.4 Hz, 1H, Ar**H**), 7.60 (dd, J_{HH} = 6.3, 2.5 Hz, 1 H, Ar**H**) 6.91 (d, J_{HH} = 8.8 Hz, Ar**H**).

^{13}C NMR ($CDCl_3$) δ 195.35, 160.46, 139.62, 35.56, 121.66, 119.74, 111.29.

m.p. 103-104°C (recrystallised from ethyl acetate/hexanes to give stout white rods), lit. melting point = 105°C

2-(3-Methyl-but-2-en-1-yloxy)-5-bromobenzaldehyde 2.38



2.37 **2.38**

K_2CO_3 (1.114 g, 8.43 mmol) was added to a solution of 2-hydroxy-5-bromobenzaldehyde **2.38** (1.538 g, 7.66 mmol), in dry degassed DMF (26.4 mL). The resulting bright green suspension was stirred for 15 min. 4-Bromo-2-methyl-but-2-ene (970 μL, 8.43 mmol) was added over 10 seconds and the resulting yellow suspension was stirred for 15 hours. 1M HCl (25 mL) was added and the resulting solution was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed successively with water (2 x 100 mL) and brine (1 x 100 mL). Removal of the solvent *in vacuo* gave the crude product as a yellow oil (2.070 g), which solidified upon standing. This was purified by flash chromatography, using 5% ethyl acetate - petroleum ether as the eluant, to give the title compound **2.39** as a yellow oil (1.895 g, 92%).

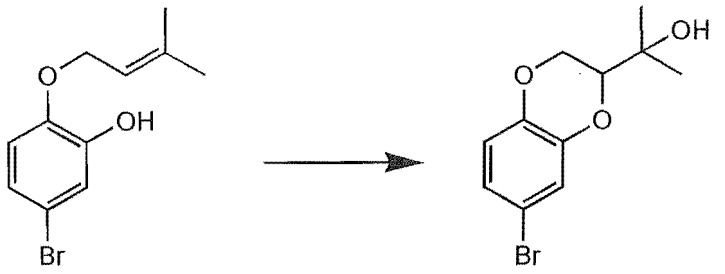
^1H NMR ($CDCl_3$) δ 10.35 (s, 1H ArC**H**O), 7.85 (d, J_{HH} = 2.9 Hz, 1H, Ar**H**), 7.55 (dd, J_{HH} = 6.4 Hz, 2.4 Hz, 1H, Ar**H**), 6.86 (d, J_{HH} = 9.3 Hz, 1H, Ar**H**), 5.41-5.46 (m, 1H, C**H**$_2$CHC(CH$_3$)$_2$), 4.58 (d, J_{HH} = 6.3 Hz, 2H, CH$_2$C**H**C(CH$_3$)$_2$), 1.77 (d, J_{HH} = 1.0 Hz, 3H, CH$_2$CHC(C**H**$_3$)$_2$), 1.72 (s, 3H, CH$_2$CHC(C**H**$_3$)$_2$)

^{13}C NMR ($CDCl_3$) δ 188.5, 160.1, 139.2, 138.1, 130.8, 126.3, 118.5, 115.0, 113.3, 65.8 , 25.76, 18.31.

HREIMS calc. for $C_{12}H_{13}O_2Br$: 268.0099; found: 268.0095.

FTIR (cm^{-1}, KBr disk) 2868.0, 1684 cm^{-1}.

Preparation of 3-Bromo-4-((2-hydroxy-2-methyl)-ethyl)-2H-1,5-benzodioxane 2.44



2.38 **2.41**

Alkene **2.39** (200 mg, 0.744 mmol) in CH_2Cl_2 (1.1 mL) was added via cannula to a solution of *m*CPBA (404 mg, 1.64 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C (ice bath). The solution was warmed to RT and after 16 h, quenched by the addition of the white suspension to an ice-cold saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was removed and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (2 x 100 mL), H_2O (2 x 100 mL) and brine (1 x 100 mL). Removal of the solvent *in vacuo* gave a mixture of the formate ester and the free phenol as a cloudy brown gum (204 mg).

In an attempt to hydrolyse the formate ester, the ester (204 mg) was dissolved in a mixture of THF (1.7 mL) and methanol (1.7 mL). LiOH (17.8 mg, 0.423 mmol) was added with stirring. After 1h, the brown solution was acidified to pH = 6 using 1M HCl and the solution diluted with H_2O (20 mL). The solution was extracted with ethyl acetate (3 x 25 mL) and the combined organic phases were washed with water (2 x 75 mL) and brine (1 x 75 mL). Removal of the solvent *in vacuo* gave the title dioxane as a yellow gum (203 mg, 100%).

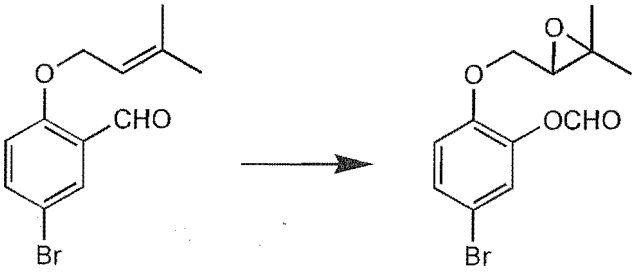
^1H NMR ($CDCl_3$) δ 7.06 (1H, d, J_{HH} = 8.4 Hz, Ar**H**), 6.92-6.96 (1H, m, Ar**H**), 6.75 (d, J_{HH} = 8.8 Hz, 1H, Ar**H**) 4.41 (dd, J_{HH} = 9.3, 12.7 Hz, 2H, ArOC**H**$_2$), 3.87-4.01 (m, 1H, ArOCH$_2$C**H**), 1.35 (s, 3H, **H**$_3$CCOHCH$_3$), 1.30 (s, 3H, H$_3$CCOHC**H**$_3$).

^{13}C NMR ($CDCl_3$) δ 144.3, 142.5, 124.3, 120.1, 118.2, 112.8, 78.9 70.6 64.7, 25.9, 25.1.

FTIR (cm^{-1}, KBr disk) 3440.8, 1585.8.

HREIMS Calc. for $C_{11}H_{13}O_3Br$: 272.0048; found: 272.0043.

2-(2,3-epoxy-3-methylbut-2-en-1-yloxy)-5-bromobenzeneformate 2.39



2.38 **2.39**

Benzaldehyde **2.38** (157 mg 0.762 mmol) in CH_2Cl_2 (1.5 mL) was added to *m*CPBA (57 mg, 0.762 mmol) in a 0.1 M NaH_2PO_4 solution, (0.4 mL). The white suspension was stirred for 16h. The reaction was quenched by the addition of the solution to saturated aqueous $NaHCO_3$ solution (25 mL), which was then extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution (2 x 100 mL) H_2O (2 x 100 mL) and brine (1 x 100 mL). Removal of the solvent *in vacuo* gave the crude product as a yellow-brown oil (180 mg).

An analytically pure sample was obtained by flash chromatography on silica using 17.5 % ethyl acetate - petroleum ether as eluant

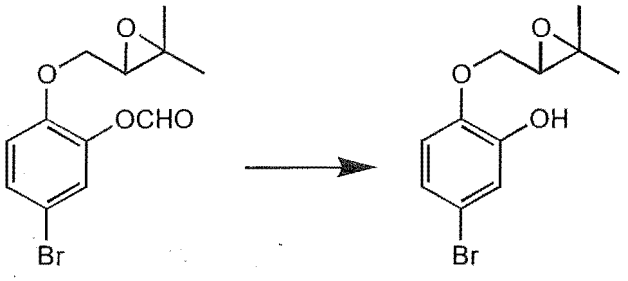
^1H NMR ($CDCl_3$) δ 8.23 (d, J_{HH} = 0.98 Hz, 1H, ArOC**H**O) 7.32-7.35 (m, 1H, Ar**H**), 7.24 (s, 1H, Ar**H**), 6.93 (d, J_{HH} = 8.8 Hz, Ar**H**), 4.16 (m, 1H, OC**H**$_2$HCOC$(CH_3)_2$), 4.06 (m, 1H, OC**H**$_2$HCOC$(CH_3)_2$), 3.07 (t, J_{HH} = 5.4 Hz, 4.9 Hz, OCH$_2$**H**COC$(CH_3)_2$)) 1.36 (s, 3H, OCH$_2$HCOC(C**H**$_3)_2$)), 1.32 (s, 3H, OCH$_2$HCOC(C**H**$_3)_2$)

^{13}C NMR ($CDCl_3$) δ 146.9, 144.8, 138.8, 122.8, 113.8, 112.3, 96.7, 68.6, 61.1, 24.6, 19.0.

HREIMS Calc. for $C_{12}H_{13}O_4Br$: 299.9997; found: 299.9990

FTIR (cm^{-1}, KBr disk) 2964.4, 1747.4, 1494.7 cm^{-1}

3-Hydroxy-4-(2,3-epoxy-3-methylbut-2-en-1-yloxy)-bromobenzene 2.40



2.39 **2.40**

The crude material from the above reaction (50 mg) was dissolved in methanol (10 mL) and refluxed for 16 hours. The solvent was removed *in vacuo* to afford the title compound **2.40** as a yellow oil. (44 mg, 100%), which was used without further purification. An analytically pure sample was obtained by flash chromatography on silica using 17.5 % ethyl acetate - petroleum ether as eluant

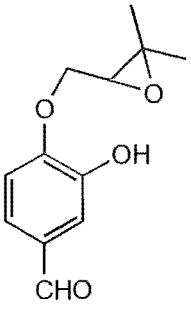
^{1}H NMR ($CDCl_3$) δ 7.08 (m, 1H, Ar**H**), 6.95 (m, 1H, Ar**H**), 6.75 (dd, J_{HH} = 6.8 Hz, 2.0 Hz, 1H, Ar**H**), 4.28 (dd, 7.3 Hz, 3.9 Hz, 1H, $OCH_2HCOC(CH_3)_2$), 4.01 (dd, 6.5 Hz, 4.4 Hz, 1H, $OCH_2HCOC(CH_3)_2$)), 3.17 (q, J_{HH} = 4.9 Hz, 2.9 Hz, 1H, $OCH_2HCOC(CH_3)_2$), 1.40 (s, 3H, $OCH_2HCOC(CH_3)_2$), 1.36 (s, 3H, $OCH_2HCOC(CH_3)_2$).

^{13}C NMR ($CDCl_3$) δ 146.9, 144.8, 138.8, 122.8, 113.8, 112.3, 96.7, 68.6, 61.1, 24.6, 19.0.

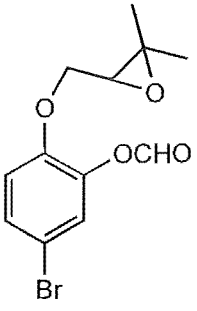
HREIMS Calc. for $C_{12}H_{13}O_4Br$: 299.9997; found: 299.9990

FTIR (cm^{-1} KBr disk) 2964.4, 1747.4, 1494.7 cm^{-1}

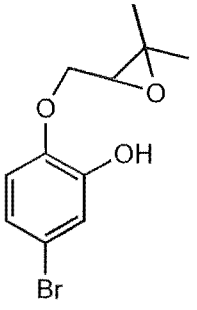
Summary of Lewis acid-catalysed cyclisation trials



2.24



2.39



2.40

All yields were determined by integration of the appropriate signals in ^1H nmr spectra.

$SnCl_4$-catalysed cyclisations of epoxide **2.24**

Conditions	Temperatures	Time (h)
$SnCl_4$ added to epoxide solution	0°C, 20°C, reflux	45 min
Epoxide solution added to $SnCl_4$ solution	0°C, 20°C	45 min
$SnCl_4$ solution added to epoxide solution	0°C, 20°C	45 min

Acid-catalysed cyclisations of epoxide **2.24**.

Method	Solvent	Temperature	% dioxepin	Time
0.1 eq CSA into epoxide solution	CH_2Cl_2	20°C	<5%	72 h
0.1 eq TFA into epoxide solution	CH_2Cl_2	20°C	<5%	1.5 h
1 eq TFA into epoxide solution	THF	20°C	0%	72 h
10 eq TFA into epoxide solution	CH_2Cl_2	20°C	15%	24 h
1 eq p-TSA into epoxide solution	CH_2Cl_2	20°C	10%	45 min
$TiCl_4$ added to epoxide solution	THF	20°C	<5%	30 min
2 eq $TiCl_4$ to epoxide solution	THF	20°C	<5%	30 min
$AlCl_3$ added to epoxide solution	THF	20°C	<5%	30 min
$BF_3.OEt_2$ added to epoxide solution	Ether	20°C	<10%	60 min
TMSOTf added to epoxide solution	THF	20°C	<10%	30 min
TMSOTf added to epoxide solution	DMSO	20°C	<10%	24 h
$LiClO_4$ added to epoxide solution	Ether	20°C	<10%	42 h
$La(OTf)_3$ added to epoxide solution	CH_2Cl_2	20°C	0%	7 days

Lewis acid-catalysed cyclisations of epoxide **2.40**

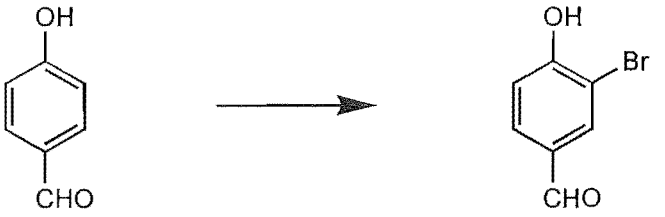
Method	Solvent	Temperature	% dioxepin	Time
$SnCl_4$ to epoxide solution	THF	20°C	10%	30 minutes
$TiCl_4$ to epoxide solution	THF	20°C	5%	30 minutes
$BF_3.OEt_2$ to epoxide solution	ether	20°C	5%	30 minutes
2 eq $LiClO_4$ to epoxide solution	ether	20°C	5%	48 hours

Lewis acid-catalysed cyclisations of formate ester **2.39**

Method	Solvent	Temperature	% dioxepin	Time
$SnCl_4$ to epoxide solution	THF	20°C	<10%	30 min
10 eq $SnCl_4$ to epoxide solution	THF	20°C	<10%	30 min
2 eq $LiClO_4$ to epoxide solution	ether	20°C	5%	44 h

5.2 Experiments described in Chapter 3

3-Bromo-4-hydroxy-benzaldehyde 3.16 [82]

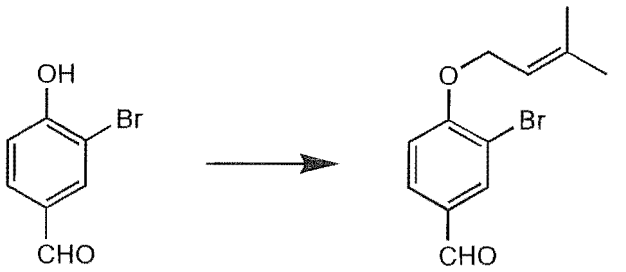


3.11 **3.16**

A solution of 4-hydroxybenzaldehyde **3.11** (1.231 g, 9.06 mmol) in $CHCl_3$ (8.9 mL) was warmed to 40°C and a solution of Br_2 (535 μL, 10.4 mmol) in $CHCl_3$ (22.2 mL) added dropwise over 40 min. After a further 75 min of heating, the pale orange solution was poured into H_2O (50 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 50 mL) and the organic extracts were combined and washed with H_2O (2 x 100 mL) and brine (1 x 100 mL). The solvent was removed *in vacuo* to give a cream solid. (1.883 g). Purification by flash chromatography on silica, using 25% ethyl acetate - petroleum ether as eluant, gave the title compound (1.570 g, 86%).

^1H NMR ($CDCl_3$) δ 9.83 (s, 1H, ArC**H**O), 8.04 (d, J_{HH} = 2.0 Hz, 1H, Ar**H**), 7.77 (dd, J_{HH} = 6.4, 1.9 Hz, 1H, Ar**H**), 7.15 (d, J_{HH} = 8.9 Hz, 1H, Ar**H**), 6.37 (br s, 1H, ArO**H**).
^{13}C NMR ($CDCl_3$) δ 189.6, 157.8, 134.2, 131.3, 130.8, 116.5, 111.1,
m.p. = 124-125 °C (recrystallised from ethyl acetate-hexanes to give white needles,),
lit. melting point = 124°C

3-Bromo-4-(2-methyl-but-2-en-1-yloxy)benzaldehyde 3.17



3.16 **3.17**

Benzaldehyde **3.16** (1.409 g, 7.01 mmol) was dissolved in DMF (21.5 mL). K_2CO_3 (1.066 g, 7.71 mmol). was added in one portion via a solid addition tube. The peach-coloured solution was stirred vigorously for 15 min at which time 4-bromo-2-methyl-but-2-ene (890 μL, 7.71 mmol) was added over 10 seconds. After 17 h, the solution was quenched by the addition of 1M HCl (15 mL). The yellow solution was extracted with ethyl acetate (3 x 50 mL) and the combined organic phases washed sequentially with H_2O (2 x 150 mL) and brine (1 x 75 mL). Removal of the solvent *in vacuo* gave a yellow solid (1.860 g). Purification by flash chromatography on silica, using 25% ethyl acetate - petroleum ether as the eluant, gave the aldehyde **3.17** as a solid (1.760 g, 93%).

^1H ($CDCl_3$) δ 9.82 (s, 1H, ArC**H**O), 8.06 (d, J_{HH} = 2.0 Hz, 1H, Ar**H**), 7.77 (dd, J_{HH} = 6.5, 2.4 Hz, 1H, Ar**H**), 6.98 (d, J_{HH} = 8.9 Hz, 1H, Ar**H**), 5.46 (m, 1H, OC**H**$_2$CHC(CH$_3$)$_2$), 4.68 (d, J_{HH} = 4.68, 2H, OCH$_2$C**H**C(CH$_3$)$_2$), 1.79 (d, J_{HH} = 2.0 Hz, OCH$_2$CHC(C**H**$_3$)$_2$), 1.76 (s, 3H, OCH$_2$CHC(C**H**$_3$)$_2$).

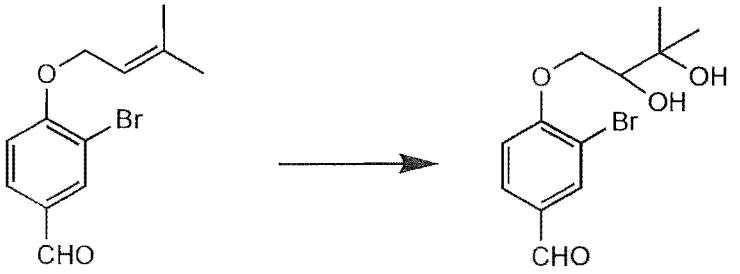
^{13}C NMR ($CDCl_3$) δ 189.5, 160.0, 139.2, 134.4, 131.0, 130.0, 118.3, 113.0, 112.7, 66.5, 25.8, 18.4.

HREIMS calc. for $C_{12}H_{13}O_2Br$: 268.0099; found 268.0094.

m.p. = 41-42 °C

FTIR (cm^{-1}, $CHCl_3$) 3024.0, 1693.4, 1593.1

3-Bromo-(2,3-dihydroxy-3-methylbut-1-yloxy)benzaldehyde 3.18



The alkene **3.17** (4.095 g, 15.2 mmol) was dissolved in acetone (2.0 mL) and the resulting yellow solution was to a solution of N-methylmorpholine-N-oxide (1.868 g, 16.1 mmol) and osmium tetroxide (38mg , 0.15 mmol) in H_2O (7.90 mL), acetone (0.5 mL) and tert-butanol (0.6 mL). The solution immediately blackened upon substrate addition. After 21.5 hours, a slurry of sodium sulfite (250 mg), H_2O (20 mL) and magnesium silicate (3 g) was added. The resulting suspension was stirred for 15 min and filtered. The brown residue was rinsed with ethyl acetate (125 mL) and the pH of the resultant light brown filtrate adjusted to pH = 2 using 1M HCl solution (15 mL). The yellow organic fraction was washed with successive portions of H_2O (2 x 100 mL) and brine (1 x 100 mL). The solvent was removed *in vacuo* to yield a golden liquid. Azeotropic distillation with 100 mL of 4:1 hexanes/ether *in vacuo* gave the title compound **3.18** as a brown solid (4.020 g, 87%) which was used without further purification.

An analytically pure sample was obtained by flash chromatography on silica using 60% ethyl acetate - petroleum ether as eluant.

^1H NMR ($CDCl_3$) δ 9.85 (s, 1H, ArC**H**O), 8.08 (d, 1H, J_{HH} = 1.9 Hz, Ar**H**), 7.8 (dd, J_{HH} = 6.7 Hz, 1.9 Hz, 1H, Ar**H**), 7.03 (d, 1H, J_{HH} = 8.3 Hz, Ar**H**), 4.33 (dd, J_{HH} = 6.4 Hz, 2.7 Hz, 1H, ArOC**H**$_2$CHOH), 4.19 (dd, J_{HH} = 6.3 Hz, 2.9 Hz, 1H, ArOC**H**$_2$CHOH), 3.86 (dd, J_{HH} = 6.4 Hz, 2.9 Hz, 1H, ArOCH$_2$C**H**OH), 3.05 (br s, 1H, O**H**), 2.55 (br s, 1H, O**H**), 1.35 (s, 1H, **H**$_3$CCCH$_3$), 1.32 (s, 1H, H$_3$CCC**H**$_3$).

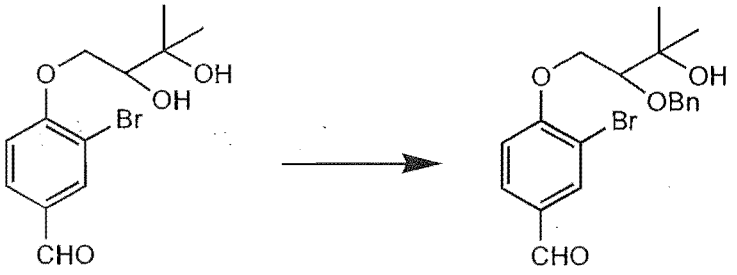
^{13}C NMR ($CDCl_3$) δ 189.48, 159.35, 134.31, 131.16, 131.00, 112.83, 112.50, 75.05, 74.97, 71.68, 70.90, 70.78, 26.52, 25.48

FTIR (cm^{-1}, $CHCl_3$) 3317.3, 2972.1, 1666.4, 1595.0.

HREIMS Calc. for $C_{12}H_{15}O_4Br$: 302.0154; found 302.1033

m.p. 93-94 °C (yellow plates)

3-Bromo-4-(3-hydroxy-2-benzyl-3-methyl-butyl-1-oxy)benzaldehyde 3.20



3.18 **3.20**

Diol **3.18** (752 mg, 2.48 mmol) was dissolved in THF (12.5 mL) and the yellow solution was cooled to 0°C. Potassium *tert*-butoxide (279 mg, 2.48 mmol) was added via solid addition tube. The solution was stirred vigourously for 5 minutes, at which time benzyl bromide (295 μL, 2.48 mmol) was added dropwise over one minute. The apricot-coloured solution was stirred for 14 hours and quenched by the addition of H_2O (100mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were washed with H_2O (2 x 150 mL) and brine (1 x 100 mL). Removal of the solvent *in vacuo* gave a yellow solid (827 mg), which was purified by flash chromatography, using 35% ethyl acetate-petroleum ethers as the eluant, to give the title compound **3.20** as a brown gum (81 mg, 9%).

^1H NMR ($CDCl_3$) δ 9.89 (s, 1H, ArC**H**O), 8.12 (s, 1H, Ar**H**), 7.81 (q, J_{HH} = 6.8, 1H, 10.7 Hz, Ar**H**), 7.38-7.30 (m, 5H, CH_2Ar**H**), 7.01 (d, J_{HH} = 8.5 Hz, 1H, Ar**H**), 5.08 (d, J_{HH} = 8.3 Hz, 1H, OCH_2Ar**H**), 4.75 (d, J_{HH} = 8.3 Hz, 1H, OCH_2ArH), 4.38-4.42 (m,

1H, CH_2HCOCH_2Ar), 4.28-4.22 (m, 1H, CH_2HCOCH_2Ar), 3.76-3.80 (m, 1H, CH_2HCOCH_2Ar), 1.33 (s, 3H, $COH(CH_3)_2$), 1.29 (s, 3H, $COH(CH_3)_2$).

^{13}C NMR ($CDCl_3$) δ 189.5 (Ar**C**HO), 159.8 (Ar**C**OCH_2), 137.5 (**C**H_2Ar) 134.5 (**Ar**H), 131.1 (**Ar**H), 130.8 (**Ar**H, 128.5 (**Ar**CH_2), 128.4 (**Ar**CH_2), 127.5 (**Ar**CH_2), 112.8 (**Ar**H), 112.1 (**Ar**Br) 83.5 (CH_2HCOCH_2Ar) 71.9 ($H_3CCOHCH_3$), 70.4 (CH_2HCOCH_2Ar) 74.9 (CH_2HCOCH_2Ar), 25.1 ($H_3CCOHCH_3$), 26.0 ($H_3CCOHCH_3$).

HREIMS calc. for $C_{19}H_{21}O_4Br$: 392.0528; found 392.0521.

FTIR (cm^{-1}, $CHCl_3$) 3014.4, 1600.4.

Additionally, the regioisomeric tertiary benzyl ether **3.21** was also isolated (271 mg, 29%).

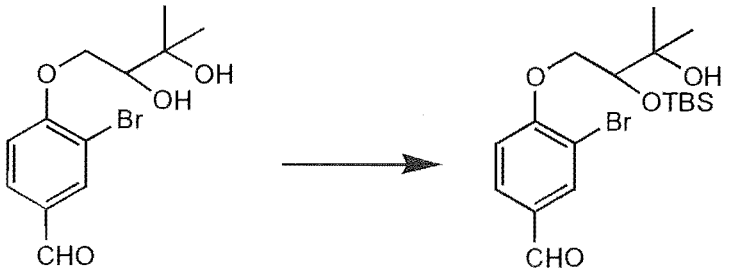
^1H NMR ($CDCl_3$) δ 9.84 (1H, s, ArC**H**O), 8.07 (d, 1H, J_{HH} = 2.5 Hz, Ar**H**), 7.77 (d, 1H, J_{HH} = 1.9 Hz, Ar**H**), 7.73 (d J_{HH} = 1.9 Hz, 1H, Ar**H**) 7.34-7.22 (m, 5H, OCH_2ArH), 4.53 (s, 2H, O**C**H_2Ar), 4.40-4.53 (m, 1H, **C**H_2HCOCH_2Ar), 3.89-3.93 (m, 2H, CH_2HCOCH_2Ar), 3.73-3.68 (m, 2H, CH_2HCOCH_2Ar), 1.33 (s, 6H, $COH(CH_3)_2$).

^{13}C NMR ($CDCl_3$) δ 189.6 (**C**HO) 160.1 (**Ar**O), 137.4 (H_2CArH), 134.6 (**Ar**H), 134.4 (**Ar**H), 131.1 (**Ar**H), 131.0 (**Ar**H), 128.5 (**Ar**H), 127.9 (**Ar**H), 127.6 (**Ar**H), 116.6 (**Ar**H), 115.1 (**Ar**H), 113.6 (**Ar**Br), 85.8, ($CH_2HCOHCOCH_2Ar$), 73.7 (O**C**H_2Ar), 72.2 (HC**C**OCH_2Ar), 69.7 (O**C**H_2CHOH) 25.8 ($COH(CH_3)_2$, 25.5 ($COH(CH_3)_2$.

HREIMS Calc. for $C_{19}H_{21}O_4Br$: 415.0521; found 415.0528.

FTIR (cm^{-1}, $CHCl_3$) - 3014.4, 1600.4.

3-Bromo-4-(tert-butyldimethylsilyl)-3-methyl-butyl-1-oxy)benzaldehyde 3.22 [88]



3.18 **3.22**

Diol **3.18** (483 mg, 1.59 mmol), imidazole (308 mg, 2.39 mmol), *tert*-butyldimethylsilylchloride (264 mg, 1.75 mmol) and *N,N*-dimethylaminopyridine (39 mg/0.32 mmol) were added to a pear-shaped flask and DMF (440 μL) was added dropwise. During the addition, the flask was gently heated with a heat gun. The resulting yellow viscous solution was stirred for 34h. The cloudy yellow suspension was added to a Na_2HPO_4/NaH_2PO_4 buffer (20 ml, pH = 7.4) and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). the combined organic phases were washed with H_2O (2 x 100 mL) and brine (1 x 100 mL). The solvent was removed *in vacuo* to give a yellow oil (480 mg). This was purified by flash chromatography, using 35% ethyl acetate - petroleum ether as eluant, to give the title alcohol **3.22** as colourless crystals (226 mg, 34%) and the starting diol (250 mg). The regiochemistry of the alkylation was confirmed by single-crystal–ray analysis. Details of which can be obtained from the author.

^1H NMR ($CDCl_3$) δ 9.84 (s, 1H, ArC**H**O), 8.08 (d, J_{HH} = 1.9Hz, 1H, Ar**H**), 7.80 (dd, J_{HH} = 2.1, 0.7 Hz, 1H, Ar**H**), 6.99 (d, J_{HH} = 8.8 Hz, 1H, Ar**H**), 4.23 (m, 1H, ArOC**H**$_2$CHOH), 4.06 (m, 1H, ArOCH$_2$C**H**OH), 3.86 (dd, J_{HH} = 6.4 Hz, 2.9 Hz, 1H, ArOCH$_2$C**H**OH), 1.28 (s, 6H, $CH_2C(CH_3)_2$), 1.26 (s, 3H, $OSiC(CH_3)_3CH_3$), 0.91(s, 9H, $OSiC(CH_3)_3CH_3$).

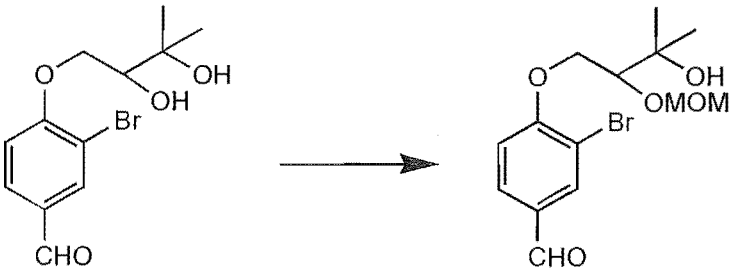
^{13}C NMR ($CDCl_3$) δ 189.5, 159.7, 134.7, 131.1, 112.3, 76.6, 72.3, 71.6, 25.9, 25.8, 25.7, 18.2.

HREIMS Calc. for $C_{14}H_{20}O_4Si$: 359.0314; found 359.0329.

FTIR (cm^{-1}, $CHCl_3$) 3018.4, 1691.5.

m.p. = 78-79 °C (recrystallised from ethyl acetate-hexanes to give colourless plates)

3-Bromo-4-(3-hydroxy-2-(2-methoxy-methyl ether)-3-methyl-butyl-1-oxy) benzaldehyde 3.23



3.18 **3.23**

Hunig's base (660 mL, 3.03 mmol) was added dropwise over 30 sec to a solution of diol **3.18** (834 mg, 2.75 mmol) in CH_2Cl_2 (28 mL) at 0°C. MOMCl (230 μL, 3.03 mmol) was immediately added dropwise over 1 minute with the evolution of a white gas. The light brown solution was warmed to RT and stirred for 14 h. The solution was then cooled to 0°C and in succession extra Hunig's base (288 μL, 1.82 mmol) and MOMCl (125 μL, 1.52 mmol) were added dropwise over 30 seconds. After a further 24 h of stirring, the yellow solution was added to saturated aqueous $NaHCO_3$ solution (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed successively with H_2O (2 x 100 mL), brine (1 x 100 mL) and the solvent removed *in vacuo* to yield a brown solid. Purification by flash chromatography on silica 40% ethyl acetate - petroleum ether as eluant, gave the title ether **3.23** as a brown solid. (361 mg, 38%).

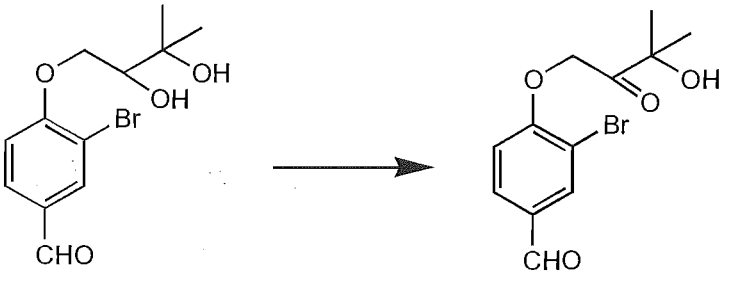
^1H NMR ($CDCl_3$) δ 9.85 (s, 1H, C**H**O), 8.09 (d, J_{HH} = 1.9 Hz, 1H, Ar**H**), 7.81 (dd, J_{HH} = 6.6, 1.9 Hz, 1H, Ar**H**), 7.01 (d, J_{HH} = 8.3 Hz, 1H, Ar**H**), 5.03 (d, J_{HH} = 6.9 Hz, 1H, $CHOCH_2OCH_3$), 4.83 (d, J_{HH} = 6.9 Hz, 1H, $ArOCH_2CHOCH_2OCH_3$), 4.20-4.34 (m, 1H, $ArOCH_2CHOCH_2OCH_3$), 3.85 (t, J_{HH} = 3.4 Hz, 1H, $ArOCH_2CHOCH_2OCH_3$) 3.45 (s, 3H, CH_2OCH_3), 1.34 (s, 3H, H_3CCCH_3), 1.31 (s, 3H, H_3CCHCH_3)

^{13}C NMR ($CDCl_3$) δ 189.6, 159.8, 134.5, 131.1, 130.8, 113.0, 112.6, 91.1, 77.9, 75.5, 70.5, 55.4, 23.0, 22.5.

HREIMS: Calc. for ($C_{14}H_{19}O_5Br$- C_2H_5O): 298.9938; found; (M^+ - C_2H_5O) = 298.9928.

FTIR (cm^{-1}, $CHCl_3$) 1697.2, 3030.0, 3022.2.

3-Bromo-4-(3-hydroxy-2-keto-3-methyl-butyl-1-oxy)-benzaldehyde 3.19 [93]



3.18 **3.19**

N-methylmorpholine-N-oxide (35 mg, 0.296 mmol), freshly-powdered activated 4 Å sieves and tetrapropylammonium perruthenate (3.5 mg, 0.010 mmol) were added to a solution of diol **3.18** (59.7 mg, 0.197 mmol), in CH_2Cl_2 (0.4 mL) via a solid addition tube. The resultant dark green suspension was stirred vigorously for 2 h and put through a 2 cm silica plug eluting with ethyl acetate (50mL). Removal of the solvent *in vacuo* gave a brown gum, which hardened upon contact with air. This was purified by flash chromatography, using 40% ethyl acetate - petroleum ether as eluant, gave 24 mg of the title ketone **3.19** (41%) as a yellow solid and 35 mg of the starting diol.

^1H *NMR* ($CDCl_3$) δ 9.85 (1H, s, ArC**H**O) 8.11 (d, J = 3.4 Hz, 1H, Ar**H**), 7.78 (dd, J_{HH} = 6.4 Hz, 1.9 Hz, 1H, Ar**H**) 6.81 (d, J_{HH} = 8.3 Hz, 1H, Ar**H**), 5.18 (s, 1H, ArOC**H**$_2$CO), 1.51 (s, 1H, COC(C**H**$_3$)$_2$).

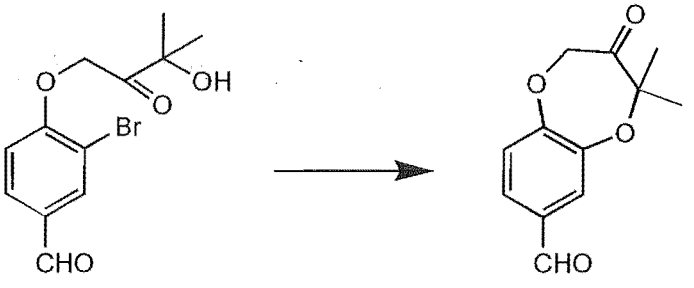
^{13}C NMR ($CDCl_3$) δ 207.4, 189.6, 160.4, 158.9, 134.9, 134.6, 131.2, 131.0, 113.0, 112.4, 77.0, 70.1, 26.8.

m.p. = 108-110°C (recrystallised from ethyl acetate-hexane to give stout lemon rods)

FTIR (cm^{-1}, $CHCl_3$) 3386.8, 2972.1, 1681.8, 1585.4.

HREIMS Calc. for $C_{12}H_{13}O_4$: 301.9978; found; 301.9981.

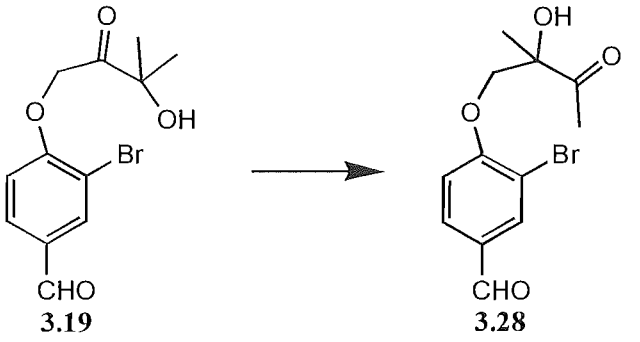
4,4-dimethyl-3-oxo-3,4-dihydro-*2H*-benzo-[b]-[1,4]-dioxepin-7-carbaldehyde 2.29



3.19 **2.29**

An oven-dried, filtered Schlenk flask was charged with $Pd(OAc)_2$ (2.5 mg, 0.013 mmol), Tol-BINAP (9.2 mg , 0.014 mmol), K_2CO_3 (37.2 mg , 0.271 mmol) and the ketol **3.19** (68 mg, 0.225 mmol). The solid mixture was dissolved in toluene (2.25 mL) and heated to 100°C. After 24 h, the reaction was cooled to 25°C and taken up in ethyl acetate (10mL), The solution was put through a silica plug (10 g), eluted with further ethyl acetate (30 mL) and the solvent removed *in vacuo* to give the crude product (110 mg). This was purified by flash chromatography on silica using 40% ethyl acetate - petroleum ether as eluant, gave the title compound **2.29** (3 mg, 6%), which gave identical spectral data to that recorded previously, (see **Section 5.2**)

The major product of the reaction (19 mg, 39%) was identified as ketone **3.28**, which arose from an α-ketol rearrangement of **3.19**.



3.19 **3.28**

^1H NMR ($CDCl_3$) δ 9.83 (s, 1H, ArC**H**O), 8.06 (d, J_{HH} = 1.9Hz, 1H, Ar**H**), 7.79 (dd, J_{HH} = 7.4, 1.9Hz, 1H, Ar**H**), 6.98 (d, J_{HH} = 8.8 Hz, 1H, Ar**H**), 4.28 (d, J_{HH} = 9.3 Hz, 1H, ArOC**H**$_2$), 4.12 (d, J_{HH} = 9.3 Hz, 1H, ArOC**H**$_2$C), 2.41 (s, 3H, $CH_2CH_3COHCOCH_3$), 1.49 (s, 3H, $CH_2CH_3COHCOCH_3$).

^{13}C NMR ($CDCl_3$) δ 210.0, 189.4, 159.0, 134.5, 131.9, 131.2, 131.0, 112.7, 78.0, 74.2, 25.0, 21.4.

FTIR (cm^{-1}, $CHCl_3$) 3361.7, 1693.4, 1612.4.

HREIMS Calc. for $C_{12}H_{12}O_4$: 220.0736 ; found : 220.0718.

General methods for Pd-catalysed aryl ether cyclisations

All manipulations were performed in a Vacuum Atmospheres glovebox under a zero-grade Ar atmosphere. All reactions were performed at a concentration of 0.1 M in the substrate alcohol.

Method 1

An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (0.03 eq), diphenylphosphinoferrocene (0.036 eq), NaO^{t}Bu (1.2 eq) and the substrate alcohol. This mixture was dissolved in toluene, protected from light and heated to 80°C with

stirring. The reaction was monitored by thin-layer chromatography and upon consumption of the starting material, cooled to room temperature. The crude reaction mixture was taken up in 25 mL ethyl acetate, put through a 10 mm silica plug and concentrated *in vacuo*.

Method 2

An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (0.05 eq), Tol-BINAP (0.06 eq), K_2CO_3 (1.2 eq). A solution of the substrate alcohol in toluene was added, the flask was protected from light and heated to 100°C with stirring. The reaction was monitored by thin-layer chromatography and upon consumption of the starting material, cooled to room temperature. The crude reaction mixture was taken up in 25 mL ethyl acetate, put through a 10 mm silica plug and concentrated *in vacuo*.

Cyclisation trials using Buchwald's conditions[78]

Substrate	Conditions	Result
3.20 Bn	1.2 eq NaO^tBu, 0.03 eq $Pd(OAc)_2$, 0.036 eq dppf, Toluene, 80°C, 24 hours	No reaction
3.20 Bn	1.2 eq K_2CO_3, 0.05 eq $Pd(OAc)_2$, 0.06 eq Tol-BINAP, Toluene, 100°C, 36 hours	No reaction
3.22 TBDMS	1.2 eq NaO^tBu, 0.03 eq $Pd(OAc)_2$, 0.036 eq dppf, Toluene, 80°C, 24 hours	No reaction
3.22 TBDMS	1.2 eq K_2CO_3, 0.05 eq $Pd(OAc)_2$, 0.06 eq Tol-BINAP, Toluene, 100°C, 36 hours	No reaction
3.23 MOM	1.2 eq K_2CO_3, 0.05 eq $Pd(OAc)_2$, 0.06 eq Tol-BINAP, Toluene, 100°C, 48 hours	No reaction
3.23 MOM	1.2 eq NaO^tBu, 0.03 eq $Pd(OAc)_2$, 0.036 eq dppf, Toluene, 80°C, 24 hours	Dehalogenation of starting material
3.19 Ketone	1.2 eq NaO^tBu, 0.03 eq $Pd(OAc)_2$, 0.036 eq dppf, Toluene, 80°C, 24 hours	Destruction of substrate
3.19 Ketone	1.2 eq K_2CO_3, 0.05 eq $Pd(OAc)_2$, 0.06 eq Tol-BINAP, Toluene, 100°C, 48 hours	α-ketol rearrangement (39%)

		Dioxepin formation (7%)

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