The Total Synthesis of 4-Methoxy-6-methylheptadienoic Acid Natural Products

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Department of Chemistry

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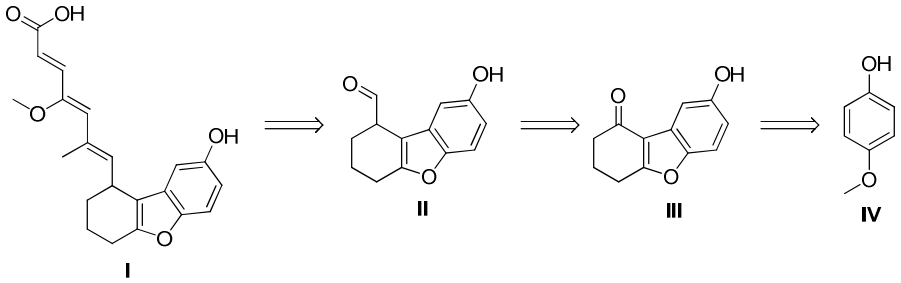
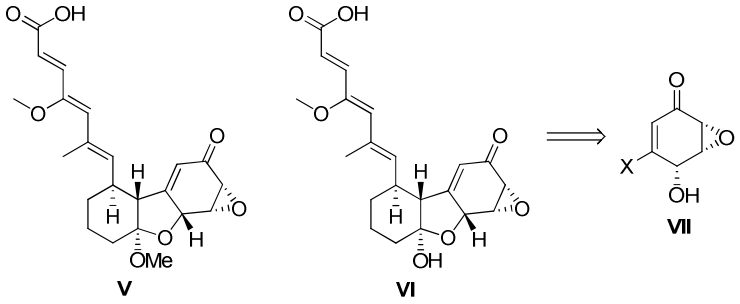
Abstract

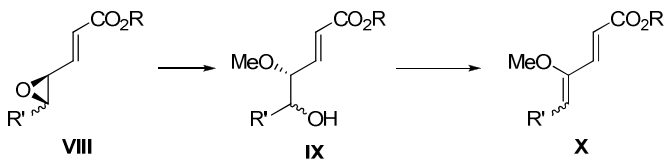
The total synthesis and first structural confirmation of the natural product (±)-cuevaene A **I**, isolated from *Streptomyces* sp. HKI 0180, and studies towards the total synthesis of natural products JBIR-23 **V** and 24 **VI**, isolated from *Streptomyces* sp. AK-AB27, are described herein. Chapter 1 gives background to these and related natural products. The previous synthesis of **I** and the resultant structural ambiguity are also discussed. In Chapter 2, the available methods of forming tetrahydrobenzofuran-1-ols are reviewed before the synthesis of the key aldehyde intermediate **II** from phenol **IV** *via* ketone **III** is discussed. The triene sidechain was then installed in a stepwise manner through a series of olefination reactions to achieve the total synthesis of **I**. The structural confirmation of **I** was then achieved through the comparison of NMR spectroscopic data with the raw isolation data.



The key intermediate for the total synthesis of JBIR-23 **V** and 24 **VI** was identified as epoxyquinol **VII** and Chapter 3 discusses the investigations into its synthesis.



Chapter 4 discusses two complementary methodologies developed to provide access to 4-methoxypentadienoates **X**, as seen in the sidechain of natural products **I**, **V** and **VI**, from the analogous γ,δ-epoxydienoates **VIII** through an initial epoxide opening and subsequent elimination of the resulting alcohols **IX**. The selectivity and substrate scope of the two processes is then investigated.



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Acknowledgements

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Special thanks have to go to a few people. Graeme, for dealing with all the breakages and problems in the labs efficiently and for all the proof-reading, and not just the thesis. Jimmy and Will, again for the proof-reading throughout my PhD, especially the thesis. And of course, Dave for making the first year in the flat such a good time, the only time I'll be allowed Sky Sports I'm sure.

Last and by no means least, an extra special thanks to Ruth, my wife. She really has been a great support throughout my PhD. She has been my motivator, soundboard, comfort and best friend. Without her I don't think I'd be here right now and she deserves absolute full credit for that.

Author's Declaration

The research presented in this Thesis was carried out at the University of York between October 2009 and September 2012. This work is, to the best of my knowledge, original except where due reference has been made to other workers.

Part of the work disclosed herein has been published, during the project, in the below articles:

Craven, P. G. E.; Taylor, R. J. K. *Tetrahedron Lett.* **2012**, *53*, 5422 – 5425.

Craven, P. G. E.; Taylor, R. J. K. *Synlett*. **2013**, *24*, 363 – 368.

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Chapter 1. Introduction

1.1. JBIR-23 and 24

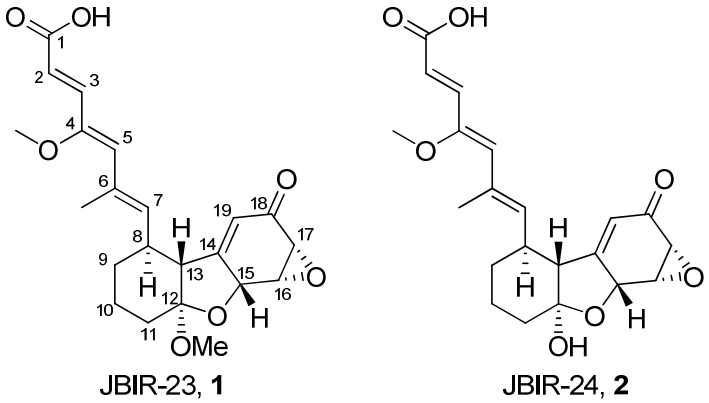


Figure 1. Structures of JBIR-23 (**1**) and JBIR-24 (**2**)

1.1.1. Isolation & biological activity

JBIR-23 (**1**) and -24 (**2**) (Figure 1) were isolated by Shin-ya *et al.* in 2009 from *Streptomyces* sp. AK-AB27.[1] Both compounds show promising cytotoxic effects against malignant pleural mesothelioma (MPM), with **1** having IC_{50} values of 10 – 50 μM over four cell-lines and **2** having IC_{50} values of 75 – 200 μM. MPM is an aggressive form of cancer which is associated with asbestos exposure.[2] Thus far, MPM is resistant to most conventional forms of cancer treatment – radiotherapy, chemotherapy and even surgery.[3] As such, novel anti-tumour agents which are active against this form of cancer are clearly of great interest.

Recently, the isolation authors have carried out further biological studies on **1** and have reinforced its potential as an anti-cancer agent.[4] *In vivo* models showed a decrease in tumour size in mice treated with **1** compared to those treated with a negative control (DMSO) (Figures 2 & 3).

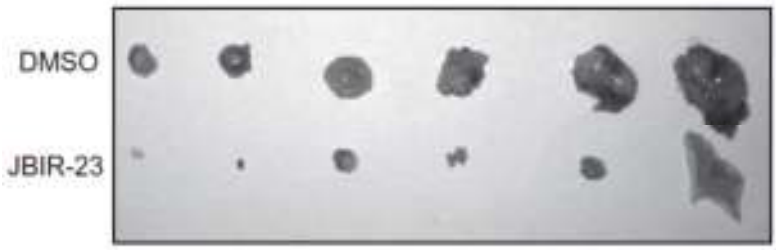


Figure 2. Inhibition of tumour growth in mice treated with JBIR-23 vs. mice treated with DMSO (diagram copied directly from ref. 4).[4]

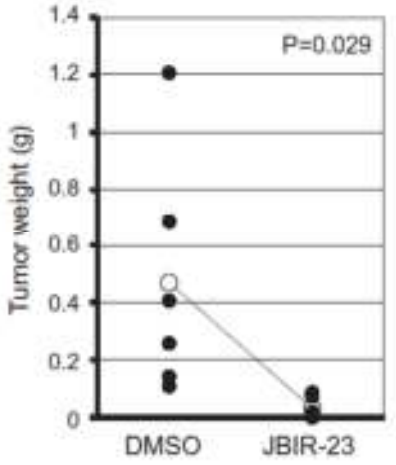


Figure 3. Comparison of tumour weight in mice treated with JBIR-23 (**1**) and DMSO (negative control) (diagram copied directly from ref. 4).[4]

The authors also conducted a series of experiments to deduce the mechanism by which this inhibition was induced. They came to the conclusion that the mechanism of action was based on the promotion of tubulin polymerisation. This is a similar mechanism to that seen in a variety of other anti-cancer drugs, most notably paclitaxel, better known as its trade name Taxol, a universally-used anti-cancer agent.

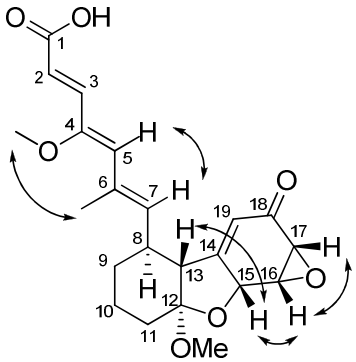
Furthermore, not only was **1** effective at inhibiting tumour growth, there were no observed adverse side-effects seen in the mice, although this was only an initial study with no detailed safety screening involved.

1.1.2. Structural elucidation

Shin-ya's group assigned the complex structure of JBIR-23 (**1**) and 24 (**2**) mainly using NMR spectroscopic techniques.[1] Indicative IR stretching frequencies revealed the presence

of an α,β-unsaturated carboxylic acid (1687 cm^{-1}). This information, alongside key peaks in the ^{13}C-NMR spectrum and various 2D NMR correlations, revealed the presence of the 4-methoxy-6-methyl-hepta-2,4,6-trienoic acid sidechain.

The *E*,*Z*,*E*-configuration of the side-chain was proved by the coupling constant (*J* = 16 Hz) between H-2 and H-3, and by strong nOe interactions between H-5 and H-7 as well as between the -Me and -OMe groups (Figure 4).



1

Figure 4. Key nOe interactions of **1**

After the determination of the core structure as a dodecahydrodibenzo[*b*,*d*]furan incorporating an α,β-unsaturated ketone and an epoxide motif, the relative stereochemistry was determined using 2D NMR techniques. ROE spectroscopy confirmed the relative stereochemistry of the left hand ring and further proved the ring exists in the chair conformation (Figure 5).

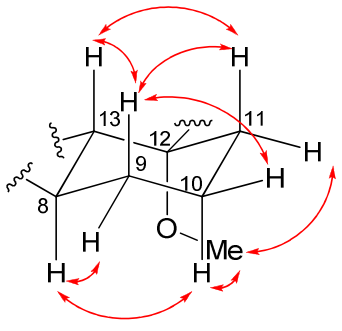


Figure 5. Key ROE interactions showing chair confirmation of cyclohexane ring of **1**

Once this was assigned, the strong nOe interactions linking H-13, H-15, H-16 and H-17, suggested all these protons exist in a *cis*-configuration (Figure 4); thus confirming the relative stereochemistry of **1**.

1.1.3. Related epoxyquinol natural products

The epoxyquinol motif is found in a range of natural products, including some isolated from *Streptomyces* bacteria, and many show biological activity.[5] Figure 6 shows a selection of the epoxyquinol natural products isolated to date.

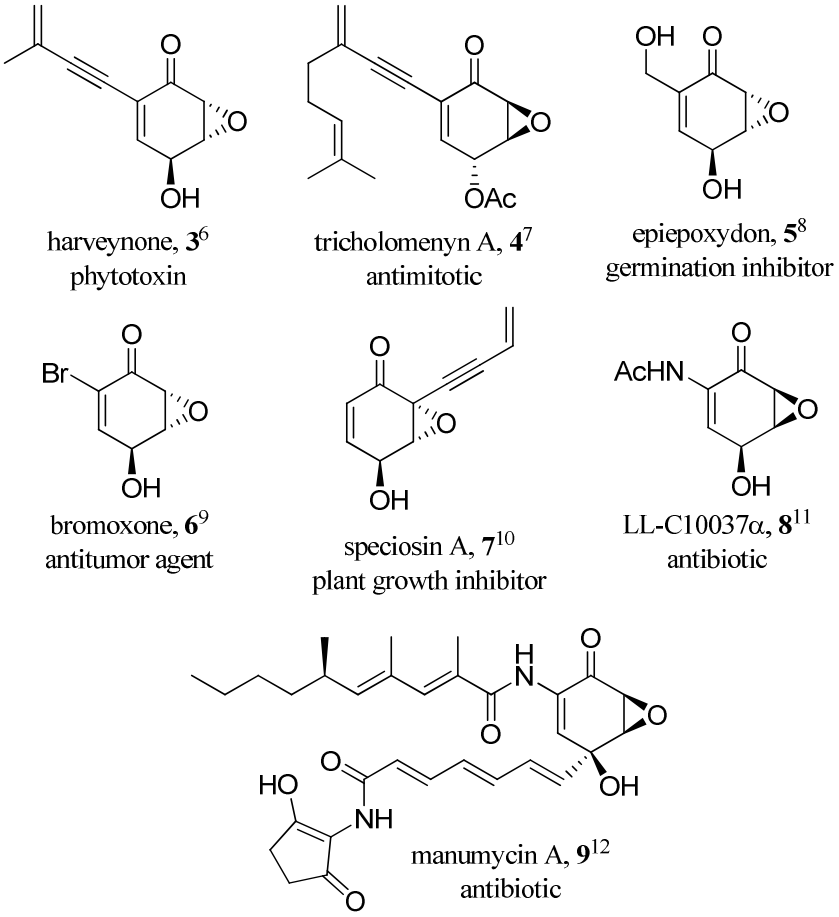
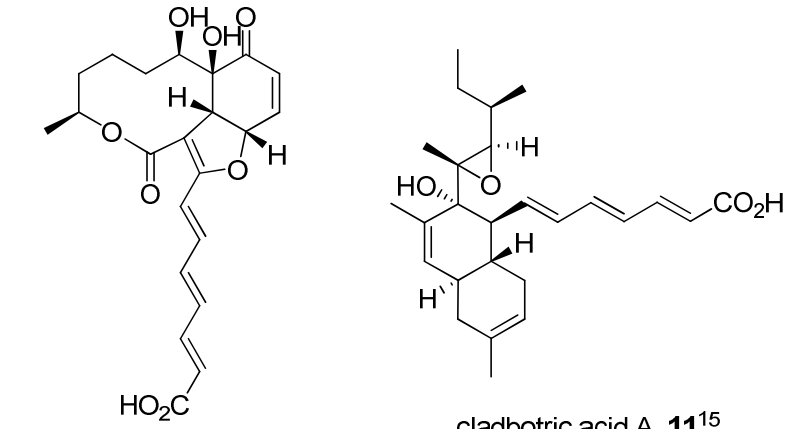


Figure 6. Selection of epoxyquinol natural products

Due to the varied biological activity of these epoxyquinol natural products there has been a large amount of study towards their total syntheses.[5] As such, a number of general methods have been developed over the years to install the epoxyquinol motif. A selection of these synthetic strategies will be discussed later in Chapter 3.

1.1.4. Related *E*,*Z*,*E*-4-methoxy-6-methylhepta-2,4,6-trienoic acid natural products

As with the epoxyquinol motif, trienoic acid sidechains are also commonly found in natural products (Figure 7).[13]



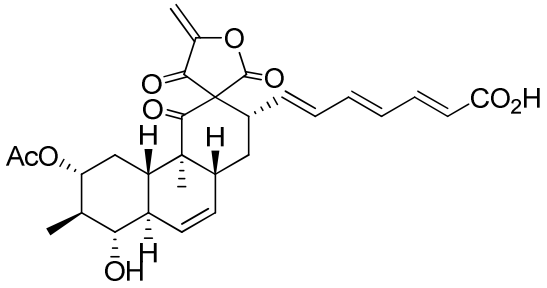


Figure 7. Representative selection of trienoic acid natural products

The commonplace nature of the trienoic acid sidechain means that many synthetic strategies have been developed towards their synthesis. However, the majority of these natural products do not incorporate the enol ether moiety seen in JBIR-23 (**1**) and 24 (**2**), and as such, this particular trienoic acid sidechain represents a novel synthetic challenge. However, one set of natural products, isolated in 2000 by Grafe *et al.* contain an identical sidechain to **1** and **2**, namely cuevaenes A (**13**) and B (**14**) (see next section).[17]

1.2. Cuevaenes A and B

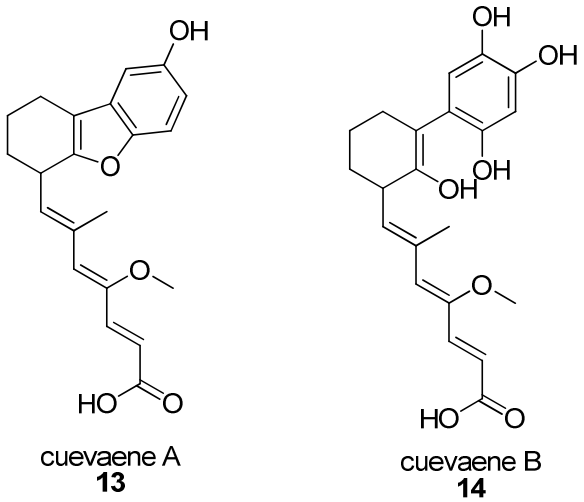


Figure 8. Gräfe's structures of the cuevaene natural products

1.2.1. Isolation and biological activity

Cuevaenes A (**13**) and B (**14**) were isolated from a strain of bacteria, *Streptomyces* sp. HKI 0180, found in a Spanish cave.[17] While **13** and **14** only show moderate antibacterial activity against Gram-positive bacteria, they were not tested against MPM cell lines and it would be interesting to see, in light of their structural similarities, if **13** and **14** display similar activity to JBIR-23 (**1**) and JBIR-24 (**2**).

1.2.2. Structural elucidation

Gräfe *et al*. used a variety of techniques to determine the structures of **13** and **14**.[17] Mass spectrometry revealed their chemical formula and molecular mass, and furthermore fragmentation peaks suggested the presence of the tetrahydrodibenzofuran motif. A range of NMR spectroscopic experiments, including COSY and HMBC experiments, were then used to determine the position and geometry of the triene sidechain (Figure 9).

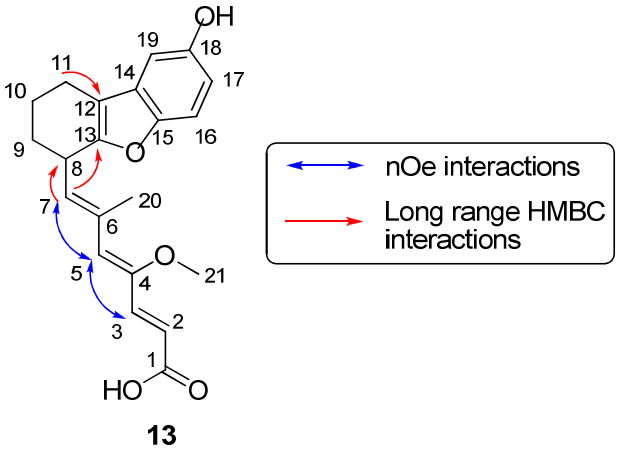


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Figure 9. Key NMR interactions of **13** used for structural determination

1.2.3. Structural ambiguity

Despite the extensive work done on the structural elucidation of cuevaenes A and B by Gräfe,[17] the assignment of their structures as **13** and **14** was questioned by Shin-ya *et al.* during their isolation of JBIR-23 (**1**) and 24 (**2**).[1] They drew on the structural similarity of **1** and cuevaene A (**13**), as well as the fact they were isolated from a very similar strain of *Streptomyces* bacteria, to propose that these natural products share a common biosynthetic pathway. They further suggested that if there was a common biosynthetic pathway, then the positioning of the sidechain would be likely to be the same on all the natural products. Therefore, they proposed that the true structure of cuevaene A was more likely to be that of **15** (Figure 10), whereby the sidechain positioning on the tetrahydrobenzofuran moiety has been altered to match that seen in **1**.

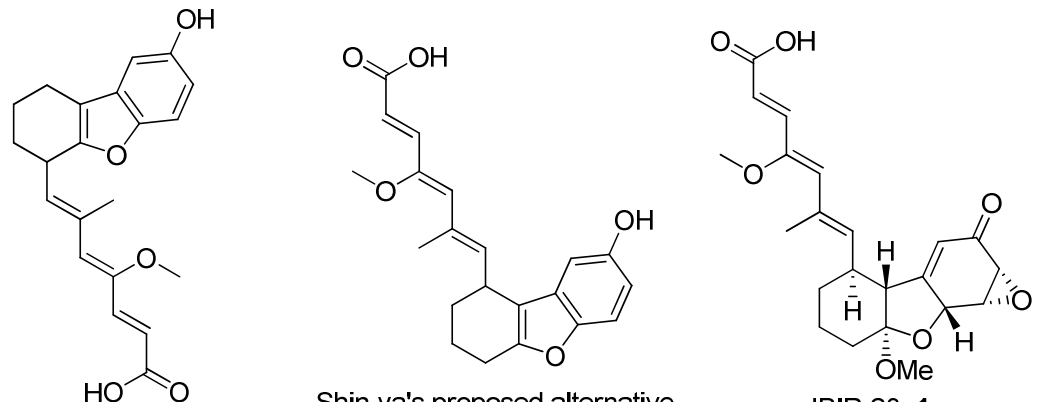
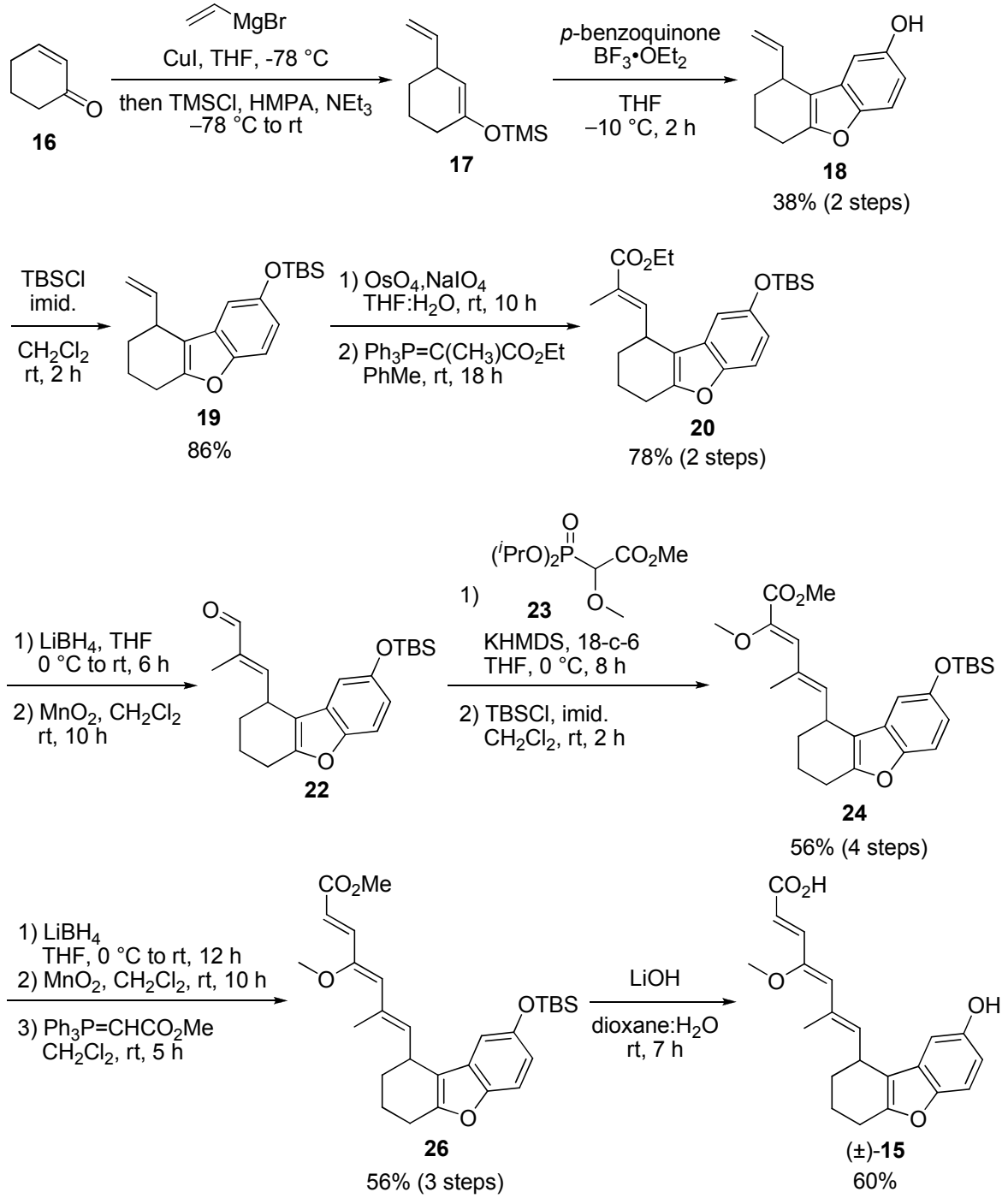


Figure 10. Gräfe's and Shin-ya's proposed structures of cuevaene A

1.2.4. Previous syntheses of (±)-13 and (±)-15



Scheme 1. Liu's synthesis of Shin-ya's structure of cuevaene A (±)-**15**

During the course of this research, Liu and co-workers reported the synthesis of both Gräfe's original structure (±)-**13** and Shin-ya's revised structure (±)-**15** of cuevaene A.[18] Their synthesis of (±)-**15** began with a vinyl cuprate addition in cyclohex-2-enone (**16**) and trapping of the intermediate enolate with TMSCl. Treatment of the subsequent TMS enol ether **17** with *p*-benzoquinone and a catalytic amount of BF_3•OEt_2, a modified version of a

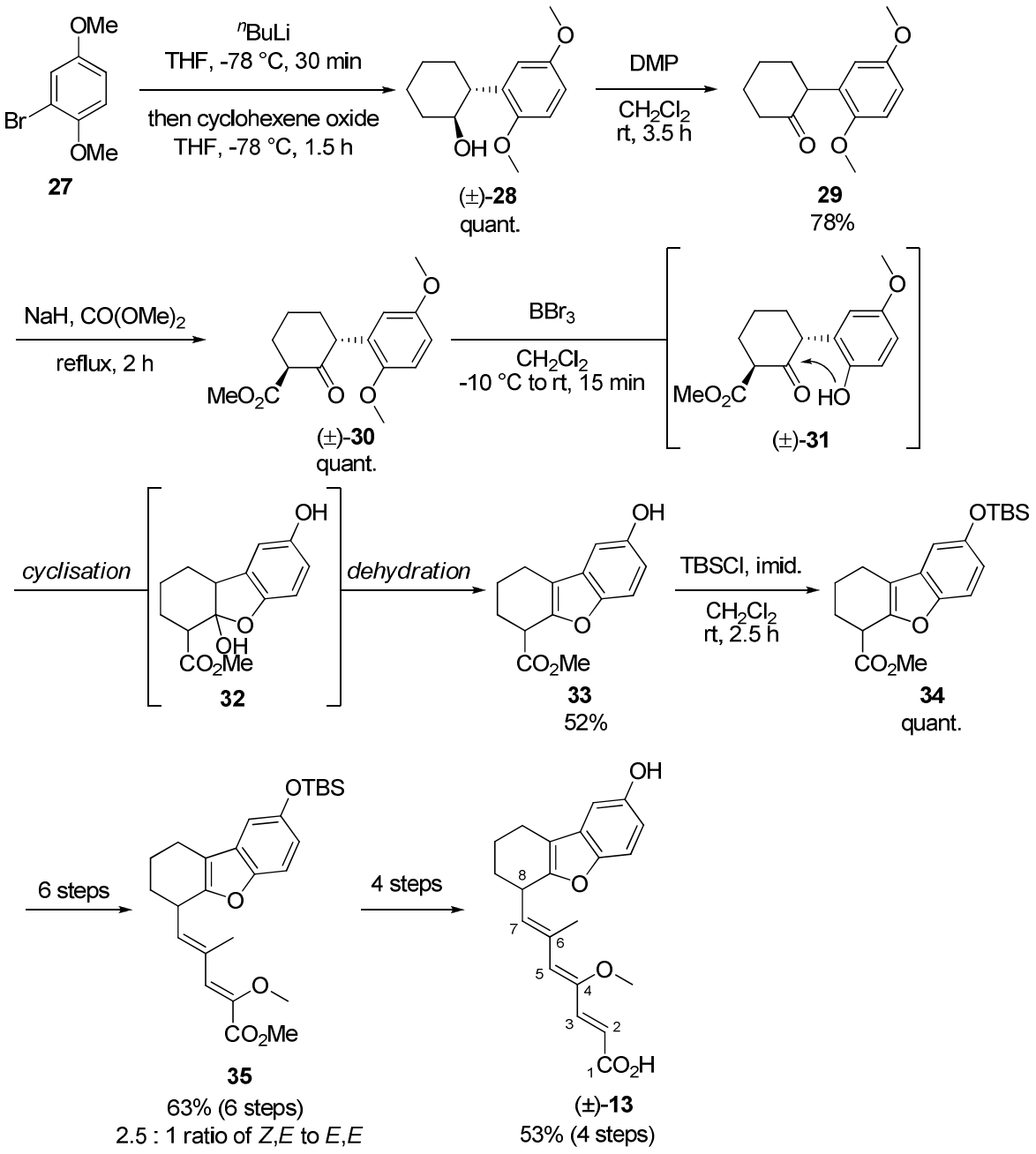
known procedure,[19] afforded the desired tetrahydrobenzofuran **18** in a reasonable yield over two steps (Scheme 1).

The vinyl group appended to this benzofuran core allowed further manipulation. Thus, after TBS protection, a Johnson-Lemieux oxidation[20] of terminal alkene **19** afforded the desired aldehyde, which, after treatment with commercially available ethyl 2-(triphenylphosphoranylidene)propanoate under Wittig conditions, delivered alkene **20** in excellent yield over the two steps. Subsequent reduction of ethyl ester **20** with $LiBH_4$, oxidation of the resulting alcohol using MnO_2 yielded aldehyde **22**.

A Horner-Wadsworth-Emmons olefination was then effected using phosphonate **23** and LiHMDS. However, Liu observed concomitant deprotection of the TBS group under these conditions and therefore an additional protection step was required. Eventually, diene **24** was obtained in good yield over the four steps from ethyl ester **21**. A similar reduction-oxidation-olefination procedure yielded to the desired triene **26**, again in good yield. Subsequent hydrolysis of the methyl ester and simultaneous deprotection of the TBS ether with LiOH, delivered Shin-ya's revised structure (±)-**15**. Overall, the total synthesis was achieved in a yield of 5% over 13 steps.

Liu then compared the NMR spectroscopic data of their synthetic material against that of the isolated natural product. They discovered that the data did not match and therefore proposed that (±)-**15** was not the structure of the natural product.[18]

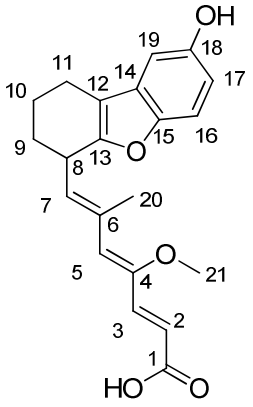
With this information in hand, Liu's group turned their attentions to Gräfe's original structure ((±)-**13**). This time the synthesis began with lithiation of bromide **27** and addition of the subsequent organolithium into cyclohexene oxide (Scheme 2). Oxidation of the subsequent alcohol (±)-**28** was achieved using DMP and installation of the α-ester group, using NaH and $CO(OMe)_2$, delivered ester (±)-**30** in quantitative yield. The key benzofuran moiety was then formed *via* an intramolecular cyclisation of (±)-**30**. This was achieved by initially deprotecting the methyl ether with BBr_3 to deliver the free phenol (±)-**31** which then underwent intramolecular cyclization onto the adjacent ketone moiety. Dehydration of the resulting alcohol **32** delivered the desired benzofuran, which after a TBS protection took the group to tricycle **34**, the corresponding compound to vinyl **18** (Scheme 1).



Scheme 2. Liu's synthesis Gräfe's structure (±)-**13**

Following a similar reduction-oxidation-olefination sequence as they used to access (±)-**15**, Liu completed the synthesis of Gräfe's original structure (±)-**13** in ten further steps in an overall yield of 10% over 15 steps.

However, as with (±)-**15**, the ^{1}H-NMR spectroscopic data of (±)-**13** also did not match that reported by Gräfe (Table 1).



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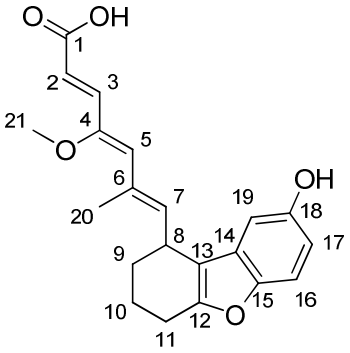

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Table 1. Comparison of ^{1}H-NMR spectroscopic data of synthetic (±)-**13** and (±)-**15** and the natural product

Proton	Isolation paper[17] 400 MHz, $CDCl_3$ δ_H (multi, *J* in Hz)	Liu's synthetic (±)-**13**[18] 400 MHz, $CDCl_3$ δ_H (multi, *J* in Hz)	Liu's synthetic (±)-**15**[18] 400 MHz, $CDCl_3$ δ_H (multi, *J* in Hz)
2	6.00 (d, 16.0)	6.05 (d, 15.2)	6.04 (d, 15.6)
3	7.06 (d, 16.0)	7.12 (d, 15.2)	7.12 (d, 15.6)
5	5.95 (s)	5.83 (s)	5.84 (s)
7	5.69 (d, 10.1)	5.81 (d, 10.4)	5.77 (d, 10.0)
8	3.85 (ddd, 10.1, 4.1, 2.2)	3.87 – 3.91 (m)	3.83 – 3.82 (m)
9	1.59 – 2.01 (m)	1.57 – 1.88 (m)	1.52 – 1.89 (m)
10	1.85 – 2.08 (m)	1.98 – 2.13 (m)	1.98 – 2.11 (m)
11	2.69 – 2.71 (m)	2.60 (t, 5.6)	2.72 – 2.73 (m)
16	7.16 (d, 9.1)	7.22 (d, 8.4)	7.23 (d, 8.0)
17	6.62 (dd, 9.1 , 2.5)	6.70 (dd, 2.4, 8.8)	6.68 (d, 8.4)
19	6.70 (d, 2.5)	6.84 (d, 2.4)	6.69 (s)
20	2.24 (s)	2.17 (s)	2.22 (s)
21	3.62 (s)	3.66 (s)	3.66 (s)

As can be seen above, the biggest differences in the spectroscopic data appear to exist in the sidechain protons (H-2, 3 and 5). Furthermore, the data for the aromatic protons (H-16, 17 and 19) in Shin-ya's structure (±)-**15** are in closer agreement to the natural product than that of Gräfe's structure (±)-**13**. Rather than clarifying the structure of cuevaene A, Liu's results added to the air of ambiguity surrounding this problem.

1.3. Aims of the Project

At the outset, the aims of the project were as follows:

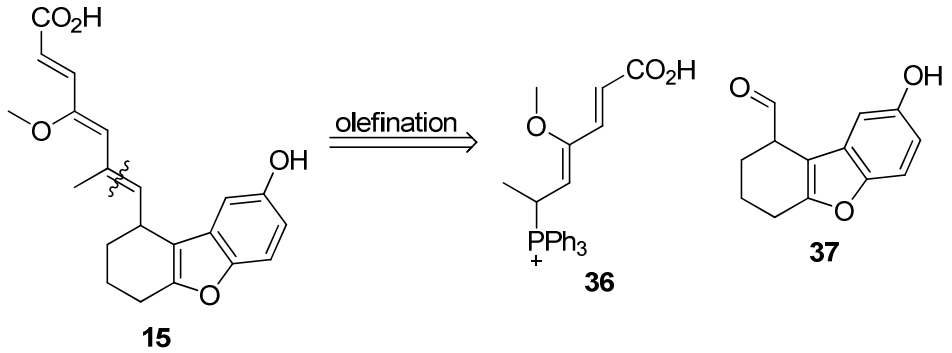
(i) To prepare Shin-ya's revised structure **15** for cuevaene A and to confirm that this is the natural product,
(ii) To apply the methodology devised in the cuevaene A study to devise synthetic approaches to the JBIR compounds **1** and **2**.

With the publication of Liu's study part-way through this research period, the first objective had to be modified (as described in Chapter 2).

Chapter 2. Total Synthesis and Structural Confirmation of (±)-Cuevaene A

2.1. Retrosynthesis of Shin-ya's Revised Structure of (±)-Cuevaene A (15)

As previously discussed, our initial objective was the total synthesis and structural elucidation was Shin-ya's revised structure **15** for cuevaene A. Retrosynthetically, we envisioned that a convergent strategy could be achieved through a late stage olefination between aldehyde **37** and a suitable olefinating reagent such as phosphonium salt **36** (Scheme 3).



Scheme 3. Retrosynthetic analysis of **15**

The major advantage of this retrosynthetic plan was the ability for phosphonium salt **36**, or a suitable equivalent, to be also used in the total synthesis of JBIR-23 (**1**) and 24 (**2**). The work undertaken towards the synthesis of **36** is discussed later in Chapter 4.

2.2. Tetrahydrodibenzofuran-2-ols: Literature Routes

The key intermediate in the total synthesis was aldehyde **37** and so we investigated routes to similar tetrahydrodibenzofuran-2-ol compounds in the literature (Figure 11).

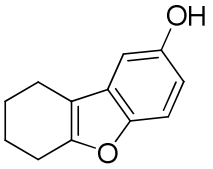


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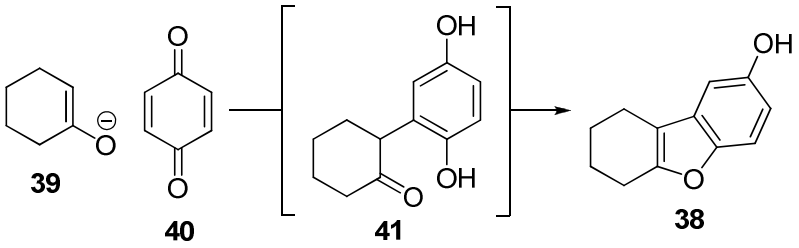
Figure 11. Core tetrahydrodibenzofuran-2-ol structure of both cuevaene A structures **13** and **15**

The major strategy for the synthesis of tetrahydrodibenzofuran structures (**38**) disclosed in the literature involves the intramolecular cyclisation of a bicyclic intermediate **41** and subsequent aromatisation (Scheme 4).



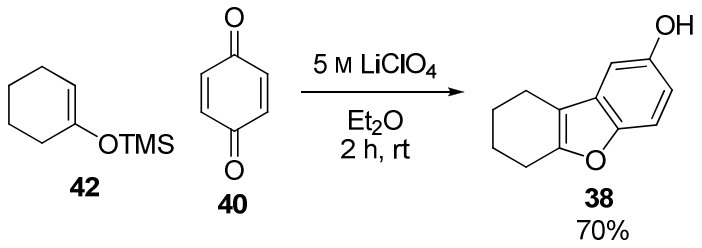
Scheme 4. First route for the formation of **38**

Bicycle **41** can be formed in a number of ways, but the most common method is a conjugate addition of an enolate **39** into *p*-benzoquinone (**40**), or suitable equivalents thereof. The advantage of this method is **41** generally cyclises *in situ* rather than requiring a second step.

A selection of examples from the literature using this strategy will be discussed, alongside an interesting example that differs from this strategy.

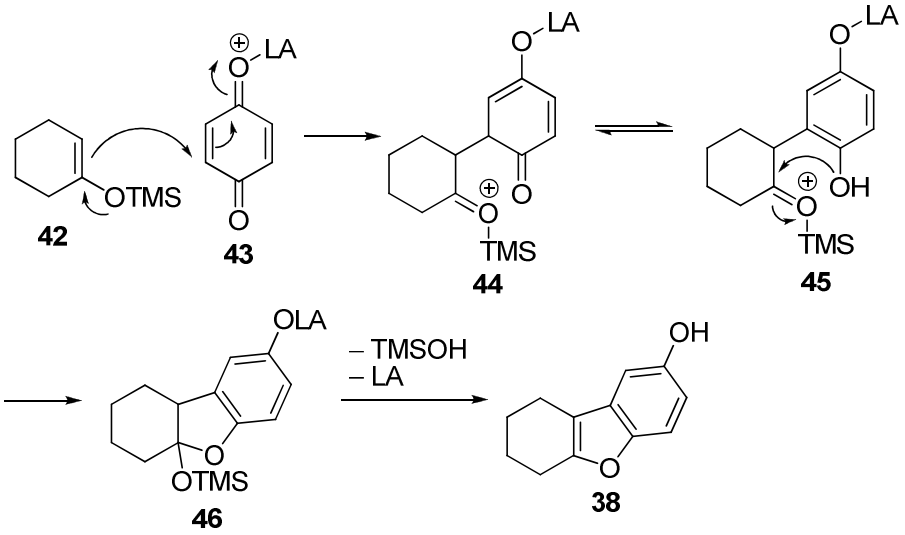
2.2.1. Conjugate addition strategies

The one-pot conjugate addition-cyclisation-aromatisation sequence is by far the most common method of forming this type of structural motif. A typical example of this strategy was discussed by Sankararaman *et al*. in 1995.[19] They developed a novel set of conditions whereby they treated preformed silyl ether **42** with $LiClO_4$ in the presence of *p*-benzoquinone (**40**) to afford the desired tetrahydrodibenzofuran **38** (Scheme 5).



Scheme 5. Sankararaman's conditions for tetrahydrodibenzofuran formation[19]

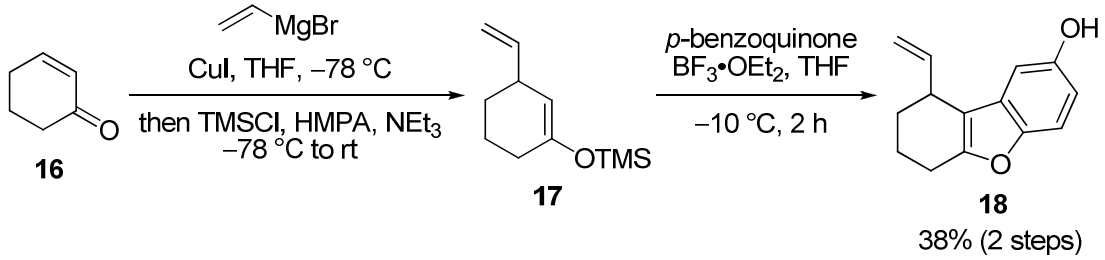
Mechanistically, the reaction initiates with the conjugate addition of silyl enol ether **42** into the Lewis-acid activated *p*-benzoquinone **43** to yield the intermediate bicycle **44** (Scheme 6).



Scheme 6. Mechanism of Sankararaman's formation of **38**

Tautomerism of **44** to the phenol **45** and subsequent intramolecular cyclisation onto the TMS activated ketone then delivers the tricyclic intermediate **46**. Subsequent aromatisation by elimination of TMSOH then yields the desired tetrahydrodibenzofuran **38**.

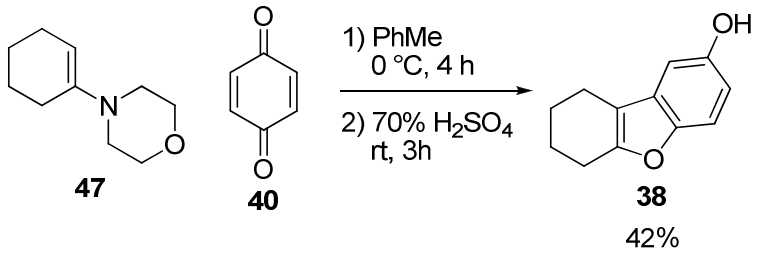
Unfortunately, the substrate scope of these conditions was not fully investigated. Further, there has been a suggestion in a subsequent report that the method may not be amenable to larger scales. In Liu's synthesis of Shin-ya's structure of cuevaene A (**15**), they attempted to use Sankararaman's procedure to synthesise their key vinyl intermediate **17** (Scheme 7).[18]



Scheme 7. Liu's modification of Sankararaman's conitions[18]

Liu *et al*. found that, after using Sankararaman's $LiClO_4$ procedure, they encountered problems with the purification preventing the clean recovery of **18**. However, they overcame this problem by the use of BF_3•OEt_2 in place of the $LiClO_4$. They also showed the substrate scope of these conditions could be extended beyond basic silyl enol ethers.

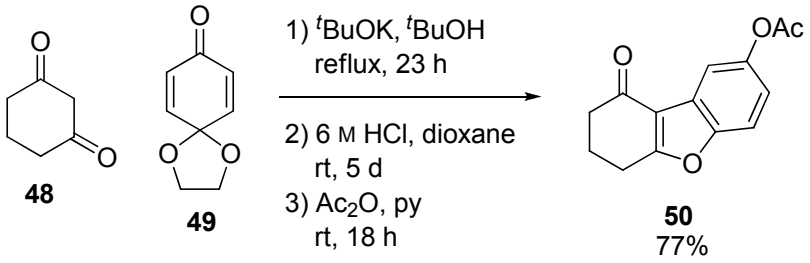
Other varieties of enolate equivalents, beyond silyl enol ethers, can also be used to form these benzofuran structures. One such example is morpholine enamine **47**, which has been utilised to this end many times in the literature (Scheme 8).[21, 22]



Scheme 8. Use of morpholine enamine **47** for the formation of tetrahydrodibenzofuran **38**[21]

For example, in 2007 Janin *et al*. found that by mixing enamine **47** with *p*-benzoquinone (**40**) for 4 h and subsequent treatment with 70% sulfuric acid delivered the desired benzofuran **38** in good yield.[21] Janin found that the use of more complex enamines was unsuccessful in forming the desired benozfurans.

There have also been some reports into the use of alternative *p*-benzoquinone substrates for these reactions. For example, while not a one-pot procedure, Duthaler and co-workers showed the efficient conversion of quinone monoketal **49** into benzofuran **50** (Scheme 9).[23]



Scheme 9. Duthaler's formation of benzofuran **50**[23]

Quinone monoketal **49** was treated with dione **48** and ^{t}BuOK followed by 6 M HCl to afford the desired benzofuran structure. Subsequent acetylation of the free phenol with Ac_2O and pyridine allowed the isolation of benzofuran **50** in an excellent yield over the three steps.

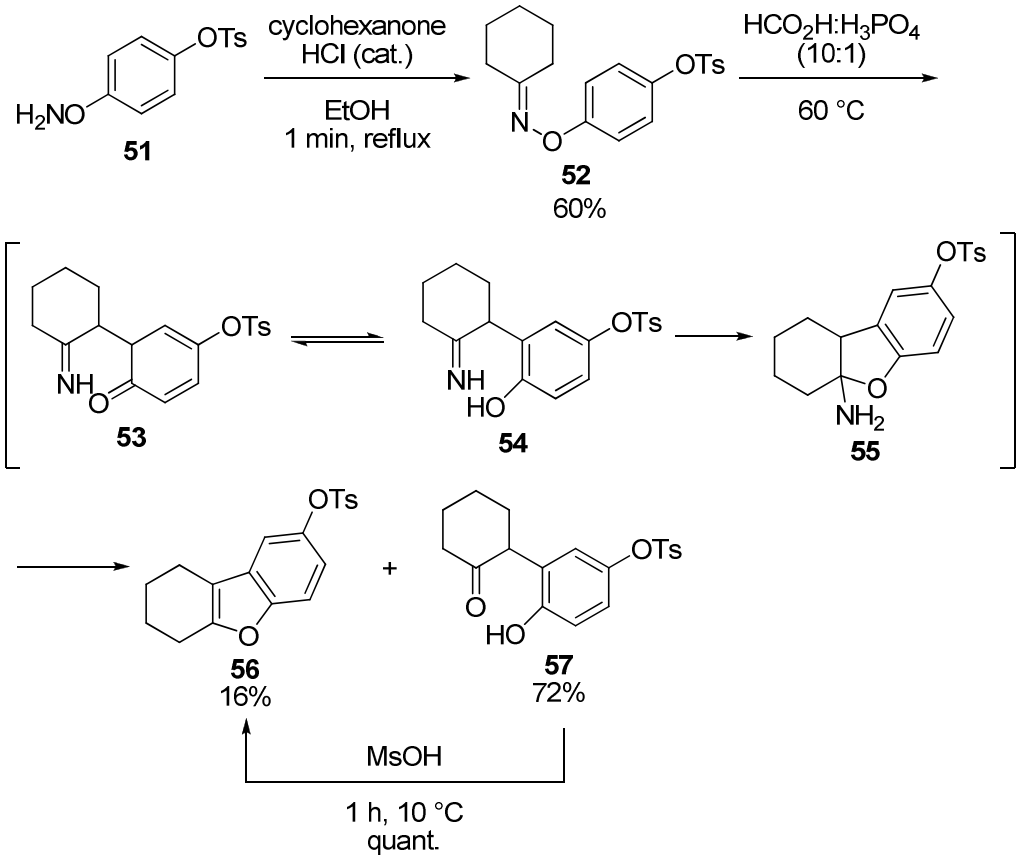
Duthaler *et al*. investigated a number of variations on this reaction with different starting materials to attempt to achieve the desired transformations. However, they found the products formed were highly dependent on the starting materials and no discernible pattern was observed.

Overall, while a common method of forming tetrahydrodibenzofurans, this conjugate addition-cyclisation-aromatisation procedure generally proceeds in only moderate yields and the reaction scope is very limited to a small range of substrates.

2.2.2. Alternative formation of bicyclic intermediate

While the conjugate addition methodology thus far discussed is the most common method of forming the bicyclic intermediate **41** (Scheme 4), a number of alternative methods have also been developed. These methods generally provide products with a greater degree of functionality than the aforementioned conjugation addition strategy.

An early example of this strategy was described in 1984 by Rapoport *et al*. whereby they formed their desired benzofuran motif **56** from an aryl hydroxylamine **51** (Scheme 10).[24]

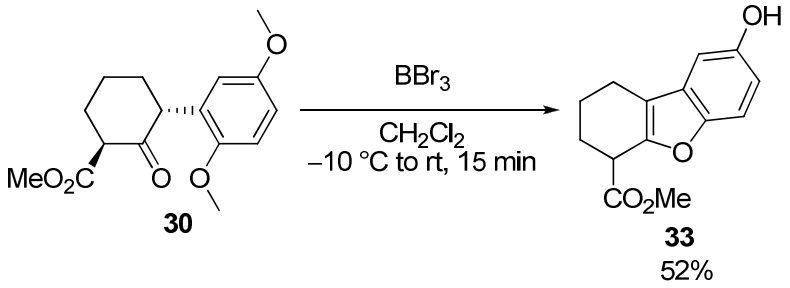


Scheme 10. Rapoport's method of forming benzofuran **56**[24]

Initial condensation of hydroxylamine **51** with cyclohexanone forms the desired *O*-aryloxime **52**. Subsequent treatment of **52** with a 10:1 mixture of formic acid:phosphoric acid starts a cascade sequence involving a sigmatropic rearrangement, intramolecular cyclisation of the free phenol onto the adjacent imine to form hemiacetal **55** and a final elimination of ammonia to deliver the desired benzofuran **56** in a poor yield. While this procedure does not fit the strategy outline of a phenol attack in a preformed bicyclic system, the side-product of the desired reaction is bicycle **57**, formed through the hydrolysis of the imine **54**.

Rapoport found that treatment of **57** with MsOH delivered the desired benzofuran **56** in quantitative yield, presumably through initial attack of the free phenol onto the adjacent ketone, to produce an overall yield of **56** of 88%.

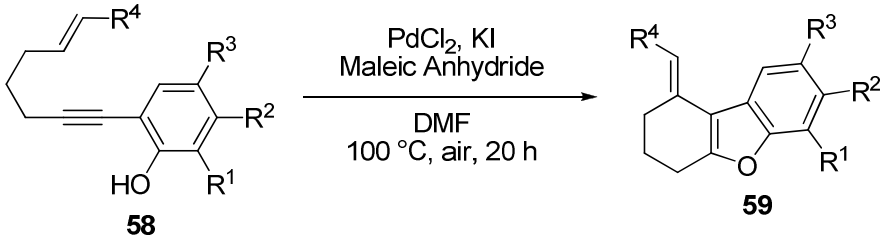
The possibility of extra functionalisation with this two-step strategy was exemplified in Liu's synthesis of Gräfe's structure of cuevaene A (**15**) (Scheme 11).[18]



Scheme 11. Liu's formation of tetrahydrodibenzofuran **33**[18]

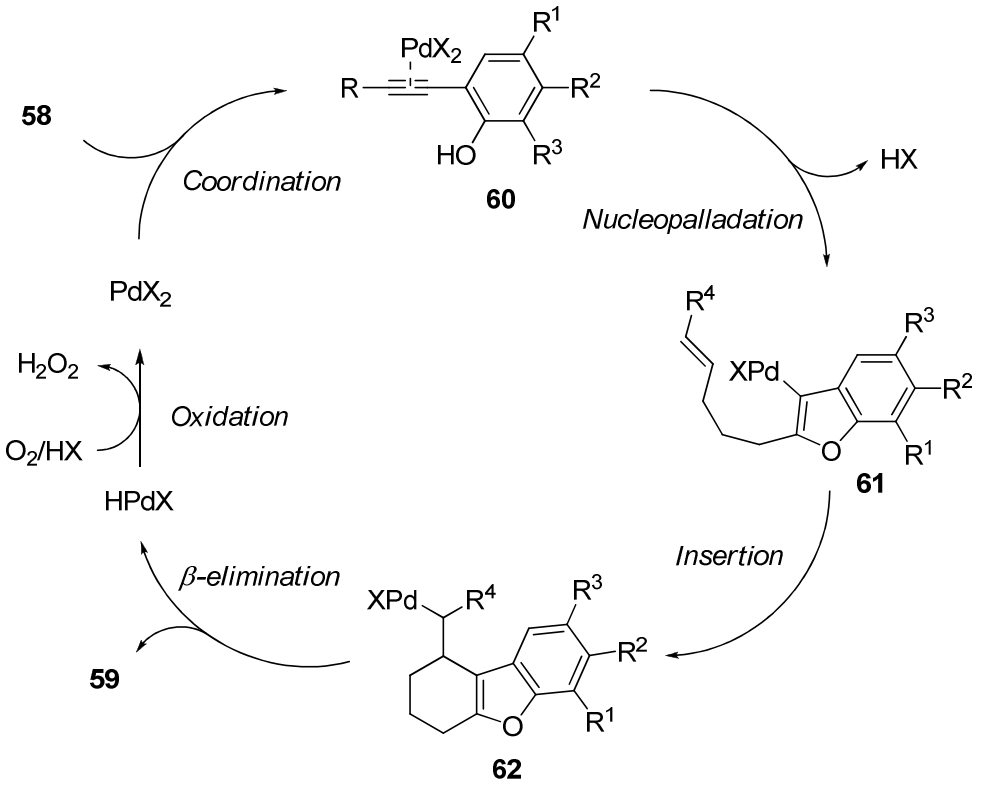
A sequence of deprotection of the methyl ether with BBr_3, attack of the nascent phenol into the adjacent ketone and a final dehydration, as described earlier, leads to the desired benzofuran **33** in moderate yield. As can be seen, these conditions allow for the presence of the α-ester group, albeit with a decrease in the obtained yield.

Ketone equivalents are not the only suitable electrophiles for the phenol attack. In 2012, Álvarez and co-workers reported the use of a palladium-alkyne complex as the electrophile (Scheme 12).[25]



Scheme 12. Álvarez's Pd-mediated formation of the tetrahydrodibenzofuran moiety[25]

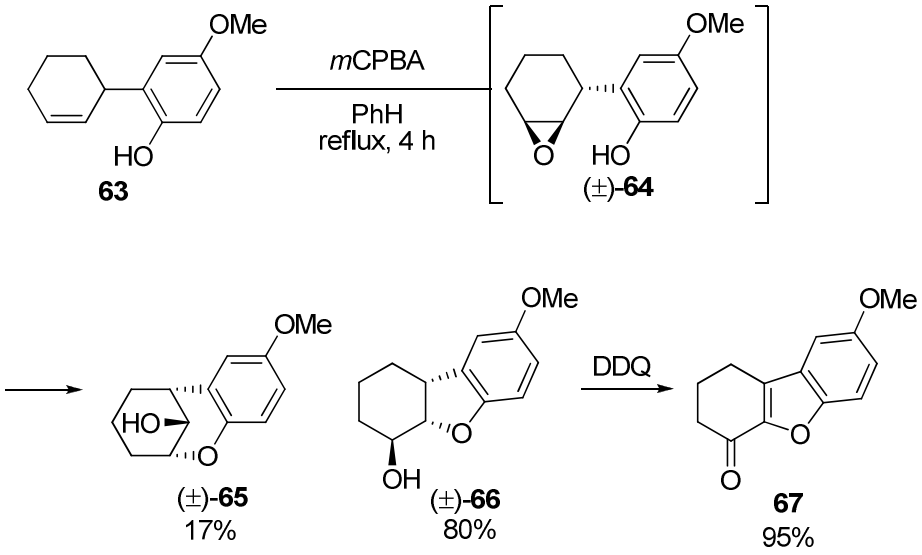
They found that treatment of alkynes **58** with a source of Pd(II) delivered their desired benzofurans **59** in good to excellent yields and excellent selectivity. The initial nucleopalladation step proceeds with excellent *endo*-selectivity forming the palladated benzofuran species **61** (Scheme 13).



Scheme 13. Mechanistic cycle for formation of benzofurans **59**[25]

The subsequent intramolecular Heck reaction of **61** then forms the desired tetrahydrodibenzofurans with excellent *E*-selectivity in the external double bond. Álvarez showed this methodology worked on a small range of different substrates (six examples) and further showed its utility with arylamides as well as phenols.

Another example of a suitable electrophile was described by Majumbar *et al*. in 1996.[26] They found that treatment of alkene **63** with *m*CPBA initiated an epoxidation-cyclisation cascade delivering alcohol **80** (Scheme 14).

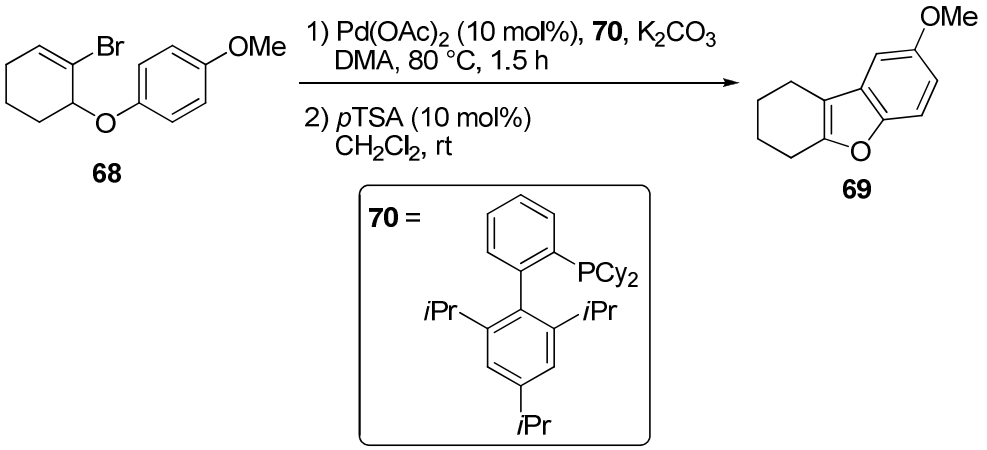


Scheme 14. Majumbar's synthesis of benzofuran **67**[26]

Subsequent oxidation to tetrahydrodibenzofurans **67** was then achieved in excellent yield using DDQ. Although they used a range of substrates, these only involved varying the substitution pattern on the aromatic ring and not on the cyclohexane. Furthermore, the group also reported a propensity for the reactions to deliver the 6,6,6-fused analogue **65**, formed by nucleophilic attack of the phenol on the remote site of the epoxide moiety in **64**.

2.2.3. Alternative approaches

As well as the two major strategies outlined above, a variety of alternative methodologies have also been described in the literature. One such method involved forming the C-C bond of the central furan ring rather than one of the C-O bonds as described in the strategies above (Scheme 15).[27]



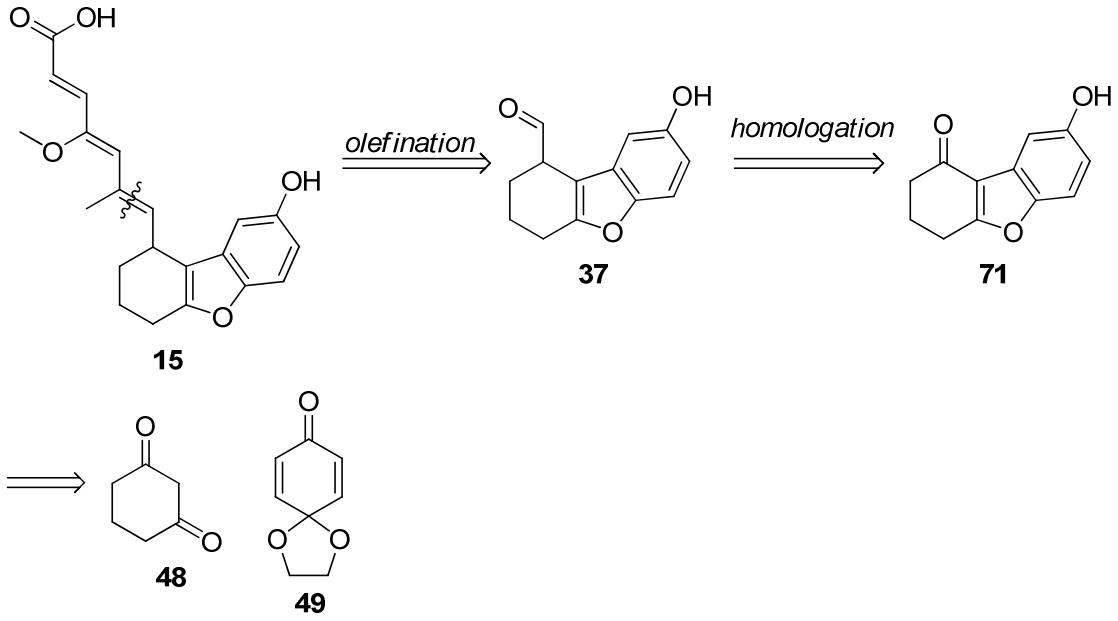
Scheme 15. Willis's methodology for benzofuran formation[27]

In their report,[27] Willis and co-workers described the synthesis of an extensive range of indoles using a Pd-catalysed intramolecular Heck reaction, and then developed their methodology for the synthesis of benzofurans. They achieved moderate to excellent yields under their conditions, with excellent results shown for the formation of tetrahydrodibenzofurans, such as **69**. However, despite these excellent results, minimal substitution was investigated on the cyclohexane ring and so was of lower interest for our project.

2.3. Synthesis of Ketone 71

2.3.1. Retrosynthetic analysis of aldehyde 37

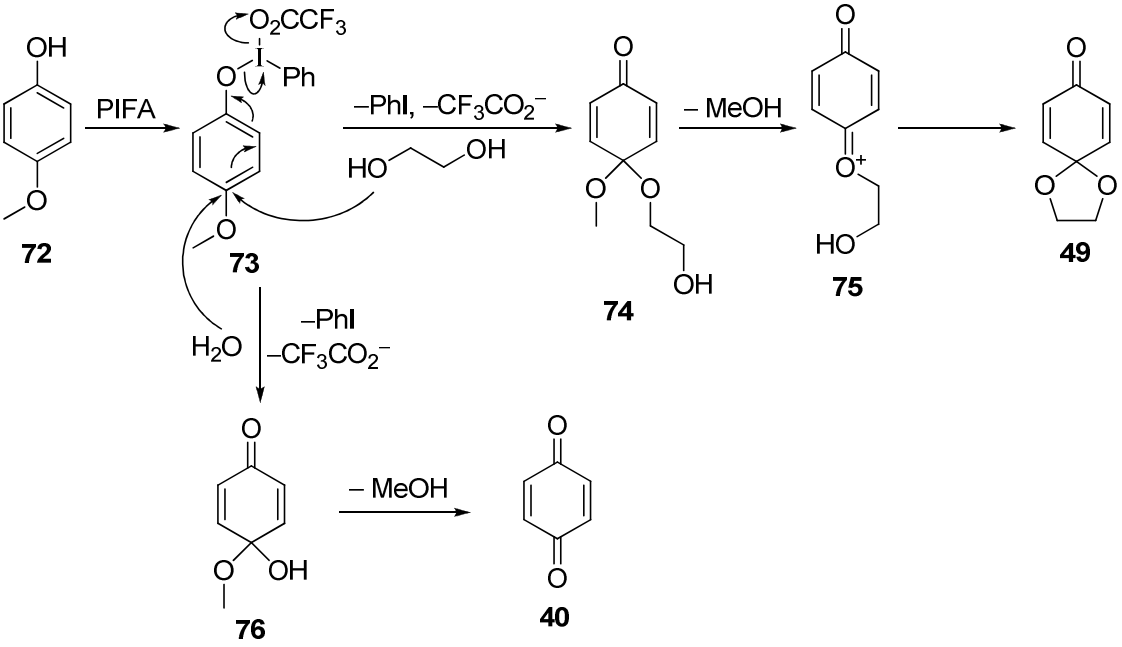
Of all the literature examples described above, at the outset of the project, the most interesting to our proposed synthesis of **15** was the report of Duthaler *et al*. (Scheme 9).[23] Specifically, we envisioned that their product, ketone **71**, could be utilised to synthesise the key aldehyde **37** through a homologation reaction as shown in Scheme 16.



Scheme 16. Retrosynthetic analysis of **15**

2.3.2. Synthesis of quinone monoketal 49

As described in Scheme 13, ketone **71** is formed through the double conjugate addition of diketone **48** into quinone monoketal **49** with a subsequent acidic rearrangement. While diketone **48** is commercially available, quinone monoketal **49** can be accessed in one step by the known PIFA-promoted oxidation of 4-methoxyphenol (**72**) in the presence of ethylene glycol (Scheme 17).[28]

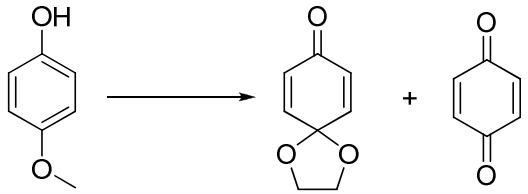


Scheme 17. Mechanism of formation of quinone monoketal **49**

Following the literature procedures, the yields for this oxidation were very good on a small scale (Table 2, entry i) and the mechanism is outlined above in Scheme 17.

Initial activation of the phenol moiety with PIFA forms the hypervalent iodine complex **73** in which the *para*-position has been activated to nucleophilic attack. Thus attack by ethylene glycol leads to mixed acetal **74** which undergoes subsequent transacetalization, eliminating methanol, and forming the desired bicyclic system **49**.

While the literature conditions formed the desired acetal **49** in excellent yield (Table 2), in our hands, detrimental effects were experienced upon scale-up. When using more than 1 g (~6.5 mmol) of **72**, yields were seen to decrease and increasing amounts of *p*-benzoquinone (**40**) were formed (Table 2, entry ii).



72 **49** **40**

Table 2. The effects of scale on the yield of oxidation of **72**

Entry	Amount of **72** (g)	Yield of **49** (%)
i	0.5	91% (lit. 83%)[28]
ii	1	55%
iii	2	0%

Conditions: Phenol (1 eq.) in CH_2Cl_2 (1.6 M) added to solution of PIFA (1.3 eq.) and ethylene glycol (1.5 eq.) in CH_2Cl_2 (0.2 M).

Above 2 g of **72** (~13 mmol), the ^{1}H-NMR spectrum of the unpurified material showed only the formation of **40** and no evidence for the formation of **49** (Table 2, entry iii). A plausible mechanism for the formation of side-product **40** is outlined above in Scheme 17. Instead of the desired nucleophilic attack of ethylene glycol on activated phenol **73**, a competing hydrolysis reaction occurs, giving hemiacetal **76**. In turn **76** then hydrolyses to deliver the unwanted side-product *p*-benzoquinone (**40**). It was thought that this mechanism was likely to be concentration-dependent and so a variety of concentrations was investigated.

Pleasingly, it was found that using ethylene glycol as the solvent for the reaction, rather than just as a reagent, allowed the reaction to be carried out on larger scales. It should be noted that a small amount of CH_2Cl_2 was still required in the reaction mixture to aid the dissolution of the phenol starting material **72**. With this alteration, this transformation could be performed on an 8 g scale in comparable yield to smaller scales (Table 3).

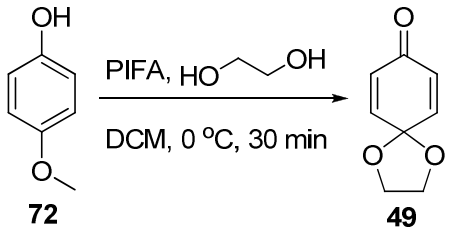


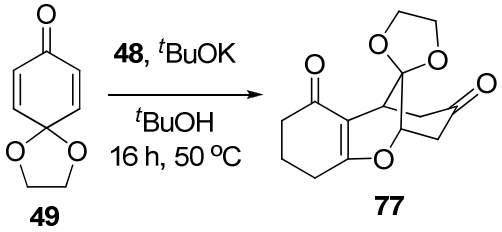
Table 3. Effect of concentration on yield of phenol oxidation

Entry	Amount of **72** (g)	Method	Yield of **49** (%)
1	1	1	55
2	1	2	91
3	2	1	0
4	2	2	78
5	8	2	74

Method 1: Phenol (1 eq.) in CH_2Cl_2 (1.6 M) added to solution of PIFA (1.3 eq.) and ethylene glycol (1.5 eq.) in CH_2Cl_2 (0.2 M). Method 2: Phenol (1 eq.) in CH_2Cl_2 (1.6 M) added to solution of PIFA (1.3 eq.) in ethylene glycol (0.2 M).

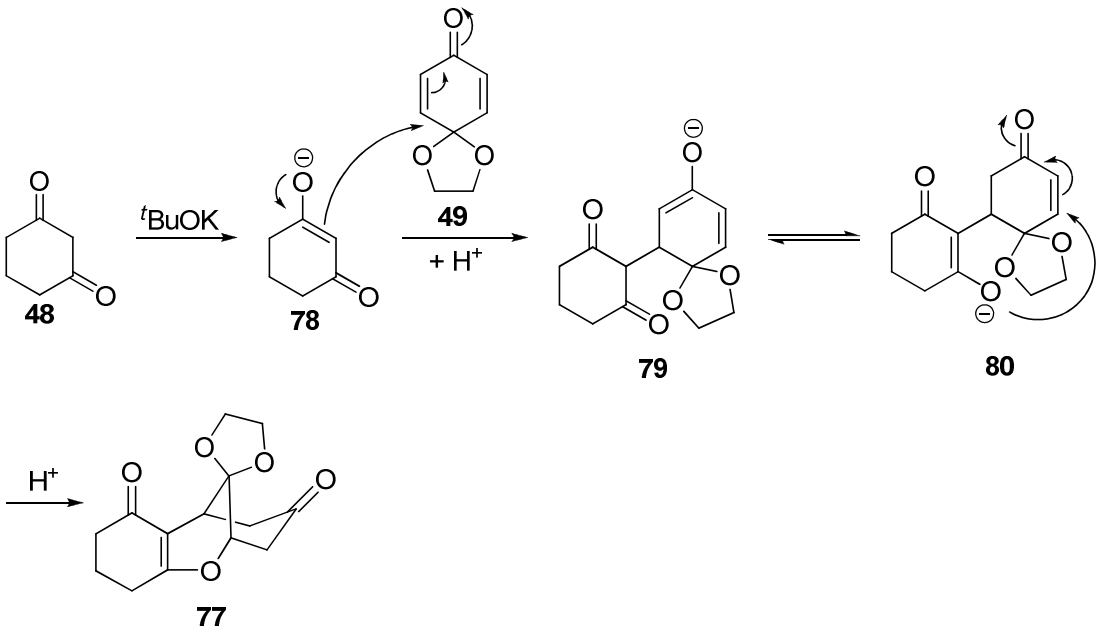
2.3.3. Double conjugate of dione 48 into quinone monoketal 49

Once in hand, quinone **49** was treated with cyclohexa-1,3-dione and potassium *tert*-butoxide, using Duthaler's procedure,[23] to form the tetracycle **77** (Scheme 18).



Scheme 18. Formation of tetracycle **77**

While this is a known literature procedure, the mechanism has not been previously discussed. Therefore, a possible mechanism is outlined, whereby cyclohex-1,3-dione **48** undergoes a double conjugate addition into quinone **49** (Scheme 19).

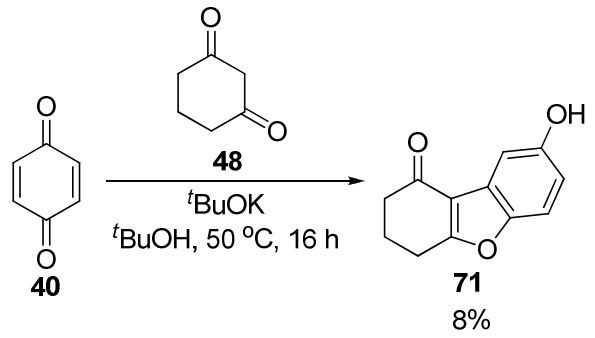


Scheme 19. Proposed mechanism for formation of tetracycle **77**

Cyclohexadione **48** initially undergoes a base-promoted Michael addition into quinone **49** to form bicycle **79**. A proton transfer then reforms the enolate, which undergoes a further conjugate addition, this time through the oxygen atom, to deliver final product **77**.

2.3.4. Attempted one-pot formation of benzofuran 71

An analogous reaction between cyclohexadione **48** and *p*-benzoquinone **40** was attempted; as if it was successful this would negate the need to do the expensive PIFA oxidation (Scheme 20). This reaction has not been reported previously.

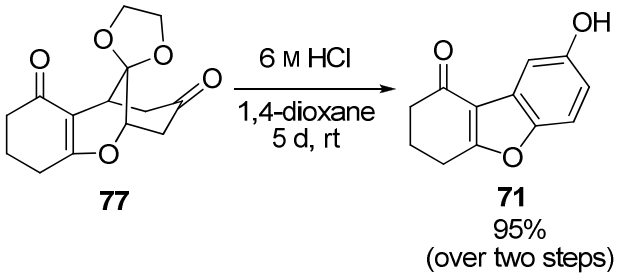


Scheme 20. Condensation of *p*-benzoquinone (**40**) and dione **48**

Whilst treatment of *p*-benzoquinone (**40**) with dione **48** and ^{t}BuOK did deliver the desired benzofuran **71**, the yield was very poor and attempted optimisation, such as alternative bases and increases temperatures, failed to increase the yield to any significant extent.

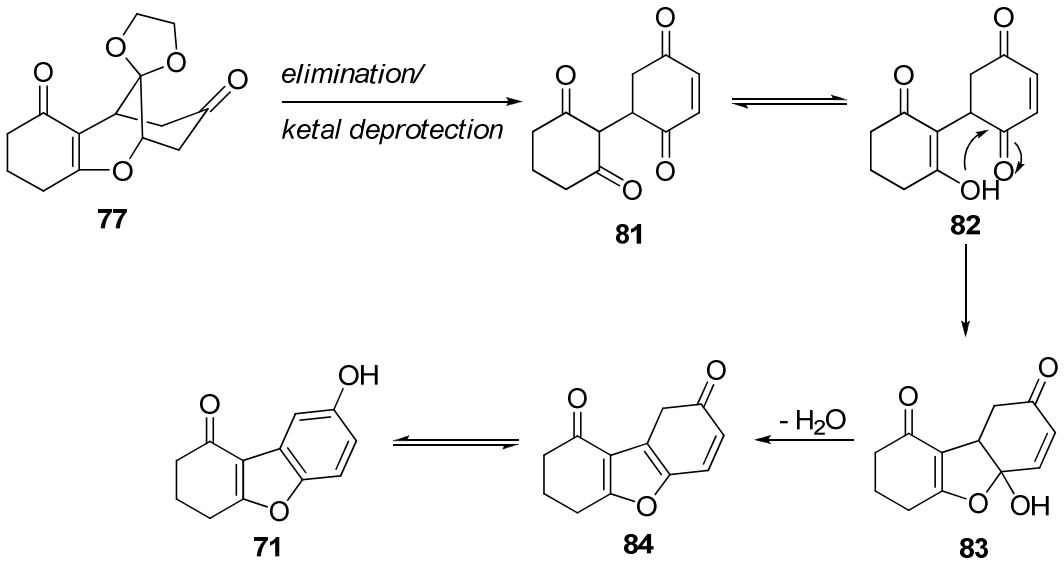
2.3.5. Completion of the synthesis of ketone 71

The final step in the synthesis of ketone **71** was to treat tetracycle **77** with 6 M aq. HCl for 5 days to deliver **71** in an excellent yield over the two steps (Scheme 21).



Scheme 21. Acid-promoted rearrangement to form ketone **71**

Again, while there is no literature discussion of the mechanism of this reaction, a plausible mechanism is outlined in Scheme 22.



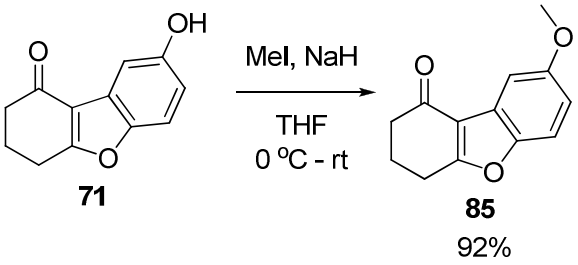
Scheme 22. Proposed mechanism of formation of ketone **71**

First, the acidic conditions promote an elimination and ketal deprotection, *via* known mechanisms, to deliver the bicyclic intermediate **81**. Ketone **81** then tautomerises to enol **82** and intramolecular nucleophilic addition of **82**, through the oxygen atom, into the ketone delivers acetal **83**. Subsequent dehydration and aromatisation delivers the desired benzofuran **71**.

Overall, ketone **71** was accessed in three steps and an excellent 86% yield from the commercially available 4-methoxyphenol (**72**) and we were now in a position to attempt the desired homologation reaction to deliver the key aldehyde intermediate **37**.

2.3.6. Protection of ketone 71

Before the homologation of ketone **71** was investigated, we decided to initially protect the free phenol moiety. In the literature this substrate has been protected as the acetate, but since we envisaged using basic conditions in later chemistry, its use in this situation was not ideal. As discussed in great detail later, attempts at protecting the phenol with a silyl group, such as a TBS group, proved ineffective. However, protection as the novel methyl ether proceeded in excellent yield using sodium hydride and methyl iodide (Scheme 23).



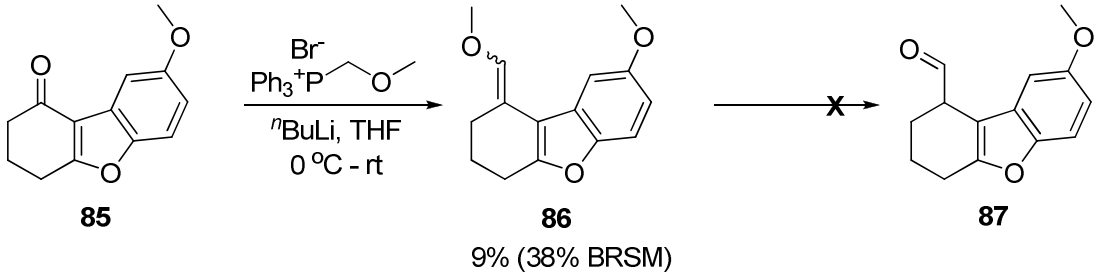
Scheme 23. Methyl protection of ketone **71**

With methyl ether **85** in hand, the envisioned homologation to deliver aldehyde **87** was investigated.

2.4. Homologation of Ketone 85 to Aldehyde 87

2.4.1. Direct methods of homologation

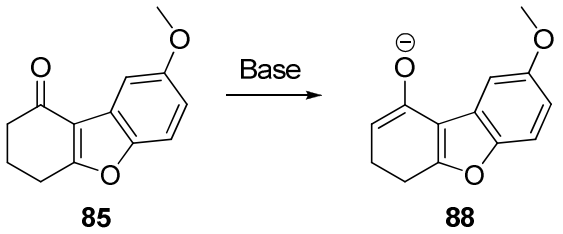
Initially, it was envisioned that we could treat ketone **85** with the commercially available (methoxymethyl)triphenylphosphonium bromide in the presence of ^{n}BuLi to deliver methyl enol ether **86** (Scheme 24).[29]



Scheme 24. Proposed homolgation utilising (methoxymethyl)triphenylphosphonium bromide

Enol ether **86** could then be hydrolysed into the desired aldehyde **87** by treatment under acidic conditions. However, the initial Wittig reaction, while providing desired enol ether **86** as a 2:1 mixture of the *E* and *Z*-isomers, gave a poor yield, and the subsequent hydrolysis also proved non-trivial and none of compound **31** was yielded. Unfortunately, attempts at using Darzen's chemistry or the Corey-Chaykovsky reaction to effect the desired homologation were also unsuccessful.[30]

Although no detailed studies have been undertaken, two plausible explanations for the low reactivity in the above reactions have been suggested. First, it could be that ketone **85** is sensitive to basic conditions and forms the unreactive enolate **88** under the reaction conditions (Scheme 25).

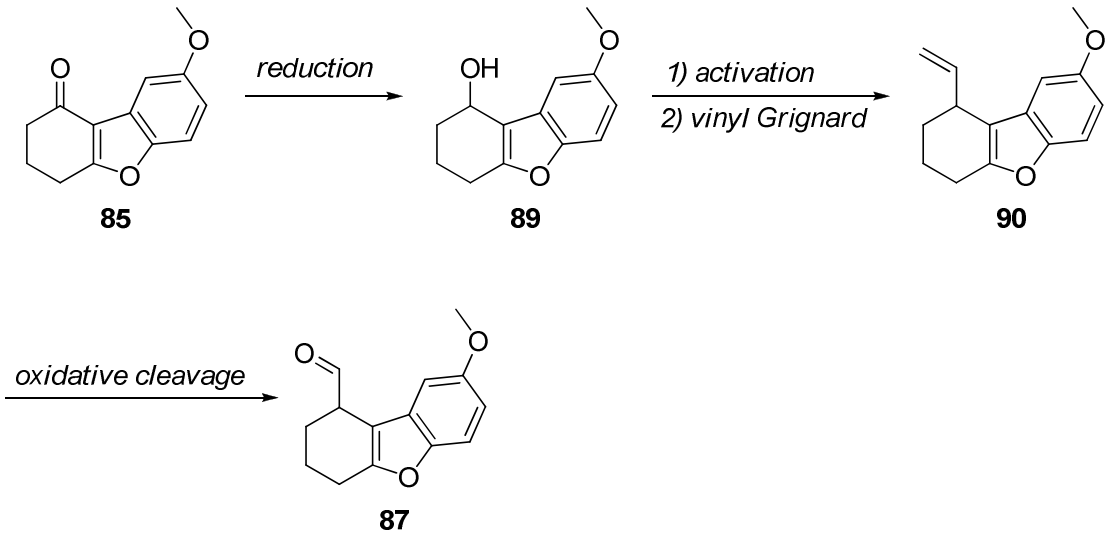


Scheme 25. Possible base-promoted enolisation of ketone **85**

The second explanation is that ketone **85** may not be as electrophilic as a normal ketone moiety. It could be that the large steric bulk surrounding the ketone alongside the fact that there is a large enone character to ketone **85** (in fact it is a vinylogous ester) reduces the electrophilic nature of the carbonyl. Both these explanations would go some way to explaining the disappointing results seen when trying to perform these direct homologations.

2.4.2. Reduction-substitution strategy

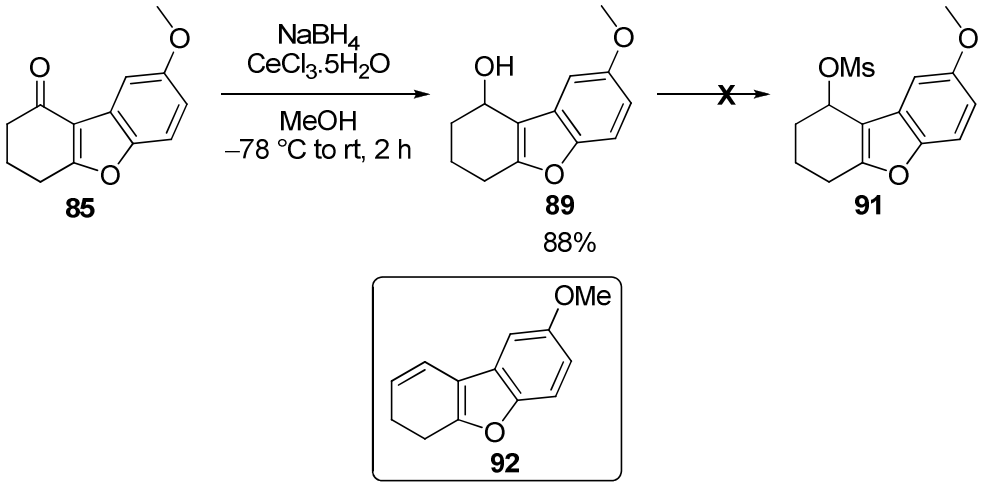
Due to the ineffectiveness of the direct homologation methods, an alternative route to aldehyde **87** was investigated (Scheme 30).



Scheme 26. Reduction-substitution strategy

It was proposed that reducing the ketone **85** to the alcohol **89**, and subsequent activation and displacement with vinyl Grignard reagent, would deliver alkene **90** which could be converted into the desired aldehyde **87** using ozonolysis or a Johnson-Lemieux reaction.

Pleasingly, the reduction of ketone **85** under Luche[31] conditions delivered the desired alcohol **89** in excellent yield (Scheme 27).

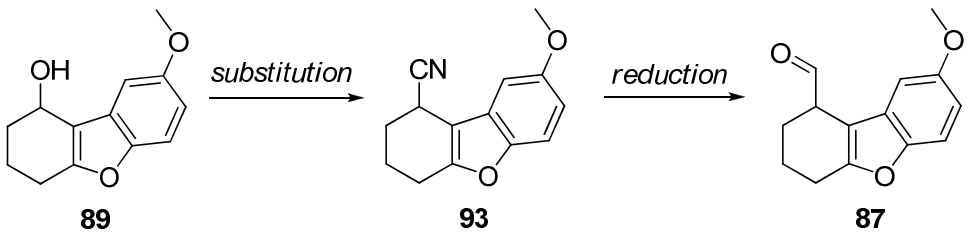


Scheme 27. Attempted mesylation procedure

However, attempts to activate the alcohol as the mesylate (or tosylate) were unsuccessful, with evidence of the eliminated product **92** being formed in the unpurified reaction mixtures (as indicated by δ_H shifts of 5.65 and 6.51 ppm in the ^{1}H-NMR spectrum of the unpurified material corresponding to the two new alkene protons).

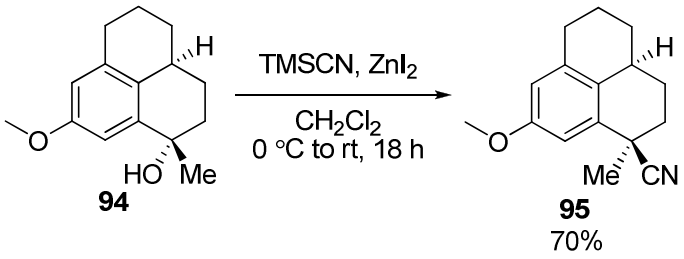
2.4.3. Nitrile formation and reduction route

Despite the lack of success in activating alcohol **89**, it could still be of use in an alternative route. It was envisioned that alcohol **89** could be converted into the analogous nitrile **93**, which could subsequently be converted into the desired aldehyde **87** (Scheme 28).



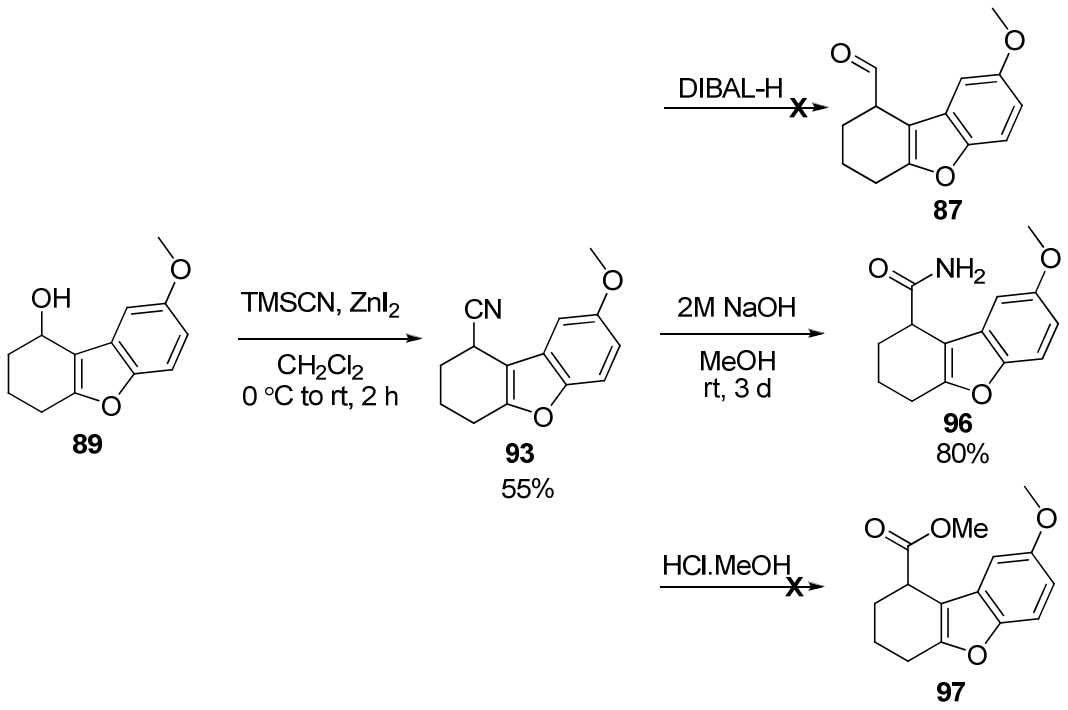
Scheme 28. Envisioned conversion of alcohol **89** into aldehyde **87** *via* nitrile **93**

In 2002, Schwarz *et al*. described a Lewis-acid mediated procedure for the conversion of secondary alcohols into the corresponding nitrile, without the need for prior activation of the alcohol (Scheme 29).[32]



Scheme 29. Schwarz's ZnI_2-mediated alcohol to nitrile conversion[32]

Pleasingly, this methodology was successful on alcohol **89**, delivering the desired nitrile **93**, albeit in moderate yield (Scheme 30).



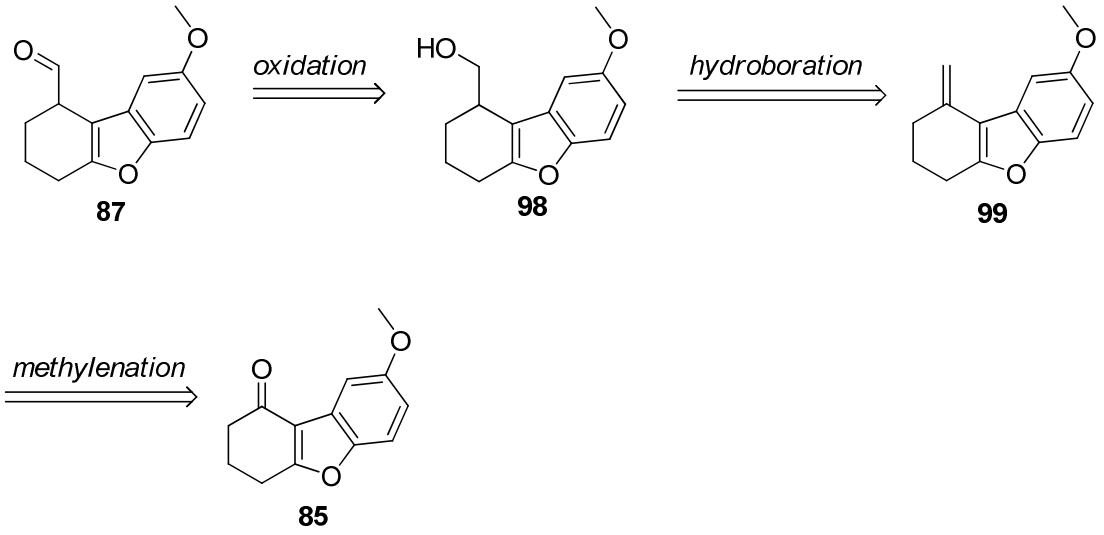
Scheme 30. Attempted manipulations of nitrile **93**

It was planned to then reduce nitrile **93** using DIBAL-H to afford the desired aldehyde **87**. However, no reaction was observed on treatment of the nitrile with one equivalent of DIBAL-H. Increasing the equivalents of DIBAL-H only led to the decomposition of the nitrile starting material **93**. Treating nitrile **93** with methanolic HCl, in an attempt to deliver

the methyl ester **97**, was also unsuccessful, again with only decomposition being observed. Indeed the only transformation of **93** we could accomplish was the hydrolysis delivering the corresponding amide **96** using 2 M NaOH. Attempts to utilise **96** for further reactions were again unsuccessful.

2.4.4. Methylenation-hydroboration strategy

With alcohol **89** failing to prove a viable intermediate to the desired aldehyde **87** an alternative route was investigated (Scheme 31).



Scheme 31. Proposed synthesis of aldehyde **87** *via* alkene **99**

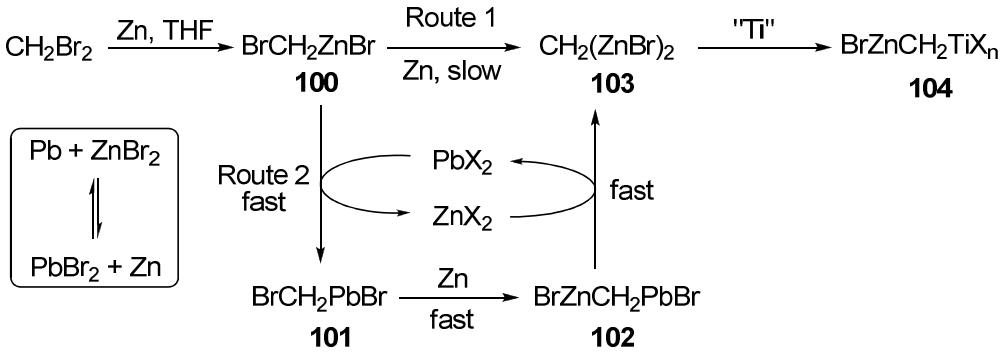
The new strategy involved accessing aldehyde **87** by the oxidation of the analogous alcohol **98**. Compound **98** could in turn be accessed from the hydroboration of methylene **99**. The advantage of this route is the existence of many methylenation procedures that utilise Lewis acidic conditions,[33] such the Tebbe reagent, Petasis reagent or the Lombardo reaction, and so do not require the use of a base, one of the proposed reasons behind the lack of reactivity of ketone **85**.

Unfortunately, attempts at utilising the Tebbe or Petatasis reagents to effect the desired methylenation were unsuccessful. Since these procedures are all non-basic, these results heavily suggest that it cannot only be the basicity of a reaction causing problems in the reactivity of ketone **85** and there must be an element of reduction in the electrophilicity of the carbonyl.

With the failure of the above reagents, the Lombardo reaction was next investigated.

2.4.5. Mechanism of the Lombardo methylenation

The Lombardo reaction is a methylenating procedure pioneered by Takai and Lombardo.[34,35] This procedure involves the *in situ* formation of methylenating agent **104** from zinc dust, $TiCl_4$ and dibromomethane, catalysed by lead (Scheme 32).

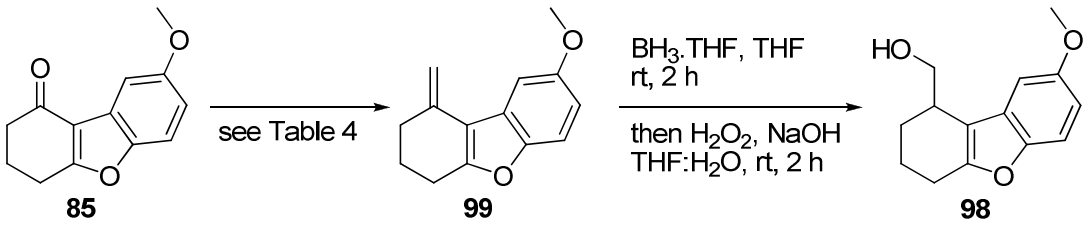


Scheme 32. Proposed formation of geminal dimetallic compound **104**[34]

The zinc reagent **104** then reacts with ketones or aldehydes to deliver the corresponding methylene. Takai reported that the addition of lead to the mixture increases the rate that dizinc compound **103** is formed. Transmetallation of zinc-carbenoid **100** with PbX_2 delivers lead-carbenoid **101**, which is readily reduced by zinc to give the geminal lead-zinc compound **102**. Subsequent transmetallation from lead to zinc, with ZnX_2, affords geminal dizinc compound **103**. Takai postulates that the reduction of lead-carbenoid **101** with zinc proceeds faster than that of the zinc-carbenoid **100**, since the lead-carbon bond is more covalent than the zinc-carbon bond.[36]

2.4.6. Results of Lombardo methylenation on ketone 85

Satisfyingly, this methylenation was successful and delivered the desired novel alkene **99** in moderate yield. Subsequent hydroboration, using a borane/THF complex, and oxidation with H_2O_2 and NaOH, then delivered the required alcohol **98**, not previously reported in the literature, in a poor yield (Table 4, entry i).



85 **99** **98**

Table 4. Optimisation of Lombardo/hydroboration procedure

Entry	Molarity (mmol/mL)	TMEDA (eq.)	Pb (eq.)	Telescoped	Yield of **98** (%)
i	0.1	0.0	0.0	No	3%
ii	0.1	0.0	0.0	Yes	15%
iii	0.1	0.0	0.05	Yes	31%
iv	0.1	2.2	0.05	Yes	16%
v	0.05	0.0	0.05	Yes	39%

All Lombardo reactions were carried out in THF using 4.5 eq. Zn, 1.1 eq. $TiCl_4$ (1.0 M solution in CH_2Cl_2) and 1.5 eq. CH_2Br_2 at rt for 2 h.

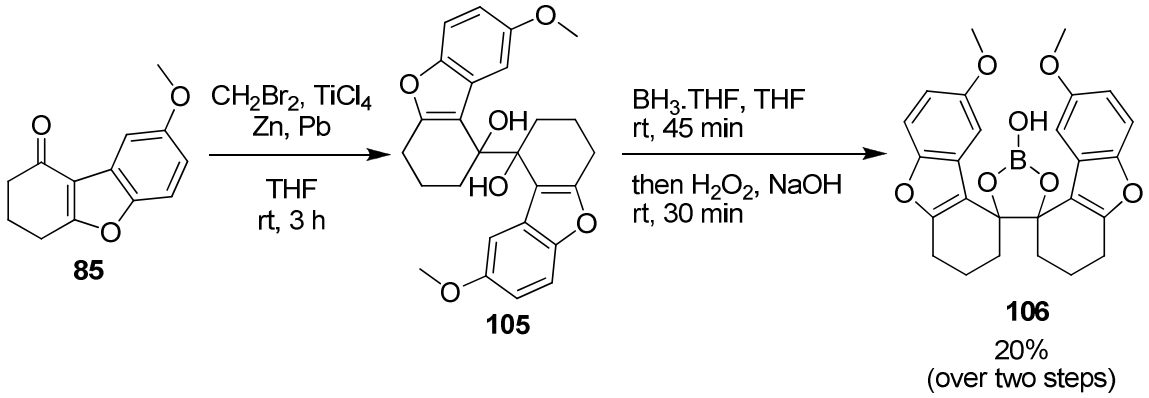
During optimisation of the conditions it was found that telescoping the reaction through the two steps improved the yields (entry i vs. entry ii). Furthermore, diluting the reaction increased the yield of the reaction (entry iii vs. entry v) as did the addition of a catalytic amount of lead shot (entry ii vs. entry iii).[36] Interestingly, while it has been reported that the use of TMEDA as an additive improves the yields of these reactions,[37] in this instance this was found not to be the case, rather the yield was suppressed (entry iii vs. entry iv).

2.4.7. Pinacol side-reaction

While this reaction was now optimised and gave reproducible results on a small scale, when the scale was increased, problems were observed. As usual, the material was telescoped through the Lombardo reaction and the subsequent hydroboration but when purifying alcohol **98**, a new side-product was isolated that had not thus far been observed on the smaller scale.

In order to determine the source of this side-product, the reaction was repeated on the same scale but this time purifying after the Lombardo reaction instead of telescoping the reaction. Purification gave another related side-product alongside the desired alkene **99**.

These observations showed that the side-product was being formed during the Lombardo reaction. Analysis of the NMR spectroscopic and MS data revealed the side-products to be diol **105** and borate ester **106** (Scheme 33).

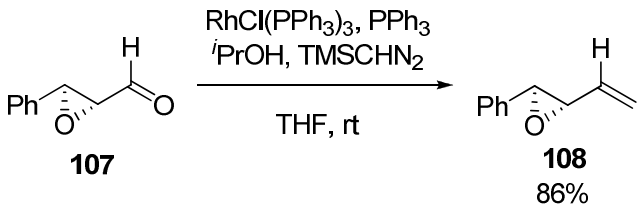


Scheme 33. Formation of by-products **105** and **106**

It is proposed that diol **105** is formed from a competing pinacol coupling reaction under the Lombardo conditions. Compound **105** is then converted into borate ester **106** under the hydroboration/oxidation conditions. Interestingly, previous reports have shown that Lombardo reactions can suffer from competing pinacol coupling reactions, but only when using readily enolizable ketones,[38] suggesting that the enolization of ketone **85** may be facile and may contribute to the problems thus far observed with the attempted formation of aldehyde **87**. Unfortunately, further optimisation to improve the yield and prevent the pinacol coupling was unsuccessful and so further methods of methylenation were investigated.

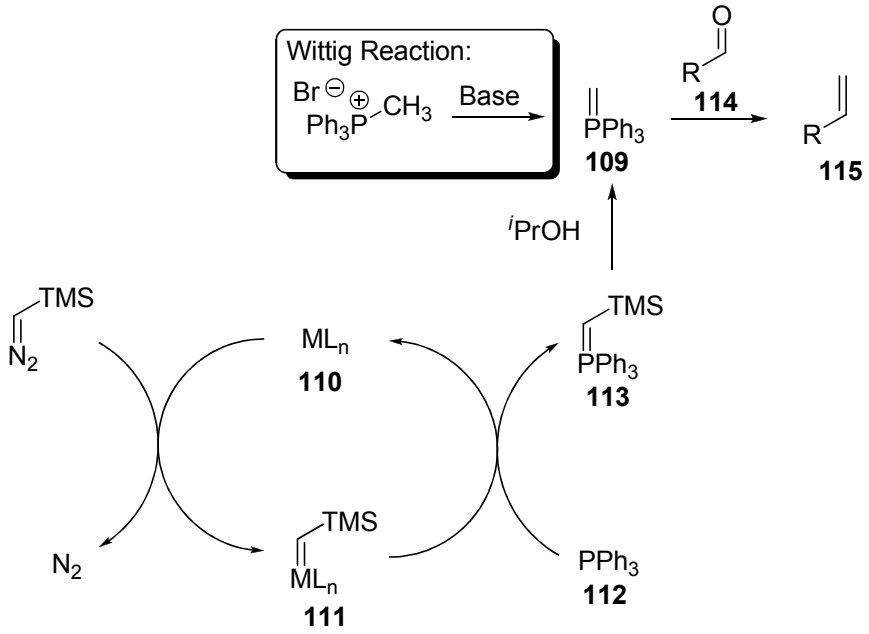
2.4.8. Rh-mediated methylenation

An interesting report in 2001 by Lebel's group reported an alternative method for the methylenation of a range of aldehyde substrates mediated by Wilkinson's catalyst (Scheme 34).[39]



Scheme 34. Lebel's Base-free 'Wittig' Reaction[39]

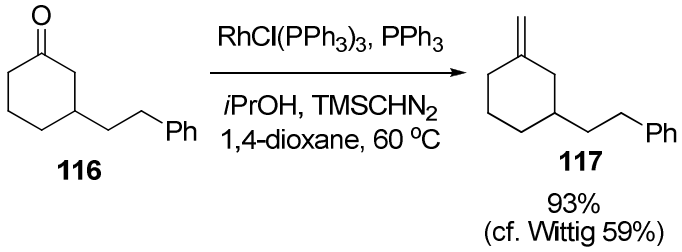
Mechanistically, the reaction proceeds *via* the same ylide **113** as the analogous Wittig reaction (Scheme 35).[40]



Scheme 35. Mechanism of Lebel's procedure[40]

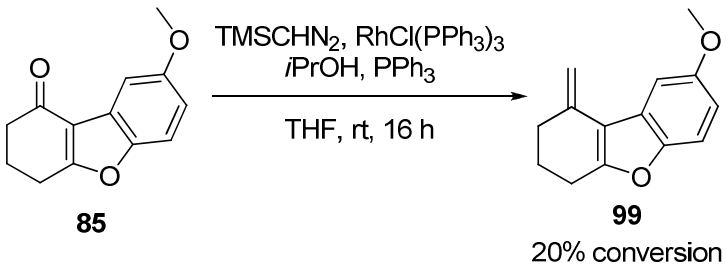
In a Wittig reaction, ylide **109** is formed by treatment of methyl(triphenyl)phosphonium bromide with a base, such as BuLi or NaHMDS. However, in Lebel's work, **109** is formed through an initial transmetallation of (trimethylsilyl)diazomethane with Wilkinson's catalyst to form the rhodium complex **111**, with the release of nitrogen. Triphenylphosphine (**112**) then displaces the rhodium, generating ylide **113**. It had been previously shown that when **113** is treated with an alcohol, it hydrolyses to give the desired ylide **109**.[41] In Lebel's procedure, 2-propanol is used as the alcohol additive. Once **113** is formed it can react with aldehyde **114** to form the desired alkene **115**.

A further report by Lebel in 2004,[42] showed an increase in the equivalents of 2-propanol allowed the reaction to proceed with ketones as well as aldehydes (Scheme 36).



Scheme 36. Lebel's modified procedure[42]

It was hoped that the lack of a base in the reaction alongside conditions designed to react with less reactive carbonyls may mean that this method of methylenation would achieve better results than the Lombardo reaction. Unfortunately, when **85** was subjected to Lebel's conditions, the reaction did not go to completion (Scheme 37).

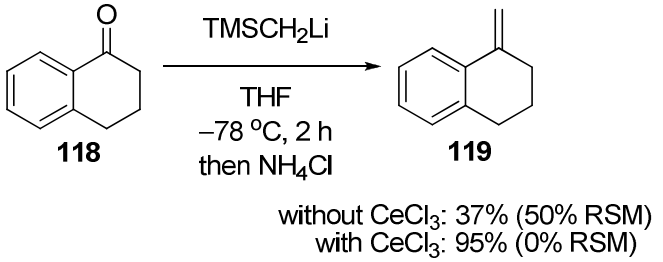


Scheme 37. Methylenation of Ketone **85** using Lebel's Procedure

While alkene **99** was formed, after 16 h the ^{1}H-NMR spectrum of the unpurified material showed only ~20% conversion had taken place. Extending the reaction time or increasing the equivalents of the reagents failed to provide a significant increase in this conversion.

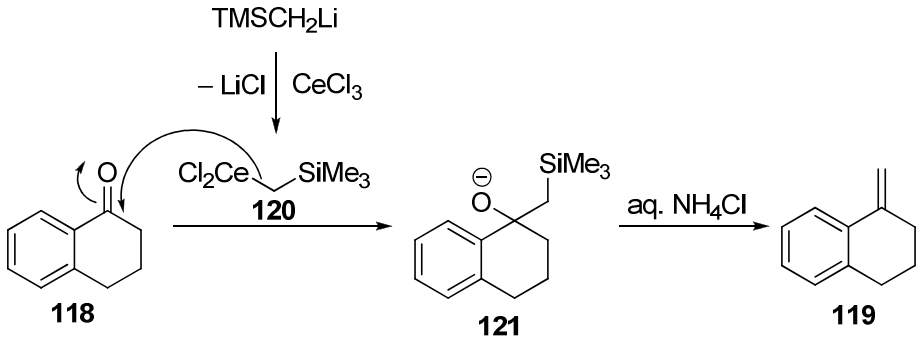
2.4.9. Peterson methylenation

Another interesting method of performing a methylenation using a Peterson reaction was first reported by Chan *et al*. in 1970.[43] Of more interest for the desired methylenation of ketone **118** was a report by Johnson *et al*. in 1987 where they utilise a Peterson reaction mediated by cerium(III) chloride to perform the methylenation of readily enolizable carbonyl compounds (Scheme 38).[44]



Scheme 38. Johnson's cerium-mediated Peterson methylenation[44]

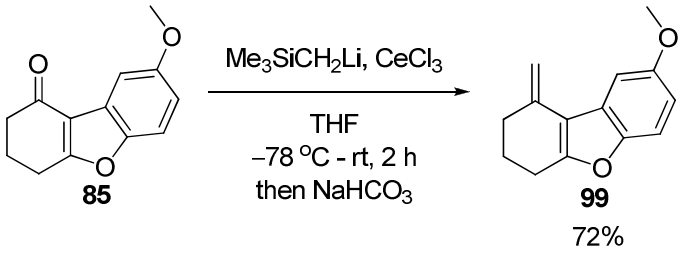
Mechanistically, Johnson postulated (trimethylsilyl)methyllithium initially transmetallates with $CeCl_3$ to generate the organocerium species **120** (Scheme 39).



Scheme 39. Mechanism of cerium-mediated Peterson methylenation reaction

Since **120** is less basic than the analogous organolithium, it is less likely to form the undesired enolate when ketone **118** is added to the reaction mixture. The reaction is then quenched by adding the reaction mixture into a saturated aqueous NH_4Cl solution, which hydrolises silane **121** to deliver the desired methylene **119**.

Pleasingly, this methodology was successfully applied to the methylenation of ketone **85** (Scheme 40), although $NaHCO_3$ was used for the quench rather than NH_4Cl.

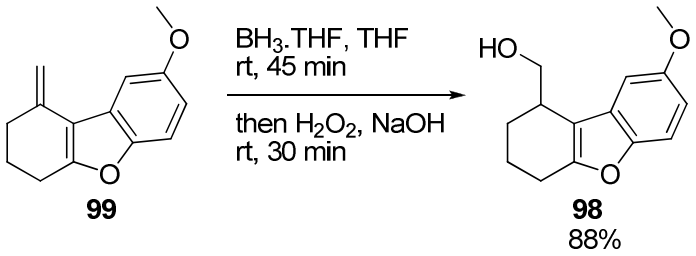


Scheme 40. Cerium-mediated methylenation of ketone **85**

Ketone **85** was treated with a pre-mixed suspension of $CeCl_3$, dried overnight under high vacuum, and (trimethylsilyl)methyllithium. After 2 h, $NaHCO_3$ was added and after a work-up and purification alkene **99** was obtained in a 72% yield, compared to a 29% yield under Lombardo's conditions (Scheme 37 and Scheme 45). Unsurprisingly, when this reaction was attempted without the cerium(III) chloride, no reaction was observed and only starting material was recovered.

2.4.9. Synthesis of aldehyde 87

As previously shown, methylene **99** was readily converted into the desired alcohol through use of the standard hydroboration and oxidative work-up conditions, whereby treatment of **99** with borane-THF complex and subsequent work-up with H_2O_2 and NaOH delivered the desired alcohol in an excellent yield. (Scheme 41).



Scheme 41. Synthesis of alcohol **98**

With alcohol **98** in hand, the oxidation to deliver the desired aldehyde **87** proved successful using Dess-Martin Periodinane. Interestingly, when a range of alternative oxidation conditions were also utilised, none delivered useful amounts of the novel aldehyde **87** (as shown by the lack of a peak at 9.75 ppm in the ^{1}H-NMR of the unpurified material) (Table 5).

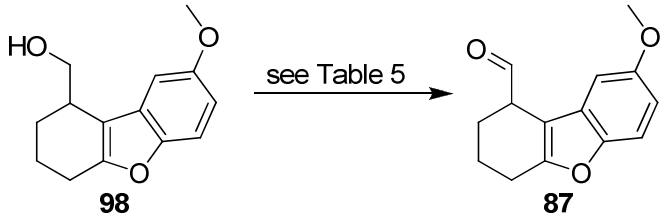
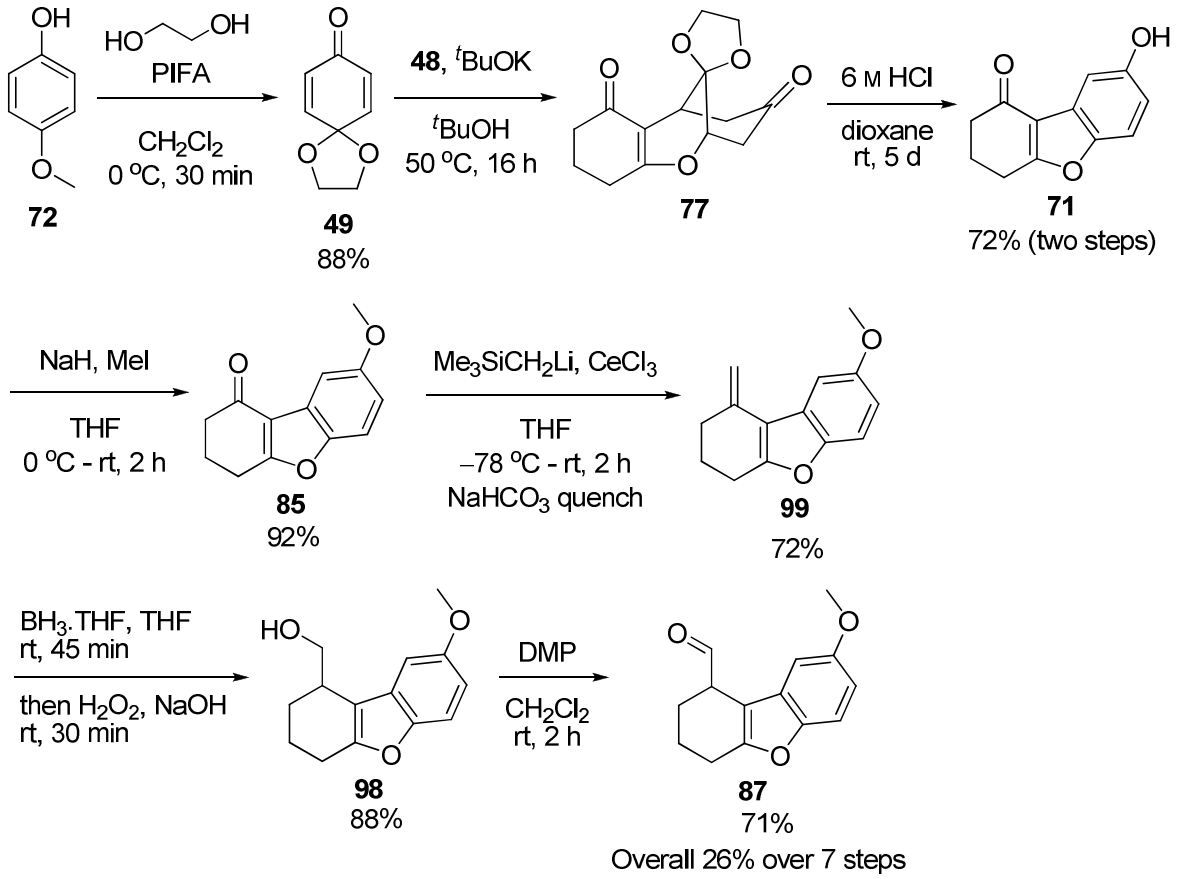


Table 5. Alternative oxidation conditions

Entry	Oxidation Conditions	Yield of 87(%)
i	$(COCl)_2$, NEt_3, DMSO	0
ii	SO_3.py, NEt_3, DMSO	0
iii	PDC, CH_2Cl_2	5
iv	DMP, CH_2Cl_2	71

Overall, the synthesis of the key aldehyde **87** was achieved in seven steps and in an overall yield of 26% (Scheme 42).



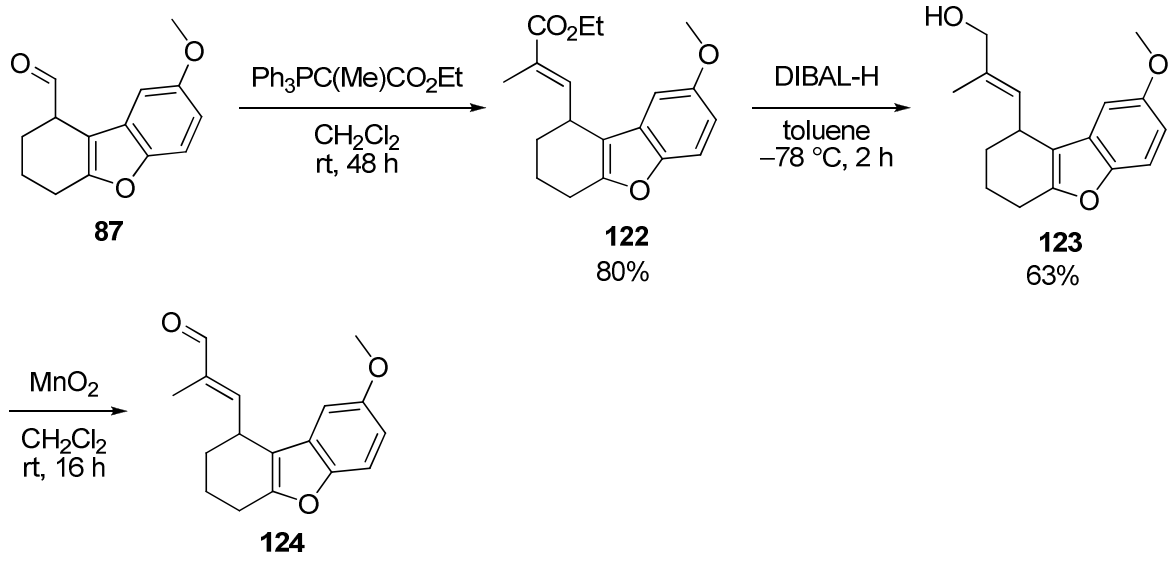
Scheme 42. Synthesis of aldehyde **87** from phenol **72**

2.5. Linear Route to Shin-ya's Structure of Cuevaene A (15)

While, the initial retrosynthesis envisioned a convergent strategy (Scheme 3), it was decided that, with aldehyde **87** in hand, Shin-ya's structure of cuevaene A (**15**) could be approached using a linear strategy similar to that later used by Liu (Schemes 1 and 2).

2.5.1. Synthesis of aldehyde 124

The initial step was to install the first of the three double bonds using ethyl 2-(triphenylphosphoranylidene)propanoate in a Wittig reaction (Scheme 43).



Scheme 43. Synthesis of aldehyde **124**

Pleasingly, the desired alkene **122** was isolated as a single isomer in a moderate yield. Subsequent reduction to alcohol **123** using DIBAL-H was then successfully achieved again in good yield. Oxidation of the activated alcohol **123** with MnO_2 gave the aldehyde **124**, which was now ready for the key Horner-Wadsworth-Emmons reaction to install the second double bond.

2.5.2. Crystal structure of aldehyde 124

At this point, the structure of aldehyde **124** was proved through single crystal X-ray analysis of a crystal of **124** (Figure 12).

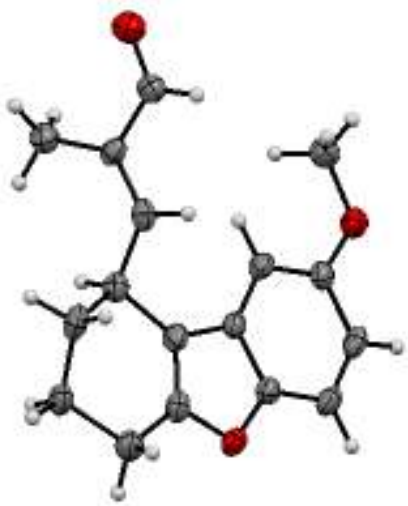
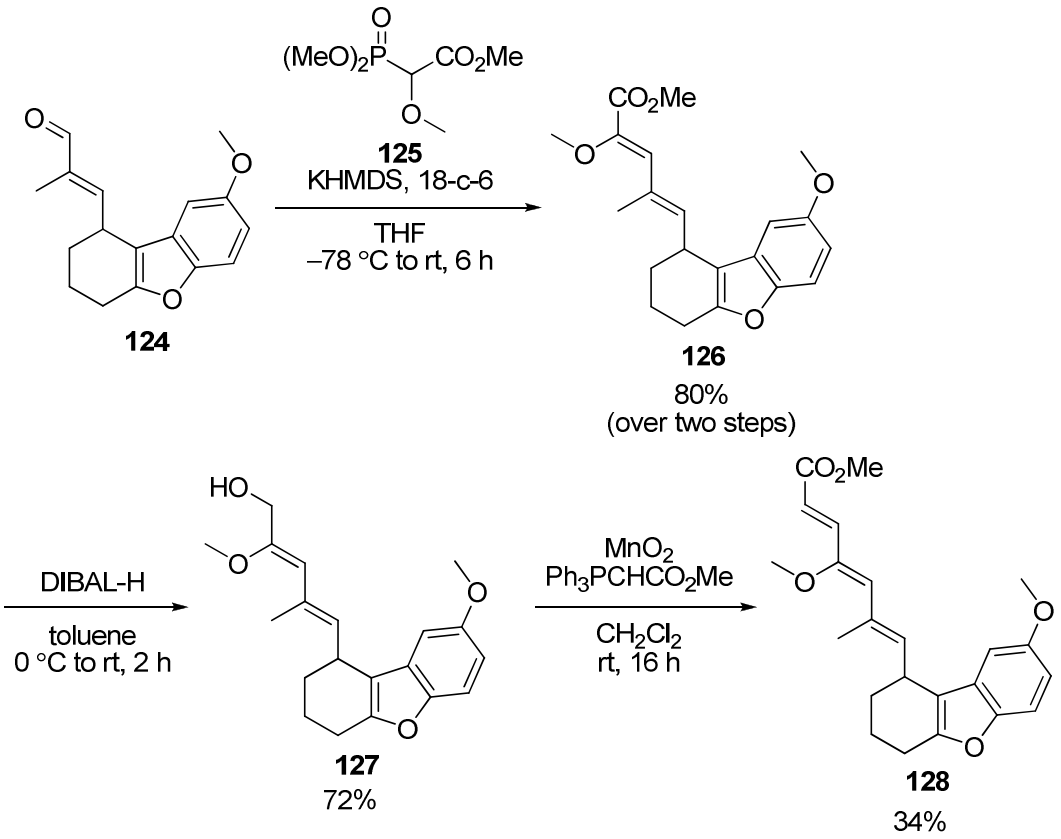


Figure 12. X-ray crystal structure of aldehyde **124** (the structure was originally modelled in two positions, the minor position has been eliminated for clarity) depicted using Mercury 3.0 (CCDC 914596)

This crystal structure proves the sidechain in aldehyde **124** is in the desired position on the cyclohexane ring and also that the double bond in the sidechain exists as the *E*-isomer.

2.5.3. Completion of the carbon skeleton of 15

With aldehyde **124** now in hand, the key Horner-Wadworth-Emmons reaction using phosphonate **125** to install the second double bond was investigated. The synthesis of phosphonate **125** is discussed later in this Chapter. Pleasingly, the HWE reaction was successful and delivered the desired diene **126** as a single isomer in excellent yield (Scheme 44).

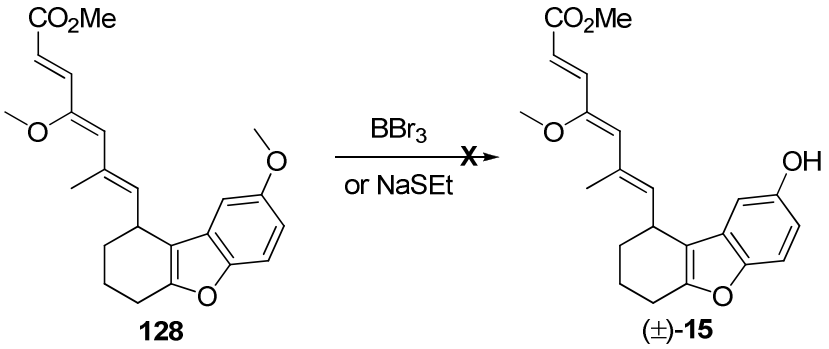


Scheme 44. Synthesis of the carbon skeleton of Shin-ya's structure of cuevaene A **128**

Subsequent reduction to deliver alcohol **127** was achieved in good yield using DIBAL-H. It was found that **127** was unstable as a solution in $CDCl_3$ but could be converted into the desired triene **128** in low yield by use of a tandem oxidation process (TOP), first developed within the Taylor group,[45] whereby the oxidation of alcohol, effected by MnO_2, and Wittig olefination, with (triphenylphosphoranylidene)acetate, are both achieved in a single reaction.

2.5.4. Attempted deprotection of triene 128

In order to complete the total synthesis of **15**, the methyl ether moiety protecting the phenol group in triene **128** needed to be removed and the methyl ester needed to be hydrolysed to the analogous acid. The common method for removal of a methyl ether protecting group is to use BBr_3 or BCl_3. Thus triene **128** was treated with 1.0 eq. of BBr_3 (Scheme 45).



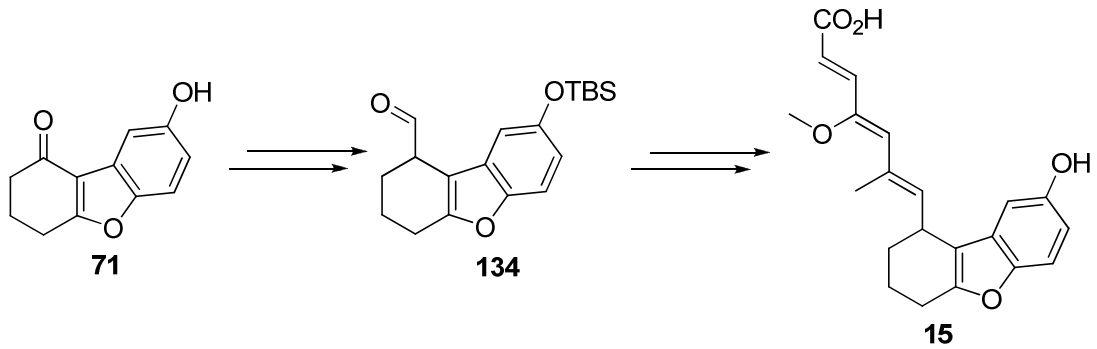
Scheme 45. Attempted deprotetion of methyl ether **128**

Unfortunately, no tractable product could be observed by TLC or NMR spectroscopy and the starting material completely decomposed. An alternative, less harsh reagent for methyl ether removal, NaSEt, was also tried but again only decomposition was observed after 1 h.

By this point, Liu *et al*. had published their total synthesis of Shin-ya's structure of cuevaene A (±)-**15**. Therefore, it was decided to attempt the total synthesis of **15** but this time using the TBS protecting group utilised by Liu. While this would involve following their chemistry very closely, compound **15** would be accessed and therefore the true structure of cuevaene A investigated.

2.6. Synthesis of TBS-protected Aldehyde 129

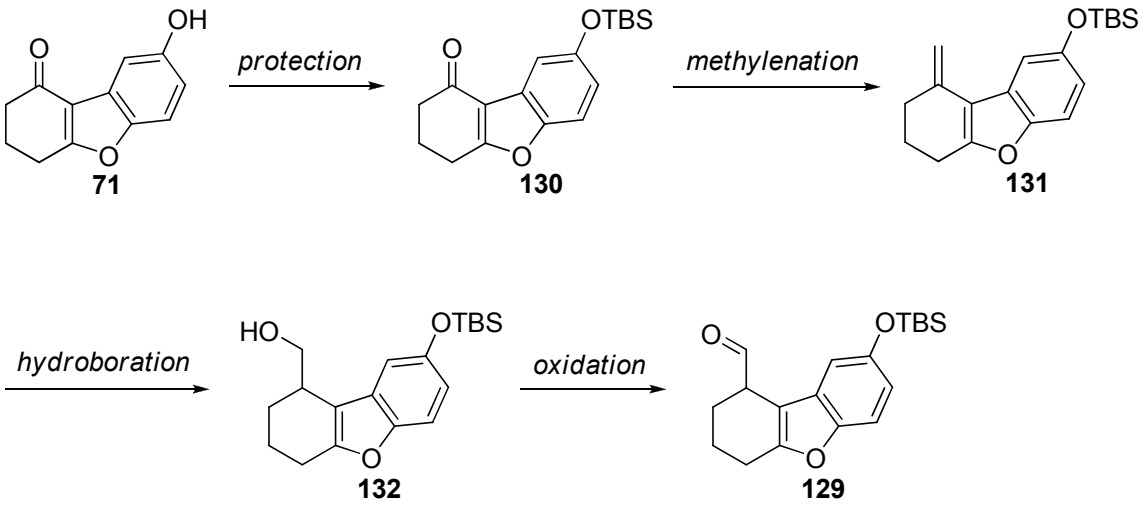
In the new strategy for the synthesis of **15**, the initial target was aldehyde **129**, an intermediate in Liu's synthesis (Scheme 1).



Scheme 46. New synthetic plan for the synthesis of **15**

2.6.1. Attempted TBS protection of ketone 71

The first step in the new synthetic strategy was to protect phenol **71** as the corresponding TBS ether **130** (Scheme 47).



Scheme 47. Strategy for conversion of ketone **71** to aldehyde **129**

However, the attempted formation of the desired TBS ether **130** was unsuccessful under a variety of conditions and in the majority of occasions the starting material was recovered. However, when ketone **71** was treated with TBSOTf and NEt_3, ^{1}H-NMR spectroscopy and MS analysis of the unpurified material suggested the formation of the TBS enol ether **133** (indicative enol ether peak at 4.70 ppm and [MH^+] peak at 317) (Figure 13).

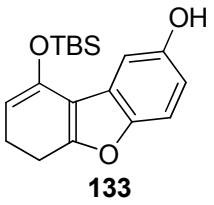
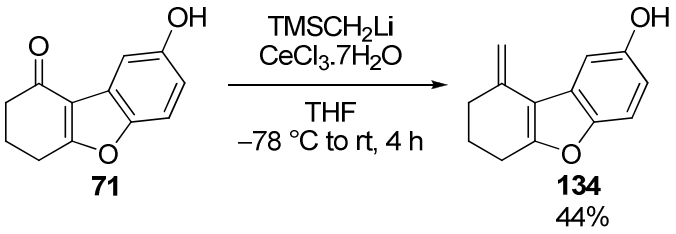


Figure 13. Structure of TBS enol ether **133**

With the TBS protection unsuccessful, the methylenation was attempted on the unprotected ketone **71**, in the hope that the resultant alkene **134** would be more amenable to TBS protection.

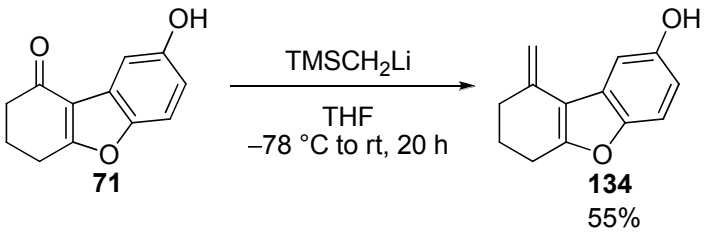
2.6.2. Methylenation of ketone 71

Despite the presence of the free phenol group, treatment of ketone **71** under the cerium-mediated Peterson reaction conditions, discussed previously (Scheme 40), delivered the desired alkene in fair yield (Scheme 48).



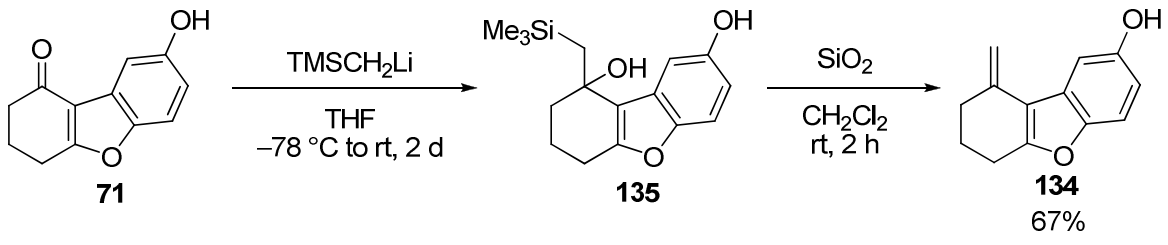
Scheme 48. Cerium-mediated Peterson methylenation of ketone **71**

Intriguingly, when performing a test reaction without any $CeCl_3$ present, some of the desired product **139** was observed in the ^{1}H-NMR spectrum, although the conversion was only ~40%. Therefore, an excess of the organolithium reagent was added (2.2 eq.) and, pleasingly, the desired alkene was formed in a moderate yield (Scheme 49).



Scheme 49. Cerium-free Peterson methylenation of ketone **71**

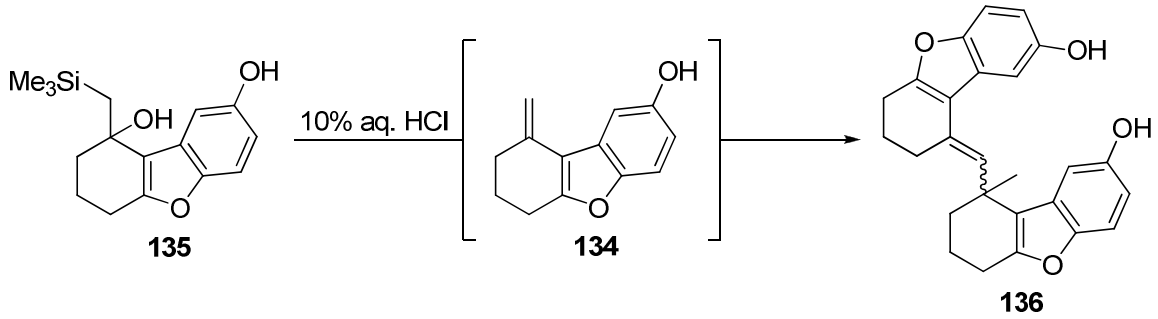
Thus the use of $CeCl_2.7H_2O$ was avoided along with the required dehydration procedure. However, this Peterson reaction, upon occasions, delivered a mixture of alkene **134** and the hydroxysilane intermediate **135**. It was found that treatment of **135** with an excess of silica at rt promoted the desired elimination and formation of alkene **134** (Scheme 50).



Scheme 50. Conversion of silane **135** into alkene **134**

Indeed it was found that this two-step procedure delivered alkene **134** in a greater yield than the initial one-step variant, presumably due instability of the intermediate hydroxysilyl to the work-up conditions.

Alternative methods of hydrolysing intermediate **135** to the desired alkene **134** under acidic conditions were investigated but ultimately proved problematic (Scheme 51).



135 **134** **136**

Scheme 51. Attempted acidic elimination of hydroxysilane **135**

While the elimination was successful, the alkene **134** then underwent a subsequent acid-catalysed dimerization to form alkene **136**. The reasons for the surprising success of the cerium-free Peterson reaction (Scheme 49) are still elusive and need further investigation. However, one theory is that the excess organolithium reagent initially deprotonates the phenol moiety in **71** and therefore preventing the formation of the inactive enolate due to dianionic interactions. Therefore, the ketone functionality is maintained and is amenable to the desired Peterson reaction. This theory may also explain why the Peterson partially stalls at the hydroxylsilane intermediate **135**.

However, this theory does not explain other observations in the reactivity of ketone **71**. Any attempt at performing the remainder of the homologation strategies, previously attempted on ketone **85**, such as Wittig chemistry and Darzens chemistry, were unsuccessful on the phenol substrate **71**. This was even the case if excesses of reagents were used in these reactions.

An alternative theory explaining this unexpected result, could be the formation of a lithium aggregate of the lithium phenolate salt of ketone **71** and (trimethylsilyl)methyllithium (Figure 14).

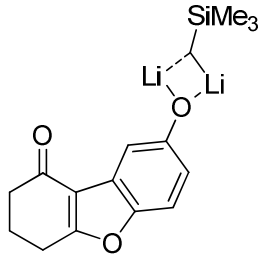
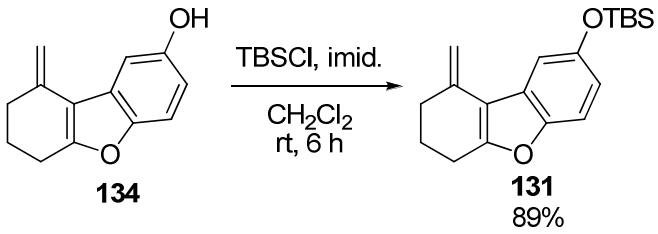


Figure 14. Structure of the aggregate of ketone **71** and (trimethylsilyl)methyl lithium

The theory is that the α-silylcarbanion in this aggregate maybe made more nuleophilic by coordination to the two lithium atoms. This increase in nucleophilicity would therefore promote the desired attack of the ketone and subsequent olefination. However, as of yet there is no proof of this aggregate formation and ultimately, the reason for the success of the Peterson reaction remains elusive.

2.6.3. TBS protection of alkene 134

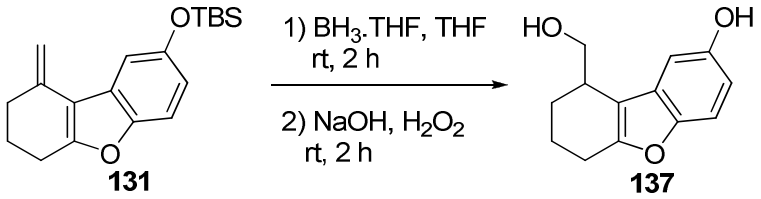
Unlike ketone **71**, the TBS protection of alkene **134** through treatment with TBSCl and imidazole provided the novel TBS-protected alkene **131** in an excellent yield (Scheme 52).



Scheme 52. TBS protection of methylene **134**

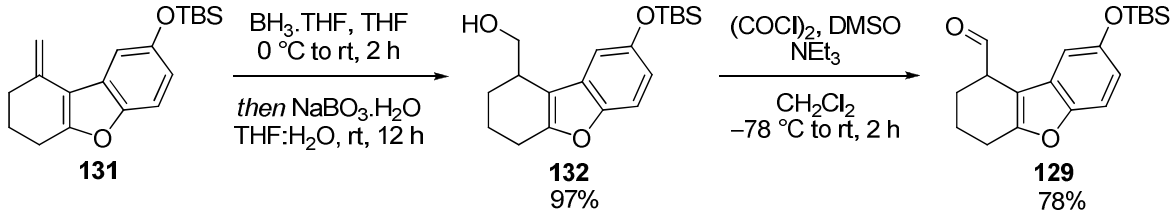
2.6.4. Synthesis of aldehyde 134

With alkene **131** in hand, the final steps to deliver the key aldehyde intermediate **129** were a hydroboration and oxidation. Hydroboration under the conditions previously used, BH_3.THF followed by a H_2O_2, NaOH work-up (Scheme 411), proceeded but with unwanted deprotection of the TBS ether observed in the ^{1}H-NMR spectrum (Scheme 53).



Scheme 53. Attempted hydroboration of alkene **131**

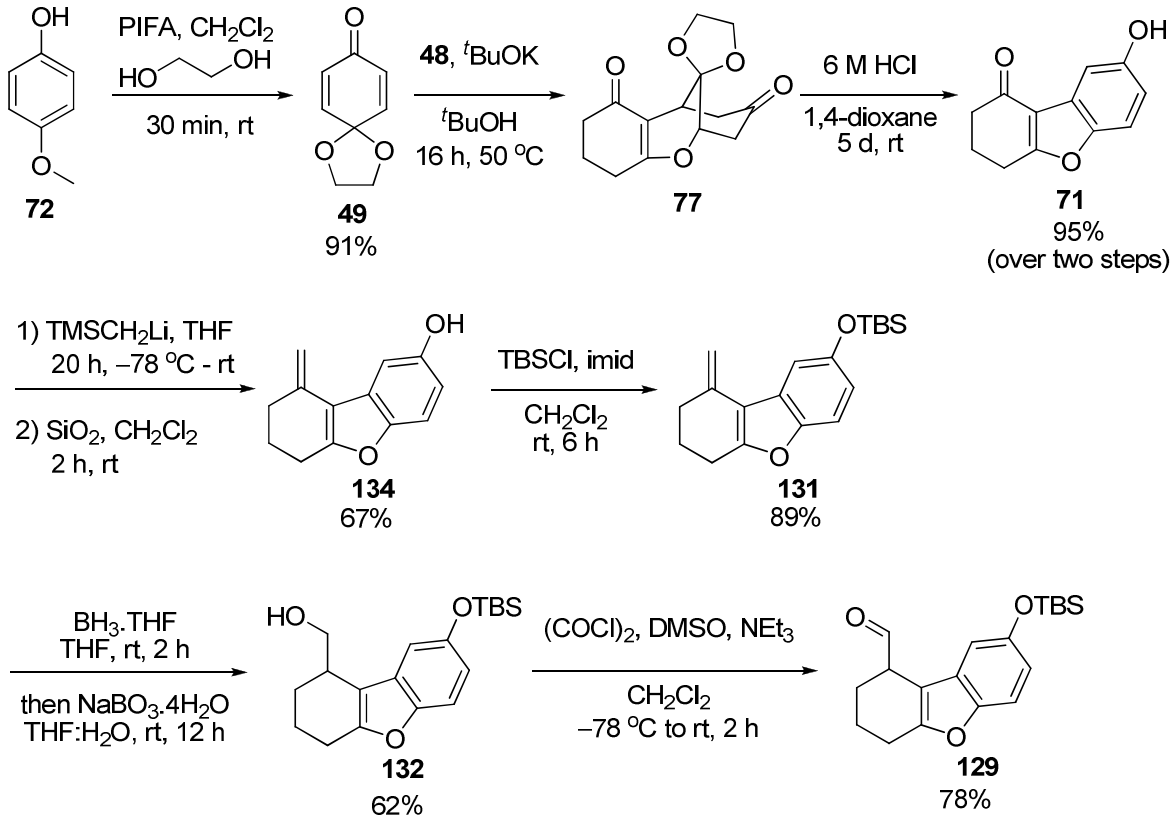
Presumably, this deprotection occurs during the basic work-up and so alternative conditions were sought. After a thorough investigation of the literature, a work-up procedure described by Carreria *et al*. using $NaBO_3.4H_2O$ proved successful and delivered the desired alcohol **132** in good yield (Scheme 54).[46]



Scheme 54. Synthesis of aldehyde **129**

Subsequent oxidation under Swern's conditions then afforded the key aldehyde intermediate **129** in good yield. It should be noted that attempted use of DMP, as used with the methyl ether variant **98**, proved unsuccessful with only decomposition observed.

Overall, the formation of aldehyde **129** was completed in 8 steps and an overall yield of 39% (Scheme 55).



Scheme 55. Synthesis of core aldehyde unit **129**

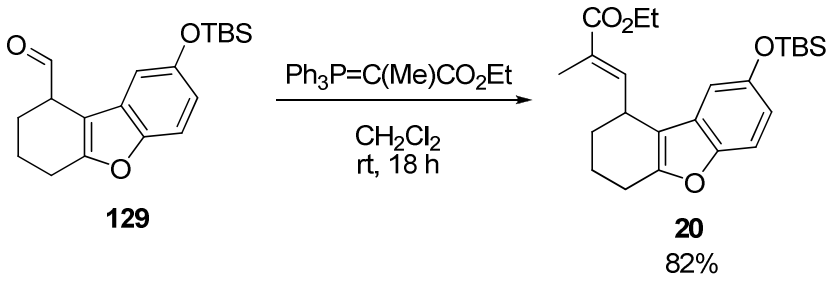
At this point, the synthesis intersects with Liu's total synthesis of **15**, however, they do not directly isolate aldehyde **129** and so it was not possible to directly compare the respective routes at this stage.

2.7. Synthesis of Shin-ya's Structure of Cuevaene A (15)

As with the methyl protected aldehyde **87**, it was decided that with a robust, reproducible route to aldehyde **129** in hand, **15** should be directly synthesised using the linear strategy essentially as described by Liu (Scheme 1).

2.7.1. Synthesis of alkene 20

The first of the three double bonds was again installed using a Wittig reaction with the commercially available ethyl 2-(triphenylphosphoranylidene)propanoate (Scheme 56).

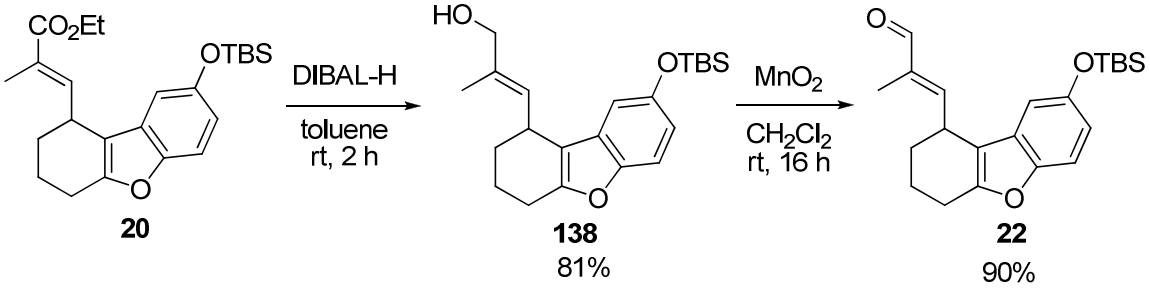


Scheme 56. Synthesis of alkene **20**

Thus treatment of aldehyde **129** with ethyl 2-(triphenylphosphoranylidene)propanoate overnight delivered the desired alkene **20** as a single isomer in good yield. It is important to note, that unlike aldehyde **129**, Liu isolates alkene **20** and achieves its synthesis in 5 steps from cyclohexenone (**16**) with an overall yield of 25% (Scheme 1).[18] This compares with our route to **20** which involves 9 steps from 4-methoxyphenol (**72**) and an overall yield of 29%.

2.7.2. Preparation of aldehyde 22

The transformation of alkene **20** into aldehyde **22**, ready for the key HWE reaction, was achieved in two steps (Scheme 57).

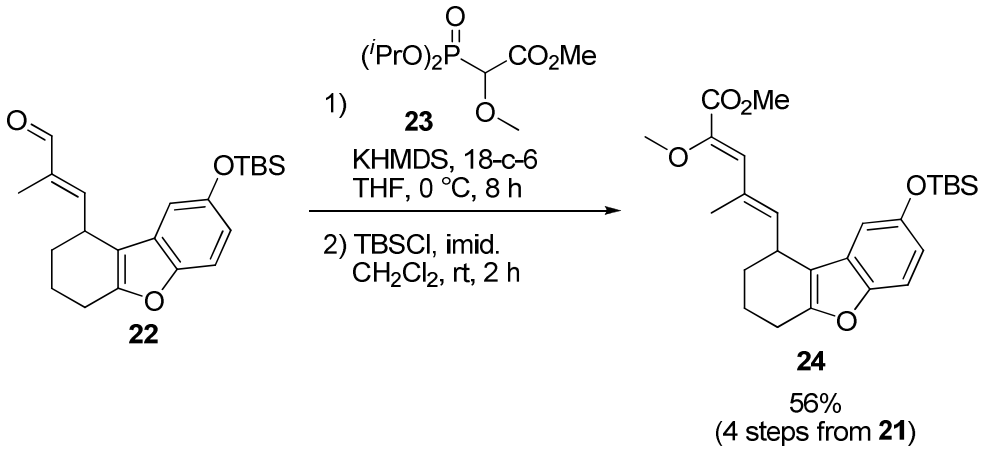


Scheme 57. Synthesis of aldehyde **22**

First, alkene **20** was treated with DIBAL-H to effect the desired reduction to alcohol **138** in excellent yield. Oxidation of the activated alcohol **138** was then achieved using MnO_2, delivering aldehyde **22**, again in an excellent yield.

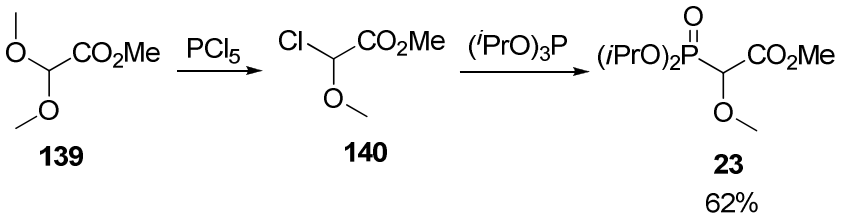
2.7.3. Synthesis of phosphonate 125

For their synthesis of **15**, Liu *et al*. used phosphonate **23** to install the second double bond in the sidechain (Scheme 58).[18]



Scheme 58. Liu's synthesis of methyl ester **24**[18]

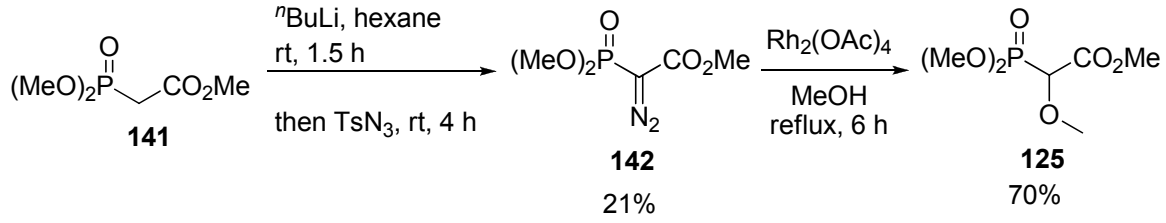
They synthesised phosphonate **23** through the known Arbuzov reaction of chloride **140** and triisopropyl phosphite (Scheme 59).[47]



Scheme 59. Liu's synthesis of phosphonate **23**[18]

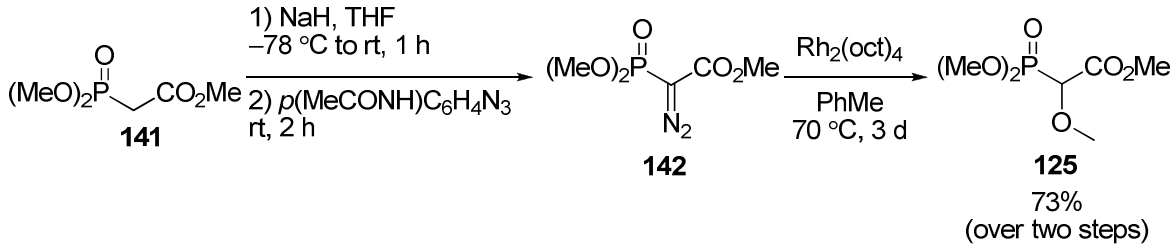
It was envisaged that the phosphonate **23** could also be utilised to install the second double bond in our synthesis. However, in our hands, the synthesis of **23** was unsuccessful following the above procedure and so an alternative synthesis was sought.

In 2002, Lu *et al*. reported an interesting transformation whereby they perform the insertion of the carbene, formed by treatment of diazo **142** with rhodium acetate dimer, into the O-H bond in methanol (Scheme 60).[48]



Scheme 60. Lu's synthesis of phosphonate **125**[48]

It was hoped that Lu's procedure could be repeated to deliver phosphonate **125** for use in the Horner-Wadsworth-Emmons reaction with aldehyde **22**. Pleasingly, phosphonate **125** was successfully synthesised using a modified version of Lu's conditions (Scheme 61).



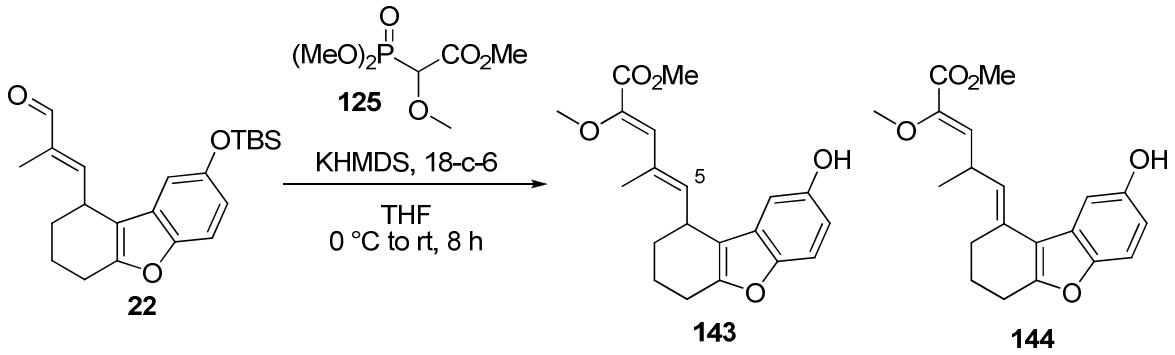
Scheme 61. Synthesis of phosphonate **125**

It was found that using NaH and *para*-acetoamidobenezensulfonyl azide, instead of ^{n}BuLi and tosyl azide, delivered diazo-compound **142** in a greater yield and clean enough to be telescoped through the carbene insertion step. The change of azide reagent was made due to lack of availability of the tosyl azide. In the subsequent carbene insertion step, the rhodium acetate dimer was substituted for the analogous octanoate dimer and the solvent was changed to toluene. These alterations provided the desired phosphonate **125** more efficiently than Lu's original conditions (73% vs. 15% for Lu's two-step procedure) and allowed **125** to be synthesised on a large scale.

2.7.4. Preparation of alkene 24 through a HWE reaction

As previously described, Liu used a HWE reaction using phosphonate **23** and KHMDS to install the second of the sidechain double bonds (Scheme 58).[18] However, their conditions suffered from unwanted deprotection of the TBS ether and so they required an extra step to reprotect the phenol group.

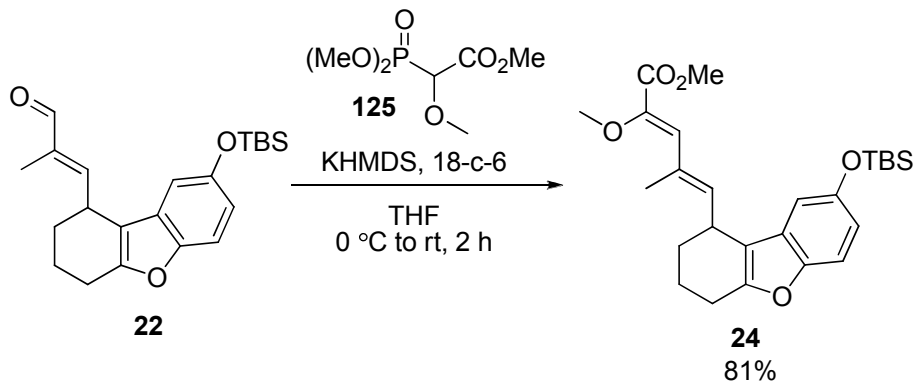
Initially Liu's conditions for this HWE reaction were repeated, although using phosphonate **125**, previously used for the HWE reaction on the methyl ether protected system (Scheme 54), rather than **23** (Scheme 62).



Scheme 62. Attempted use of Liu's conditions for formation of methyl ester **24**

As expected, the unwanted deprotection as experienced by Liu was seen in this reaction.[18] However, analysis of the ^{1}H-NMR spectrum of the reaction product suggested that a second side-reaction had taken place. Namely, the double bond adjacent to the core tetrahydrodibenzofuran unit had moved into conjugation with the aromatic system to give diene **144**. This transformation was indicated by the appearance of a peak at 5.19 ppm compared to the expected peak at roughly 5.8 ppm for H-5 in **143**.

While no detailed investigation was carried out into the mechanism of formation of **144**, it is possible that the excess of KHMDS (2.0 eq.) used in Liu's conditions could be the cause of these problems. Therefore, in order to circumvent this unwanted side-reaction, the reaction was repeated with fewer equivalents of KHMDS (1.0 eq.) (Scheme 63).



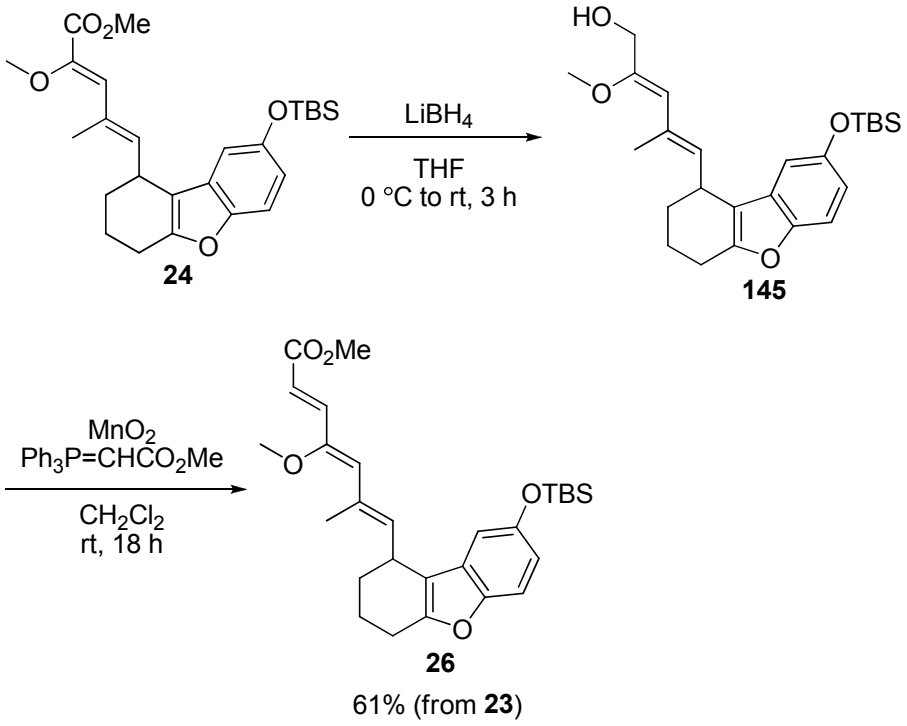
Scheme 63. HWE reaction with reduced equivalents of KHMDS

Pleasingly, the ^{1}H-NMR spectrum showed no indication of the side-product **144** and, after purification, the desired alkene **24** was isolated in excellent yield. Remarkably, it was also found that the undesired deprotection was also avoided under these conditions; thus eliminating the need for a reprotection step.

Thus the synthesis of alkene **24** was completed from alkene **20** in a 59% yield over three steps, compared to Liu's four-step procedure achieved in 56% yield.[18]

2.7.5. Completion of the carbon skeleton of (±)-15

With alkene **24** now in hand, the third and final double bond of the sidechain could now be installed. For this, Liu's reduction-oxidation-olefination procedure was again followed (Scheme 64).



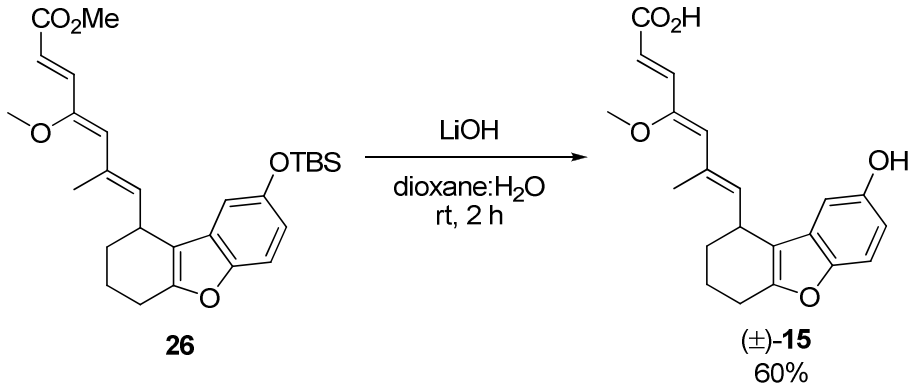
Scheme 64. Completion of the carbon skeleton of (±)-**15**

The initial reduction was achieved using $LiBH_4$ to deliver alcohol **145**, which, since instability issues had been previously observed, was carried forward to the next reaction without purification. For the formation of the final double bond, Liu used a two-step procedure (Scheme 1),[18] whereby the oxidation was achieved with MnO_2 and then olefination using a Wittig reaction with methyl (triphenylphosphoranylidene)acetate.

However, the Taylor group has previously shown that both these reactions could be achieved in a one-pot procedure using a tandem oxidation process (TOP).[47] Therefore, following this procedure, unpurified alcohol **145** was directly treated with MnO_2 and methyl (triphenylphosphoranylidene)acetate in one-pot and the desired triene **26** was afforded in a reasonable yield over the two steps from ester **24** (61% compared to 56% for Liu's three-step procedure).

2.7.6. Completion of total synthesis of Shin-ya's structure (±)-15

The final deprotection of the TBS ether and saponification of the methyl ester was achieved using the conditions used in Liu's synthesis (Scheme 65).[18]



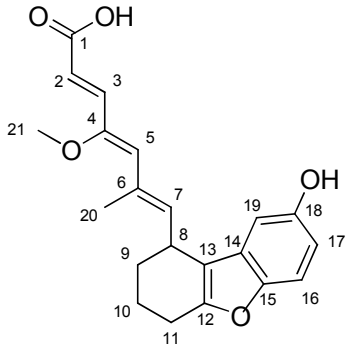
Scheme 65. Synthesis of Shin-ya's structure of cuevaene A ((±)-**15**)

Triene **26** was treated with LiOH for 2 h to deliver the final product (±)-**15** in a moderate yield (identical to Liu's yield for the same step). Pleasingly, the saponification conditions also gave the desired desilylation. Overall the synthesis of (±)-**15** was achieved in 15 steps and an overall yield of 7%, compared to Liu's synthesis in 13 steps and 5% yield.

2.8. Structural Confirmation of Cuevaene A

2.8.1. Comparison of ^{1}H-NMR spectroscopy data

Once the synthesis of (±)-**15** was complete, the ^{1}H-NMR spectroscopic data of the natural product and (±)-**15** [both our synthetic sample (Appendix 1) and Liu's synthetic sample] could be compared (Table 6).[17,18]



15

Table 6. ^{1}H-NMR spectroscopic data comparison of (±)-**15** and cuevaene A

Proton	Cuevaene A[17] δ_H ($CDCl_3$, 300 MHz)	Liu's Synthetic **15**[18] δ_H ($CDCl_3$, 400 MHz)	Our Synthetic **15** δ_H ($CDCl_3$, 400 MHz)
16	7.15 (d, 8.7)	7.23 (d, 8.0)	7.22 (d, 8.3)
3	7.07 (d, 15.4)	7.12 (d, 15.2)	7.11 (d, 15.4)
19	6.69 (d, 2.4)	6.69 (s)	6.70 (d, 2.6)
17	6.63 (dd, 2.4, 8.7)	6.68 (d, 8.4)	6.68 (dd, 2.6, 8.3)
2	5.99 (d, 15.4)	6.04 (d, 15.6)	6.03 (d, 15.4)
5	5.91 (s)	5.84 (s)	5.83 (s)
7	5.80 (d, 10.0)	5.77 (d, 10.0)	5.76 (d, 9.9)
8	3.80-3.91 (m)	3.82-3.83 (m)	3.78-3.87 (m)
21	3.65 (s)	3.66 (s)	3.65 (s)
11	2.66-2.74 (m)	2.72-2.73 (m)	2.68-2.76 (m)
20	2.24 (s)	2.22 (s)	2.21 (s)
	1.96-2.15 (m)	1.98-2.11 (m)	1.95-2.11 (m)
9&10	1.81-1.95 (m)	1.82-1.89 (m)	1.80-1.92 (m)
	1.50-1.66 (m)	1.52-1.60 (m)	1.50-1.61 (m)

As can be seen in the above table, our spectroscopic data for (±)-**15** matches very closely with that reported by Liu, as would be expected. Obviously, this means that the data also fails to match that supplied by Gräfe in the original isolation paper.

2.8.2. Discrepancies in the isolation paper

In order to gather a clearer picture as to the discrepancies observed in the ^{1}H-NMR spectroscopic data, the original NMR spectroscopic data were requested directly from the isolation authors. Upon receipt and subsequent processing of the raw data (Appendix 2), discrepancies came to light between these data and that presented in the original isolation paper.[17]

When comparing the received data against that reported in the paper we noted that the original ^{1}H-NMR spectrum was not run in $CDCl_3$ as the solvent, as reported,[17] but instead in CD_3OD (Table 7).

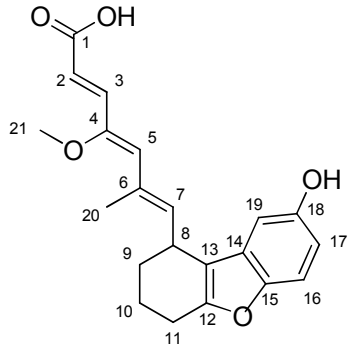


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Table 7. Comparison of ^{1}H-NMR spectroscopic data of originally reported data and the processed raw data for cuevaene A

Proton	Originally reported data[17] δ_H ($CDCl_3$, 300 MHz)	Processed raw data δ_H (CD_3OD, 300 MHz)
16	7.16 (d, 9.1)	7.15 (d, 8.7)
3	7.06 (d, 16.0)	7.07 (d, 15.4)
19	6.70 (d, .5)	6.69 (d, 2.4)
17	6.62 (dd, 9.1, 2.5)	6.63 (dd, 2.4, 8.7)
2	6.00 (d, 16.0)	5.99 (d, 15.4)
5	5.95 (s)	5.91 (s)
7	5.69 (d, 10.1)	5.80 (d, 10.0)
8	3.85 (ddd, 10.1, 4.1, 2.2)	3.80-3.91 (m)
21	3.62 (s)	3.65 (s)
11	2.69 (m) & 2.71 (m)	2.66-2.74 (m)
20	2.24 (s)	2.24 (s)
9&10	1.59 (m), 1.85 (m) 2.01 (m), 2.08 (m)	1.96-2.15 (m) 1.81-1.95 (m) 1.50-1.66 (m)

Furthermore, the reported δ_H shift values of some protons (especially H-7) did not match the raw data (5.69 vs. 5.80 ppm).

2.8.3. Comparsion of new ^{1}H-NMR spectroscopic data and structural confirmation of cuevaene A

With this new knowledge in hand, the ^{1}H-NMR spectrum for (±)-**15** was re-run but this time using CD_3OD as the solvent (Appendix 1, Table 8).

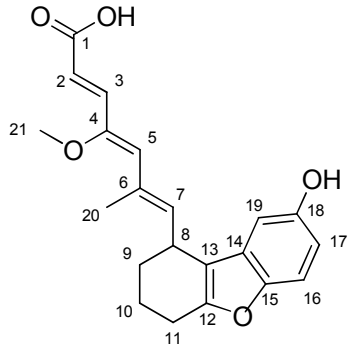

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Table 8. Final ^{1}H-NMR comparison of (±)-**15** and cuevaene A

Proton	Cuevaene A δ_H (CD_3OD, 300 MHz)	Synthetic (±)-**15** δ_H (CD_3OD, 400 MHz)
16	7.15 (d, 8.7)	7.15 (d, 8.7)
3	7.07 (d, 15.4)	7.07 (d, 15.4)
19	6.69 (d, 2.4)	6.69 (d, 2.4)
17	6.63 (dd, 2.4, 8.7)	6.63 (dd, 2.4, 8.7)
2	5.99 (d, 15.4)	5.99 (d, 15.4)
5	5.91 (s)	5.91 (s)
7	5.80 (d, 10.0)	5.79 (d, 10.1)
8	3.80-3.91 (m)	3.84 (ddd, 5.7, 7.7, 10.1)
21	3.65 (s)	3.65 (s)
11	2.66-2.74 (m)	2.67-2.74 (m)
20	2.24 (s)	2.24 (s)
9&10	1.96-2.15 (m) 1.81-1.95 (m) 1.50-1.66 (m)	1.96-2.14 (m) 1.81-1.93 (m) 1.50-1.63 (m)

Pleasingly, upon comparison of the spectroscopic data, it was confirmed that Shin-ya's structure of cuevaene A (**15**) was correct and the original structural assignment (**13**) was therefore incorrect.

2.8.4. Comparison of ^{13}C-NMR spectroscopic data

To further confirm (±)-**15** was the true structure, the ^{13}C-NMR spectroscopic data were also compared (Table 9).

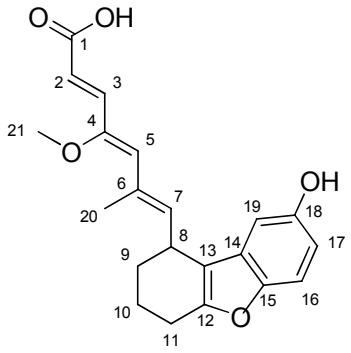

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Table 9. ^{13}C-NMR spectroscopic data comparison of cuevaene A and (±)-**15**

Carbon	Cuevaene A δ_C (CD_3OD, 125 MHz)	Synthetic (±)-**15** δ_C (CD_3OD, 100 MHz)
1	170.5	170.5
2	118.1	118.1
3	143.7	143.8
4	153.4	153.5
5	130.9	130.9
6	133.0	133.0
7	140.8	140.8
8	33.5	33.6
9	31.0	31.0
10	22.5	22.5
11	24.3	24.3
12	115.6	115.7
13	156.1	156.1
14	130.3	130.3
15	153.7	153.8
16	111.7	111.8
17	112.3	112.3
18	150.3	150.3
19	105.3	105.3
20	15.3	15.4
21	60.7	60.7

Again this comparison showed a close match between the data of (±)-**15** and those of the natural product. These observations confirm the structural reassignment of cuevaene A to (±)-**15**.

2.8.5. Structural reassignment of cuevaene B

With the true structure of cuevaene A now confirmed, it was possible to theorise that cuevaene B's structure should also be altered to match the substitution pattern seen in (±)-**15**, giving new structure **146** (Figure 14).

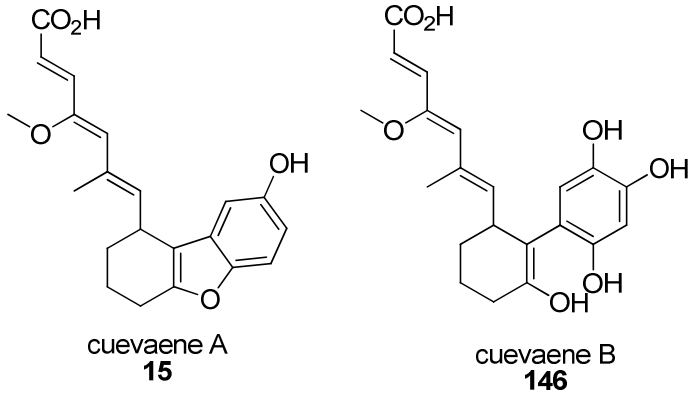


Figure 15. True structures of cuevaene A and B

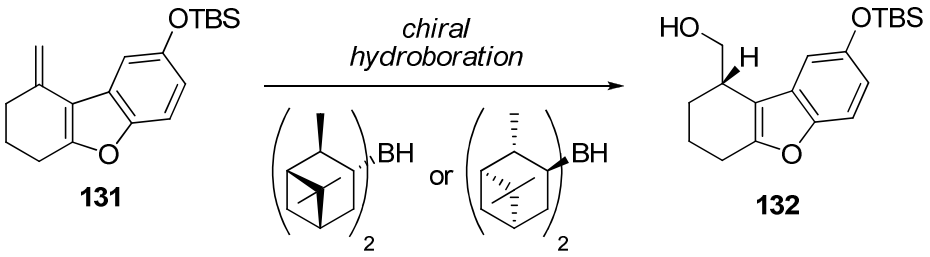
2.9. Summary & Future Work

2.9.1. Summary

In summary, the total synthesis of Shin-ya's structure of cuevaene A ((±)-**15**) was completed in 15 steps and an overall yield of 7% from 4-methoxyphenol (**72**) (Scheme 74). The key steps included a PIFA-mediated phenol oxidation, a Peterson methylenation and HWE reaction using phosphonate **125**. Once the synthesis of (±)-**15** was complete, comparison of the ^{1}H-NMR spectroscopic data and the correction of the data reported in the isolation paper revealed that (±)-**15** was the true structure of cuevaene A; thus correcting the original misassignment in the isolation paper.

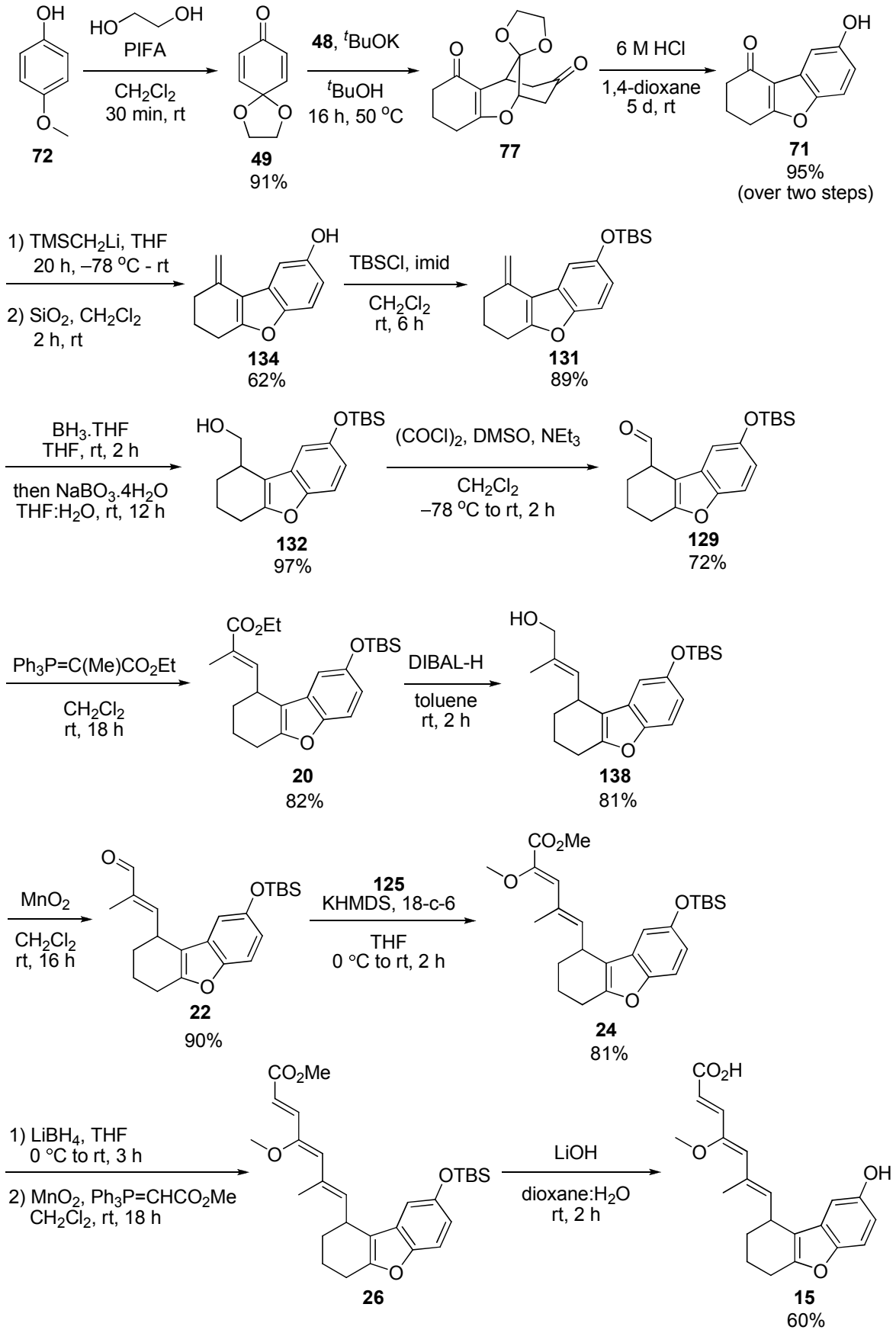
2.9.2. Future work

The major focus of any future work on the synthesis of cuavene A (**15**) should be the determination of the absolute stereochemistry of the natural product. It is envisioned that the single chiral centre in **15** could be set using a chiral hydroboration of alkene **131** (Scheme 66). The advantage of this strategy is two-fold: first it is an extension of a reaction already shown to work (Scheme 54) and second it allows access to both isomers of alcohol **132** by the use of either isomer of the pinene-derived hydroborating agent.



Scheme 66. Possible chiral hydroboration of alkene **131**

The work discussed in this Chapter was recently the subject of a publication.[49]



Scheme 74. Total synthesis of (±)-cuevaene A ((±)-**15**)

Chapter 3. Studies towards the Total Synthesis of JBIR-23 and 24

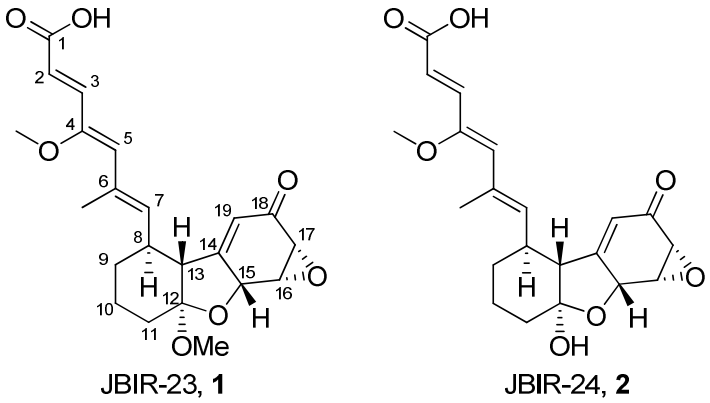
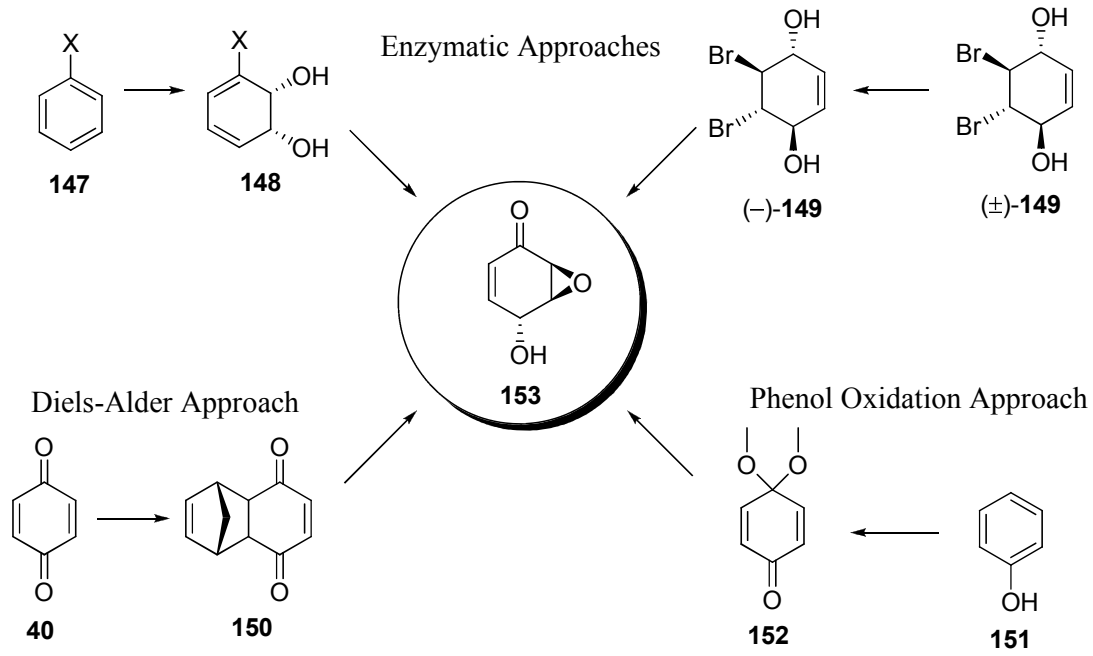


Figure 16. Structures of JBIR-23 (**1**) and JBIR-24 (**2**)

3.1. Introduction

3.1.1. Epoxyquinol natural products

As discussed in Chapter 1, there are many natural products which contain the epoxyquinol motif seen in **1** and **2** (Figure 16). Due to the widespread nature of this motif, an array of methods for the syntheses of these compounds have been disclosed in the literature;[5] some of the common routes are laid out below in Scheme 75 and then discussed in greater depth.



Scheme 75. General approaches to epoxyquinol natural products

3.1.2. Diels–Alder approach

The Diels–Alder approach towards epoxyquinol natural products involves the manipulation of a Diels–Alder adduct (**150**) to functionalise the cyclohexene core and a final retro-Diels–Alder reaction to reveal the natural product. The major advantage of this strategy is the cage-like structure of the Diels–Alder adducts, which facilitates diastereoselective reactions on the less hindered *exo*-face (Figure 15).

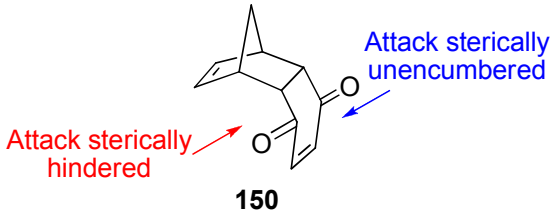
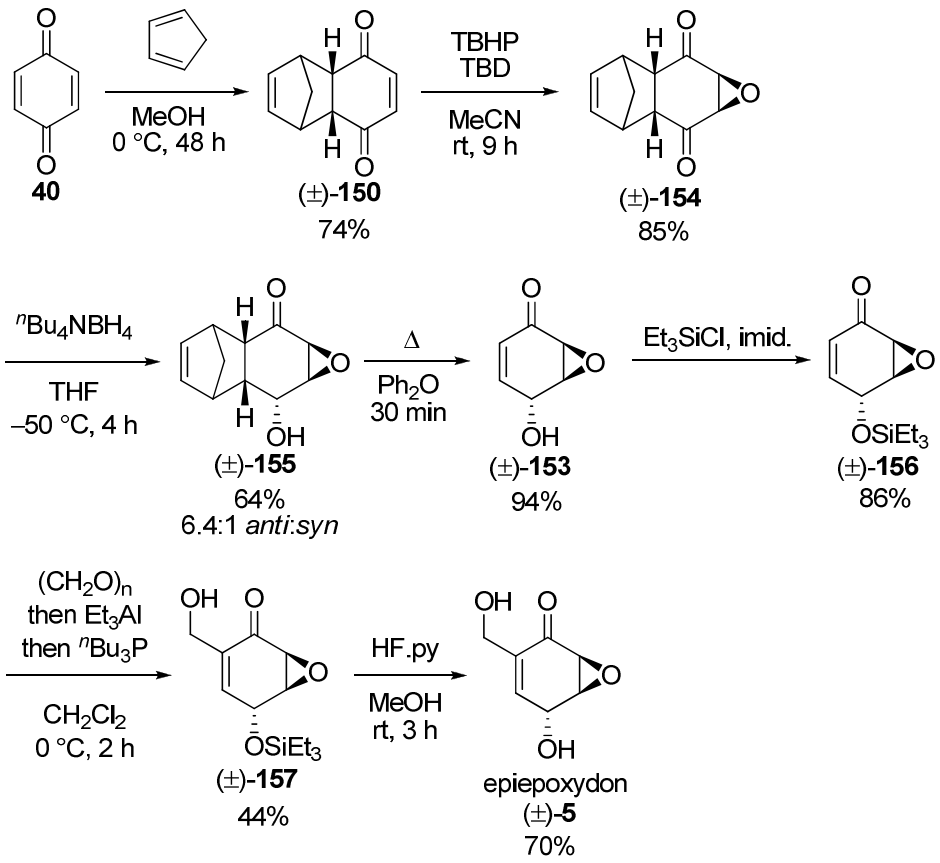


Figure 17. Cage-like structure of tricycle **150**

This approach has been utilised many times during the total syntheses of epoxyquinol natural products, for example Taylor's synthesis of epiepoxydon (±)-**5** (Scheme 76).[50]

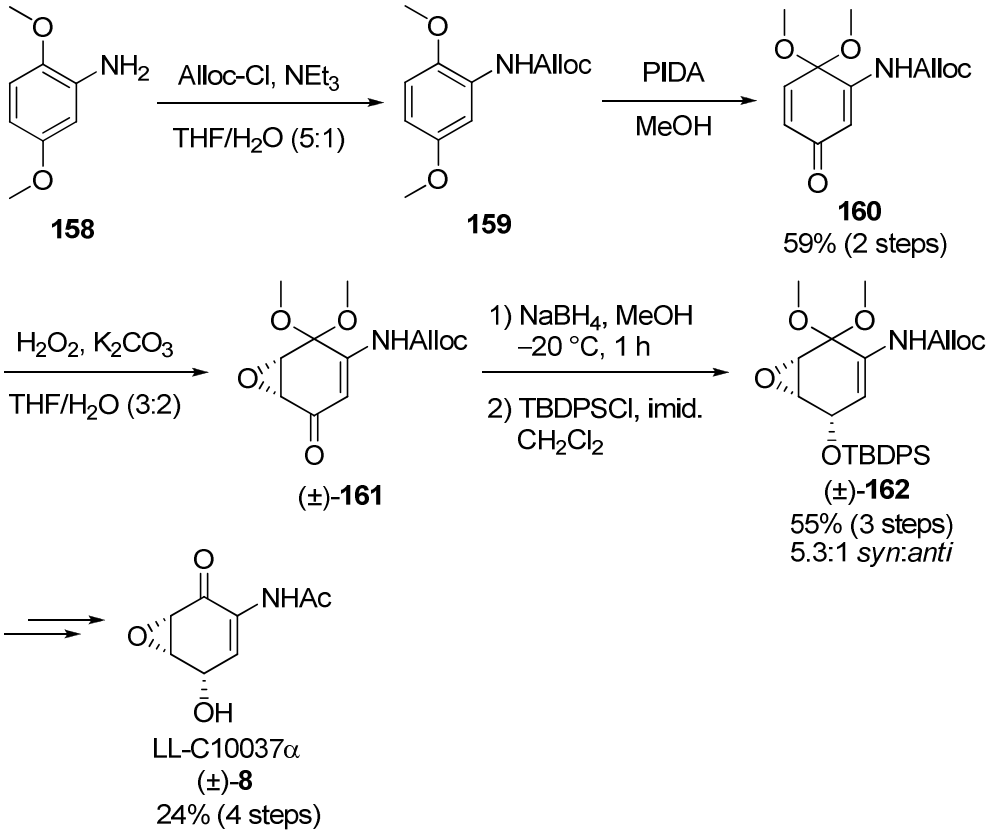


Scheme 76. Taylor's synthesis of epiepoxydon (±)-**5**[50]

The sequence initiated with the Diels–Alder reaction between cyclopentadiene and *p*-benzoquinone (**40**). The subsequent epoxidation with TBHP and reduction with $^{n}Bu_4NBH_4$ to deliver alcohol (±)-**155** were both performed with high levels of diastereoselectivity, demonstrating the major advantage of the cage-like tricyclic structure (Figure 15). The retro-Diels–Alder reaction of alcohol (±)-**155** was then achieved in excellent yield by heating in Ph_2O. The key Baylis–Hillman reaction with paraformaldehyde was found to be more efficient on the silyl ether (±)-**156** rather than the analogous unprotected system (±)-**153**. A final deprotection with HF.py then delivered epiepoxydon ((±)-**5**) in good yield.

3.1.3. Phenol oxidation approach

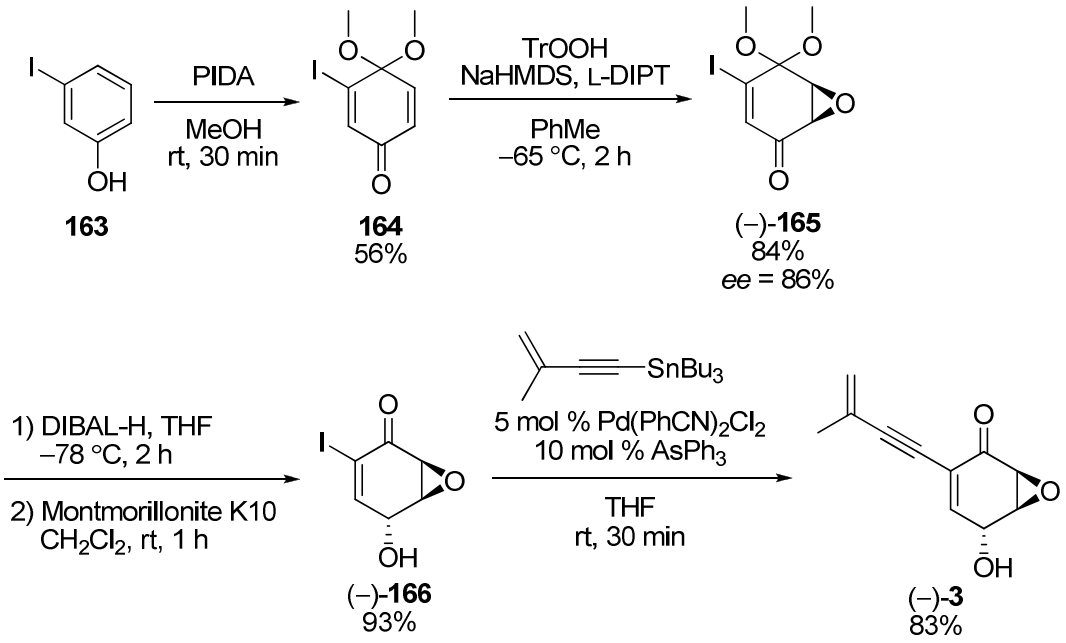
An alternative synthetic approach involves the oxidation of a phenol to a quinone intermediate and these quinone intermediates can then be manipulated to deliver a series of epoxyquinol natural products. An example of this approach is displayed in Wipf's total synthesis of LL-C10037α ((±)-**8**) (Scheme 77).[51]



Scheme 77. Wipf's first synthesis of LL-C10037α ((±)-**8**)[51]

Wipf used the hypervalent iodine compound (diacetoxyiodo)benzene (PIDA), in the presence of methanol to perform the oxidation of the anisole **159** to generate the desired quinone monoketal **160** in good yield. Subsequent epoxidation with hydrogen peroxide and potassium carbonate and further functional group manipulations delivered LL-C10037α ((±)-**8**). A similar approach towards the total synthesis of (±)-**8** and a range of other natural products was subsequently described by Taylor *et al*. in 1998.[52]

More recently, Taylor and co-workers have reported the synthesis (–)-harveynone ((–)-**3**) using a similar PIDA oxidation approach (Scheme 78).[53]



Scheme 78. Taylor's synthesis of (–)-harveynone ((–)-**3**)[53]

During this work, a procedure for the double oxidation of halophenols to haloquinones using PIDA in the presence of methanol was developed, the first time such an oxidation had been performed on halophenols. They then utilised one of the haloquinone products, namely iodide **164**, for the total synthesis of (–)-harveynone ((–)-**3**) in four further steps. The desired chirality was introduced through an enantioselective L-DIPT epoxidation procedure. The total synthesis of (–)-**3** from iodophenol **163** was completed in five steps and an overall 36% yield.

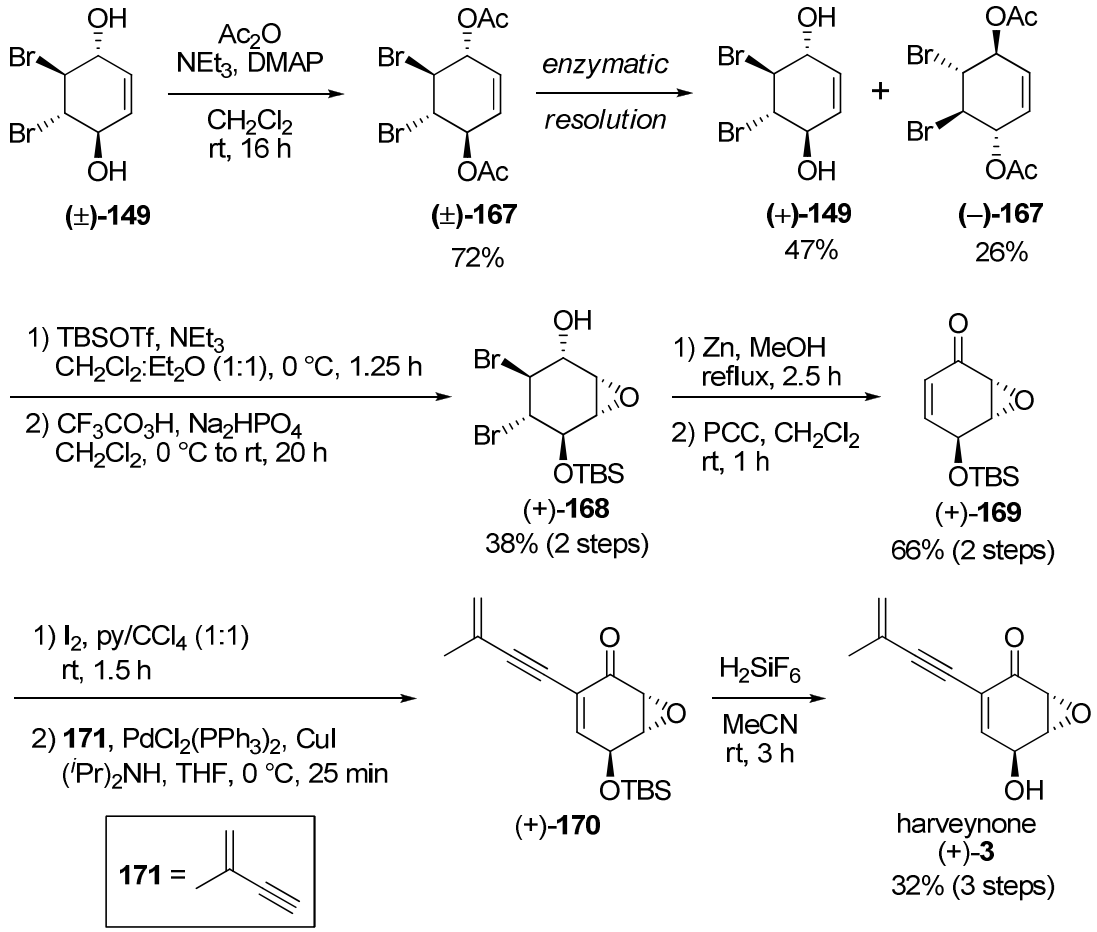
While in these reports Wipf and Taylor utilised PIDA for the key phenol oxidation, there are other methods of performing this type of oxidation in the literature, such as the use of

$Tl(NO_3)_2$ or electrochemical techniques.[54] However, these methods are usually less favourable than using hypervalent iodine compounds, due to the difficulty of using the electrochemical technique and the toxicity of thallium compounds.

3.1.4. Enzymatic approaches

There are many synthetic methods towards epoxyquinols that utilise enzymes to install the desired stereochemistry,[55,56] and two representative examples of this strategy are discussed below.

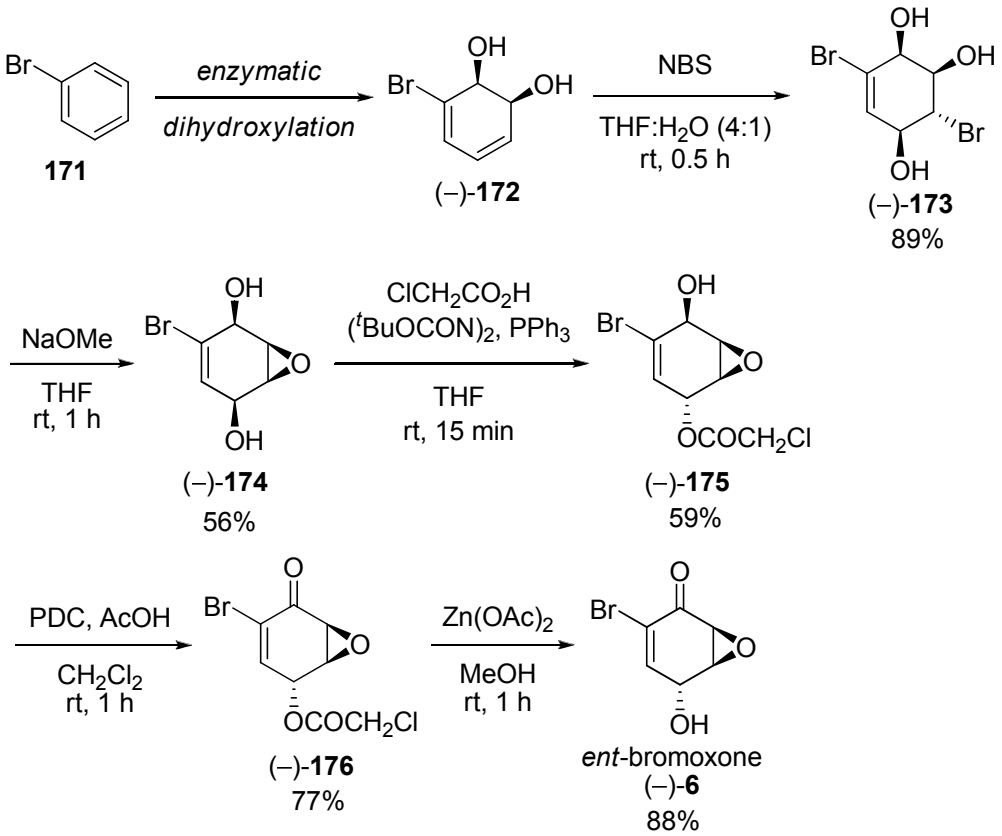
The first, reported by Johnson's group in the synthesis of a variety of epoxyquinol natural products, is the enzymatic resolution of diacetate (±)-**167** to deliver enantiopure diol (+)-**149** (Scheme 79).[55]



Scheme 79. Johnson's synthesis of harveynone ((+)-**3**)[55]

Monoprotection and epoxidation of enantioenriched diol (+)-**149** delivered epoxide (+)-**168** in a moderate yield over the two steps. Treatment of (+)-**168** with zinc metal, to reduce and eliminate the dibromide moiety, and oxidation of the alcohol with PCC delivered Johnson's key epoxyquinol scaffold (+)-**169**. Johnson then utilised (+)-**169** in the synthesis of a range of natural products, for example iodination followed by a Sonogashira cross-coupling and deprotection completed the synthesis of enantioenriched harveynone ((+)-**3**).

An alternative enzymatic process towards epoxyquinol natural products was described recently by Banwell and co-workers (Scheme 80).[56]



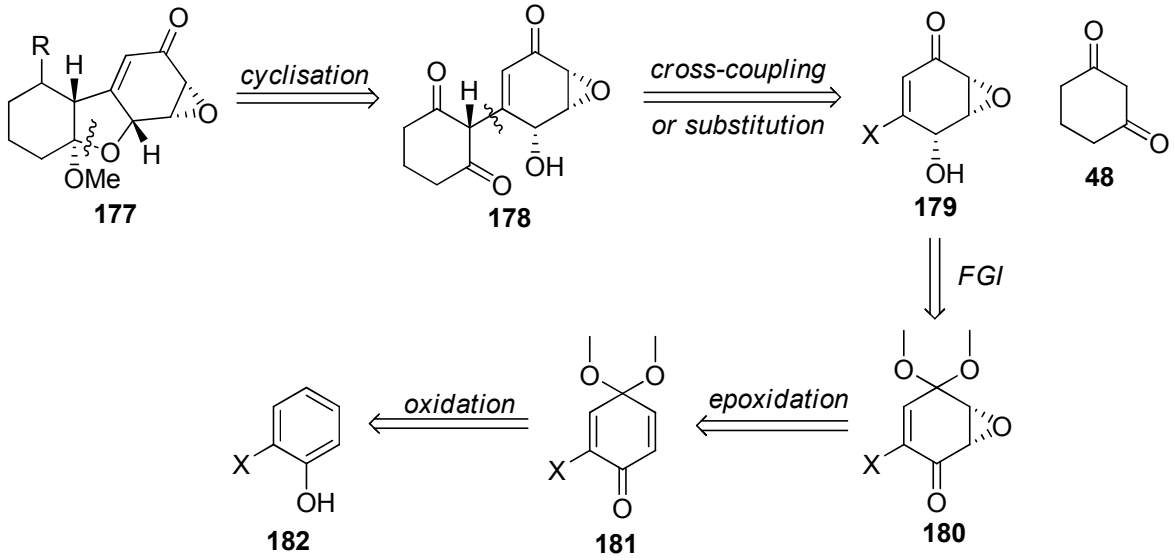
Scheme 80. Banwell's synthesis of *ent*-bromoxone ((–)-**6**)[56]

The key step, which installs the desired stereochemistry is an enzymatic dihydroxylation of bromobenzene **171** delivering chiral diol (–)-**172**. Upon treatment with *N*-bromosuccinimide in the presence of water, (–)-**172** is then converted into bromohydrin (–)-**173**. Subsequent intramolecular cyclisation is promoted by NaOMe to deliver epoxide (–)-**174**, albeit in a moderate yield. A Mitsunobu reaction and oxidation then yields what

Banwell describes as the 'epoxyquinol synthon' (–)-**176**. Banwell's group then demonstrates the utility of (–)-**176** by using it as a basis for the synthesis of five epoxyquinol natural products, including *ent*-bromoxone ((–)-**6**) through the deprotection of the chloroacetate group with zinc(II) acetate and MeOH.

3.1.5. Retrosynthesis of JBIR-23/24

Due to work undertaken in this group by Hookins (Scheme 78),[53] of the approaches described above, the strategy of greatest interest was that involving phenol oxidation mediated by hypervalent iodine compounds and the retrosynthesis based on this strategy is outlined below in Scheme 81.



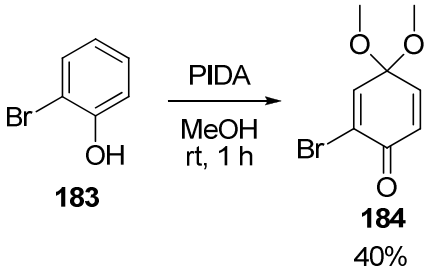
Scheme 81. Retrosynthetic analysis of key intermediate **177**

It was envisioned that tricycle **177** would be the key intermediate for the synthesis of JBIR-23 (**1**), with the R group being a suitable appendage for the development of the triene sidechain. It was hoped that **177** could be accessed from epoxyquinol **179** through a cross-coupling or substitution reaction with dione **48**, or a suitable alternative, followed by an intramolecular cyclisation. The initial plan for synthesising the key epoxyquinol intermediate **179** was the oxidation of phenol **182**, a regioselective epoxidation and further functional group manipulations.

3.2. PIDA oxidation routes

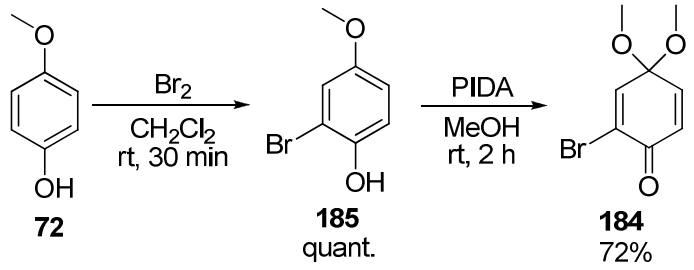
3.2.1. Single vs. double PIDA oxidation

As described above (Scheme 81), the initial step of the synthesis was the double oxidation of phenol **183** (Scheme 82), which was achieved using a literature procedure affording bromide **184** in a moderate yield.[53]



Scheme 82. Synthesis of monoketal **184**

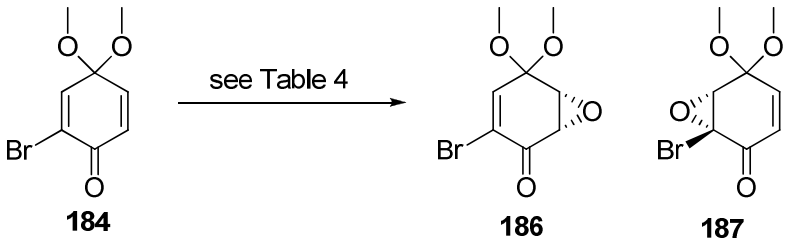
Due to the disappointing yield of this double oxidation procedure, the single oxidation of 2-bromo-4-methoxyphenol (**185**) was attempted in the hope of increasing the overall yield (Scheme 85). Pleasingly, the treatment of phenol **185**, readily accessible from *p*-methoxyphenol (**72**),[58] with PIDA in the presence of methanol delivered the desired bromquinone **184** in an increased yield when compared to the double oxidation (72% vs. 40%). In fact, this single oxidation of **185** with PIDA has since been disclosed by Reisman's group in comparable yield (87%).[59]



Scheme 82. Synthesis of monoketal **184**

3.2.2. Attempted epoxidation of quinone 184

With quinone **184** in hand, the next step was to introduce the epoxide moiety. Unfortunately, a variety of attempted epoxidation conditions failed to deliver any of the desired product **186** (Table 10).

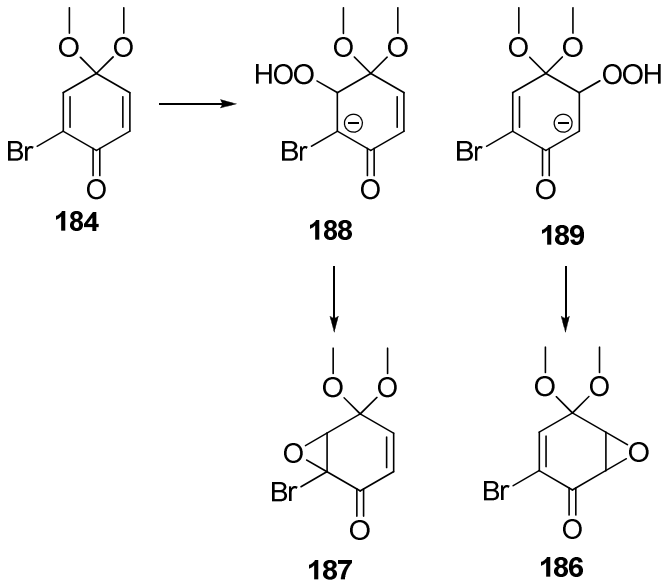


184 **186** **187**

Table 10. Attempted conditions for the epoxidation of **184**

Entry	Conditions	Result
i	*m*CPBA	No reaction
ii	TrOOH, NaHMDS	**187** formation observed
iii	^{t}BuOOH, DBU	**187** formation observed
iv	Cumene hydroperoxide, NaH	**187** formation observed
v	H_2O_2, K_2CO_3	**187** formation observed
vi	*In situ* TFDO	Deprotected SM
vii	H_2O_2, NaOH	**187** formation observed
viii	Cumene hydroperoxide, NaOH	**187** formation observed

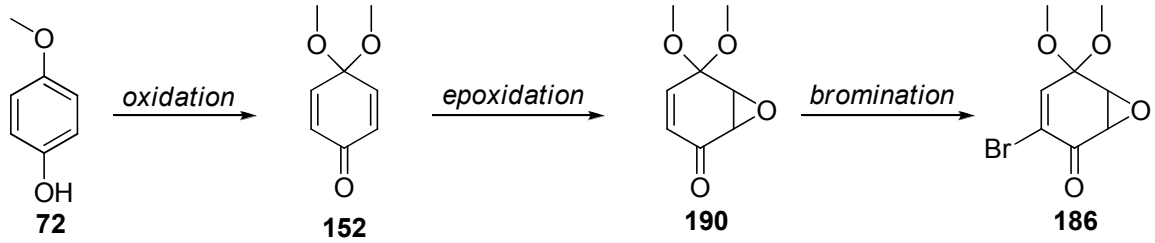
The only product observed in the ^{1}H-NMR spectra of the unpurified material, albeit in small amounts, was the unwanted regioisomer **187**. It is postulated that the inductive effect of the bromo-substituent on quinone **184** provides additional stabilisation for the intermediate anion **188** and promotes the formation of the alternative isomer **187** (Scheme 84).



Scheme 84. Postulated mechanism for formation of the epoxide side-product **187**

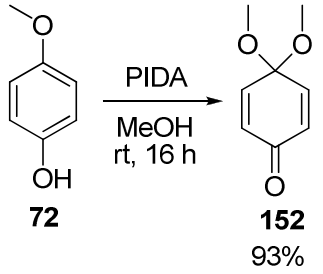
3.2.3. Alternative strategy

Following the failure of the above strategy, an alternative was sought. The new strategy involved the oxidation n of *p*-methoxyphenol (**72**),[60] followed by epoxidation of the resultant quinone **152** and then an α-bromination to deliver the desired bromoquinone **186** (Scheme 85).



Scheme 85. Alternative route to bromoquinone **186**

The initial oxidation was successfully achieved in excellent yield following the published procedure by the treatment of phenol **72** with PIDA in the presence of the methanol to deliver quinone **152** (Scheme 86).[61]



Scheme 86. PIDA oxidation of phenol **72**

With **152** in hand, the subsequent epoxidation was investigated (Table 11).

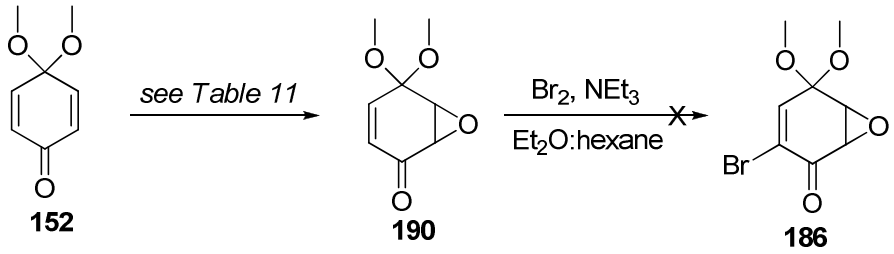


Table 11. Conditions for epoxidation of quinone **152**

Entry	Conditions	Ratio **152**:**190**[a]
i	H_2O_2, K_2CO_3	1:2.6
ii	H_2O_2, NaOH	1:3.33
iii	^{t}BuOOH, DBU	1:1.67
iv	Cumene hydroperoxide, NaH	No reaction
v	*In situ* TFDO	No reaction
vi	TrOOH, NaHMDS	No reaction

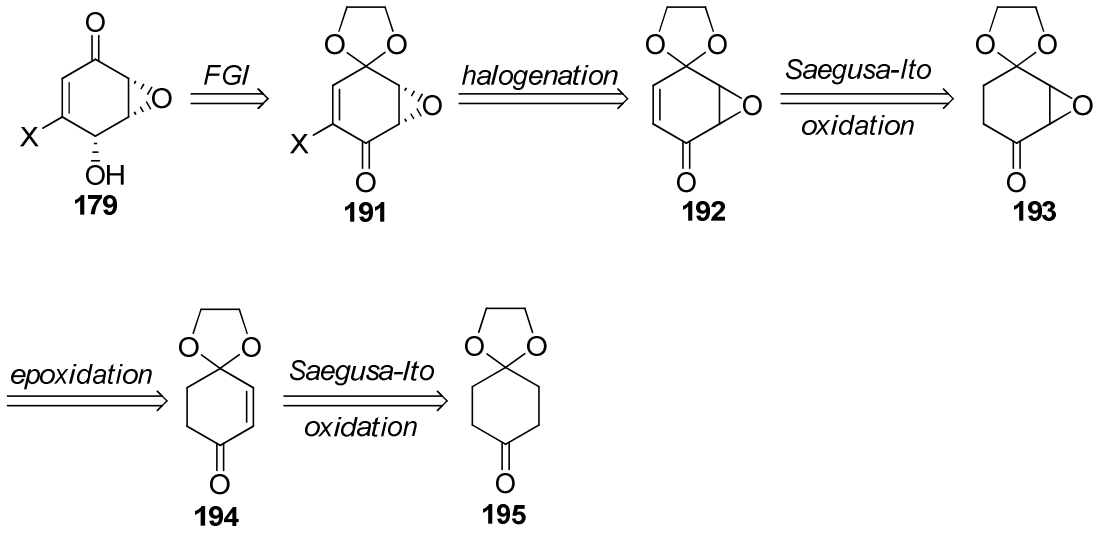
a As determined by analysis of the crude ^{1}H-NMR sprectoscopic data

In fact the epoxidation of quinone **152** is a known procedure reported in 2008 by Bachu *et al*.[61] However, repeating the literature conditions gave a mixture of starting material **152** and epoxide **190** (entry i). Unfortunately, despite a number of attempts, the separation of **152** and **190** was unsuccessful. A range of differing epoxidation conditions were attempted (Table 11) but, while an increase in the ratio of **152**:**190** was observed (entry ii), full conversion was never achieved. The attempted bromination of the mixture of **152** and **190** using Br_2/NEt_3 was unfortunately unsuccessful and delivered no tractable product.

3.3. Saegusa-Ito Oxidation Route to Epoxyquinol 179

3.3.1. New retrosynthesis of epoxyquinol 179

With the failure to synthesise the key epoxyquinol **179** *via* the desired PIDA oxidation routes, an alternative retrosynthesis was considered (Scheme 87).

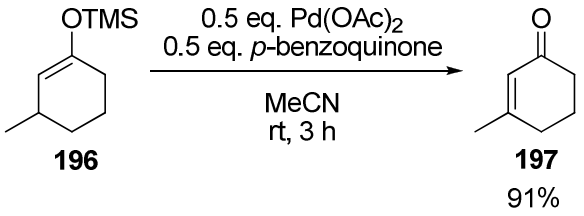


Scheme 87. New retrosynthesis of epoxyquinol **179**

In the new strategy, epoxyquinol **179** was envisioned to come from haloenone **191** through a series of functional group manipulations. In turn, enone **191** should be accessed from the halogenation of the parent enone **192**. Enone **192** could then be synthesised *via* a Saegusa-Ito oxdiation from ketone **193**, itself available from the epoxidation of enone **194**. A second Saegusa-Ito oxidation from commercially available ketone **195** completes the retrosynthesis. Although not as direct as the phenol oxidation route previously described (Scheme 81), this route avoids the problematic epoxidation of quinones **152** and **184** (Scheme 84 and Table 11).

3.3.2. Literature Background of the Saegusa-Ito Oxidation

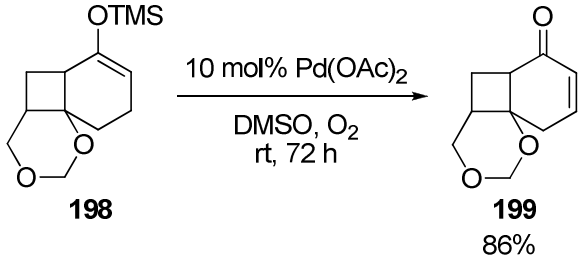
The Saegusa-Ito oxidation is the oxidation of a silyl enol ether to the analogous enone using palladium(II) acetate (Scheme 88).[62]



Scheme 88. First report of a Saegusa-Ito oxidation[62]

The original conditions described by Saegusa and co-workers used 0.5 equivalents of the palladium species and 0.5 equivalents of *p*-benzoquinone to effect the oxidation of silyl enol ether **196** to enone **197**. However, they also report that the use of stoichiometric palladium(II) acetate, in the absence of *p*-benzoquinone, gave a quantitative yield of enone **197**.[62]

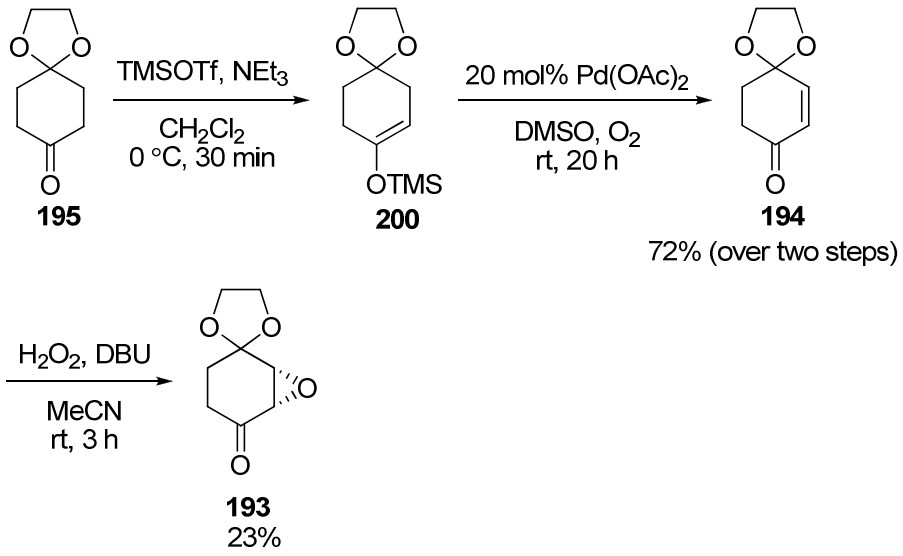
In 1995, Larock described an improved version of the Saegusa-Ito conditions whereby only 10 mol% of palladium(II) acetate was used, compared to either 50 or 100 mol% previously required, under an atmosphere of oxygen to allow the regeneration of the catalyst (Scheme 89).[63]



Scheme 89. Larock's modified Saegusa-Ito oxidation[62]

3.3.3. Synthesis of epoxide 193 *via* Saegusa-Ito oxidation

The initial step in the new strategy for the synthesis of epoxyquinol **179** was the formation of enone **194** (Scheme 87). This oxidation has been disclosed in literature by Kerr and co-workers using stoichiometric palladium(II) acetate,[64] and the first step was the formation of silyl enol ether **200** through the treatment of ketone **195** with triethylamine and TMSOTf (Scheme 90).

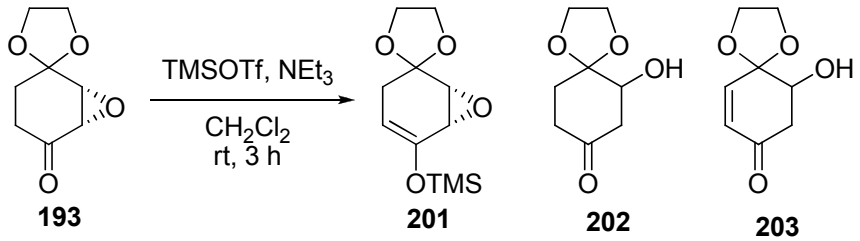


Scheme 90. Synthesis of epoxide **193**

Unlike Kerr *et al*.,[64] the Saegusa-Ito oxidation of the unpurified enol ether **200** was then performed using Larock's modified conditions to deliver the desired enone **194** in good yield over the two steps. Whilst the subsequent epoxidation of enone **194** was achieved, the desired epoxide **193** was only afforded in a poor yield (Scheme 90).

3.3.4. Attempted Synthesis of Enone 192

The next step in the synthesis was the oxidation of epoxide **193** to enone **192** through a second Saegusa-Ito reaction (Scheme 91).



Scheme 91. Attempted formation of TMS enol ether **201**

Unfortunately, the initial attempt to form of the required TMS enol ether **201** using TMSOTf and triethylamine was unsuccessful. Under these conditions, the majority of the starting epoxide **193** was recovered alongside a small amount of an inseparable 1:1 mixture of two compounds, tentatively assigned as ketone **202** and enone **203**. As of yet, the mechanism of their formation is not clear.

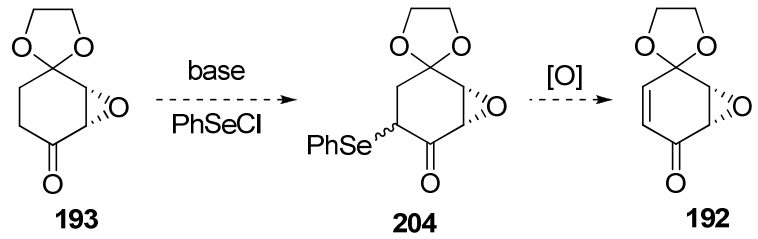
3.4. Summary and Future Work

3.4.1. Summary

The main focus of the work thus far undertaken towards the total synthesis of JBIR-23 (**1**) and 24 (**2**) has been the attempted synthesis of the haloepoxyquinol **179**, a key intermediate in the proposed retrosynthesis (Scheme 81), but unfortunately the two strategies thus far investigated, the phenol oxidation approach and the Saegusa-Ito oxidation approach, have proved unsuccessful.

3.4.2. Future Work

Further investigation into the Saegusa-Ito oxidation approach is still needed. Specifically, there are many methods by which the oxidation of ketone **193** to enone **192** could be achieved. Initially, alternative conditions for the formation of silyl enol ether **201** would be investigated and, if successful, the Saegusa-Ito oxidation could be investigated. If unsuccessful, alternative strategies for the conversion of ketone **193** to enone **192** could be investigated such as the use of selenium chemistry (Scheme 92).

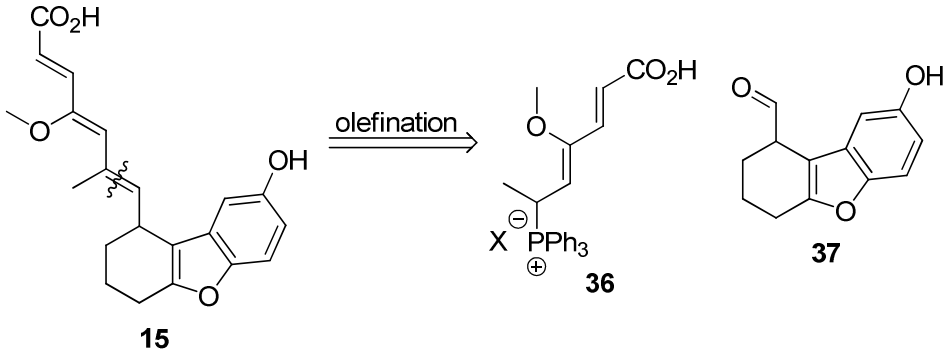


Scheme 92. Possible access to enone **192** through selenium chemistry

Chapter 4. Synthesis of 4-Methoxypentadienoates

4.1. Introduction

As discussed in Chapter 2, the initial retrosynthesis for cuevaene A (**15**) and JBIR-23 (**1**) and 24 (**2**) envisioned a late stage olefination between the aldehyde **37** and phosphonium salt **36** (Scheme 93).

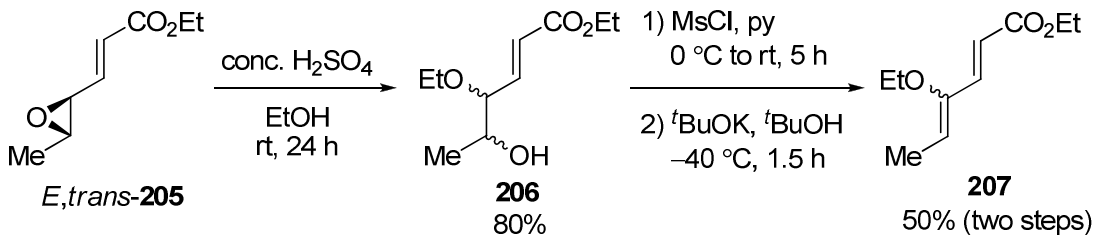


Scheme 93. Retrosynthetic analysis of **15**

Ultimately, as described in Chapter 2 a step-wise elaboration of aldehyde **37** was employed to prepare cuevaene A (**15**). However this route was lengthy and a more efficient route to 4-methoxypentadienoates was sought, which could possibly be applied to prepare reagents such as phosphonium salt **36**.

4.1.1. Watt's ethyl enol ether formation

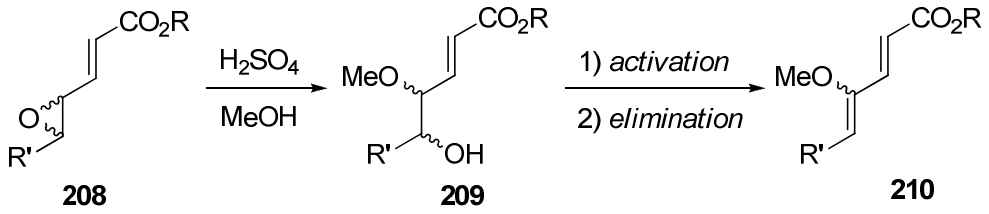
The starting point for the development of a new route to phosphonium salt **36** was a report by Watt *et al*. in 1983 where they achieved the synthesis of ethoxydienoate **207** from epoxide *E*,*trans*-**205** in three steps (Scheme 94).[65]



Scheme 94. Watt's synthesis of ethyl enol **207**[65]

The initial step was the regioselective epoxide-opening of *E*,*trans*-**205** with ethanol, under acidic conditions, to deliver alcohol **206** in an excellent yield. Subsequent mesylation and elimination delivered their desired ethoxydienoate **207** in a good yield over the two steps. While Watt does not discuss the stereochemical outcome of the reaction sequence, only one isomer of alcohol **206** and one isomer of the ethoxydienoate product **207** were described in their experimental data suggesting that the sequence was diastereoselective.

It was envisioned that a similar strategy could be used for the synthesis of the desired methoxydienoate moiety by switching from ethanol to methanol (Scheme 95). We also assumed that this process should be stereoselective (see later).



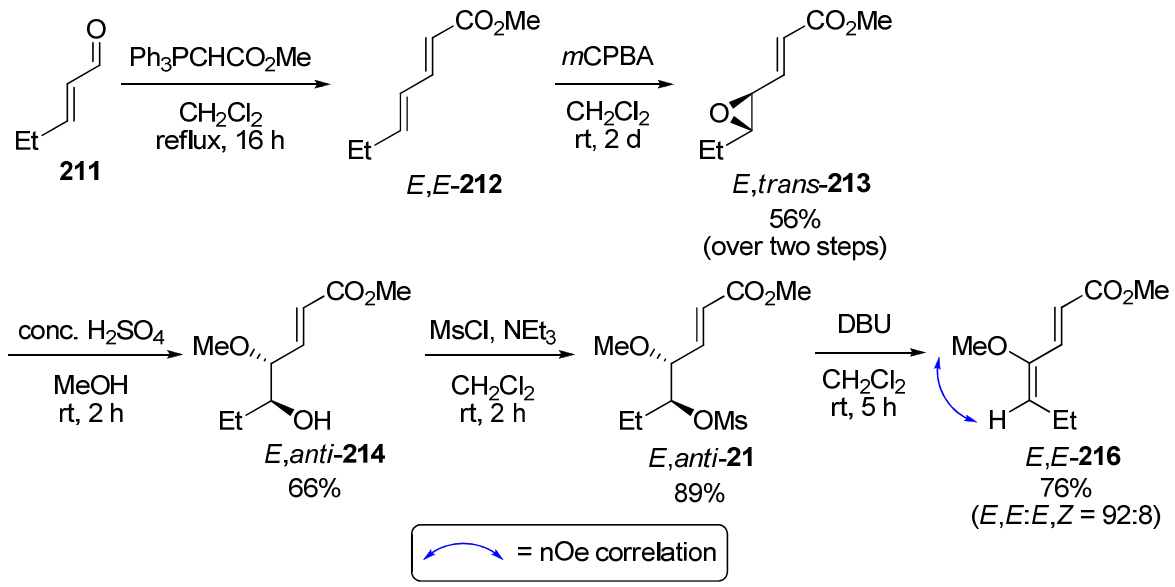
208 **209** **210**

Scheme 95. Envisioned strategy for methoxydienoate formation

4.2. Development and Substrate Scope of Methoxydienoate Synthesis

4.2.1. Initial results

The strategy outlined above (Scheme 95) was tested using epoxide *E*,*trans*-**213**, itself available from commercially available aldehyde **211** in two known steps (Scheme 96).[66,67]



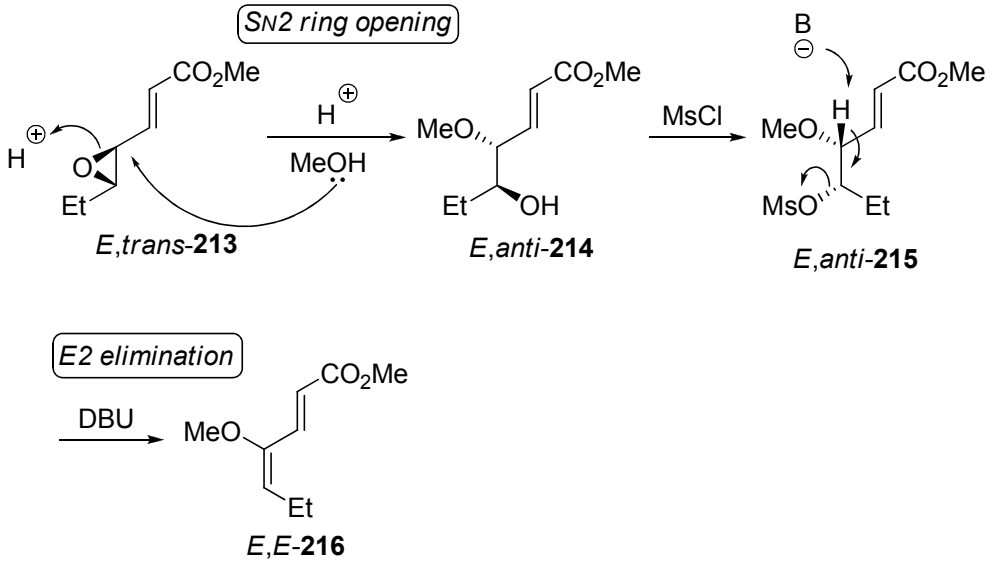
Scheme 96. Formation of methoxy dienoate *E*,*E*-**216** using a modified version of Watt's conditions

Thus, the treatment of aldehyde **211** with methyl (triphenylphosphoranylidene)acetate and subsequent epoxidation of diene *E*,*E*-**212** using *m*CPBA delivered the desired epoxide *E*,*trans*-**213** in moderate yield. The formation of methoxydienoate *E*,*E*-**216**, using a modified version of Watt's conditions, was next investigated (Scheme 96).

Pleasingly, the desired epoxide-opening with methanol under acidic conditions was successful and delivered alcohol *E*,*anti*-**214** as a single diastereomer in a moderate yield. Subsequent activation with mesyl chloride and elimination using DBU, which was found to be more efficient than Watt's use of ^{t}BuOK (Scheme 94),[65] then delivered the desired methoxydienoate *E*,*E*-**216** in a good yield. The reaction sequence proceeded in a diastereoselective manner (92:8 major:minor) and the major isomer was determined as *E*,*E*-**216** using nOe NMR-spectroscopic experiments, which showed a strong correlation between H-5 and the –OMe group. Unfortunately, the two isomers proved inseparable using chromatographic methods.

4.2.2. Proposed mechanism

While the mechanism of the above reaction sequence has not been fully investigated, a likely mechanism explaining the observed selectivity is outlined below (Scheme 97).



Scheme 97. Proposed mechanism of methoxydienoate synthesis

The initial regioselective acid-promoted ring-opening with methanol is thought to occur *via* an S_N2 mechanism, inverting the stereocentre at C-4 and delivering alcohol *E*,*anti*-**214** as a single diastereomer. The subsequent DBU-promoted elimination of mesylate *E*,*anti*-**215** then proceeds through an E2 elimination mechanism, with the hydrogen atom and mesylate in the required antiperiplanar relationship shown below (Figure 17), to deliver the desired methoxydienoate *E*,*E*-**216**.

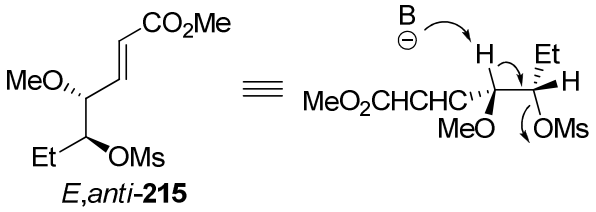
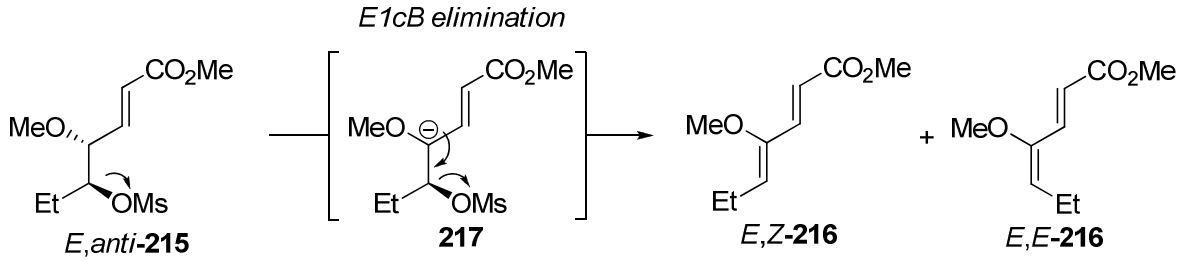


Figure 18. Antiperiplanar conformation of mesylate *E*,*anti*-**215** for E2 elimination

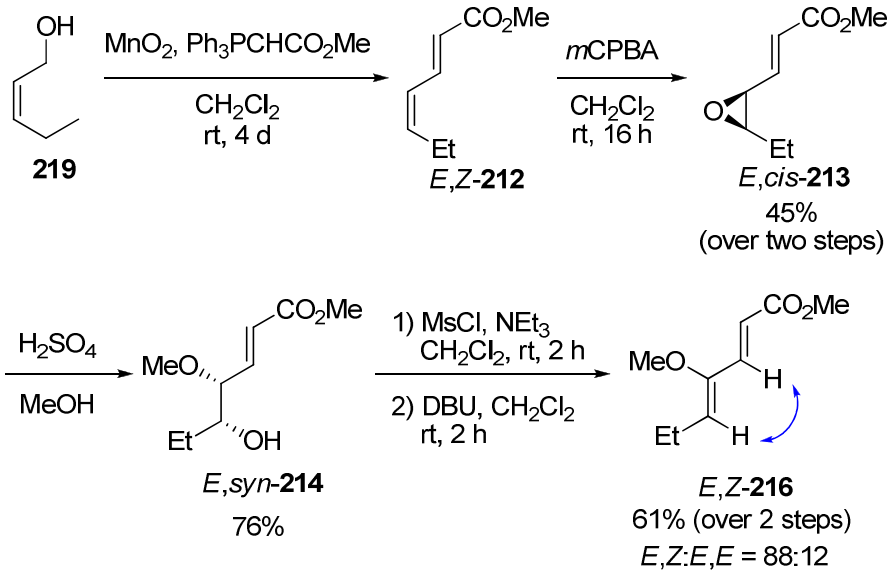
The presence of small amount of the isomeric *E*,*Z*-**216** is most likely due to a competing E1cB elimination through the intermediate carbanion **217** (Scheme 98).



Scheme 98. Possible E1cB elimination pathway causing isomerisation

4.2.3. Formation of methoxydienoate *E*,*Z*-216

To confirm the selective nature of the reaction sequence, the diastereoisomeric epoxide *E*,*cis*-**213**, available in two steps from alcohol **219**,[68] was subjected to the same conditions (Scheme 99). As expected, treating *E*,*Z*-**213** under the reaction conditions delivered the opposite isomer *E*,*Z*-**216** in good yield, although a small amount of the *E*,*E*-isomer was isolated as well. The stereochemistry was again confirmed using nOe experiments, which showed a strong correlation between H-3 and H-5. The isolation of the alternate isomer correlates with what was expected from the proposed mechanism (Scheme 97).



Scheme 99. Formation of methoxy dienoate *E*,*Z*-**216**

4.2.4. Synthesis of epoxide substrates

With a robust reaction sequence for the synthesis of methoxydienoates in hand, the substrate scope of the sequence was investigated. For this investigation a range of epoxides were required. The most common method used for their formation was the epoxidation of

the analogous diene using *m*CPBA.[66] The epoxides synthesised by this procedure are shown below (Figure 18).

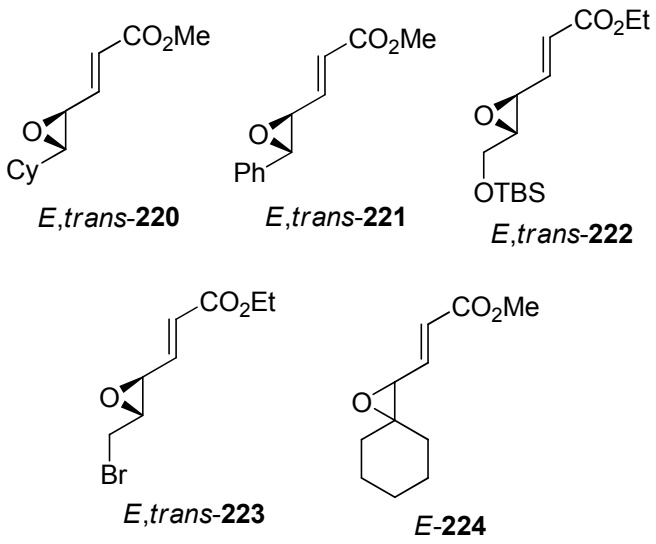
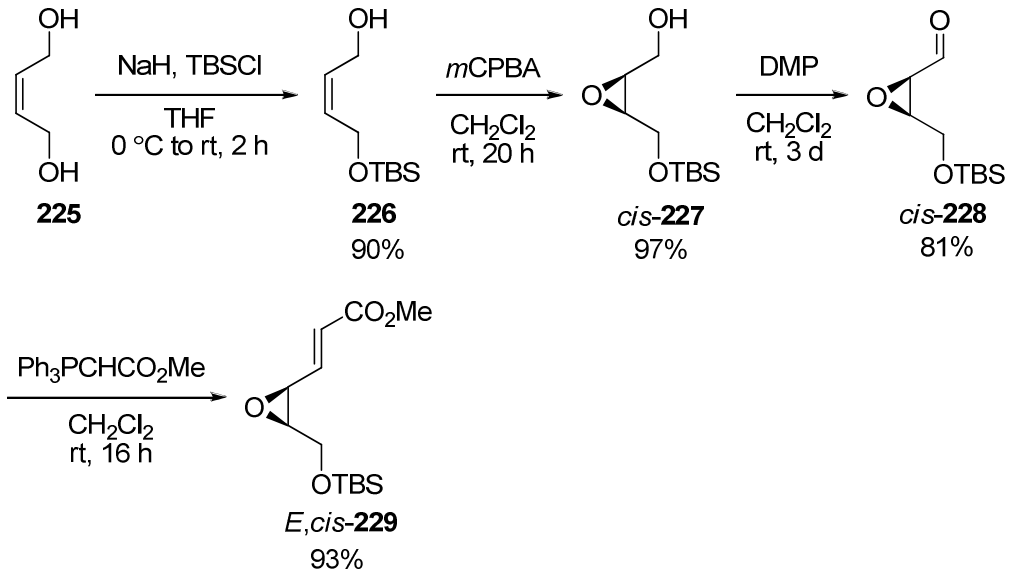


Figure 18. Synthesised epoxides for substrate scope investigation

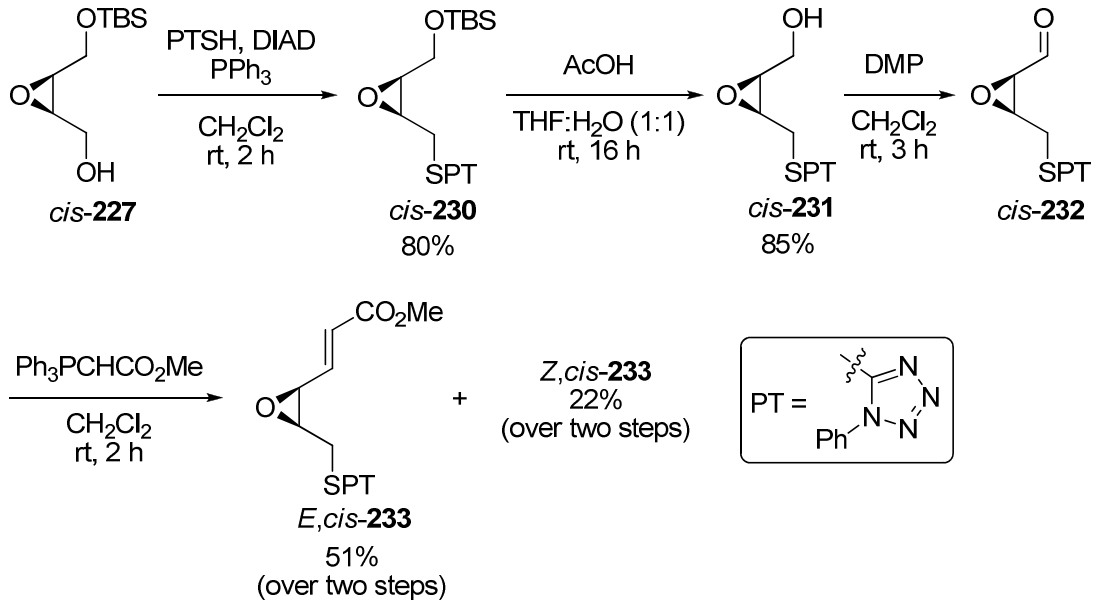
While the majority of the epoxide substrates were synthesised *via* this strategy, two substrates, *E*,*cis*-**229** and *E*,*cis*-**233**, required alternative synthetic routes. Instead of the epoxide being installed at the final stage of the synthetic sequence, it was installed earlier as shown (Schemes 100 and 101).



Scheme 100. Synthesis of epoxide *E*,*cis*-**229**

Thus epoxide *cis*-**227** was synthesised through two known reactions.[69,70] Subsequent oxidation with DMP and a Wittig olefination with methyl (triphenylphosphoranylidene)acetate then delivered the desired epoxide *E*,*cis*-**229**.

Epoxide *cis*-**227** was then used for the synthesis of sulfide epoxide *E*,*cis*-**233** (Scheme 101).



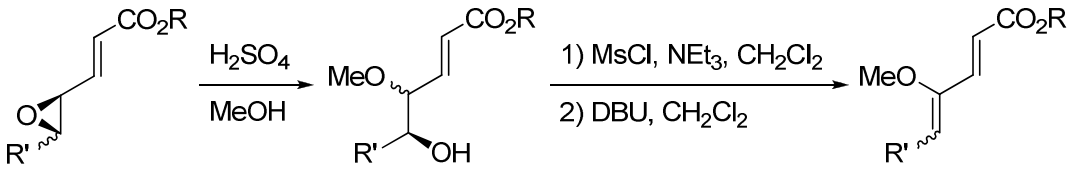
Scheme 101. Synthesis of epoxide *E*,*cis*-**233**

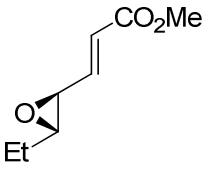
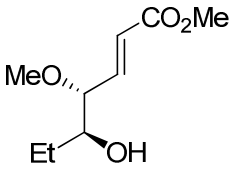
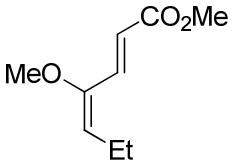
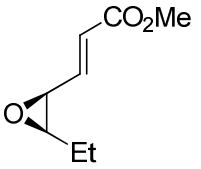
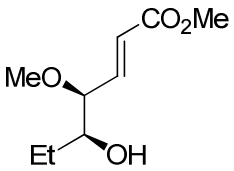
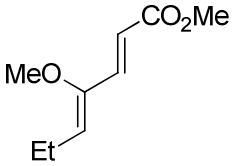
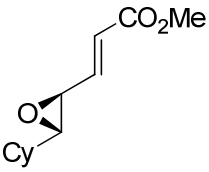
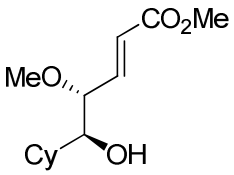
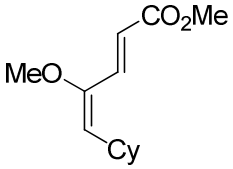
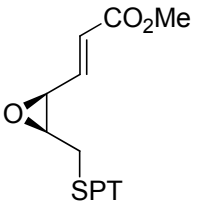
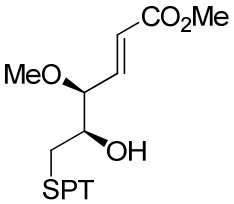
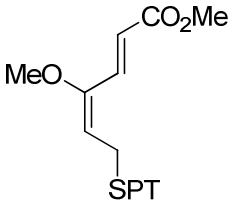
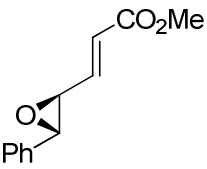
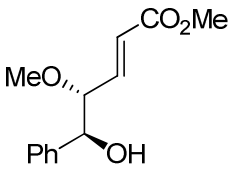
A Mitsunobu reaction to install the desired sulfide functional group proceeded in excellent yield. Deprotection with acetic acid followed by oxidation and Wittig olefination then delivered the desired epoxide *E*,*cis*-**233** in an excellent overall yield.

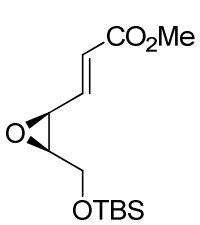
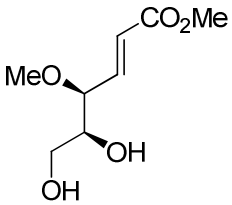
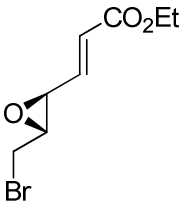
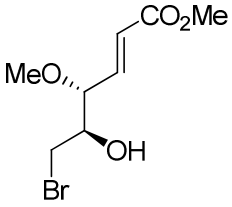
4.2.5. Investigation of substrate scope

The methodology could now be tested on all the epoxides described above and the results are shown below (Table 12).

Table 12. Substrate scope of methoxydienoate formation



Entry	Epoxide	Alcohol	Diene
i	 *E*,*trans*-**213**	 *E*,*anti*-**214** (66%, 2 h)	 *E*,*E*-**216** (76%, 5 h) *E*,*E*:*E*,*Z* = 92:8
ii	 *E*,*cis*-**213**	 *E*,*syn*-**214** (76%, 1 h)	 *E*,*Z*-**216** (61%, 2 h) *E*,*Z*:*E*,*E* = 88:12
iii	 *E*,*trans*-**220**	 *E*,*anti*-**234** (80%, 2 h)	 *E*,*E*-**235** (56%, 48 h) *E*,*E*:*E*,*Z* = 72:28
iv	 *E*,*cis*-**233**	 *E*,*syn*-**236** (72%, 1 h)	 *E*,*E*-**237** (84%, 18 h) *E*,*E*:*E*,*Z* = >95:5
v	 *E*,*trans*-**221**	 *E*,*anti*-**238** (63%, 16 h)	–

vi	 *E*,*cis*-**229**	 *E*,*syn*-**239** (33%, 0.5 h)	–
vii	 *E*,*trans*-**223**	 *E*,*anti*-**240** (80%, 15 h)	–

[a] Epoxide opening reactions were performed with a catalytic amount of H_2SO_4 in 0.1 M MeOH at rt for the indicated time.

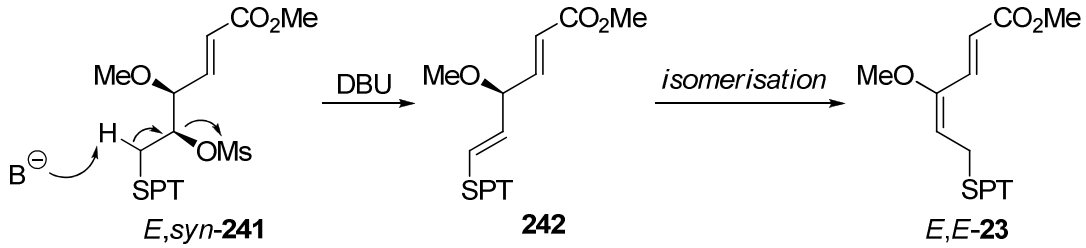
[b] Mesylation reactions were performed with MsCl (1.5 eq.) and triethylamine (3.0 eq.) in 0.1 M CH_2Cl_2 at rt for 2 h.

[c] Elimination reactions were performed with DBU (1.2 eq.) in 0.1 M CH_2Cl_2 at rt for the indicated time (the ratio of major:minor diene isomers is indicated).

4.2.7. Problems with the Elimination Procedure

As can be seen in Table 12, one of the fundamental problems with this methodology was observed in those substrates with electron-donating groups (entries i, ii, iii) which all delivered significant proportions of the minor methoxydienoate isomer.

It is also interesting to note that the sulfide substrate *E*,*cis*-**233** gave the opposite isomer to that expected (entry iv). While this anomalous result has yet to be fully investigated, an alternative mechanism for its occurrence is proposed (Scheme 102); instead of deprotonating the desired proton, the acidic α-sulfur proton is deprotonated giving diene **242** and subsequent isomerisation then delivers the methoxydienoate product *E*,*E*-**237**.



Scheme 102. Proposed mechanism of formation of *E*,*E*-**237**

Furthermore, the attempted elimination of alcohol *E*,*anti*-**238** (entry v) proved ineffective with no reaction occurring. It is believed that this lack of elimination may be due to steric hindrance caused by the Gauche interactions between the phenyl group and the α,β-unsaturated ester in the required antiperiplanar conformation of the intermediate mesylate *E*,*anti*-**243** (Figure 19).

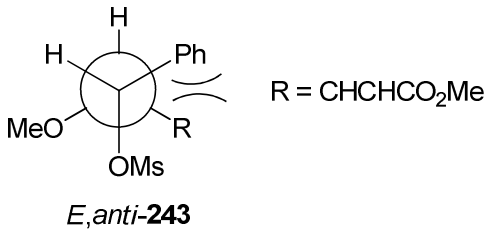


Figure 19. Steric hindrance in antiperiplanar conformation

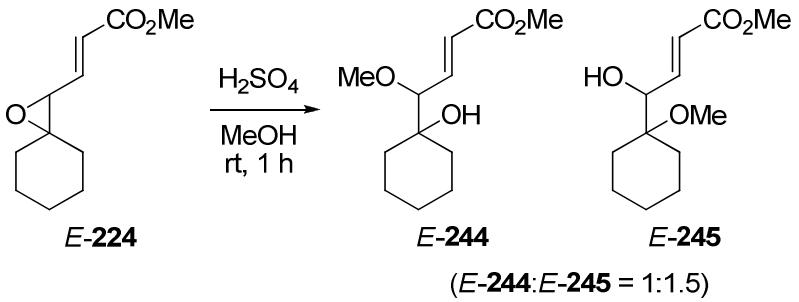
A similar unreactivity was seen with bromide alcohol *E*,*anti*-**240** (entry vii) and it is plausible that this alcohol suffers the same problem seen above with phenyl analogue *E*,*anti*-**238** (Figure 19).

Attempted optimisation of the elimination step, such as the use of different bases and increased temperatures, provided no solution to the problems outlined above.

4.2.8. Problems with Watt's Epoxide Opening Procedure

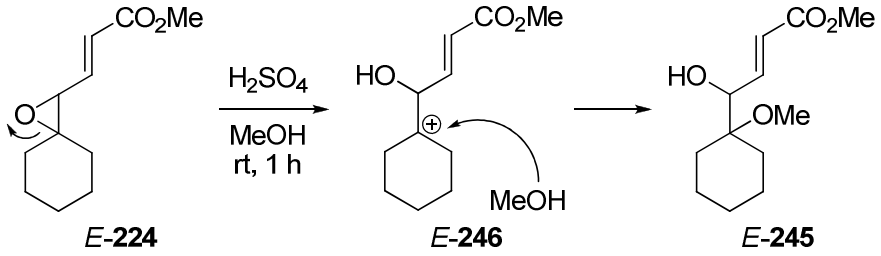
Alongside difficulties with the elimination step of the reaction sequence, further problems were experienced in the epoxide-opening step. The main problem was the incompatibility of certain substrates to the acidic conditions employed for this step. For example, under the standard conditions the TBS group of *E*,*cis*-**229** was cleaved, alongside the desired epoxide opening, to give diol *E*,*syn*-**239** (entry vi).

As well as this compatibility problem, a further problem involving the regioselectivity of the epoxide opening was observed when using cyclohexyl epoxide *E*-**224** (Scheme 103).



Scheme 103. Attempted epoxide opening of *E*-**224**

Treatment of *E*-**224** under Watt's conditions gave a mixture of two products in the ^{1}H-NMR spectrum of the unpurified material. Analysis of the ^{1}H-NMR spectrum is consistent with the formation of the unwanted regioisomer *E*-**245** through a competing S_N1 ring-opening reaction facilitated by the formation of a stabilised carbocation (Scheme 104).



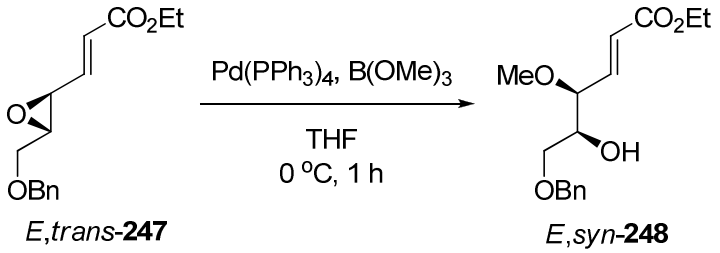
Scheme 104. Mechanism of formation of *E*-**245**

4.3. Alternative Epoxide Opening Conditions

4.3.1. Miyashita's epoxide opening conditions

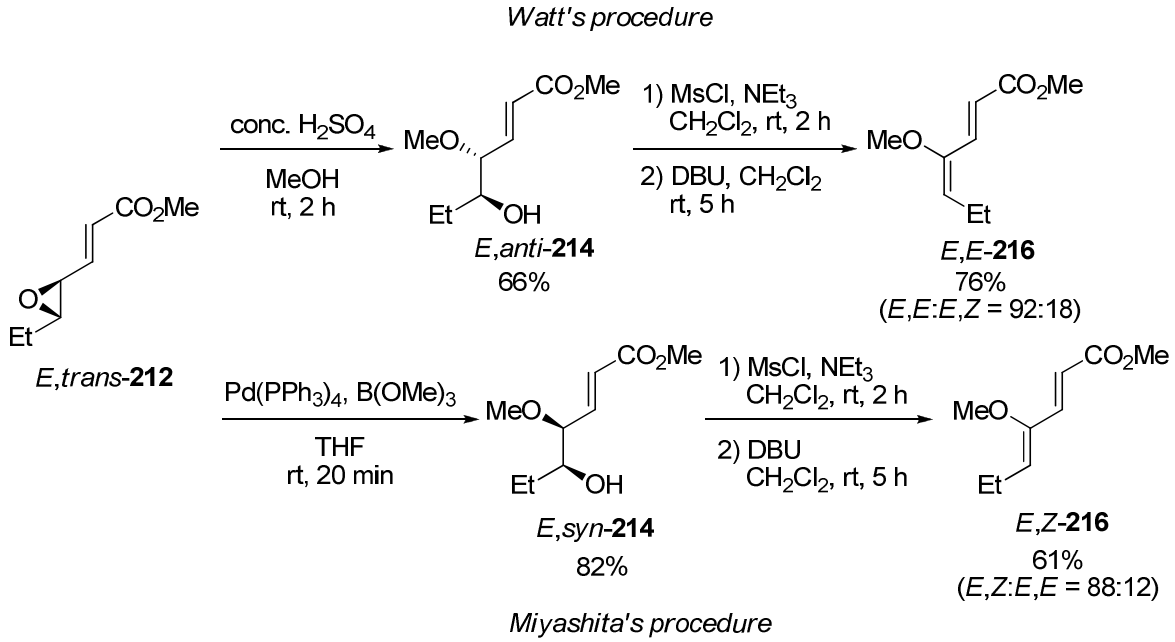
With Watt's conditions for epoxide opening proving ineffective in a number of instances, alternative methods were investigated and in fact a suitable set of conditions had been recently reported by Miyashita and co-workers.[71]

Miyashita *et al*. found that treating epoxide *E*,*trans*-**247** with $Pd(PPh_3)_4$ and $B(OMe)_3$ delivered a range of desired 1,2-methoxyalcohols **248** (Scheme 105).[71]



Scheme 105. Miyashita's palladium-catalysed epoxide opening[71]

This methodology also appears advantageous compared to Watt's methodology, since the conditions used were much milder and so should avoid the incompatibilities observed above. To confirm the utility of this methodology to the desired methoxydienoate formation, it was initially tested on epoxide *E*,*trans*-**212** (Scheme 106). The treatment of *E*,*trans*-**212** with $Pd(PPh_3)_4$ and $B(OMe)_3$ pleasingly afforded desired alcohol *E*,*syn*-**214** as a single diastereomer in excellent yield (Scheme 104). This represents a reversal in diastereoselectivity compared to that seen under the modified Watt conditions.

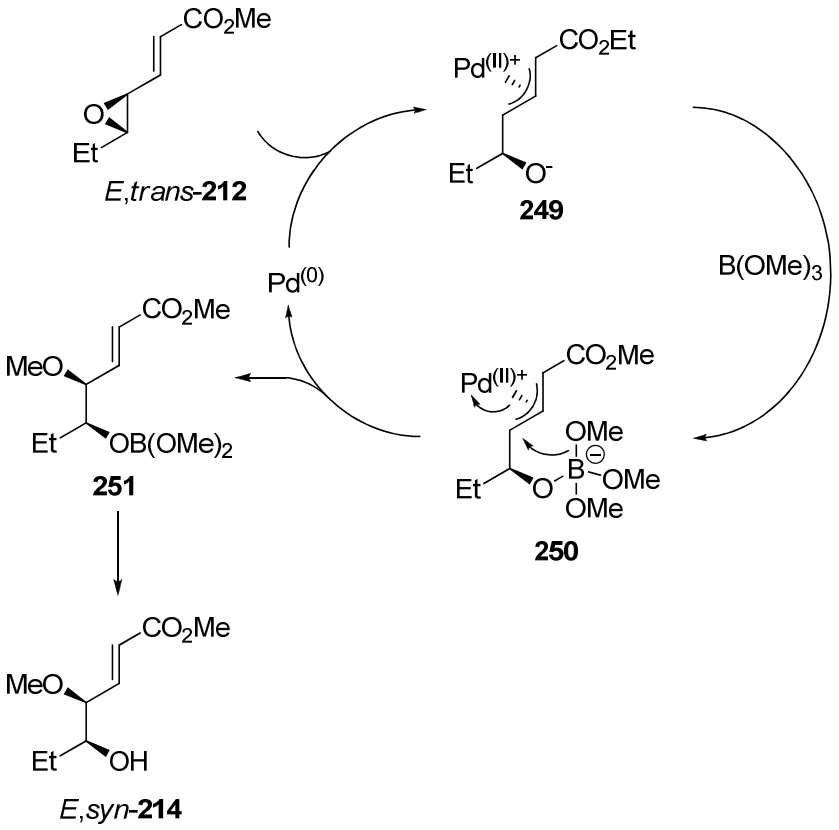


Scheme 106. Formation of enol ether *E*,*Z*-**216** using the procedure of Miyashita

This change in diastereoselectivity was then confirmed through the subsequent elimination to deliver *E*,*Z*-**216**, compared to Watt's procedure which delivered the isomeric *E*,*E*-**216**.

4.3.2. Mechanistic Discussion of Miyashita's Conditions

The change in stereoselectivity can be explained by the mechanism postulated by Miyashita *et al*. (Scheme 107).[71]



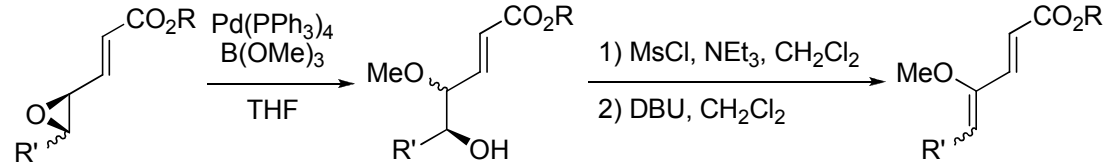
Scheme 107. Mechanism of Miyashita's epoxide opening[71]

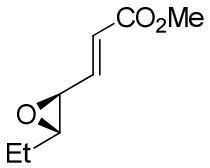
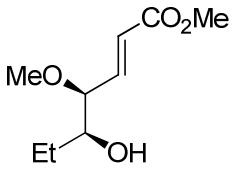
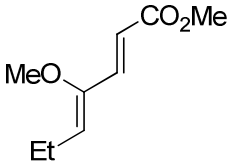
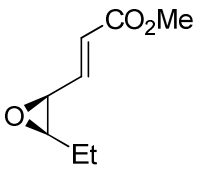
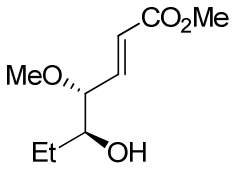
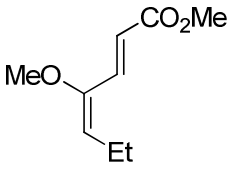
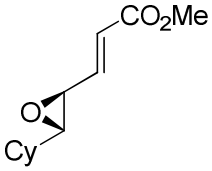
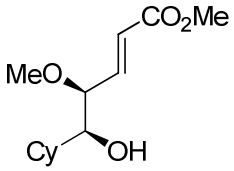
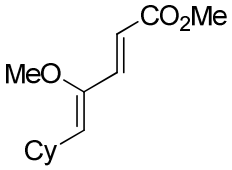
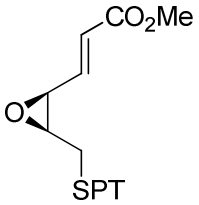
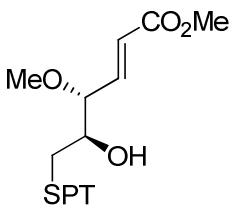
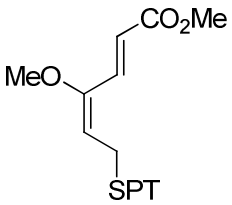
Mechanistically, the reaction resembles the Tsuji-Trost allylation procedure.[72] Initial oxidative addition of the palladium(0) species into enoate *E*,*trans*-**212** forms a η^3-π-allyl complex **249** through the ring-opening of the epoxide. Importantly, the palladium species adds from the opposite face to the epoxide, leading to inversion at the carbon centre. The free alkoxide then attacks the vacant *p*-orbital in $B(OMe)_3$ to form borate **250**. The B-O bond then attacks the η^3-π-allyl complex intramolecularly forming borate **251**, regenerating the palladium(0) catalyst. This second attack occurs from the opposite face from the palladium complex leading to double inversion of the carbon centre, compared to the single inversion seen in the modified Watt conditions (Scheme 95). Subsequent hydrolysis of borate **251** affords the desired alcohol *E*,*syn*-**214**.

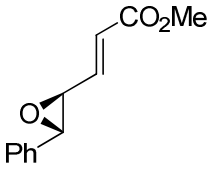
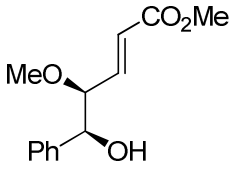
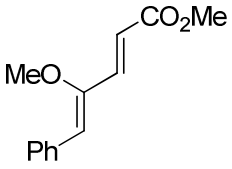
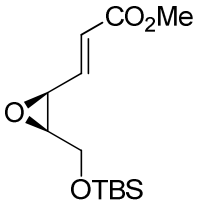
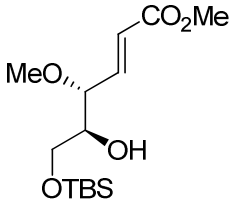
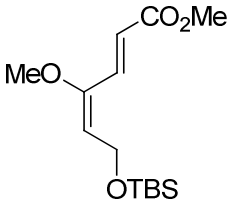
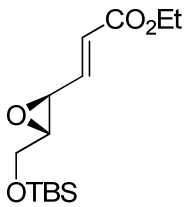
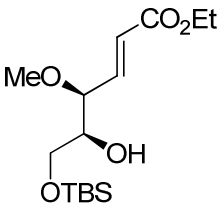
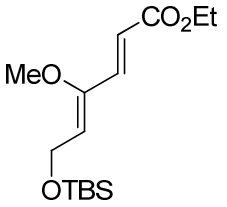
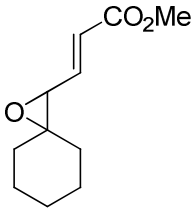
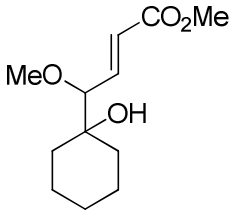
4.3.2. Substrate scope of modified Miyashita's route

With these new conditions for the epoxide opening in hand, the substrate scope of the reaction was investigated and the results detailed below in Table 13.

Table 13. Substrate scope of methoxy dienoate formation using Miyashita's epoxide opening conditions



Entry	Epoxide	Alcohol	Diene
i	 *E*,*trans*-**213**	 E,*syn*-**214** (82%, 1 h)	 *E*,*Z*-**216** (61%, 2 h) *E*,*Z*:*E*,*E* = 88:12
ii	 *E*,*cis*-**213**	 *E*,*anti*-**214** (80%, 1 h)	 *E*,*E*-**216** (76%, 2 h) *E*,*E*:*E*,*Z* = 92:8
iii	 *E*,*trans*-**220**	 E,*syn*-**234** (70%, 1 h)	 *E*,*Z*-**235** (62%, 2 h) *E*,*Z*:*E*,*E* = 83:17
iv	 *E*,*cis*-**233**	 *E*,*anti*-**236** (52%, 2 h)	 *E*,*E*-**237** (84%, 7 h) *E*,*E*:*E*,*Z* = >95:<5

v	 *E*,*trans*-**221**	 E,*syn*-**238** (84%, 1 h)	 *E*,*Z*-**252** (72%, 2 h) *E*,*E*:*E*,*Z* = >95:<5
vi	 *E*,*cis*-**229**	 *E*,*anti*-**253** (82%, 1 h)	 *E*,*E*-**254** (90%, 2 h) *E*,*E*:*E*,*Z* = >95:<5
vii	 *E*,*trans*-**222**	 *E*,*syn*-**235** (57%, 1 h)	 *E*,*Z*-**256** (69%, 2 h) *E*,*Z*:*E*,*E* = >95:<5
viii	 *E*-**224**	 *E*-**244** (38%, 2 h)	–

[a] Epoxide opening reactions were performed with $Pd(PPh_3)_4$ (10 mol%) and $B(OMe)_3$ (1.2 eq.) in THF (0.2 M) at rt for the indicated time.

[b] Mesylation reactions were performed with MsCl (1.5 eq.) and triethylamine (3.0 eq.) in 0.1 M CH_2Cl_2 at rt for 2 h.

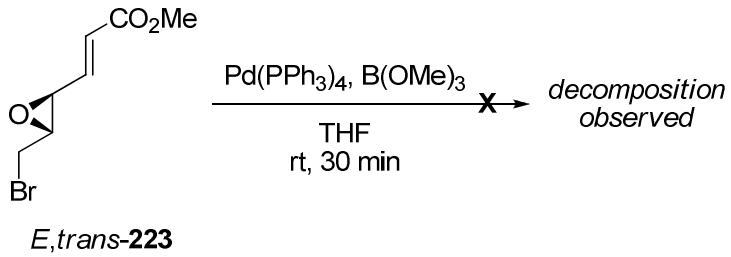
[c] Elimination reactions were performed with DBU (1.2 eq.) in 0.1 M CH_2Cl_2 at rt for the indicated time.

4.3.3. Discussion of Epoxide Opening Step

As can been seen from Table 13, the scope of epoxide substrates successfully converted into the intermediate alcohols by Miyashita's methodology was increased compared to Watt's methodology (Table 12).

The regioselectivity problems previously observed with *E*-**224** (Scheme 103), were not seen under Miyashita's conditions. This observation indicates that there is no competing mechanistic pathway for opening the epoxide under this set of conditions. Furthermore, acid-sensitive substrates *E*,*trans*-**222** and *E*,*cis*-**229** were both successfully converted into their analogous alcohols in good yield (entries vi and vii). This compares favourably with the incompatibility of these substrates with Watt's conditions (Table 12, entry vi).

With only one substrate was a problem encountered with this methodology, namely bromide *E*,*trans*-**223**. Treatment of *E*,*trans*-**223** under the standard conditions delivered a complex mixture of products from which no discernible product could be isolated or identified (Scheme 108). It is thought that the palladium(0) species may be inserting into the C-Br bond, starting a series of side-reactions that prevent the formation of the desired alcohol.



E,*trans*-**223**

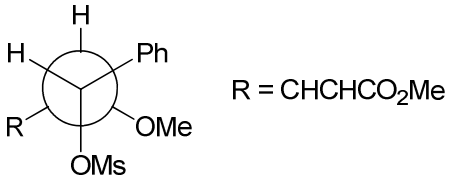
Scheme 108. Attempted epoxide opening of *E*,*trans*-**223** under Miyashita's conditions

It should also be noted that not only is the scope of Miyashita's conditions improved compared to Watt's conditions, they also generally give the alcohol intermediates in a greater yield; for example, under Watt's conditions, ethyl epoxide *E*,*trans*-**213** was converted into alcohol *E*,*anti*-**214** in a 66% yield (Table 12, entry i) and under Miyashita's conditions *E*,*trans*-**213** was converted into alcohol *E*,*anti*-**214** in a 82% yield.

4.3.4. Discussion of elimination step

In most cases the elimination occurred as previously seen (Table 12). However, it was found that phenyl alcohol *E*,*syn*-**238** eliminated cleanly to give the desired methoxydienoate (*E*,*Z*-**252**) in good yield (entry v), whereas its diastereomer, *E*,*anti*-**238** failed to undergo this elimination (Table 12, entry v). An explanation for this observation may be that the gauche interactions seen in *E*,*anti*-**243** (Figure 19) being relieved in

E,*syn*-**243** allowing the mesylate and hydrogen to sit in the required antiperiplanar relationship (Figure 20).



E,*syn*-**243**

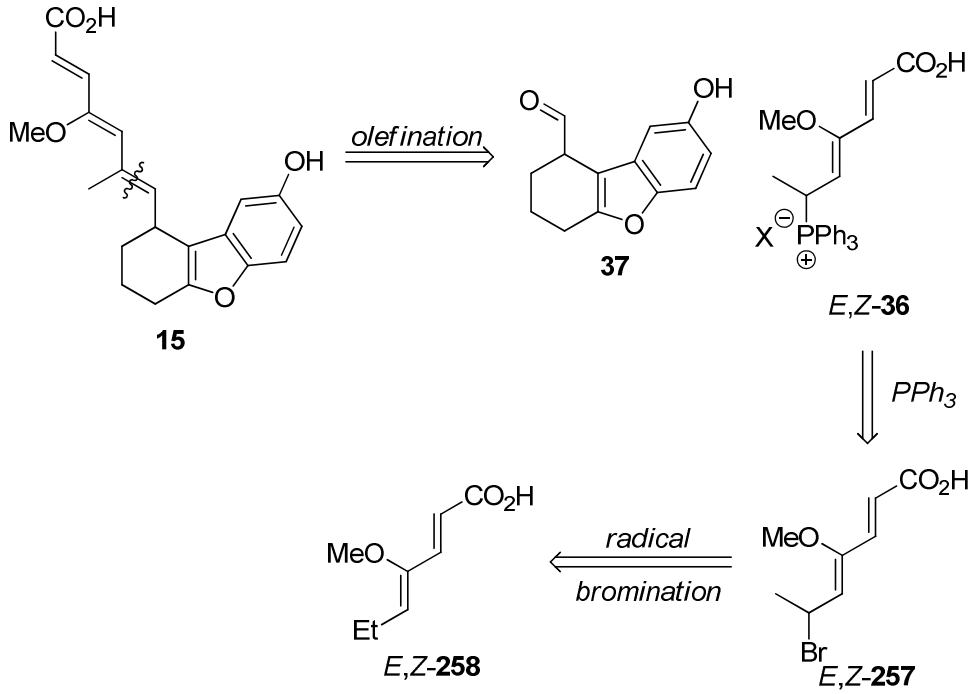
Figure 20. Antiperiplanar conformation of *E*,*syn*-**243**

Intriguingly, the attempted elimination of cyclohexyl alcohol *E*-**244** proved ineffective under a variety of conditions and no reasons for this lack of reactivity have yet been identified.

4.4. Attempted Synthesis of Olefination Reagents

4.4.1. Retrosynthesis of phosphonium salt *E*,*Z*-36

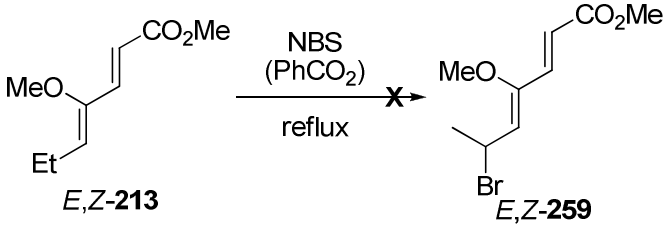
With two sets of complementary methodology for the formation of methoxydienoates now developed, attention turned to using these methodologies to form the desired phosphonium salt *E*,*Z*-**36** required for the total syntheses of JBIR-23 (**1**) and 24 (**24**) and cuevaene A (**15**) (Scheme 109). It was envisioned that phosphonium salt *E*,*Z*-**36** could itself be synthesised from bromide *E*,*Z*-**257** through nucleophilic displacement with triphenylphosphine (Scheme 109).



Scheme 109. Retrosynthesis of cuevaene A (**15**) and phosphonium salt *E*,*Z*-**36**

4.4.2. Attempted radical bromination approach

Since it has already been shown that the synthesis of bromo-methoxydienoates is problematic (Table 12, entry vii and Scheme 108), it was thought that bromide *E*,*Z*-**255** could be accessed directly from ethyl methoxydienoate *E*,*Z*-**258** through a radical bromination reaction. Unfortunately, the attempted bromination of *E*,*Z*-**213** (Scheme 110) was unsuccessful under a variety of conditions (such as NBS, $(PhCO_2)_2$) and so an alternative approach was needed.

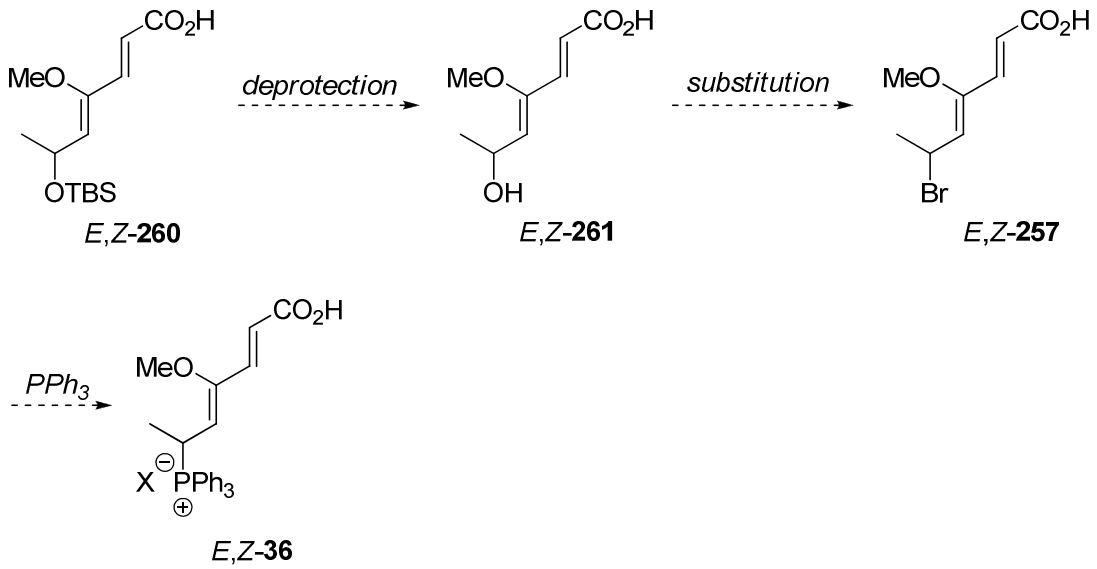


Scheme 110. Attempted radical bromination of methoxydienoate *E*,*Z*-**213**

4.4.3. Proposed conversion of alcohol *E*,*Z*-252 to phosphonium salt *E*,*Z*-36

The next approach considered was to convert TBS-protected *E*,*Z*-**260**, known to be compatible with the developed methodology, into phosphonium salt *E*,*Z*-**36** *via*

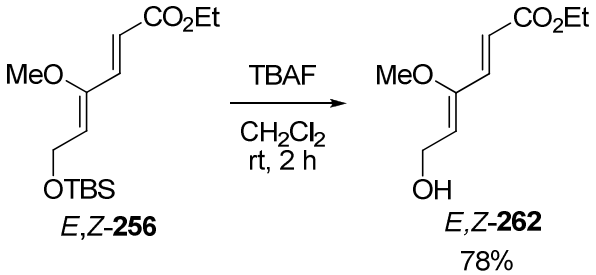
deprotection followed by conversion of the resultant alcohol into bromide *E*,*Z*-**257** and then phosphonium salt *E*,*Z*-**36** (Scheme 111). There are also methods described in literature of converting alcohols directly into their phosphonium salt analogues, avoiding the need for an extra step in the synthesis. Since the synthesis of the demethylated analogue of *E*,*Z*-**259** had already been completed (Table 13, entry vii), the proposed synthetic sequence was tested using this model substrate *E*,*Z*-**256**.



E,*Z*-**260** *E*,*Z*-**261** *E*,*Z*-**257** *E*,*Z*-**36**

Scheme 111. Proposed synthesis of phosphonium *E*,*Z*-**36** from TBS-protected *E*,*Z*-**260**

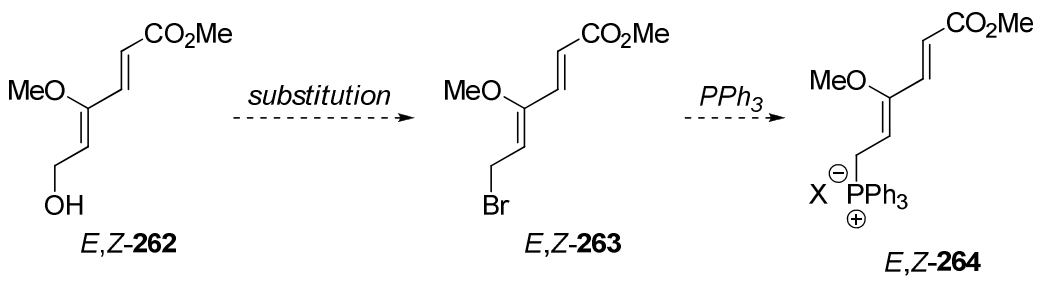
The initial step of the proposed route was the cleavage of the silyl protecting group (Scheme 112).



E,*Z*-**256** *E*,*Z*-**262** 78%

Scheme 112. Deprotection of TBS-protected *E*,*Z*-**256**

Pleasingly, treatment of *E*,*Z*-**256** with TBAF successfully deprotected the TBS group and delivered free alcohol *E*,*Z*-**262** in good yield. Now with a robust route to *E*,*Z*-**262** in hand, the transformation of the alcohol into bromide *E*,*Z*-**263** or phosphonium *E*,*Z*-**264** could be investigated (Scheme 113).



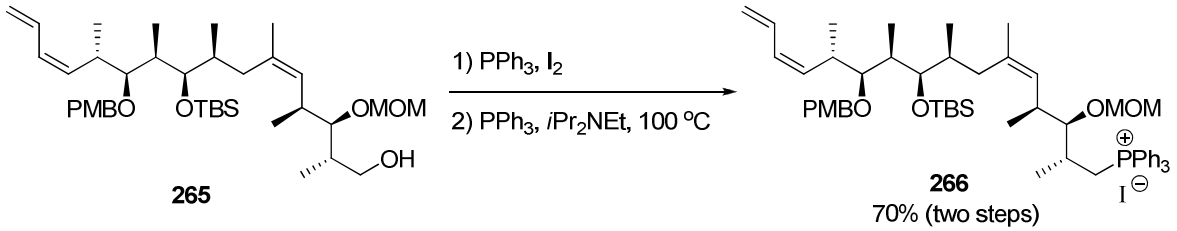
E,*Z*-**262** *E*,*Z*-**263** *E*,*Z*-**264**

Scheme 113. Proposed synthesis of phosphonium salt *E*,*Z*-**264**

4.4.4. Literature examples of converting primary alcohols into phosphonium salts

The most common method of transforming primary alcohols into their corresponding phosphonium salts in the literature is to initially convert the alcohol into an intermediate iodide or bromide. Once in hand, these halides can be converted into the desired phosphonium salt by heating with triphenylphosphine.

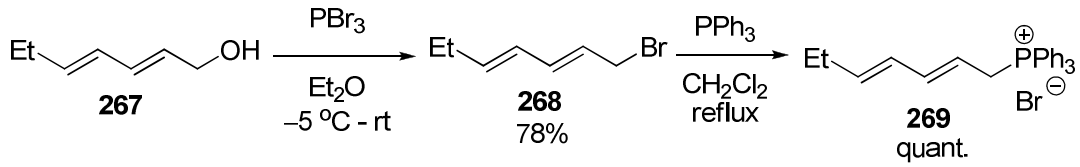
For example, Smith's group utilised this strategy in their synthesis of (+)-discodermolide (Scheme 114).[73] They initially converted alcohol **265** into the corresponding iodide, under Appel conditions, and its subsequent treatment with triphenylphosphine delivered desired phosphonium salt **266** in good yield over the two steps.



265 **266** 70% (two steps)

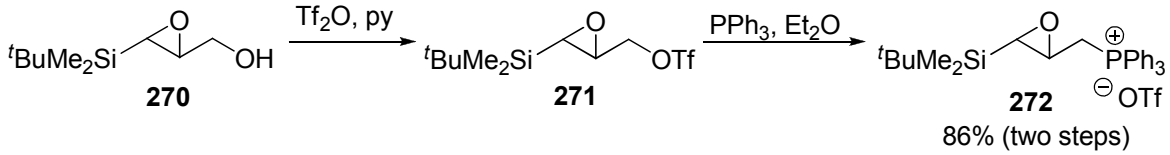
Scheme 114. Smith's conversion of alcohol **265** into phosphonium salt **266** *via* an intermediate iodide[73]

Intermediate bromides can also be used, as shown by Koskinen and co-workers in the synthesis of amaminol A (Scheme 115).[74] Alcohol **267** was converted into bromide **268** using phosphorus tribromide. Bromide **268** was in turn transformed into the desired phosphonium salt **269** by heating with triphenylphosphine.



Scheme 115. Koskinen's conversion of alcohol **267** into phosphonium salt **269** *via* an intermediate bromide **268**[74]

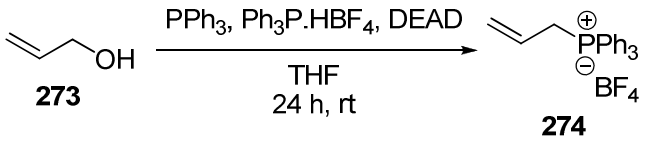
Another two step method was described by Takeda *et al*. in 2006 (Scheme 116).[75] Rather than isolate the corresponding halide, they instead isolated the intermediate triflate **271**. Displacement of the triflate with triphenylphosphine then afforded the desired phosphonium salt **272** in excellent yield over two steps.



Scheme 116. Takeda's covnersion of alcohol **270** into phosphonium salt **272** *via* an intermediate triflate **271**[75]

While the transformation of alcohols to phosphonium salts is generally performed *via* a two-step method, such as those described above, a few reports discussing one-step methods of completing this conversion have also been published.

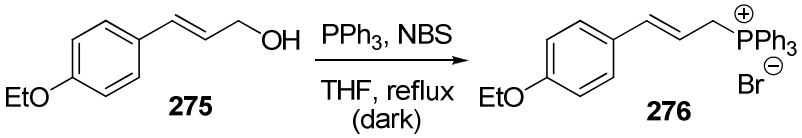
The first, described by Mazurkiewicz's and co-workers, using a modified Mitsunobu reaction to effect this conversion (Scheme 117).[76]



Scheme 117. Mazurkiewicz's one step conversion of alcohols into phosphonium salts[76]

The Mitsunobu reaction requires the presence of an acidic proton to activate DEAD. Mazurkiewicz uses the tetrafluoroborate salt of triphenylphosphine to act as both the nucleophile and the source of acidic protons, allowing the transformation of primary alcohols to the corresponding phosphonium salt in one step; for example allylic alcohol **273** was efficiently converted in 57% yield into the analogous phosphonium salt **274**.

Another example was reported in 2008 by Aitken's group in the synthesis of microclerodermins C, D and E (Scheme 118).[77]



Scheme 115. Aitken's one pot transformation of alcohol **275**[77]

Aitken found that treatment of allylic alcohol **275** with triphenylphosphine and *N*-bromosuccinimide in THF at reflux in the absence of light, delivered the required phosphonium salt **276** in a good yield. While there is no discussion of the reaction mechanism in the paper, presumably, the reaction goes through the intermediate bromide which is then converted *in situ* into the desired phosphonium salt **276**.

4.4.5. Attempted conversion of alcohol *E*,*Z*-262 into phosphonium salt *E*,*Z*-264

With alcohol *E*,*Z*-**262** in hand, the transformation into phosphonium salt *E*,*Z*-**264** was attempted using the literature methods described above (Table 14). Unfortunately, under a range of the reported conditions only decomposition was observed in the ^{1}H-NMR spectra of the unpurified material. Therefore, this synthetic route toward phosphonium salt *E*,*Z*-**264** was abandoned.

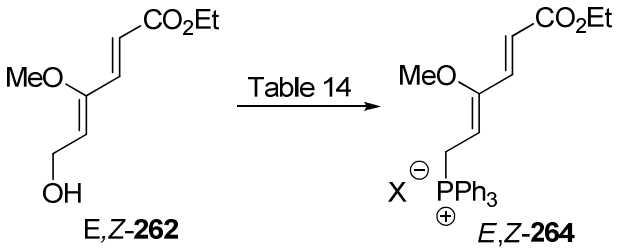
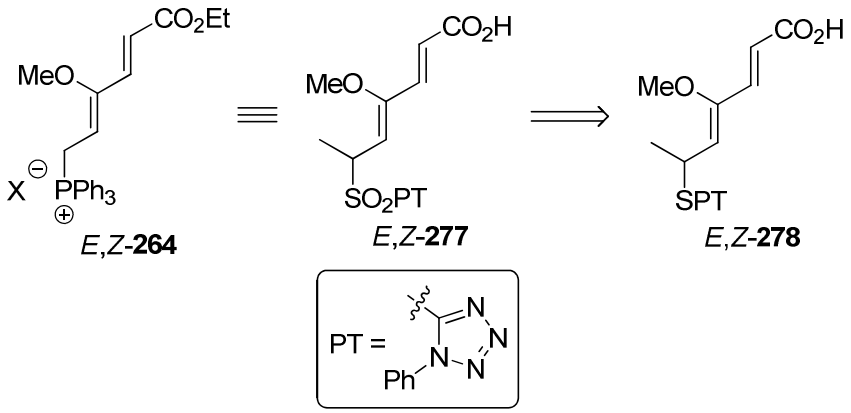


Table 14. Conditions used for the attempted conversion of alcohol *E*,*Z*-**262**

Entry	Conditions	Yield (%)
i	PPh_3, PPh_3.HBr, DEAD	Decomposition
ii	PPh_3, NBS	Decomposition
iii	MsCl, NEt_3 then PPh_3	Decomposition
iv	CBr_4, PPh_3	Decomposition
v	MsCl, NEt_3 then NBS	Decomposition

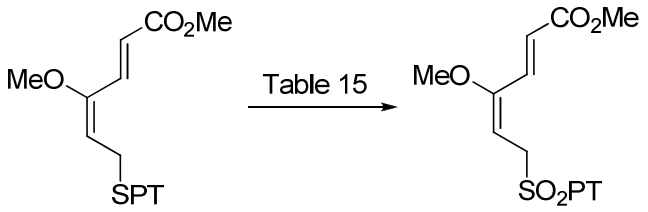
4.4.6. Attempted synthesis of Julia reagents

With access to phosphonium salt *E*,*Z*-**36** proving difficult it was decided to synthesise an alternative olefination reagent, namely sulfone *E*,*Z*-**277** (Scheme 119).



Scheme 119. Sulfone equivalent of phosphonium salt *E*,*Z*-**36**

It was hoped that sulfone *E*,*Z*-**277** could be accessed through the oxidation of sulfide *E*,*Z*-**278**. As with the TBS-protected analogue previously discussed, the demethylated analogue of sulfide *E*,*Z*-**278** has already been synthesised (Table 13, entry iv), although as the geometric isomer *E*,*E*-**237**. Unfortunately, the attempted oxidation of sulfide *E*,*E*-**237** under a variety of conditions proved ineffective, with only decomposition observed (Table 15).



E,*E*-**237** *E*,*E*-**279**

Table 15. Attempted oxidation of sulfide *E*,*E*-**237** to sulfone *E*,*E*-**279**

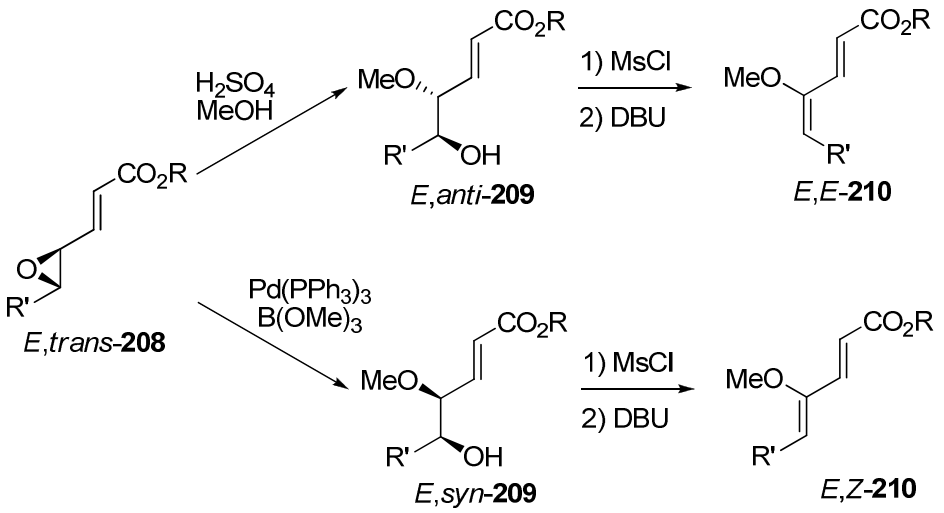
Entry	Conditions	Yield
1	*m*CPBA, CH_2Cl_2	Decomposition
2	H_2O_2	Decomposition
3	$NaIO_4$, CH_2Cl_2	Decomposition

It is postulated that the methyl enol ether moiety within the methoxydienoate products is relatively unstable and it may be this instability causing the decomposition of the products when further reactions are attempted. Alternatively, the oxidation of the enol ether may occur preferentially.

4.5. Summary and Future Work

4.5.1. Summary

In summary, two complementary stereoselective methodologies for the synthesis of 4-methoxypentadienoates **210** from γ,δ-epoxydienoates **208** have been developed. The first, based off a report by Watt, uses an acid-promoted epoxide-opening and the second uses a palladium-catalysed epoxide opening originally reported by Miyashita. The intermediate alcohol can then mesylated and subjected to a DBU-promoted elimination (Scheme 120).



Scheme 120. The two methodologies for the synthesis of 4-methoxypentadienoates **210**

The two strategies deliver complementary isomers of the methoxydienoate product **210**, determined by their mechanism. The methodology based on Watt's report proceeds with a single inversion of the C-4 centre while that based on Miyashita's method proceeds with double inversion. Overall, due to an increase in substrate scope and yields, Miyashita's palladium-catalysed methodology would seem to be the better of the two strategies in the majority of cases.

Unfortunately, as of yet, the syntheses of the desired phosphonium salt *E*,*Z*-**36** or sulfone *E*,*Z*-**277** have yet to be successful, with the manipulation of the methoxydienoate products proving difficult.

4.5.2. Future work

Future work should first focus on the installation of either the phosphonium salt or sulfone prior to the epoxide-opening, elimination methodology described in this Chapter. Therefore the initial targets would be epoxides *E*-**280** and *E*-**281** (Figure 21).

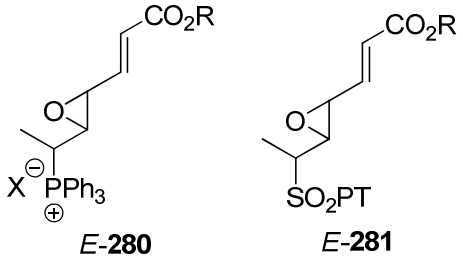
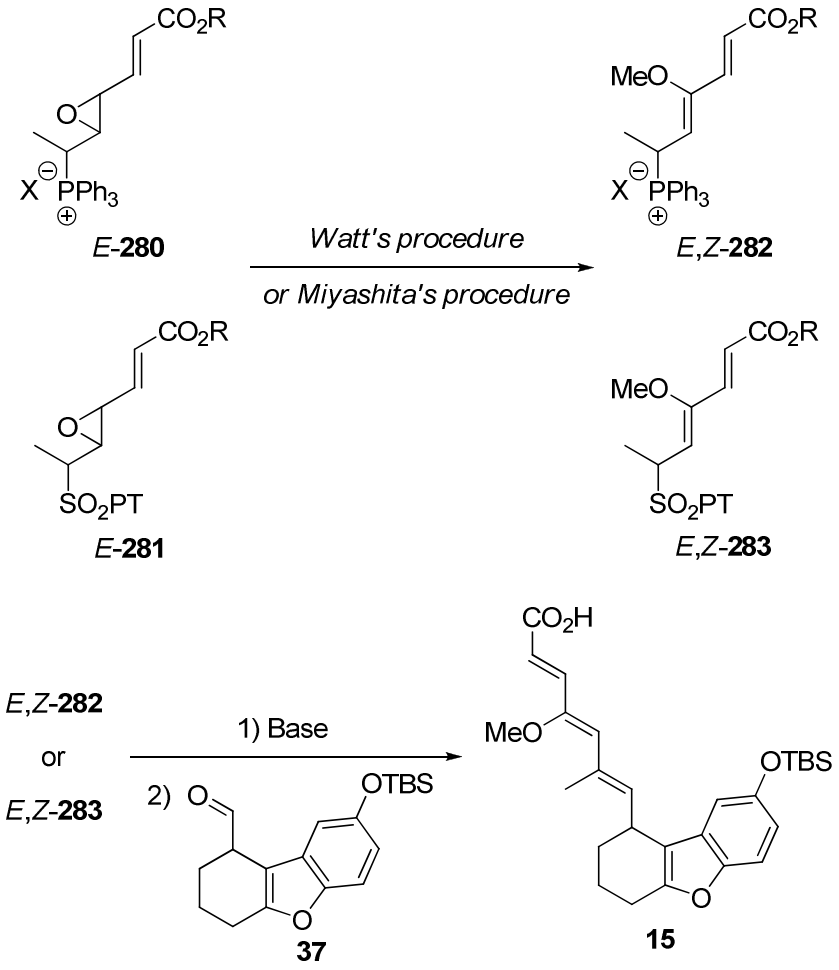


Figure 21. Potential targets for future work

Once the synthesis of these compounds is completed, they can be subjected to the methodology described in this Chapter. If successful then the subsequent dienes *E,Z*-**282** and *E,Z*-**283** can then be used to attempt the desired late-stage olefination with aldehyde **37** to complete the carbon skeleton of cuevaene A (**15**) or JBIR-23 (**1**) (Scheme 121).



Scheme 120. Possible future synthesis of **15**

The work discussed in this Chapter was recently the subject of a publication.[89]

Chapter 5. Experimental

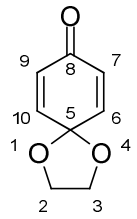
5.1. General Experimental

Except where stated, all reagents were purchased from commercial sources and used without further purification, and all experimental procedures were carried out under an atmosphere of argon. Anhydrous CH_2Cl_2, Et_2O, DMF, MeCN and toluene were obtained from an Innovative Technology Inc. PureSolv® solvent purification system. Anhydrous THF was obtained by distillation over sodium benzophenone immediately before use. Except where stated, triethylamine refers to anhydrous triethylamine purchased from commercial sources. DMP was prepared using the procedure described by Boeckmann *et al*.[78] ^{1}H NMR and ^{13}C NMR were recorded on a JEOL ECX400 or JEOL ECS400 spectrometer, operating at 400 MHz and 100 MHz, respectively or a Bruker DRX500 spectrometer, operating at 500 MHz and 125 MHz respectively. All spectral data was acquired at 295 K. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peak, δ_H 7.26 and δ_C 77.0 for $CDCl_3$ and δ_H 3.31 and δ_C 49.0 for CD_3OD was used as a reference. Coupling constants (*J*) are reported in Hz to the nearest 0.1 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet. Signal assignment was achieved by analysis of DEPT, COSY, NOESY, HMBC and HSQC experiments where required. Infrared (IR) spectra were recorded on a ThermoNicolet IR-100 spectrometer with NaCl plates as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. Mass-spectra (low and high-resolution) were obtained by the University of York Mass Spectrometry Service, using electrospray ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer. CHN elemental analyses were performed by the University of York CHN service and were determined using an Exeter Analytical CE440 Elemental Analyser. Melting points were determined using Gallenkamp apparatus and are uncorrected. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$ pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with either basic aqueous potassium permanganate or ethanolic *p*-anisaldehyde as appropriate. Flash column chromatography was carried out using slurry packed Fluka silica gel (SiO_2), 35-70 μm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Petrol refers to petroleum ether 40 - 60 °C. The naming of compounds conforms to IUPAC rules throughout. The numbering of compounds is for characterisation purposes and, while it

conforms to IUPAC where possible, it may vary from the numbering in the compound name.

5.2. Experimental Procedures and Product Characterisation for Chapter 2

1,4-Dioxaspiro[4.5]deca-6,9-dien-8-one, 49



To a stirred suspension of phenyliodonium ditrifluoroacetate (4.50 g, 10.5 mmol) in ethylene glycol (40 mL) at rt was added, *via* cannula, a solution of 4-methoxyphenol (**72**) (1.00 g, 8.06 mmol) in CH_2Cl_2 (5 mL) and ethylene glycol (5 mL). After 20 min, the reaction mixture was quenched with $NaHCO_3$ (sat. aq. solution, 50 mL). After a further 10 min, the resultant solution was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a dark yellow oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford monoketal **49** (1.12 g, 91%) as a yellow solid.

Mp: 50 – 51 °C (Lit.[28] 54 °C);

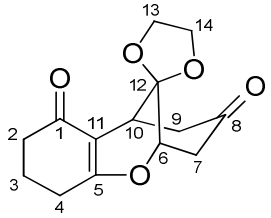
***R*$_f$ (SiO_2, 3:2 Et_2O:petrol):** 0.33;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 4.14 (4 H, s, H-2 and H-3), 6.16 (2 H, d, *J* 10.0 Hz, H-7 and H-9), 6.62 (2 H, d, *J* 10.0 Hz, H-6 and H-10).

Obtained data in accord with those reported in the literature.[28]

Lab. Notebook Reference: PC/1/63.

6',8',9',10'-Tetrahydro-2'*H*-spiro[1,3-dioxolane-2,11'-[2,6]methano[1]benzoxocine]-4',7'(3'*H*,5'*H*)-dione, 77[23]



To a stirred solution of quinone **49** (11.9 g, 78.2 mmol) in ^{t}BuOH (280 mL) at 50 °C (under an air atmosphere) was added cyclohexa-1,3-dione (12.3 g, 109.5 mmol), followed by ^{t}BuOK (1 M solution in ^{t}BuOH, 27.4 mL, 27.4 mmol). The resulting brown solution was stirred at 50 °C for 16 h. The reaction mixture was cooled to rt and quenched with HCl (10% aq. solution, 100 mL) and diluted with CH_2Cl_2 (300 mL) and H_2O (100 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (300 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude ketone **77** as a brown oil. The crude material was usually used immediately in the next reaction without further purification.

***R*$_f$ (SiO_2, 1:1 CH_2Cl_2:EtOAc):** 0.30;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.92 – 2.01 (2 H, m, H-3), 2.31 – 2.44 (4 H, m, H-2 and H-4), 2.48 (1 H, td, *J* 2.7, 15.7 Hz, H-7a), 2.65 (1 H, td, *J* 2.5, 17.0 Hz, H-9a), 2.92 (1 H, dd, *J* 4.5, 17.0 Hz, H-9b), 2.94 (1 H, dd, *J* 4.4, 15.7 Hz, H-7b), 3.09 – 3.13 (1 H, m, H-10), 4.09 – 4.18 (4 H, m, H-13 and H-14), 4.35 (1 H, ddd, *J* 2.3, 3.2, 4.4 Hz, H-6);

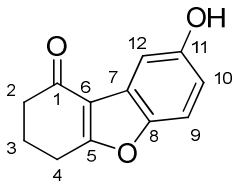
MS (ESI): 265 $[MH]^+$, 287 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{14}H_{16}O_5$, 265.1071. Found: $[MH^+]$, 265.1074 (1.2 ppm error).

Obtained data in accord with those reported in the literature.[23]

Lab. Notebook Number: PC/7/6.

8-Hydroxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2H)-one, 71[23]



To a stirred solution of the crude ketone **77** (78.2 mmol, 100% purity assumed from previous reaction) in dioxane (400 mL) at rt (under an air atmosphere) was added HCl (6 M aq. solution, 200 mL). The resulting solution was stirred at rt for 5 d. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (200 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a white solid. The crude material was purified by flash column chromatography (SiO_2, 4:1 CH_2Cl_2:EtOAc) to afford ketone **71** (15.4 g, 95% from **49**) as a white solid.

Mp: 154 – 156 °C (Lit.[23] 156 – 157 °C);

***R*f (4:1 CH_2Cl_2:EtOAc)** 0.36;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.24 – 2.32 (2 H, m, H-3), 2.64 (2 H, dd, *J* 5.7, 7.3 Hz, H-4), 3.03 (2 H, t, *J* 6.3 Hz, H-2), 6.87 (1 H, dd, *J* 2.7, 8.8 Hz, H-10), 7.34 (1 H, d, *J* 8.8 Hz, H-9), 7.81 (1 H, d, *J* 2.7 Hz, H-12);

^{13}C-NMR (100 MHz, CD_3OD): δ_C 22.3 (C-3), 23.3 (C-4), 37.3 (C-2), 106.0 (C-12), 111.1 (C-9), 113.0 (C-10), 115.8 (C-6), 124.3 (C-8), 149.0 (C-7), 154.6 (C-5), 172.9 (C-11), 196.3 (C-1);

MS (ESI): 203 $[MH]^+$;

HRMS (ESI): Calculated for $C_{12}H_{11}O_3$, 203.0703. Found: $[MH]^+$, 203.0705 (1.0 ppm error);

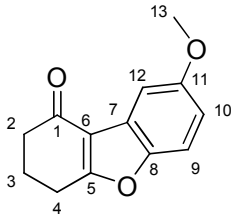
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3280, 2924, 2853, 1642, 1581, 1539, 1462, 1390, 1256, 1225, 1068;

Microanalysis: Found C, 71.1; H, 4.98%. $C_{12}H_{10}O_3$ requires C, 71.3; H, 4.98%.

Obtained data in accord with those reported in the literature.[23]

Lab. Notebook Number: PC/7/8.

8-Methoxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2H)-one, 85



To a stirred solution of benzofuran **71** (5.20 g, 25.7 mmol) in THF (200 mL) and MeOH (5 mL) at 0 °C was added portionwise NaH (60% w/w in mineral oil, 1.44 g, 36.0 mmol). Once bubbling had ceased, methyl iodide (3.2 mL, 51.4 mmol) was added. After 7 h, additional NaH (60% w/w in mineral oil, 720 mg, 18.0 mmol) was added portionwise, followed by methyl iodide (1.6 mL, 25.7 mmol). The reaction mixture was stirred at rt for a further 16 h and then quenched with NH_4Cl (sat. aq. solution, 100 mL). The resulting suspension was separated between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to deliver a light brown solid. The crude material was purified by flash column chromatography (SiO_2, 9:1 CH_2Cl_2:EtOAc) to deliver ketone **85** (5.11 g, 92%) as a white solid.

Mp: 94 – 95 °C;

***R*$_f$ (SiO$_2$, 1:1 petrol:Et$_2$O):** 0.26;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 2.22 – 2.31 (2 H, m, H-3), 2.57 – 2.62 (2 H, m, H-2), 3.02 (2 H, t, *J* 6.3 Hz, H-4), 3.87 (3 H, s, H-13), 6.88 (1 H, dd, *J* 2.7, 9.0 Hz, H-10), 7.34 (1 H, d, *J* 9.0 Hz, H-9), 7.52 (1 H, d, *J* 2.7 Hz, H-12);

^{13}C-NMR (100 MHz, CD$_3$OD): δ_C 22.6 (C-3), 24.0 (C-4), 38.0 (C-2), 56.1 (C-13), 103.9 (C-12), 111.7 (C-9), 114.0 (C-10), 116.8 (C-6), 124.4 (C-8), 149.4 (C-7), 157.3 (C-5), 171.5 (C-11), 194.9 (C-1);

MS (ESI): 217 $[MH]^+$, 239 $[MNa]^+$;

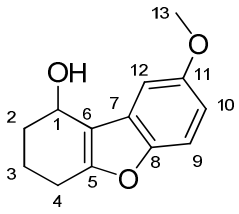
HRMS (ESI): Calculated for $C_{13}H_{13}O_3$, 217.0859. Found: $[MH^+]$, 217.0862 (1.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 1664, 1587,1454, 1433, 1393, 1275, 1226, 1155, 1027, 1006;

Microanalysis: Found C, 72.2; H, 5.60. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.59%.

Lab. Notebook Reference: PC/1/90/P1.

8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-ol, 89



To a stirred solution of ketone **85** (72 mg, 0.333 mmol) in MeOH (5 mL) was added $CeCl_3.5H_2O$ (140 mg, 0.374 mmol). The resulting solution was stirred at rt for 10 min. The reaction mixture was then cooled to -78 °C and $NaBH_4$ (14 mg, 0.356 mmol) was added. The reaction mixture was warmed to rt and stirred for 2 h. The reaction was quenched with $NaHCO_3$ (sat. aq. solution, 5 mL) and EtOAc (10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a light brown oil. The crude oil was purified by flash column chromatography (SiO_2, 3:2 Et_2O:petrol) to deliver alcohol **89** (64 mg, 88%) as a clear, colourless oil.

***R*$_f$ (SiO_2,7:3 Et_2O:petrol):** 0.27;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.85 – 2.10 (4 H, m, H-2 and H-3), 2.55 – 2.80 (2H, m, H-4), 3.84 (3 H, s, H-13), 5.01 (1 H, m, H-1), 6.82 (1 H, dd, *J* 2.6, 8.9 Hz, H-10), 7.09 (1 H, d, *J* 2.6 Hz, H-12), 7.30 (1 H, d, *J* 8.9 Hz, H-9);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 18.5 (C-3), 23.3 (C-4), 32.4 (C-2), 55.8 (C-13), 63.3 (C-1), 101.7 (C-12), 111.2 (C-9), 111.7 (C-10), 115.6 (C-6), 127.6 (C-8), 149.2 (C-7), 155.8 (C-5), 156.7 (C-11);

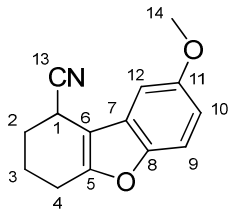
MS (ESI): 241 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{13}H_{14}NaO_3$ 241.0835. Found $[MNa^+]$: 241.0827, (2.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3393, 2923, 1624, 1463,1266, 1213, 1189, 1132, 1062, 1031, 799.

Lab Notebook Reference: PC/2/7.

8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-carbonitrile, 93



To a stirred solution of alcohol **89** (80 mg, 0.367 mmol) and TMSCN (0.14 mL, 1.099 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added ZnI_2 (351 mg, 1.099 mmol). The reaction mixture was stirred at rt for 3 h and then quenched with pyridine (10 mL), washed with $NaHCO_3$ (sat. aq. solution, 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a light brown solid. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to deliver nitrile **93** (46 mg, 55%) as a yellow gum.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.41;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.95 – 2.25 (4 H, m, H-2 and H-3), 2.70 – 2.85 (2 H, m, H-4), 3.86 (3 H, s, H-14), 3.90 – 3.95 (1 H, m, H-1), 6.86 (1 H, dd, *J* 2.6, 8.9 Hz, H-10), 7.04 (1 H, d, *J* 2.6 Hz, H-12), 7.32 (1 H, d, *J* 8.9 Hz, H-9);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 20.7 (C-3), 23.0 (C-4), 24.1 (C-1), 27.2 (C-2), 56.0 (C-14), 101.2 (C-12), 107.6 (C-13), 111.7 (C-9), 112.6 (C-10), 120.1 (C-6), 127.0 (C-8), 149.2 (C-7), 156.0 (C-5), 156.2 (C-10);

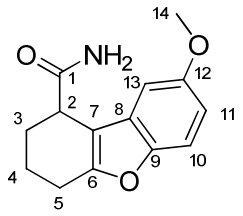
MS (ESI): 228 $[MH]^+$, 250 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{14}H_{14}NO_2$, 228.1019. Found: $[MH^+]$, 228.1020 (0.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2940, 2867, 2845, 2239 (-CN), 1625, 1592, 1477, 1456, 1438, 1383, 1327, 1268, 1215, 1194, 1131, 1059, 1030, 936, 889, 859, 812, 782, 736.

Lab Notebook Reference: PC/2/24.

8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-amide, 96



To a stirred solution of nitrile **93** (100 mg, 0.440 mmol) in MeOH (5 mL) at rt was added NaOH (2 M in H_2O, 4 mL, 8.00 mmol). The resulting solution was stirred at rt for 3 d. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown oil. The crude material was purified by flash column chromatography (SiO_2, 9:1 CH_2Cl_2:MeOH) to afford amide **96** (86 mg, 80%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 9:1 CH_2Cl_2:MeOH):** 0.24;

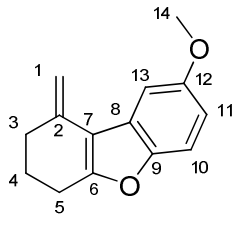
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.93 – 2.01 (2 H, m, H-3a and H-4a), 2.01 – 2.10 (1 H, m, H-3b or 4b), 2.24 – 2.32 (1 H, m, H-3b or 4b), 2.70 – 2.85 (2 H, m, H-5), 3.63 (1 H, m, H-5), 3.82 (3 H, s, H-14), 5.65 (2 H, br s, -$CONH_2$), 6.84 (1 H, dd, *J* 2.6, 8.9 Hz, H-11), 6.89 (1 H, d, *J* 2.6 Hz, H-13), 7.32 (1 H, d, *J* 8.9 Hz, H-10);

MS (ESI): 246 $[MH]^+$, 268 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{14}H_{16}NO_3$, 246.1125. Found: $[MH^+]$, 246.1118 (2.5 ppm error).

Lab Notebook Reference: PC/2/28.

8-Methoxy-1-methylene-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan, 99



Lombardo Method:

To a stirred solution of zinc dust (680 mg, 10.4 mmol), lead shot (25 mg, 0.120 mmol) and CH_2Br_2 (0.24 mL, 3.47 mmol) in THF (25 mL) at rt was added $TiCl_4$ (1.0 M in CH_2Cl_2, 2.54 mL, 2.54 mmol). Once effervescence had ceased, a solution of ketone **85** (500 mg, 2.31 mmol) in THF (25 mL) was added to the reaction mixture. After 3 h, K_2CO_3 (sat. aq. solution, 50 mL) was added and the resulting blue suspension was stirred for 18 h. The mixture was diluted with Et_2O (50 mL) and H_2O (50 mL) and the aqueous layer was extracted with Et_2O (50 mL). Combined organic layers were passed through a short silica plug eluting with Et_2O, the filtrate was dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a yellow gum. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford alkene **99** (146 mg, 29%) as a clear oil and diol **105** (123 mg, 12 %) as a white solid.

Rh-mediated Wittig Method:

To a stirred solution of chlorotris(triphenylphosphine)rhodium (23 mg, 0.025 mmol), triphenylphosphine (289 mg, 1.10 mmol) and 2-propanol (0.77 mL, 10.0 mmol) in THF (10 mL) at rt was added ketone **85** (216 mg, 1.00 mmol) followed by $TMSCHN_2$ (2.0 M in Et_2O, 0.80 mL, 1.60 mmol). After 16 h, the reaction mixture was concentrated *in vacuo* to deliver a red gum. The crude material was characterised by ^{1}H-NMR spectroscopy and shown to be a 4:1 mixture of ketone **85** and alkene **99**.

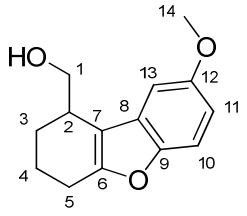
Peterson Method:

$CeCl_3.6H_2O$ (604 mg, 1.62 mmol) was dried *in vacuo* at 140 ^oC for 16 h. After cooling to rt, THF (5 mL) was added. After 30 min, the solution was cooled to -78 ^oC and $TMSCH_2Li$ (1.0 M in pentane, 1.39 mL, 1.39 mmol) was added. After stirring for 20 min, a solution ketone **85** (200 mg, 0.925 mmol) in THF (1 mL) was added. The reaction was warmed to rt

and after 2 d the reaction mixture was quenched with $NaHCO_3$ (sat. aq. solution, 10 mL) and diluted with Et_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organics were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a clear oil. The crude oil was purified by flash column chromatography (SiO_2, 95:5 petrol:Et_2O) to afford alkene **99** (142 mg, 72%) as a clear oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.57;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.98 – 2.06 (2 H, m, H-4), 2.50 – 2.55 (2 H, m, H-3), 2.84 (2 H, t, *J* 6.3 Hz, H-5), 3.87 (3 H, s, H-14), 5.02 (1 H, d, *J* 1.0 Hz, H-1a), 5.37 (1 H, d, *J* 1.0 Hz, H-1b), 6.85 (1 H, dd, *J* 2.6, 8.9 Hz, H-11), 7.23 (1 H, d, *J* 2.6 Hz, H-13), 7.33 (1 H, d, *J* 8.9 Hz, H-10);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 22.7 (C-4), 23.6 (C-5), 32.1 (C-3), 55.8 (C-14), 103.7 (C-10), 105.8 (C-1), 110.7 (C-11/C-13), 110.8 (C-11/C-13), 113.8 (C-7), 126.1 (C-8), 138.5 (C-2), 149.1 (C-9), 155.6 (C-6), 157.7 (C-12);
MS (ESI): 215 $[MH]^+$;
HRMS (ESI): Calculated for $C_{14}H_{15}O_2$, 215.1067. Found: $[MH^+]$, 215.1069 (0.9 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2935, 2834, 1638, 1592, 1470, 1434, 1273, 1227, 1193, 1177, 1161, 1066, 1034, 909, 871, 855, 828, 802, 772, 733.
Lab Notebook Reference: PC/3/77.

(8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)methanol, 98



To a stirred solution of alkene **99** (198 mg, 0.925 mmol) in THF (10 mL) at rt was added BH_3.THF (1 M in THF, 0.93 mL, 0.93 mmol). After 45 min, NaOH (2 M, 2 mL) was added and once the effervescence had ceased, H_2O_2 (30% w/w in H_2O, 1.0 mL, 9.25 mmol) was added. After 30 min, the reaction was diluted with Et_2O (10 mL) and H_2O (10

mL). The aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to deliver alcohol **98** (189 mg, 88%) as a clear colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.15;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.80 – 2.05 (4 H, m, H-3a and H-4), 2.65 – 2.75 (2 H, m , H-3b), 3.05 – 3.15 (1 H, m, H-2), 3.83 (1 H, dd, *J* 7.3, 10.8 Hz, H-1a), 3.83 (3 H, s, H-14), 3.94 (1 H, dd, *J* 4.9, 10.8 Hz, H-1b), 6.79 (1 H, dd, *J* 2.6, 8.9 Hz, H-11), 7.01 (1 H, d, *J* 2.6 Hz, H-13), 7.28 (1 H, d, *J* 8.9 Hz, H-10);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 19.8 (C-4), 23.5 (C-5), 25.2 (C-3), 35.1 (C-2), 55.9 (C-14), 65.2 (C-1), 102.4 (C-13), 111.0 (C-11), 111.2 (C-10), 112.7 (C-7), 128.6 (C-9), 149.2 (C-8), 155.6 (C-6), 156.4 (C-12);

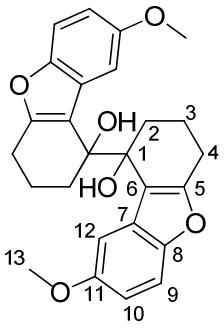
MS (ESI): 233 $[MH]^+$, 255 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{14}H_{17}O_3$, 233.1172. Found: $[MH^+]$, 233.1178 (2.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3396, 2937, 2880, 1614, 1591, 1473, 1437, 1264, 1212, 1191, 1152, 1132, 1076, 1033, 909, 803, 732.

Lab Notebook Reference: PC/2/91.

8,8'-Dimethoxy-3,3',4,4'-tetrahydro-1,1'-bidibenzo[*b*,*d*]furan-1,1'(2*H*,2'*H*)-diol, 105



For procedure see Lombardo method for **99**.

***R*$_f$ (SiO_2, 3:2 Et_2O:petrol):** 0.22;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.46 – 1.55 (2 H, m, H-3/H-4), 1.75 -2.02 (6 H, m, H-3/H-4), 2.60 (2 H, ddd, *J* 5.4, 11.4, 16.9 Hz, H-2a), 2.72 – 2.81 (2 H, m, H-2b), 3.44 (2 H,

d, *J* 0.9 Hz, -OH), 3.84 (6 H, s, H-14), 6.85 (2 H, dd, *J* 2.7, 8.9 Hz, H-9), 7.31 (2 H, d, *J* 8.9 Hz, H-8), 7.85 (2 H, d, *J* 2.7 Hz, H-11);

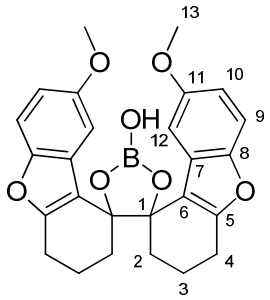
MS (ESI): 457 ($[MNa]^+$), 417 ($[(M-H_2O)H]^+$);

HRMS (ESI): Calculated for $C_{26}H_{25}O_5$, 417.1697. Found: $[(M-H_2O)H]^+$, 417.1695 (0.4 ppm error). Calculated for $C_{26}H_{26}O_6Na$, 457.1627. Found: $[MNa]^+$, 457.1627 (0.0 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3366, 3083, 2915, 2886, 1696, 1574, 1416, 1305, 1262, 1143, 1114.

Lab Notebook Reference: PC/3/22.

8,8''-Dimethoxy-3,3'',4,4''-tetrahydro-2*H*,2''*H*-dispiro[dibenzo[*b*,*d*]furan-1,4'-[1,3,2]dioxaborolane-5',1''-dibenzo[*b*,*d*]furan]-2'-ol, 106



To a stirred solution of an impure mixture of methylene **99** and diol **105** (4.63 mmol, assumed 100% yield from previous reaction) in THF (25 mL) at rt was added BH_3.THF (1 M in THF, 6.95 mL, 6.95 mmol). After 45 min, NaOH (2 M, 10 mL) was added and once the effervescence had ceased, H_2O_2 (30% w/w in H_2O, 2.4 mL, 20.8 mmol) was added. After 30 min, the reaction was diluted with Et_2O (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver an orange oil. The crude residue was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to deliver alcohol **98** (354 mg, 33% over two steps) as a clear colourless oil and borate ester **106** (419 mg, 20%) as a white solid.

Mp: 144 – 146 °C;

***R*$_f$ (SiO_2, 1:1 petrol: Et_2O):** 0.30;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.66 – 1.78 (2 H, m, H-2/H-3), 1.81 – 1.93 (4 H, m, H-2/H-3), 2.08 – 2.17 (2 H, m, H-2/H-3), 2.57 – 2.66 (2 H, m, H-4), 2.76 (2 H, dt, *J* 5.1, 16.7

Hz, H-4), 3.84 (6 H, s, H-13), 4.16 (1 H, s, -OH), 6.87 (2 H, dd, *J* 2.5, 8.9 Hz, H-10), 7.25 (2 H, d, *J* 2.5 Hz, H-12), 7.43 (2 H, d, *J* 8.9 Hz, H-9);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 20.0 (C-2), 23.5 (C-4), 33.5 (C-3), 55.9 (C-13), 85.7 (C-1), 104.5 (C-12), 111.5 (C-9/C-10), 111.6 (C-9/C-10), 115.2 (C-6), 126.9 (C-8), 149.4 (C-7), 156.1 (C-11), 158.0 (C-5);

MS (ESI): 461 ($[MH]^+$);

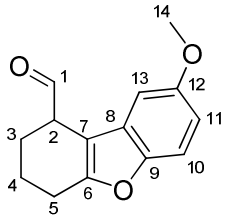
HRMS (ESI): Calculated for $C_{26}H_{26}BO_7$, 461.1771. Found: $[MH^+]$, 461.1754 (3.7 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3373, 2939, 1615, 1473, 1358, 1218, 1197, 1131, 1080, 1034;

CHN analysis: Found C, 68.1; H, 5.74%. $C_{26}H_{25}BO_7$ requires C, 67.8; H, 5.47%.

Lab Notebook Reference: PC/3/2.

8-Methoxy-1,2,3,4-tetrahydrodibenzo[b,d]furan-1-carbaldehyde, 87



To a stirred solution of alcohol **98** (97 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) at rt (under an air atmosphere) was added Dess-Martin periodinane (177 mg, 0.42 mmol). The resulting suspension was stirred at rt for 16 h. Additional Dess-Martin periodinane (89 mg, 0.21 mmol) was added. After 2 h, the resulting suspension was diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a yellow oil. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to deliver aldehyde **87** (68 mg, 71%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O)** 0.50;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.93 – 2.02 (3 H, m, H-3a and H-4), 2.14 – 2.24 (1 H, m, H-4b), 2.74 – 2.80 (2 H, m, H-5), 3.62 – 3.69 (1 H, m, H-2), 3.83 (3 H, s, H-14), 6.84 (1 H,

dd, *J* 8.8, 2.4 Hz, H-11), 6.87 (1 H, d, *J* 2.4 Hz, H-13), 7.32 (1 H, d, *J* 8.8 Hz, H-10), 9.75 (1 H, d, *J* 2.4 Hz, H-1);

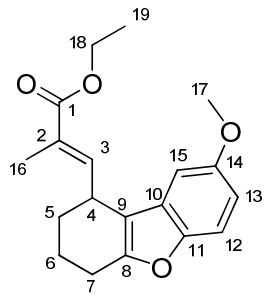
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 20.5 (C-4), 22.8 (C-3), 23.2 (C-5), 45.7 (C-2), 55.8 (C-14), 108.4 (C-7), 109.0 (C-13), 111.0 (C-10), 111.5 (C-11), 128.1 (C-9), 149.3 (C-8), 151.4 (C-6), 156.7 (C-12), 200.7 (C-1);

MS (ESI): 231 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{14}H_{15}O_3$, 231.1016. Found: $[MH^+]$, 231.1016 (2.9 ppm error).

Lab Notebook Reference: PC/2/95.

Ethyl (*E*)-3-(8-methoxy-1,2,3,4-tetrahydrodibenzo[b,d]furan-1-yl)-2-methylacrylate, 122



To a solution of aldehyde **87** (702 mg, 3.05 mmol) in CH_2Cl_2 (15 mL) at rt was added ethyl 2-(triphenylphosphoranylidene)propanoate (1.66 g, 4.57 mmol). After 48 h, the resulting solution was concentrated *in vacuo* to afford a yellow solid. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford alkene **122** (769 mg, 80%) as a clear, yellow oil.

***R*$_f$ (SiO_2, 8:2 petrol:EtOAc):** 0.42;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.27 (3 H, t, *J* 7.1 Hz, H-19), 1.59 – 1.70 (1 H, m, H-5/H-6), 1.82 – 1.95 (1 H, m, H-5/H-6), 1.96 – 2.15 (2 H, m, H-5/H-6), 2.10 (3 H, d, *J* 1.4 Hz, H-16), 2.70 -2.81 (2 H, m, H-7), 3.78 (3 H, s, H-17), 3.80 – 3.89 (1 H, m, H-4), 4.18 (2 H, q, *J* 7.1 Hz, H-18), 6.72 (1 H, d, *J* 2.6 Hz, H-15), 6.76 (1 H, dq, *J* 10.3, 1.4 Hz, H-3), 6.78 (1 H, dd, *J* 2.6, 8.8 Hz, H-13), 7.28 (1 H, d, *J* 8.8 Hz, H-12);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 12.8 (C-16), 14.2 (C-19), 21.1 (C-6), 23.4 (C-7), 29.0 (C-5), 32.6 (C-4), 55.8 (C-17), 60.6 (C-18), 102.3 (C-15), 110.8 (C-12), 111.1 (C-13),

113.9 (C-9), 127.7 (C-11), 128.7 (C-2), 143.8 (C-3), 149.2 (C-10), 155.3 (C-8), 155.5 (C-14), 168.1 (C-1);

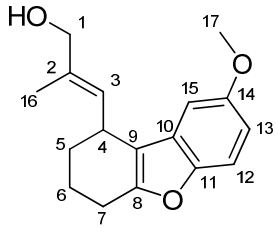
MS (ESI): 315 $[MH]^+$, 337 $[MNa]^+$;

HRMS (ESI): Calculated for $C_{19}H_{23}O_4$, 315.1591. Found: $[MH^+]$, 315.1592 (0.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2985, 2938, 2254, 1703, 1474, 1382, 1295, 1243, 1212, 1178, 1133, 1093, 1031.

Lab Notebook Reference: PC/2/96.

(2*E*)-3-(8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methylprop-2-en-1-ol, 123



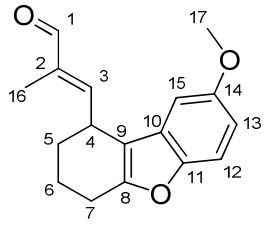
To a stirred solution of ester **122** (55 mg, 0.175 mmol) in toluene (5 mL) at –78 °C was added DIBAL-H (1.0 M in hexanes, 0.35 mL, 0.35 mmol). After 2 h, the resulting solution was quenched with Rochelle's salt (sat. aq. solution, 5 mL) and further diluted with EtOAc (5 mL). The resulting biphasic system was stirred vigorously for 4 h and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petrol:Et_2O) to afford the desired alcohol **123** (30 mg, 63%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.21;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.50 – 1.60 (1 H, m, H-5/H-6), 1.71 (1 H, br s, -OH), 1.79 – 1.90 (1 H, m, H-5/H-6), 1.94 (3 H, d, *J* 1.4 Hz, H-16), 1.92 – 2.11 (2 H, m, H-5/H-6), 2.72 (2 H, ddd, *J* 2.0, 5.3, 7.2 Hz, H-7), 3.71 – 3.78 (1 H, m, H-4), 3.79 (3 H, s, H-17), 4.07 (2 H, s, H-1), 5.43 (1 H, dq, *J* 1.4, 10.0 Hz, H-3), 6.76 (1 H, dd, *J* 2.7, 8.7 Hz, H-13), 6.79 (1 H, dd, *J* 0.6, 2.7 Hz, H-15), 7.27 (1 H, dd, *J* 0.6, 8.7 Hz, H-12);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 14.0 (C-16), 21.3 (C-5/C-6), 23.4 (C-7), 30.1 (C-5/C-6), 31.7 (C-4), 55.8 (C-17), 68.8 (C-1), 102.8 (C-15), 110.4 (C-13), 111.0 (C-12), 115.0 (C-9), 128.9 (C-3), 129.0 (C-11), 134.8 (C-2), 149.3 (C-10), 155.0 (C-8), 155.3 (C-14);
MS (ESI): 273 ($[MH]^+$), 295 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_{17}H_{20}NaO_3$, 295.1305. Found: [MNa^+], 295.1319 (4.2 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3371, 2936, 2855, 1614, 1473, 1456, 1437, 1264, 1211, 1191, 1138, 1032, 801.
Lab Notebook Reference: PC/6/25.

(2*E*)-3-(8-Methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methylacrylaldehyde, 124



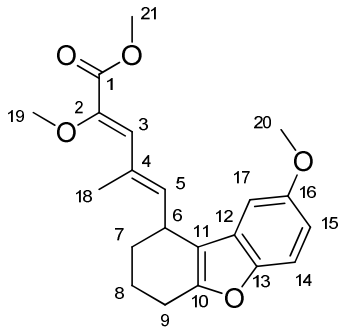
To a stirred solution of alcohol **123** (388 mg, 1.42 mmol) in CH_2Cl_2 (15 mL) at rt was added MnO_2 (1.24 g, 14.2 mmol). After 48 h, the resulting suspension was filtered through a celite pad (eluting with EtOAc) and concentrated *in vacuo* to deliver impure aldehyde **124** as a yellow solid. The crude material was used in the next reaction without purification.

A crystal was grown by slow evaporation from $CDCl_3$.

Mp: 123 – 124 °C;
***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.33;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.62 – 1.74 (1 H, m, H-5/H-6), 1.86 – 1.99 (1 H, m, H-5/H-6), 2.01 (3 H, d, *J* 1.4 Hz, H-16), 2.03 – 2.18 (2 H, m, H-5/H-6), 2.79 (2 H, ddd, *J* 1.8, 5.3, 7.2 Hz, H-7), 3.76 (3 H, s, H-17), 3.99 – 4.07 (1 H, m, H-4), 6.50 (1 H, dq, *J* 1.4, 10.2 Hz, H-3), 6.63 (1 H, dd, *J* 0.4, 2.6 Hz, H-15), 6.79 (1 H, dd, *J* 2.6, 8.9 Hz, H-13), 7.30 (1 H, dd, *J* 0.4, 8.9 Hz, H-12), 9.45 (1 H, s, H-1);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 9.6 (C-16), 21.1 (C-5/C-6), 23.3 (C-7), 28.9 (C-5/C-6), 32.8 (C-4), 55.8 (C-17), 102.0 (C-15), 111.0 (C-9), 111.3 (C-10), 113.2 (C-16), 128.4 (C-11), 138.8 (C-2), 149.3 (C-10), 155.5 (C-8), 155.7 (C-14), 156.0 (C-3), 195.3 (C-1);
MS (ESI): 271 ($[MH]^+$), 293 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_{17}H_{18}NaO_3$, 293.1148. Found: [MNa^+], 293.1158 (3.1 ppm error);
Lab Notebook Reference: PC/6/30.

Methyl (2*Z*,4*E*)-2-methoxy-5-(8-methoxy-1,2,3,4-tetrahydrodibenzo[b,d]furan-1-yl)-4-methyl-2,4-dienoate, 126



To a stirred solution of phosphonate **125** (154 mg, 0.728 mmol) and 18-C-6 (192 mg, 0.728 mg) in THF (2 mL) at 0 °C was added KHMDS (0.7 M in THF, 0.87 mL, 0.607 mmol). After 15 min, a solution of aldehyde **124** (0.303 mmol, assume 100% purity from previous step) in THF (1 mL) was added. The resulting red solution was warmed to rt and after 48 h was quenched with NH_4Cl (sat. aq. solution, 5 mL) and further diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford diene **126** (86 mg, 80% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.47;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.49 – 1.64 (1 H, m, H-7a), 1.78 – 1.92 (1 H, m, H-8a), 1.94 – 2.13 (2 H, m, H-7b and H-8b), 2.24 (3 H, d, *J* 1.0 Hz, H-18), 2.68 – 2.78 (2 H, m, H-9), 3.70 (3 H, s, H-19), 3.78 (6 H, br s, H-20 and H-21), 3.81 – 3.89 (1 H, m, H-6), 5.82

(1 H, d, *J* 10.1 Hz, H-5), 6.63 (1 H, d, *J* 1.0 Hz, H-3), 6.74 – 6.80 (2 H, m, H-15 and H-17), 7.28 (1 H, dd, *J* 0.7, 8.6 Hz, H-14);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 15.0 (C-18), 21.3 (C-8), 23.4 (C-9), 29.7 (C-7), 32.2 (C-6), 52.0 (C-21), 55.8 (C-20), 60.3 (C-19), 102.5 (C-17), 110.6 (C-15), 111.0 (C-14), 114.5 (C-11), 128.7 (C-13), 129.2 (C-3), 131.3 (C-4), 141.2 (C-5), 143.3 (C-2), 149.2 (C-12), 155.1 (C-10), 155.4 (C-16), 165.2 (C-1);

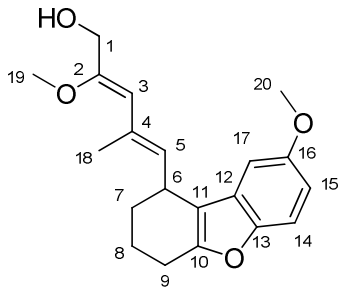
MS (ESI): 357 ($[MH]^+$), 379 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{21}H_{24}NaO_5$, 379.1516. Found: [MNa^+], 379.1511 (0.7 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2892, 1692, 1596, 1415, 1326, 1231, 1192, 1086, 1015.

Lab Notebook Reference: PC/6/62.

(2*Z*,4*E*)-2-Methoxy-5-(8-methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-4-methylpenta-2,4-dien-1-ol, 127



To a stirred solution of ester **126** (59 mg, 0.166 mmol) in toluene (5 mL) at –78 °C was added DIBAL-H (1 M in hexanes, 0.36 mL, 0.36 mmol). The resulting solution was warmed to rt and after 2 h was quenched with Rochelle's salt (sat. aq. solution, 5 mL). The resulting biphasic system was stirred vigorously for 1 h and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford the desired alcohol **127** (40 mg, 73%) as a clear, colourless oil.

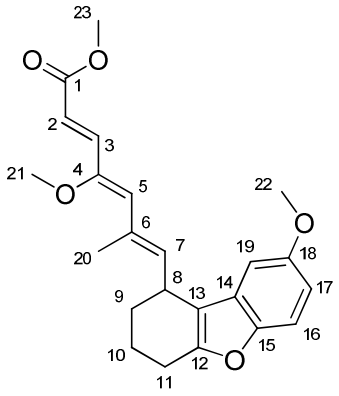
***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.15;

^{1}H-NMR (400 MHz, CD_3OD): δ_H 1.47 – 1.65 (1 H, m, H-7a), 1.78 – 1.91 (1 H, m, H-8a), 1.95 – 2.10 (2 H, m, H-7b and H-8b), 2.15 (3 H, d, *J* 1.4 Hz, H-18), 2.69 – 2.76 (2 H, m,

H-9), 3.71 (3 H, s, H-19), 3.78 – 3.81 (1 H, m, H-6), 3.79 (3 H, s, H-20), 4.16 (2 H, s, H-1), 5.25 (1 H, s, H-3), 5.50 (1 H, d, *J* 9.9 Hz, H-5), 6.76 (1 H, dd, *J* 2.6, 8.8 Hz, H-15), 6.83 (1 H, d, *J* 2.6 Hz, H-17), 7.27 (1 H, d, *J* 8.8 Hz, H-14).

Lab Notebook Reference: PC/6/63/P1.

Methyl (2*E*,4*Z*,6*E*)-4-methoxy-7-(8-methoxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan -1-yl)-6-methylhepta-2,4,6-trienoate, 128



To a stirred solution of alcohol **127** (101 mg, 0.308 mmol) in CH_2Cl_2 (3 mL) at rt was added MnO_2 (2.95 g, 3.39 mmol) and methyl (triphenylphosphoranylidene) acetate (136 mg, 0.407 mmol). The resulting suspension was stirred at rt for 16 h and then filtered through celite. The filtrate was concentrated *in vacuo* to afford a brown oil. The crude material was purified by flash column chromatography (SiO_2, 8:1 petrol:Et_2O) to afford the desired triene **128** (40 mg, 34%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.24;

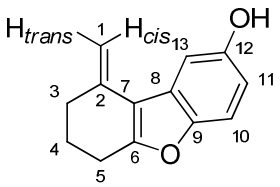
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.44 – 1.54 (1 H, m, H-9a), 1.76 – 1.85 (1 H, m, H-10a), 1.87 – 2.05 (2 H, m, H-9b and H-10b), 2.17 (3 H, d, *J* 1.4 Hz, H-20), 2.60 – 2.67 (2 H, m, H-11), 3.56 (3 H, s, H-23), 3.63 – 3.68 (1 H, m, H-8), 3.65 (3 H, s, H-21), 3.66 (3 H, s, H-22), 5.69 (1 H, d, *J* 10.1 Hz, H-7), 5.86 (1 H, s, H-5), 5.95 (1 H, d, *J* 15.5 Hz, H-2), 6.66 (1 H, d, *J* 2.6 Hz, H-19), 6.68 (1 H, dd, *J* 2.6, 8.6 Hz, H-17), 7.02 (1 H, d, *J* 15.5 Hz, H-3), 7.16 (1 H, d, *J* 8.6 Hz, H-16);

MS (ESI): 383 ($[MH]^+$), 405 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{23}H_{27}O_5$, 383.1854. Found: [MH^+], 383.1853 (0.2 ppm error).

Lab Notebook Reference: PC/6/80.

9-Methylidene-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-ol, 134



To a solution of ketone **71** (4.95 g, 24.5 mmol) in THF at −78 °C was added, *via* cannula, $TMSCH_2Li$ (1.0 M in pentane, 53.8 mL, 53.8 mmol). The reaction was stirred at −78 °C for 1 h and then warmed to rt and stirred for 2 d. The reaction was quenched with $NaHCO_3$ (sat. aq., 55 mL) and stirred at rt for 2 h. The resulting mixture was diluted with EtOAc (55 mL) and the layers separated. The inorganic layer was then extracted with EtOAc (2 x 55 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a mix of alkene **134** and intermediate hydroxysilane **135** as crude brown oil. The crude mixture was taken up in CH_2Cl_2 (55 mL) and silica gel (1 g) was added and the resulting suspension was stirred at rt for 2 h and concentrated *in vacuo* to deliver a brown powder. The crude material was purified by flash column chromatography (SiO_2, 3:2 petr0l:Et_2O) to afford the desired alkene **134** (3.29 g, 67%) as a brown gum.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.38;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.97 – 2.05 (2 H, m, H-4), 2.48 – 2.54 (2 H, m, H-3), 2.83 (2 H, t, *J* 6.3 Hz, H-5), 4.67 (1 H, s, -OH), 4.99 (1 H, s, H-1$_{trans}$), 5.32 (1 H, s, H-1$_{cis}$), 6.75 (1 H, dd, *J* 2.6, 8.7 Hz, H-11), 7.18 (1 H, d, *J* 2.6 Hz, H-13), 7.27 (1 H, d, *J* 8.7 Hz, H-10);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 23.1 (C-4), 24.0 (C-3), 32.4 (C-5), 106.1 (C-13), 106.3 (C-1), 111.3 (C-10), 111.6 (C-11), 114.1 (C-2), 126.7 (C-9), 138.8 (C-7), 149.6 (C-12), 151.6 (C-8), 158.3 (C-6);

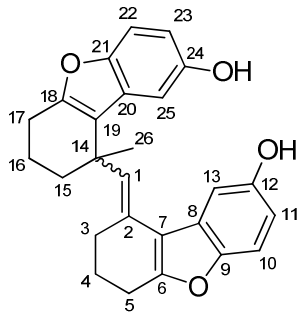
MS (ESI): 201 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{13}H_{13}O_2$, 201.0910. Found: [MH^+], 201.0908 (0.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3296, 2892, 1595, 1567, 1440, 1384, 1352, 1264, 1171, 1022, 995, 895, 832, 787, 722, 681.

Lab Notebook Reference: PC/6/87.

9-[(*E*)-(8-Hydroxy-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ylidene)methyl]-9-methyl-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-ol, 136



To a solution of ketone **71** (50 mg, 0.247 mmol) in THF (2 mL) at −78 °C was added $TMSCH_2Li$ (1.0 M in pentane, 0.54 mL, 0.544 mmol). The reaction was stirred at −78 °C for 1 h and then warmed to rt and stirred for 16 h. The reaction was quenched with $NaHCO_3$ (sat. aq. solution, 5 mL), diluted with EtOAc (5 mL) and stirred at rt for 2 h. To the resulting mixture was added HCl (10% aq. solution, 10 mL). After 2 h, the resulting solution was diluted with EtOAc (10 mL) and the layers separated. The inorganic layer was then extracted with EtOAc (2 x 15 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a crude brown oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petr0l:Et_2O) to afford the alkene **136** (15 mg, 31%) as a brown gum.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.38;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.50 – 1.72 (3 H, m, H-Cy), 1.55 (3 H, s, H-26), 1.88 – 1.95 (2 H, m, H-Cy), 1.96 – 2.03 (2 H, m, H-Cy), 2.19 (1 H, dddd, *J* 1.2, 3.3, 8.3, 14.7 Hz, H-Cy), 2.56 – 2.73 (2 H, m, H-Cy), 2.73 – 2.80 (2 H, m, H-3), 4.63 (1 H, br s, -OH), 4.86 (1 H, br s, -OH), 6.21 (1 H, s, H-1), 6.68 (1 H, dd, *J* 2.6, 8.7 Hz, H-11/23), 6.75 (1 H, dd, *J* 2.6, 8.7 Hz, H-11/23), 6.88 (1 H, d, *J* 2.6, H-13/25), 7.25 (1 H, d, *J* 8.7 Hz, H-10/22), 7.26 (1 H, d, *J* 8.7 Hz, H-10/22), 7.32 (1 H, d, *J* 2.6 Hz, H-13/25);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 19.9 (C-Cy), 22.7 (C-Cy), 23.6 (C-Cy), 23.9 (C-Cy), 25.7 (C-Cy), 29.6 (C-26), 36.2 (C-14), 37.9 (C-Cy), 105.6 (C-13/25), 106.3 (C-13/25), 111.2 (C-10/11/22/23), 111.2 (C-10/11/22/23), 111.4 (C-10/11/22/23), 111.5 (C-10/11/22/23), 115.1 (C-Fur), 120.8 (C-2), 126.9 (C-Fur), 128.3 (C-Fur), 130.0 (C-1), 132.3 (C-Fur), 149.7 (C-12/24), 149.7 (C-12/24), 150.8 (C-Fur), 151.5 (C-Fur), 153.7 (C-Fur), 157.1 (C-Fur);

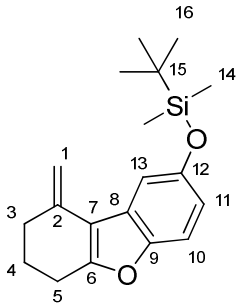
MS (ESI): 401 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{26}H_{25}O_4$, 401.1753. Found: $[MH^+]$, 401.1747 (1.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3324, 2883, 1596, 1569, 1440, 1352, 1237, 1172, 1022, 787, 721.

Lab Notebook Reference: PC/6/83.

***tert*-Butyl(dimethyl)[(9-methylene-6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-yl)oxy]silane, 131**



To a solution of alkene **134** (520 mg, 2.60 mmol) in CH_2Cl_2 (20 mL) at rt was added TBSCl (588 mg, 3.90 mmol) followed by imidazole (530 mg, 7.79 mmol). After 6 h, the resulting solution was diluted with H_2O (30 mL) and CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown oil. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford the desired alkene **131** (730 mg, 89%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.32;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.20 (6 H, s, H-14), 1.00 (9 H, s, H-16), 1.96 – 2.04 (2 H, m, H-4), 2.48 – 2.53 (2 H, m, H-3), 2.82 (2 H, t, *J* 6.3 Hz, H-5), 4.98 (1 H, s, H-1), 5.31 (1 H, s, H-1), 6.74 (1 H, dd, *J* 2.4, 8.6 Hz, H-11), 7.16 (1 H, d, *J* 2.4 Hz, H-13), 7.25 (1 H, d, *J* 8.6 Hz, H-10);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.4 (C-14), 18.2 (C-15), 23.2 (C-4), 24.0 (C-5), 25.8 (C-16), 32.4 (C-3), 106.3 (C-1), 111.0 (C-13), 111.0 (C-10), 114.2 (C-7), 116.2 (C-11), 116.8 (C-9), 138.9 (C-2), 149.9 (C-12), 151.6 (C-8), 158.0 (C-6);

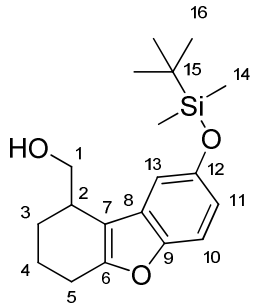
MS (ESI): 315 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{19}H_{27}O_2Si$, 315.1775. Found: [MH^+], 315.1777 (1.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2908, 2886, 2849, 2813, 1650, 1614, 1593, 1563, 1442, 1369, 1238, 1167, 904, 843, 826, 793, 768.

Lab Notebook Reference: PC/7/2.

(8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)methanol, 132



To a solution of alkene **131** (6.70 g, 21.3 mmol) in THF (200 mL) at 0 °C was added BH_3.THF (1.0 M in THF, 32.0 mL, 32.0 mmol). The resulting solution was stirred at 0 °C for 30 min and then warmed to rt for 3 h. The reaction was then cooled to 0 °C and quenched with H_2O until effervescence had ceased. A suspension of $NaBO_3.4H_2O$ (20 g, 127.8 mmol) in H_2O (80 mL) was then added portionwise and the resulting white suspension was stirred at rt for 12 h. The suspension was then diluted with ethyl acetate (100 mL) and H_2O (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petrol:Et_2O) to afford the desired alcohol **132** (6.88 g, 97%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.27;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.19 (6 H, s, H-14), 1.00 (9 H, s, H-16), 1.51 (1 H, br s, -OH), 1.82 – 1.93 (3 H, m, H-3a and H-4), 1.94 – 2.03 (1 H, m, H-3b), 2.74 – 2.66 (2 H, m, H-5), 3.05 – 3.13 (1 H, m, H-2), 3.83 (1 H, dd, *J* 7.3, 10.8 Hz, H-1a), 3.94 (1 H, dd, *J* 4.8, 10.8 Hz, H-1b), 6.71 (1 H, dd, *J* 2.5, 8.7 Hz, H-11), 6.97 (1 H, d, *J* 2.5 Hz, H-13), 7.24 (1 H, d, *J* 8.7 Hz, H-10);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.5 (C-14), 18.2 (C-15), 20.0 (C-3), 23.5 (C-5), 25.4 (C-4), 25.7 (C-16), 35.2 (C-2), 65.3 (C-1), 109.5 (C-13), 111.0 (C-10), 112.6 (C-7), 115.9 (C-11), 128.7 (C-9), 149.6 (C-12), 151.1 (C-8), 156.4 (C-6);

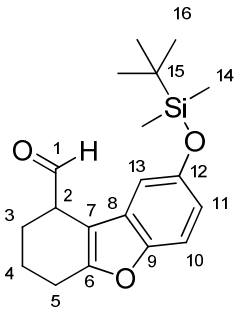
MS (ESI): 333 ($[MH]^+$), 355 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{19}H_{29}O_3Si$, 333.1880. Found: $[MH^+]$, 333.1872 (2.1 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3360, 2887, 2841, 2814, 1590, 1563, 1440, 1237, 1187, 1169, 1114, 1022, 988, 927, 887, 827, 792, 768.

Lab Notebook Reference: PC/7/7.

8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-carbaldehyde, 129



To a solution of oxalyl chloride (3.14 g, 2.1 mL, 24.8 mmol) in CH_2Cl_2 (150 mL) at −78 °C was added DMSO (3.87 g, 3.5 mL, 49.6 mmol). The resulting solution was stirred at −78 °C for 30 min and then a solution of alcohol **132** (6.86 g, 20.6 mmol) in CH_2Cl_2 (50 mL) was added. The resulting white suspension was stirred at −78 °C for a further 1 h. After this time, triethylamine (10.4 g, 14.4 mL 103.0 mmol) was added dropwise. The resulting suspension was stirred at −78 °C for 30 min and then 1 h at rt. The suspension was then diluted with CH_2Cl_2 (50 mL) and H_2O (250 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a yellow oil. The crude was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford the desired aldehyde **129** (5.34 g, 78%) as a yellow oil.

R_f (SiO_2, 9:1 petrol:Et_2O): 0.24;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.18 (6 H, s, H-14), 0.99 (9 H, s, H-16), 1.92 – 2.00 (3 H, m, 1.92 – 2.00, H-3a and H-4), 2.09 – 2.23 (1 H, m, H-3b), 2.70 – 2.79 (2 H, m, H-5), 3.61 – 3.66 (1 H, m, H-2), 6.74 (1 H, dd, *J* 2.4, 8.8 Hz, H-11), 6.83 (1 H, d, *J* 2.4 Hz, H-13), 7.26 (1 H, d, *J* 8.8 Hz, H-10), 9.74 (1 H, d, *J* 2.4 Hz, H-1);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.51 (C-14), -4.48 (C-14), 18.2 (C-15), 20.5 (C-4), 22.8 (C-3), 23.2 (C-5), 25.7 (C-16), 45.7 (C-2), 108.3 (C-7), 109.0 (C-13), 111.2 (C-10), 116.5 (C-11), 128.2 (C-9), 149.7 (C-8), 151.4 (C-12), 156.7 (C-6), 200.7 (C-1);

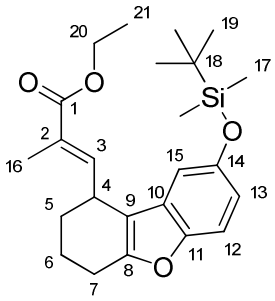
MS (ESI): 331 ($[MH]^+$), 353 ($[MNa]^+$);

HRMS (ESI): calculated for $C_{19}H_{27}O_3Si$, 331.1724. Found: [MH^+], 331.1717 (2.0 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2886, 2848, 2813, 1700, 1647, 1596, 1564, 1441, 1321, 1234, 1191, 1172, 1131, 1113, 927, 827, 793, 769.

Lab Notebook Reference: PC/7/12.

Ethyl (2*E*)-3-(8-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methylacrylate, 20



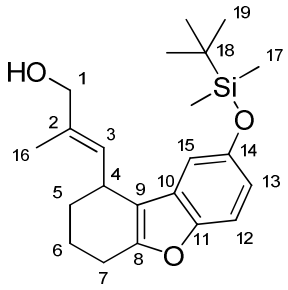
To a solution of aldehyde **129** (831 mg, 2.51 mmol) in CH_2Cl_2 (10 mL) at rt was added ethyl 2-(triphenylphosphoranylidene)propanoate (1.37 g, 3.77 mmol). After 2 d, the resulting solution was concentrated *in vacuo* to deliver a yellow solid. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:EtOAc) to afford the desired alkene **20** (853 mg, 82%) as a yellow oil.

R_f (SiO_2, 9:1 petrol:Et_2O): 0.29;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.14 (3 H, s, H-17), 0.14 (3 H, s, H-17), 0.96 (9 H, s, H-19), 1.26 (3 H, t, *J* 7.1 Hz, H-21), 1.62 (1 H, dddd, *J* 2.7, 8.0, 10.8, 13.4 Hz, H-5a), 1.81 –

1.93 (1 H, m, H-6a), 1.93 – 2.05 (2 H, m, H-5b and 6b), 2.09 (3 H, d, *J* 1.5 Hz, H-16), 2.75 (2 H, ddd, *J* 1.9, 5.2, 7.3 Hz, H-7), 3.77 – 3.87 (1 H, m, H-4), 4.17 (1 H, qd, *J* 7.1, 14.6 Hz, H-20), 4.19 (1 H, qd, *J* 7.1, 14.6 Hz, H-20), 6.66 (1 H, d, *J* 2.3 Hz, H-15), 6.69 (1 H, dd, *J* 2.3, 8.6 Hz, H-13), 6.74 (1 H, dd, *J* 1.5, 10.5 Hz, H-3), 7.22 (1 H, d, *J* 8.6 Hz, H-12).
Obtained data in accord with those reported in the literature.[18]
Lab Notebook Reference: PC/7/14.

(2*E*)-3-(8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methylprop-2-en-1-ol, 138



To a solution of ethyl ester **20** (101 mg, 0.244 mmol) in toluene (4 mL) at rt was added DIBAL-H (1.0 M in hexanes, 0.54 mL, 0.54 mmol). After 2 h, the resulting solution was quenched with Rochelle's salt (sat. aq. solution, 15 mL) and further diluted with EtOAc (10 mL). The resulting biphasic system was stirred vigorously for 16 h and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 7:3 petrol:Et_2O) to afford the desired alcohol **138** (74 mg, 81%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 7:3 petrol:Et_2O):** 0.31;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.16 (6 H, s, H-17), 0.98 (9 H, s, H-19), 1.43 (1 H, br s, -OH), 1.55 (1 H, dddd, 2.6, 7.8, 10.6, 13.2 Hz, H-5a), 1.80 – 1.90 (1 H, m, H-6a), 1.93 (3 H, d, *J* 1.4 Hz, H-16), 1.94 – 2.01 (1 H, m, H-5b), 2.02 – 2.11 (1 H, m, H-6b), 2.72 (2 H, ddd, *J* 1.9, 5.3, 7.2 Hz, H-7), 3.69 – 3.78 (1 H, m, H-4), 4.08 (2 H, d, *J* 1.1 Hz, H-1), 5.43 (1 H, qd, *J* 1.4, 10.1 Hz, H-3), 6.68 (1 H, dd, *J* 2.4, 8.7 Hz, H-13), 6.72 (1 H, d, *J* 2.4, H-15), 7.21 (1 H, d, *J* 8.7, H-12);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.5 (C-17), 14.0 (C-16), 18.2 (C-18), 21.4 (C-5/6), 23.4 (C-7), 25.7 (C-19), 30.1 (C-5/6), 31.8 (C-4), 68.8 (C-1), 109.4 (C-15), 110.8 (C-13), 114.9 (C-9), 115.8 (C-12), 128.9 (C-3), 128.9 (C-11), 134.7 (C-2), 149.6 (C-14), 150.8 (C-10), 154.8 (C-8);

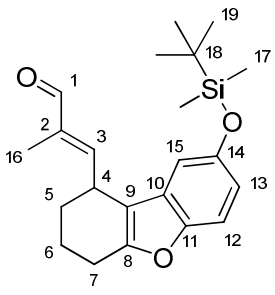
MS (ESI): 355 ([{M-H_2O}H]$^+$), 373 ([MH]$^+$), 395 ([MNa]$^+$);

HRMS (ESI): Calculated for $C_{22}H_{33}O_3Si$, 373.2193. Found: [MH$^+$], 373.2176 (4.2 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3331, 2885, 2813, 1590, 1564, 1439, 1362, 1340, 1237, 1186, 1115, 917, 842, 826, 793, 768.

Lab Notebook Reference: PC/7/54.

(2*E*)-3-(8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methylacrylaldehyde, 22



To a solution of alcohol **138** (2.30 g, 6.17 mmol) in CH_2Cl_2 (200 mL) at rt was added MnO_2 (10.7 g, 123.5 mmol). After 17 h, the resulting black suspension was filtered through celite. The filtrate was concentrated *in vacuo* to afford the desired aldehyde **20** (2.05 g, 90%) as an orange oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.21;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.13 (6 H, s, H-17), 0.95 (9 H, s, H-19), 1.62 – 1.71 (1 H, m, H-5a), 1.86 – 1.98 (1 H, m, H-6a), 2.00 (3 H, d, *J* 1.4 Hz, H-16), 2.03 – 2.18 (2 H, m, H-5b and H-6b), 2.78 (2 H, ddd, *J* 1.9, 5.2, 7.2 Hz, H-7), 3.98 – 4.06 (1 H, m, H-4), 6.48 (1 H, qd, *J* 1.4, 10.3 Hz, H-3), 6.59 (1 H, dd, *J* 0.4, 2.5 Hz, H-15), 6.71 (1 H, dd, *J* 2.5, 8.7 Hz, H-13), 7.24 (1 H, dd, *J* 0.4, 8.7 Hz, H-12), 9.44 (1 H, s, H-1);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.5 (C-17), -4.5 (C-17), 9.6 (C-16), 18.2 (C-18), 21.2 (C-6), 23.3 (C-7), 25.7 (C-19), 28.8 (C-5), 32.9 (C-4), 108.8 (C-15), 111.1 (C-12), 113.0

(C-9), 116.3 (C-13), 128.3 (C-10), 138.8 (C-2), 149.6 (C-11), 151.2 (C-14), 155.4 (C-8), 156.0 (C-3), 195.2 (C-1);

MS (ESI): 371 ($[MH]^+$), 393 ($[MNa]^+$);

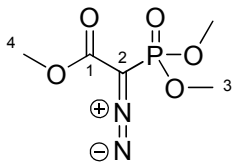
HRMS (ESI): Calculated for $C_{22}H_{31}O_3Si$, 371.2037. Found: $[MH^+]$, 371.2021 (3.8 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2886, 2813, 1663, 1590, 1441, 1239, 1187, 918, 826, 793, 768.

CHN analysis: Found C, 70.8; H, 8.10%. $C_{22}H_{30}O_3Si$ requires C, 71.3; H, 8.16%.

Lab Notebook Reference: PC/7/55.

Methyl diazo(dimethoxyphosphoryl)acetate, 142



To a suspension of NaH (70% w/w in mineral oil, 528 mg, 13.2 mmol) in THF (50 mL) at −78 °C was added methyl (dimethoxyphosphoryl)acetate **141** (2 g, 11.0 mmol). The resulting suspension was held at −78 °C for 30 min and then warmed to rt and held for 1 h. To the resulting white suspension was added 4-(acetylamino)benzenesulfonyl azide (3.17 g, 13.2 mmol). The resulting yellow suspension was stirred at rt for 2 h and then quenched with NH_4Cl (sat. aq. solution, 50 mL), diluted with Et_2O (50 mL) and the layers separated. The aqueous layer was extracted with Et_2O (2 x 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude diazo compound **142** a clear, colourless oil. The crude material was carried forward to the next step without further purification.

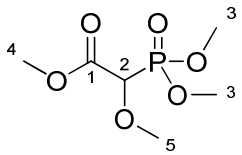
***R*$_f$ (SiO$_2$, EtOAc):** 0.17;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 3.82 (6 H, d, *J* 3.6 Hz, H-3), 3.83 (3 H, s, H-4).

Obtained data in accord with those reported in the literature.[48]

Lab Notebook Reference: PC/6/60.

Methyl (dimethoxyphosphoryl)(methoxy)acetate, 125



To a solution of crude diazo compound **142** (11.0 mmol) in PhMe (50 mL) and MeOH (10 mL) was added rhodium octanoate dimer (428 mg, 0.55 mmol). The resulting solution was heated to 70 °C for 3 d and then concentrated *in vacuo* to afford a green oil. The crude material was purified by flash column chromatography (SiO_2, EtOAc) to afford the desired phosphonate **125** (1.70 g, 73% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, EtOAc):** 0.17;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.52 (3 H, s, H-5), 3.84 (3 H, d, *J* 5.4 Hz, H-3), 3.84 (3 H, s, H-4), 3.86 (3 H, d, *J* 5.4 Hz, H-3), 4.26 (1 H, d, *J* 18.6 Hz, H-2);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 52.9 (C-4), 54.1 (d, *J* 6.6 Hz, C-3), 54.2 (d, *J* 6.6 Hz, C-3), 60.5 (d, *J* 13.1 Hz, C-5), 77.9 (d, *J* 158.0 Hz, C-2), 167.5 (d, *J* 1.8 Hz, C-1);

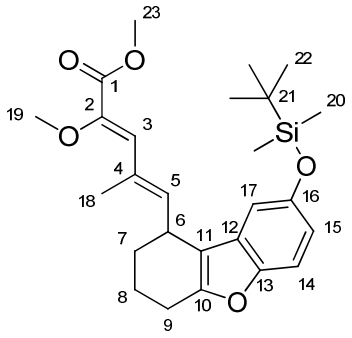
MS (ESI): 213 ($[MH]^+$), 235 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_6H_{13}NaO_6P$, 235.0342. Found: [MNa^+], 235.0341 (0.3 ppm error).

Obtained data in accord with those reported in the literature.[48]

Lab Notebook Reference: PC/6/61.

Methyl (2*Z*,4*E*)-5-(8-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methoxy-4-methylpenta-2,4-dienoate, 24



To a solution of phosphonate **125** (161 mg, 0.761 mmol) and 18-crown-6 (301 mg, 1.14 mmol) in THF (20 mL) at 0 °C was added KHMDS (0.7 M in THF, 1.09 mL, 0.761 mmol). The resulting pale yellow solution was stirred at 0 °C for 10 min, rt for 10 min and 0 °C for a further 10 min. A solution of aldehyde **22** (282 mg, 0.761 mmol) in THF (20 mL) was then added and the resulting suspension was warmed to rt and stirred for 2.5 h. The reaction mixture was then quenched with NaCl (sat. aq. solution, 30 mL) and diluted with EtOAc (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a pale brown oil. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford the desired ester **24** (282 mg, 81%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.23;

^{1}H-NMR (400 MHz, CD_3OD): δ_H 0.13 (6 H, s, H-20), 0.95 (9 H, s, H-22), 1.46 – 1.58 (1 H, m, H-7a), 1.79 – 1.92 (1 H, m, H-8a), 1.93 – 2.03 (1 H, m, H-7b), 2.04 – 2.13 (1 H, m, H-8b), 2.23 (3 H, d, *J* 1.2 Hz, H-18), 2.66 – 2.75 (2 H, m, H-9), 3.70 (3 H, s, H-19), 3.78 (3 H, s, H-23), 3.80 – 3.89 (1 H, m, H-6), 5.79 (1 H, dqd, *J* 0.9, 1.2, 10.3 Hz, H-5), 6.61 (1 H, d, *J* 0.9 Hz, H-3), 6.68 (1 H, dd, *J* 2.5, 8.7 Hz, H-15), 6.71 (1 H, d, *J* 2.5 Hz, H-17), 7.21 (1 H, d, *J* 8.7 Hz, H-14);

^{13}C-NMR (100 MHz, CD_3OD): δ_C -4.2 (C-20), -4.2 (C-20), 15.4 (C-18), 19.2 (C-21), 22.7 (C-8), 24.2 (C-9), 26.3 (C-22), 30.8 (C-7), 33.7 (C-6), 52.5 (C-23), 60.7 (C-19), 110.3 (C-17), 111.9 (C-14), 115.5 (C-11), 117.0 (C-15), 130.1 (C-3), 130.1 (C-12), 132.6 (C-4), 142.6 (C-5), 144.9 (C-2), 151.2 (C-13), 152.3 (C-10), 156.4 (C-16), 166.7 (C-1);

MS (ESI): 457 ($[MH]^+$), 479 ($[MNa]^+$);

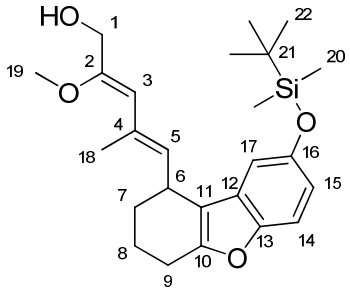
HRMS (ESI): Calculated for $C_{26}H_{37}O_5Si$, 457.2405. Found: $[MH^+]$, 457.2397 (1.9 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2886, 2812, 2487, 1693, 1675, 1643, 1625, 1566, 1438, 1231, 1185, 1086, 918, 825, 792, 766.

Obtained data in accord with those reported in the literature.[18]

Lab Notebook Reference: PC/8/19.

(2*Z*,4*E*)-5-(8-{[*tert*-Butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-2-methoxy-4-methylpenta-2,4-dien-1-ol, 145



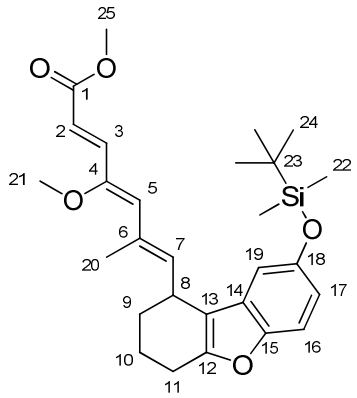
To a stirred solution of ester **24** (276 mg, 0.604 mmol) in THF (12 mL) at 0 °C was added $LiBH_4$ (4.0 M in THF, 1.51 mL, 6.04 mmol). The resulting solution was held at 0 °C for 10 min and then warmed to rt. After 18 h, the resulting solution was quenched with brine (5 mL) and further diluted with H_2O (5 mL) and EtOAc (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver the crude alcohol **145** as a clear, colourless oil. The crude material was used immediately in the next reaction without further purification.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.32;

^{1}H-NMR (400 MHz, CD_3OD): δ_H 0.14 (3 H, s, H-20), 0.14 (3 H, s, H-20), 0.96 (9 H, s, H-22), 1.45 (1 H, dddd, *J* 2.6, 8.4, 11.1, 13.4, H-7a), 1.74 – 1.82 (1 H, m, H-8a), 1.89 – 1.96 (1 H, m, H-7b), 1.97 – 2.06 (1 H, m, H-8b), 2.00 (3 H, s, H-18), 2.60 – 2.67 (2 H, m, H-9), 3.67 (3 H, s, H-19), 3.68 – 3.75 (1 H, m, H-6), 4.08 (2 H, s, H-1), 5.24 (1 H, s, H-3), 5.39 (1 H, d, *J* 10.1 Hz, H-5), 6.62 (1 H, dd, *J* 2.5, 8.7 Hz, H-15), 6.74 (1 H, d, *J* 2.5 Hz, H-17), 7.14 (1 H, d, *J* 8.7 Hz, H-14);

MS (ESI): 429 ($[MH]^+$), 451 ($[MNa]^+$), 411 ($[MH-H_2O]^+$);
HRMS (ESI): Calculated for $C_{25}H_{37}O_4Si$, 429.2456. Found: $[MH^+]$, 429.2457 (0.3 ppm error).
Lab Notebook Reference: PC/8/21.

Methyl (2*E*,4*Z*,6*E*)-7-(8-{[*tert*-butyl(dimethyl)silyl]oxy}-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-4-methoxy-6-methylhepta-2,4,6-trienoate, 26



To a solution of the impure alcohol **145** (0.604 mmol) in CH_2Cl_2 at rt was added MnO_2 (1.05 g, 12.1 mmol) and methyl (triphenylphosphoranylidene) acetate (505 mg, 1.51 mmol). After 30 h, the resulting suspension was filtered through celite. The filtrate was concentrated *in vacuo* to deliver a brown oil. The crude material was purified by flash column chromatography (SiO_2, 8:1 petrol:Et_2O) to afford the desired triene **26** (177 mg, 61% from 23) as a yellow oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.18;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.14 (6 H, s, H-22), 0.95 (9 H, s, H-24), 1.50 – 1.71 (1 H, m, H-9a), 1.80 – 1.93 (1 H, m, H-10a), 1.96 – 2.13 (2 H, m, H-9b and H-10b), 2.23 (3 H, s, H-20), 2.69 – 2.76 (2 H, m, H-11), 3.64 (3 H, s, H-21), 3.76 (3 H, s, H-25), 3.77 – 3.89 (1 H, m, H-8), 5.73 (1 H, d, *J* 10.4 Hz, H-7), 5.80 (1 H, s, H-5), 6.06 (1 H, d, *J* 15.4 Hz, H-2), 6.68 (1 H, dd, *J* 2.3, 8.7 Hz, H-17), 6.71 (1 H, d, *J* 2.3 Hz, H-19), 7.05 (1 H, d, *J* 15.4 Hz, H-3), 7.22 (1 H, d, *J* 8.7 Hz, H-16);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -4.6 (C-22), -4.5 (C-22), 14.9 (C-20), 18.2 (C-23), 21.4 (C-10), 23.4 (C-11), 25.7 (C-24), 29.7 (C-9), 32.3 (C-8), 51.6 (C-25), 60.1 (C-21), 109.3 (C-19), 110.9 (C-16), 114.5 (C-12), 115.9 (C-17), 116.6 (C-2), 128.8 (C-14), 129.9 (C-5),

131.6 (C-6), 139.5 (C-7), 142.2 (C-3), 149.6 (C-14), 150.9 (C-4), 151.9 (C-15), 154.9 (C-13), 167.5 (C-1);

MS (ESI): 483 ($[MH]^+$), 505 ($[MNa]^+$);

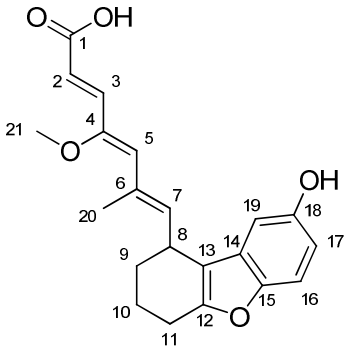
HRMS (ESI): Calculated for $C_{28}H_{39}O_5Si$, 483.2561. Found: $[MH^+]$, 483.2539 (4.0 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2888, 2813, 1691, 1594, 1440, 1283, 1239, 1185, 1148, 918, 826, 794, 768, 722.

Obtained data in accord with those reported in the literature.[18]

Lab Notebook Reference: PC/8/26.

(2*E*,4*Z*,6*E*)-7-(8-Hydroxy-1,2,3,4-tetrahydrodibenzo[*b*,*d*]furan-1-yl)-4-methoxy-6-methylhepta-2,4,6-trienoic acid, (±)-15



To a solution of methyl ester **26** (277 mg, 0.574 mmol) in dioxane:H_2O (1:1, 12 mL) was added LiOH.H_2O (482 mg, 11.5 mmol). The resulting suspension was stirred at rt for 4 d and then quenched with HCl (10% aq. solution) until pH ~3 was reached and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a brown oil. The crude material was purified by flash column chromatography (SiO_2, 9:1 CH_2Cl_2:MeOH) to afford the desired acid **15** (122 mg, 60%) as a pale yellow wax.

***R*$_f$ (SiO_2, 9:1 CH_2Cl_2:MeOH):** 0.27;

^{1}H-NMR (400 MHz, CD_3OD): δ_H 1.50 – 1.63 (1 H, m, H-9a), 1.81 – 1.93 (1 H, m, H-10a), 1.96 – 2.14 (2 H, m, (H-9b and H-10b), 2.24 (3 H, s, H-20), 2.67 – 2.74 (2 H, m, H-11), 3.65 (3 H, s, H-21), 3.84 (1 H, ddd, *J* 5.7, 7.7, 10.1 Hz, H-8), 5.79 (1 H, d, *J* 10.1 Hz,

H-7), 5.91 (1 H, s, H-5), 5.99 (1 H, d, *J* 15.4 Hz, H-2), 6.63 (1 H, dd, *J* 2.4, 8.7 Hz, H-17), 6.69 (1 H, d, *J* 2.4 Hz, H-17), 7.07 (1 H, d, *J* 15.4 Hz, H-3), 7.15 (1 H, d, *J* 8.7 Hz, H-16);

^{13}C-NMR (100 MHz, CD_3OD): δ_C 15.4 (C-20), 22.5 (C-10), 24.3 (C-11), 31.0 (C-9), 33.6 (C-8), 60.7 (C-21), 105.3 (C-19), 111.8 (C-16), 112.4 (C-17), 115.7 (C-13), 118.2 (C-2), 130.3 (C-14), 131.0 (C-5), 133.0 (C-6), 140.9 (C-7), 143.8 (C-3), 150.3 (C-18), 153.5 (C-4), 153.8 (C-15), 156.1 (C-12), 170.5 (C-1);

MS (ESI): 355 ($[MH]^+$), 377 ($[MNa]^+$);

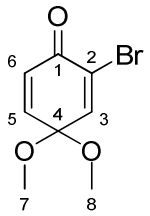
HRMS (ESI): Calculated for $C_{21}H_{23}O_5$, 355.1540. Found: [MH^+], 355.1521 (3.5 ppm error)];

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3340, 2887, 2283, 1655, 1594, 1440, 1176, 1025, 792.

Lab Notebook Reference: PC/8/27.

5.3. Experimental Procedures and Product Characterisation for Chapter 3

2-Bromo-4,4-dimethoxycyclohexa-2,5-dienone, 184



Double Oxidation Procedure:

To a stirred solution of PIDA (782 mg, 2.43 mmol) in MeOH (2 mL) at rt was added a solution of phenol **183** (200 mg, 1.16 mmol) in MeOH (2 mL). After 1 h, the resulting black solution was diluted with EtOAc (5 mL) and $NaHCO_3$ (sat. aq. solution, 10 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($NaSO_4$), filtered and concentrated *in vacuo* to deliver a dark yellow oil. The crude material was purified by flash coloumn chromatography (SiO_2, 1:1 petrol:Et_2O) to afford quinone **184** (107 mg, 40%) as a yellow oil.

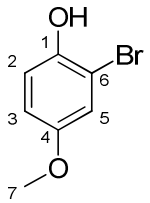
Single Oxidation Procedure:

To a stirred solution of PIDA (2.59 g, 8.04 mmol) in MeOH (17.5 mL) at rt was added a solution of phenol **185** (1.63 g, 8.04 mmol) in MeOH (17.5 mL). After 2 h, the resulting

yellow solution was diluted with EtOAc (25 mL) and $NaHCO_3$ (sat. aq. solution, 50 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 75 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to deliver a yellow oil. The crude material was purified by flash chromatography (SiO_2, 3:2 petrol:Et_2O) to afford quinone **184** (1.34 g, 72%) as a yellow oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.53;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.37 (6 H, s, H-7 and H-8), 6.36 (1 H, d, *J* 10.3 Hz, H-6), 6.84 (1 H, dd, *J* 10.3, 3.0 Hz, H-5), 7.27 (1 H, d, *J* 3.0 Hz, H-3);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 50.6 (C-7 and C-8), 94.4 (C-4), 125.9 (C-2), 128.2 (C-6), 143.6 (C-5), 143.9 (C-3), 177.8 (C-1);
MS (ESI): 255 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_8H_9{}^{79}BrNaO_3$, 254.9627. Found: $[MH^+]$, 254.9630 (1.1 ppm error).
Lab Notebook Reference: PC/1/13.

2-Bromo-4-methoxyphenol, 185



To a stirred solution of 4-methoxyphenol **72** (1 g, 8.06 mmol) in CH_2Cl_2 (30 mL) at rt was added a solution of bromine (0.41 mL, 8.06 mmol) in CH_2Cl_2 (10 mL). After 30 min, the resulting deep red solution was quenched with $NaHCO_3$ (sat. aq. solution, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a brown oil. The crude material was purified by flash coloumn chromatography (SiO_2, 7:3 petrol:Et_2O) to afford phenol **185** (1.63 g, 100%) as a brown oil.

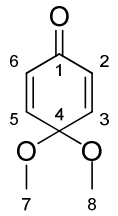
***R*f (SiO2, 7:3 petrol:Et2O):** 0.36;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.73 (3 H, s, H-7), 5.31 (1 H, br s, -OH), 6.78 (1 H, dd, *J* 2.9, 8.9 Hz, H-3), 6.92 (1 H, d, *J* 8.9 Hz, H-2), 7.00 (1 H, d, *J* 2.9 Hz, H-5).

Obtained data in accord with those reported in the literature.[69]

Lab Notebook Reference: PC/1/11.

4,4-Dimethoxycyclohexa-2,5-dienone, 152



To a stirred suspension of PIDA (2.59 g, 8.06 mmol) in MeOH (10 mL) at rt was added a solution of phenol **72** (1 g, 8.06 mmol) in MeOH (10 mL). After 16 h, the resulting yellow solution the reaction was diluted with EtOAc (20 mL) and $NaHCO_3$ (sat. aq. solution, 50 mL) and the layers separated. The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organics were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to deliver a yellow oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford quinone **152** (1.16 g, 93%) as a pale yellow oil.

***R*f (SiO2, 1:1 petrol:Et2O):** 0.57;

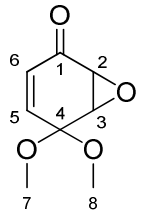
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.35 (6 H, s, H-7 and H-8), 6.27 (2 H, d, *J* 10.4 Hz, H-3 and H-5), 6.81 (2 H, d, *J* 10.4 Hz, H2 and H-6);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 50.4 (C-7 and C-8), 92.4 (C-4), 130.0 (C-3 and C-5), 143.2 (C-2 and C-6), 185.1 (C-1).

Obtained data in accord with those reported in the literature.[79]

Lab Notebook Reference: PC/1/16.

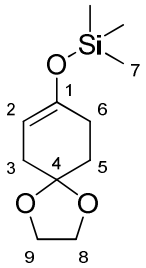
5,5-Dimethoxy-7-oxabicyclo[4.1.0]hept-3-en-2-one, 190[61]



To a stirred solution of quinone **152** (250 mg, 1.62 mmol) in THF:H_2O (15 mL, 1:1) at rt was added K_2CO_3 then H_2O_2. After 16 h, the resulting solution was diluted with Et_2O (15 mL) and the layers separated. The aqueous layer was washed with Et_2O (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver an inseparable mixture of quinone **152** and epoxide **190** (**152**:**190** = 1:2.57) as a yellow gum.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.57;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.38 (3 H, s, H-7 or H-8), 3.45 – 3.49 (1 H, m, H-2), 3.53 (3 H, s, H-7 or H-8), 3.77 – 3.81 (1 H, m, H-3), 5.99 (1 H, dd, *J* 2.0, 10.9 Hz, H-6), 6.53 (1 H, dd, *J* 2.9, 10.9 Hz, H-5).
Obtained data in accord with those reported in the literature.[61]
Lab Notebook Reference: PC/1/34.

(1,4-Dioxaspiro[4.]dec-7-en-8-yloxy)(trimethyl)silane, 200[64]

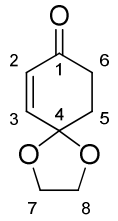


To a solution of ketone **195** (1.00 g, 6.40 mmol) and triethylamine (1.94 g, 2.68 mL, 19.2 mmol) in CH_2Cl_2 (70 mL) at 0 °C was added TMSOTf (1.56 g, 1.27 mL, 7.04 mmol) in CH_2Cl_2 (20 mL). After 30 min, the resulting green solution was quenched with $NaHCO_3$ (sat. aq. solution, 50 mL) and H_2O (50 mL) and the layers separated. The organic was dried

($MgSO_4$), filtered and concentrated *in vacuo* to deliver impure enol ether **200** as a brown oil. The crude material was used in the next reaction without purification.

***R*f (SiO2, 1:1 petrol:Et2O):** 0.66;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.18 (9 H, s, H-7), 1.80 (2 H, t, *J* 6.6 Hz, H-5), 2.18 – 2.24 (2 H, m, H-6), 2.24 – 2.28 (2 H, m, H-3), 3.94 – 3.99 (4 H, m, H-8 and H-9), 4.72 (1 H, tt, *J* 1.2, 3.9 Hz, H-2).
Obtained data in accord with those reported in the literature.[64]
Lab Notebook Reference: PC/6/12/C2.

1,4-Dioxaspiro[4.5]dec-6-en-8-one, 194



To a stirred solution of impure enol ether 200 (5.35 mmol, assumed 100% purity) in DMSO (25 mL) at rt was added $Pd(OAc)_2$ (240 mg, 1.07 mmol). The resulting brown suspension was then stirred under an atmosphere of O_2. After 20 h, the resulting suspension was diluted with CH_2Cl_2 (25 mL) and brine (30 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a brown oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford enone **194** (594 mg, 72% over two steps) as a clear, colourless oil.

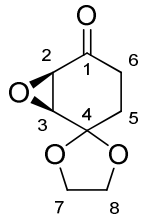
***R*f (SiO2, 1:1 petrol:Et2O):** 0.17;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.19 (2 H, ddd, *J* 7.4, 6.1, 1.0 Hz, H-5), 2.60 – 2.64 (2 H, m, H-6), 4.05 – 4.02 (4 H, m, H-7 and H-8), 6.00 (1 H, d, *J* 10.2 Hz, H-2), 6.61 (1 H, dt, *J* 10.2, 1.0 Hz, H-3);
MS (ESI): 155 ($[MH]^+$), 177 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_8H_{11}O_3$, 155.0703. Found: [MH^+], 155.0703 (0.6 ppm error).

Obtained data in accord with those reported in the literature.[64]

Lab Notebook Reference: PC/6/13/P1.

(1'*S,6'*R**)-5'*H*-spiro[1,3-dioxolane-2,2'-[7]oxabicyclo[4.1.0]heptan]-5'-one, 193**



To a stirred solution of enone **194** (100 mg, 0.649 mmol) in MeCN (7 mL) at rt was added H_2O_2 (30 wt%, 221 mg, 6.49 mmol, 0.74 mL) and DBU (494 mg, 3.25 mmol, 0.49 mL). After 3 h, the resulting brown solution was quenched with brine (10 mL) and CH_2Cl_2 (10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a brown oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford epoxide **193** (25 mg, 23%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.17;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.68 (1 H, dddd, *J* 1.5, 2.8, 6.5, 13.5 Hz, H-5_{eq}), 2.27 (1 H, ddd, *J* 6.6, 11.4, 13.5 Hz, H-5_{ax}), 2.38 (1 H, ddd, *J* 6.5, 11.4, 18.0 Hz, H-6_{ax}), 2.48 (1 H, dddd, *J* 0.5, 2.8, 6.6, 18.0 Hz, H-6_{eq}), 3.33 (1 H, dd, *J* 0.5, 4.0 Hz, H-2), 3.37 (1 H, dd, *J* 1.5, 4.0 Hz, H-3), 3.91 – 3.99 (1 H, m, H-7 or H-8), 4.06 – 4.14 (3 H, m, H-7 and H-8);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 26.2 (C-5), 33.7 (C-6), 56.0 (C-2), 56.7 (C-3), 65.2 (C-7/C-8), 65.5 (C-7/C-8), 106.8 (C-4), 203.2 (C-1);

MS (ESI): 171 ([$MH]^+$), 193 ([$MNa]^+$);

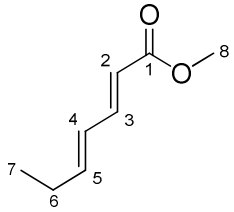
HRMS (ESI): Calculated for $C_8H_{11}O_4$, 171.0652. Found: [MH^+], 171.0652 (0.9 ppm error).

Lab Notebook Reference: PC/6/93/P1.

5.4. Experimental Procedures and Product Characterisation for Chapter 4

5.4.1. Synthesis of (*E*)-Methyl 3-(Oxiran-2-yl)acrylates

Methyl (2*E*,4*E*)-hept-2,4-dienoate, *E*,*E*-212



To a stirred solution of $Ph_3P{=}CHCO_2CH_3$ (1.99 g, 5.94 mmol) in CH_2Cl_2 (10 mL) at rt was added aldehyde **211**, (0.58 mL, 5.94 mmol) and the solution was then heated to reflux. After 16 h, the resulting solution was filtered through a short silica pad, washing with Et_2O to deliver impure diene *E,E*-**212** as a clear, colourless oil. The crude material was used in the next reaction without further purification.

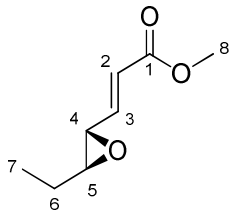
***R*$_f$ (SiO_2, 4:1 petrol:EtOAc):** 0.42

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.03 (3 H, t, *J* 7.5 Hz, H-7), 2.14 – 2.24 (2 H, m, H-6), 3.72 (3 H, s, H-8), 5.78 (1 H, d, *J* 15.6 Hz, H-2), 6.13 – 6.18 (2 H, m, H-4 and H-5), 7.22 – 7.30 (1 H, m, H-3).

Obtained data in accord with those reported in the literature.[67]

Lab Notebook Reference: PC/1/88.

Methyl (2*E*)-3-[(4*S,5*S**)-3-ethyloxiran-2-yl]acrylate, *E*,*trans*-213**

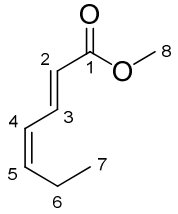


To a stirred solution of impure *E,E*-**212** (714 mg, 5.09 mmol) in CH_2Cl_2 (10 mL) was added *m*CPBA (1.29 g, 7.64 mmol). After 48 h, the resulting solution was filtered, washing with CH_2Cl_2. The filtrate was washed with brine (20 mL) and the organic layer was dried

($MgSO_4$), filtered and concentrated *in vacuo* to deliver a white solid. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to deliver epoxide *E*,*trans*-**213** (442 mg, 56% over two steps) as a clear, colourless liquid.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.3;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.99 (3 H, t, *J* 7.5 Hz, H-7), 1.59 – 1.67 (2 H, m, H-6), 2.86 (1 H, dt, *J* 2.0, 5.4 Hz, H-5), 3.21 (1 H, dd, *J* 2.0, 7.0 Hz, H-4), 3.72 (3 H, s, H-8), 6.11 (1 H, d, *J* 15.6 Hz, H-2), 6.67 (1 H, dd, *J* 7.0, 15.6 Hz);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 10.2 (C-7), 20.9 (C-6), 51.7 (C-8), 55.2 (C-4), 60.8 (C-5), 124.7 (C-2), 142.2 (C-3), 166.0 (C-1);
MS (ESI): 157 ($[MH]^+$);
HRMS (ESI): Calculated for $C_8H_{13}O_3$, 157.0859. Found: $[MH^+]$, 157.0857 (1.2 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2971, 2359, 1726, 1659, 1438, 1308, 1275, 1195, 1144, 1040, 1011, 978, 887, 852.
Lab Notebook Reference: PC/1/89.

Methyl (2*E*,4*Z*)-hept-2,4-dienoate, *E*,*Z*-212



To a stirred solution of alkene **219** (1 mL, 9.90 mmol) in CH_2Cl_2 (300 mL) at rt was added MnO_2 (8.6 g, 99.0 mmol) and Ph_3PCHCO_2Me (3.98 g, 11.9 mmol). After 4 d, the resulting suspension was filtered through a celite pad. The solvent was evaporated under a flow of air to deliver impure diene *E*,*Z*-**212** as a clear, colourless oil. The crude material was used in the next reaction without further purification.

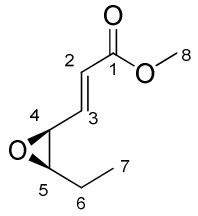
***R*f (SiO$_2$, 3:2 petrol:Et$_2$O):** 0.83;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 1.04 (3 H, t, *J* 7.5 Hz, H-7), 2.27 – 2.36 (2 H, m, H-6), 3.75 (3 H, s, H-8), 5.83 – 5.90 (2 H, m, H-2 and H-4), 6.04 – 6.13 (1 H, m, H-5), 7.62 (1 H, ddd, *J* 1.1, 11.7, 15.2 Hz, H-3).

Obtained data in accord with those reported the in literature.[68]

Lab Notebook Reference: PC/1/97.

Methyl (2*E*)-3-((2*S,3*R**)-3-ethyloxiran-2-yl)acrylate, *E*,*cis*-213**



To a stirred solution of unpurified diene *E*,*Z*-**212** (9.90 mmol) in CH_2Cl_2 (20 mL) at rt was added *m*CPBA (2.56 g, 14.9 mmol). After 16 h, the resulting suspension was filtered through a celite pad. The filtrate was separated between CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a white solid. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford the desired epoxide *E*,*cis*-**213** (442 mg, 45% over two steps) as a clear, colourless liquid.

***R*f (SiO$_2$, 4:1 petrol:EtOAc):** 0.30;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 0.99 (3 H, t, *J* 7.5 Hz, H-7), 1.39 – 1.68 (2 H, m, H-6), 3.14 (1 H, dt, *J* 4.4, 6.4 Hz, H-5), 3.51 (1 H, ddd, *J* 1.0, 4.4, 6.6 Hz, H-4), 3.73 (3 H, s, H-8), 6.12 (1 H, dd, *J* 1.0, 15.7 Hz, H-2), 6.80 (1 H, dd, *J* 6.6, 15.7 Hz, H-3);

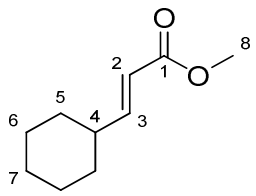
^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 10.2 (C-7), 20.9 (C-6), 51.7 (C-8), 55.2 (C-4), 60.8 (C-5), 124.7 (C-2), 142.2 (C-3), 166.0 (C-1);

MS (ESI): 157 ($[MH]^+$);

HRMS (ESI): Calculated for $C_8H_{13}O_3$, 157.0859. Found: $[MH^+]$, 157.0861 (1.5 ppm error).

Lab Notebook Reference: PC/2/2.

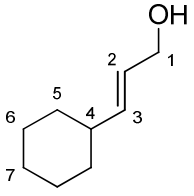
Methyl (2*E*)-3-cyclohexylacrylate, 284



To a stirred solution of Ph_3PCHCO_2Me (7.16 g, 21.4 mmol) in CH_2Cl_2 (90 mL) at rt was added cylcohexanecarbaldehyde (2 g, 17.8 mmol). After 18 h, the reaction mixture was concentrated *in vacuo* to deliver a crude white solid. The crude material was purified by flash column chromatography (SiO_2, 19:1 petrol:Et_2O) to afford ester **284** (2.85 g, 95%) as a clear colourless oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.45;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.07 – 1.37 (5 H, m, -Cy), 1.64 – 1.71 (1 H, m, -Cy), 1.71 – 1.80 (4 H, m, -Cy), 2.07 – 2.18 (1 H, m, H-4), 3.72 (3 H, s, H-8), 5.76 (1 H, dd, *J* 1.5, 15.1 Hz, H-2), 6.92 (1 H, dd, *J* 6.8, 15.8 Hz, H-3);
MS (ESI): 169 ($[MH]^+$);
HRMS (ESI): Calculated for $C_{10}H_{17}O_2$, 169.1223 Found: $[MH^+]$, 169.1223 (0.1 ppm error).
Obtained data in accord with those reported in literature.[80]
Lab Notebook Reference: PC/9/53.

(*2E*)-3-Cyclohexylprop-2-en-1-ol, 285

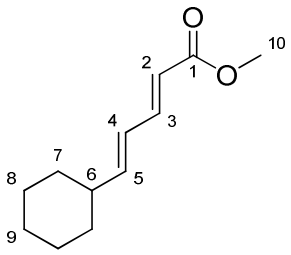


To a stirred solution of methyl ester **284** (2.83 g, 16.8 mmol) in toluene (100 mL) at 0 °C was added DIBAL-H (1 M in hexanes, 33.6 mL, 33.6 mmol). The resulting solution was stirred at rt for 1.5 h and then quenched with Rochelle's salt (sat. aq. solution, 100 mL) and further diluted with EtOAc (25 mL). The resulting biphasic system was stirred vigorously

for 2 h and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 75 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford impure alcohol **285** as a clear, colourless oil. The crude material was carried forward to the next reaction without further purification.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.16;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.99 – 1.34 (5 H, m, -Cy), 1.44 (1 H, br s, -OH), 1.60 – 1.77 (5 H, m, -Cy), 1.91 – 2.01 (1 H, m, H-4), 4.07 – 4.10 (2 H, m, H-1), 5.54 – 5.67 (2 H, m, H-2 and H-3);
MS (ESI): 163 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_9H_{16}NaO$, 163.1093. Found: $[MH^+]$, 163.1090 (0.1 ppm error).
Obtained data in accord with those reported in literature.[81]
Lab Notebook Reference: PC/9/55.

Methyl (2*E*,4*E*)-5-cyclohexylpenta-2,4-dienoate, *E*,*E*-286



To a stirred solution of impure alcohol **285** (16.8 mmol, assume 100% yield from previous reaction) in CH_2Cl_2 (50 mL) at rt was added MnO_2 (14.6 g, 168.0 mmol) and Ph_3PCHCO_2Me (6.74 g, 20.2 mmol). The resulting mixture was heated at 40 °C for 18 h, then filtered through celite, washing with EtOAc. The filtrate was concentrated *in vacuo* to afford a crude white solid. The crude material was purified by flash column chromatography (SiO_2, 19:1 petrol:Et_2O) to afford the methyl ester *E*,*E*-**286** (2.45 g, 75% over two steps) as a clear, colourless oil.

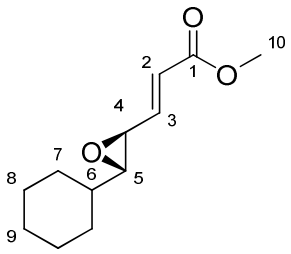
***R*f (SiO2, 4:1 petrol:Et2O):** 0.39;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.04 – 1.34 (5 H, m, -Cy), 1.61 – 1.82 (5 H, m, -Cy), 2.03 – 2.14 (1 H, m, H-4), 3.73 (3 H, s, H-10), 5.79 (1 H, dd, *J* 0.4, 15.4 Hz, H-2), 6.03 – 6.17 (2 H, m, H-4 and H-5), 7.26 (1 H, dd, *J* 10.1, 15.4 Hz, H-3).

Obtained data in accord with those reported in literature.[82]

Lab Notebook Reference: PC/9/57.

Methyl (2*E*)-3-[(2*S,3*S**)-3-cyclohexyloxiran-2-yl]acrylate, *E*,*trans*-220**



To a stirred solution of methyl ester *E*,*E*-**286** (2.43 g, 12.5 mmol) in CH_2Cl_2 (35 mL) at rt was added *m*CPBA (70% purity, 3.69 g, 15.0 mmol). After 16 h, the resulting suspension was quenched with 1:1 $Na_2S_2O_3$:$NaHCO_3$ (both sat. aq. solutions, 35 mL). The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude white solid. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford epoxide *E*,t*rans*-**220** (2.01 g, 76%) as a white solid.

Mp: 51 – 52 °C;

***R*f (SiO2, 9:1 petrol:Et2O):** 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.03 – 1.35 (5 H, m, -Cy), 1.62 – 1.80 (5 H, m, -Cy), 1.80 – 1.89 (1 H, m, H-6), 2.69 (1 H, dd, *J* 2.1, 6.8 Hz, H-5), 3.27 (1 H, dd, *J* 0.7, 2.1, 7.1 Hz, H-4), 3.74 (3 H, s, H-12), 6.11 (1 H, dd, *J* 0.7, 15.7 Hz, H-2), 6.69 (1 H, dd, *J* 7.1, 15.7 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 25.4 (C-Cy), 25.5 (C-Cy), 26.1 (C-Cy), 28.8 (C-Cy), 29.5 (C-Cy), 40.0 (C-6), 51.7 (C-12), 55.1 (C-4), 65.8 (C-5), 122.8 (C-2), 145.4 (C-3), 166.2 (C-1);

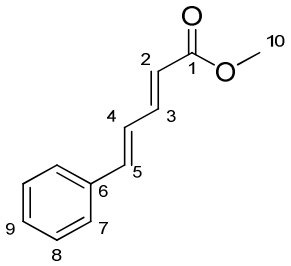
MS (ESI): 211 ($[MH]^+$), 223 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{12}H_{19}O_3$, 211.1329. Found: $[MH^+]$, 211.1323 (2.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2882, 2809, 1698, 1632, 1423, 1287, 1240, 1177, 1159, 1126, 840.

Lab Notebook Reference: PC/9/58.

Methyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate, *E*,*E*-287



To a stirred solution of (2*E*, 4*E*)-5-phenyl-2,4-pentadienoic acid (2.96 g, 17.0 mmol) in MeOH (400 mL) was added H_2SO_4 (1 mL). After 18 h, the reaction mixture was diluted with EtOAc (100 mL) and H_2O (200 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford methyl ester *E*,*E*-**287** (2.98 g, 93%) as a white solid.

Mp: 69 – 71 °C (Lit.[S] 68 – 70 °C);

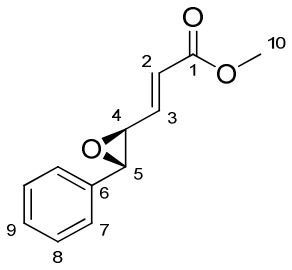
***R*$_f$ (SiO$_2$, 4:1 petrol:Et$_2$O):** 0.52;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 3.78 (3 H, s, H-10), 6.00 (1 H, d, *J* 15.3 Hz, H-2), 6.83 – 6.94 (2 H, m, H-4 and H-5), 7.28 – 7.39 (3 H, m, -Ph), 7.42 – 7.50 (2 H, m, -Ph), 7.46 (1 H, ddd, *J* 1.9, 8.4, 15.3 Hz, H-3).

Obtained data in accord with those reported in literature.[83]

Lab Notebook Reference: PC/8/28.

Methyl (2*E*)-3-[(2*S,3*S**)-3-phenyloxiran-2-yl]acrylate, *E*,*trans*-221**



To a stirred solution of methyl ester *E*,*E*-**287** (1.12 g, 5.95 mmol) in CH_2Cl_2 (30 mL) at rt was added, portionwise, *m*CPBA (70% purity, 3.23 g, 13.1 mmol). After 16 h, the resulting suspension was quenched with 1:1 $Na_2S_2O_3$:$NaHCO_3$ (both sat. aq. solutions, 35 mL). The biphasic mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a crude white solid. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford epoxide *E*,*trans*-**221** (656 mg, 54%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.39;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.47 (1 H, ddd, *J* 0.8, 1.8, 6.9 Hz, H-4), 3.76 (3 H, s, H-10), 3.83 (1 H, d, *J* 1.8 Hz, H-5), 6.20 (1 H, dd, *J* 0.8, 15.7 Hz, H-2), 6.83 (1 H, dd, *J* 6.9, 15.7 Hz, H-3), 7.27 – 7.50 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 51.8 (C-10), 60.5 (C-4), 61.1 (C-5), 123.6 (C-2), 125.5 (C-Ph), 127.2 (C-Ph), 128.6 (C-Ph), 136.0 (C-6), 143.9 (C-3), 166.1 (C-1);

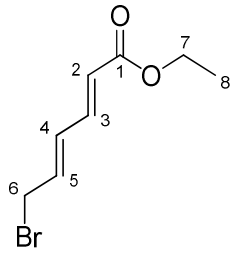
MS (ESI): 205 ($[MH]^+$), 227 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{12}H_{13}O_3$, 205.0859. Found: [MH^+], 205.0857 (0.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2906, 1695, 1633, 1600, 1414, 1327, 1288, 1245, 1157, 1119, 961, 833, 745, 687.

Lab Notebook Reference: PC/8/30.

Ethyl (2*E*,4*E*)-6-bromohexa-2,4-dienoate, *E*,*E*-288



To a stirred suspension of ethyl sorbate (2.64 mL, 2.5 g, 17.8 mmol) and NBS (4.75 g, 26.7 mmol) in chlorobenzene (11 mL) at 100 ^{o}C was added $(PhCO_2)_2$ (1:1 with plasticiser, 431 mg, 0.890 mmol). After 6 h, the reaction mixture was cooled to rt and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 95:5 petrol:Et_2O) to afford bromide *E*,*E*-**288** (4.53 g, 29%) as a yellow oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.23;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.30 (3 H, t, *J* 7.1 Hz, H-8), 4.03 (2 H, dd, *J* 0.7, 7.6 Hz, H-6), 4.21 (2 H, q, *J* 7.1 Hz, H-7), 5.93 (1 H, d, *J* 15.4 Hz, H-2), 6.24 (1 H, dt, *J* 7.6, 15.0 Hz, H-5), 6.38 (1 H, ddd, *J* 0.7, 10.9, 15.0 Hz, H-4), 7.25 (1 H, dd, *J* 10.9, 15.4 Hz, H-3);

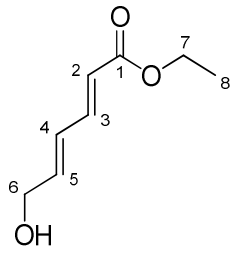
MS (ESI): 219 ($[MH]^+$);

HRMS (ESI): Calculated for $C_8H_{12}{}^{79}BrO_2$, 219.0015. Found: $[MH^+]$, 219.0016 (-0.5 ppm error).

Obtained data in accord with those reported in literature.[84]

Lab Notebook Reference: PC/4/40.

Ethyl (2*E*,4*E*)-6-hydroxyhexa-2,4-dienoate, *E*,*E*-289

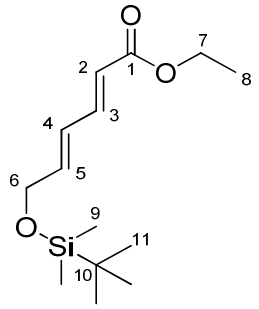


To a stirred solution of bromide *E*,*E*-**288** (928 mg, 4.24 mmol) in acetone (12 mL) at rt was added $NaHCO_3$ (sat. aq. solution, 8 mL). The reaction mixture was heated to reflux. After 5 h, the reaction was cooled to rt and concentrated *in vacuo*. The biphasic system was

diluted with Et_2O (25 mL). The aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford impure alcohol *E*,*E*-**289** as a yellow oil. The crude material was carried forward to the next reaction without further purification.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.18;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.30 (3 H, t, *J* 7.1 Hz, H-8), 4.20 (2 H, q, *J* 7.1 Hz, H-7), 4.30 (2 H, dd, *J* 1.7, 5.0 Hz, H-6), 5.89 (1 H, d, *J* 15.4 Hz, H-2), 6.22 (1 H, dt, *J* 5.0, 15.2 Hz, H-5), 6.41 (1 H, ddt, *J* 1.7, 10.9, 15.2 Hz, H-4), 7.29 (1 H, dd, *J* 10.9, 15.4 Hz, H-3);
MS (ESI): 157 ($[MH]^+$);
HRMS (ESI): Calculated for $C_8H_{13}O_3$, 157.0859. Found: $[MH^+]$, 157.0861 (0.8 ppm error).
Obtained data in accord with those reported in literature.[85]
Lab Notebook Reference: PC/4/50.

Ethyl (2*E*,4*E*)-6-(*tert*-butyldimethylsilyloxy)hexa-2,4-dienoate, *E*,*E*-290



To a stirred solution of impure alcohol *E*,*E*-**289** (4.24 mmol, assumed 100% purity) in CH_2Cl_2 (10 mL) at rt was added imidazole (866 mg, 12.7 mmol) followed by TBSCl (959 mg, 6.36 mmol). After 1.5 h, the reaction mixture was diluted with H_2O (20 mL) and CH_2Cl_2 (10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a yellow oil. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford diene *E*,*E*-**290** (780 mg, 68% over two steps) as a clear, colourless oil.

R_f (SiO_2, 4:1 petrol:Et_2O): 0.67;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.08 (6 H, s, H-9), 0.92 (9 H, s, H-11), 1.29 (3 H, t, *J* 7.1 Hz, H-8), 4.20 (2 H, q, *J* 7.1 Hz, H-7), 4.30 (2 H, dd, *J* 1.9, 4.3 Hz, H-6), 5.86 (1 H, d, *J* 15.4 Hz, H-2), 6.17 (1 H, dt, *J* 4.3, 15.1 Hz, H-5), 6.40 (1 H, d, *J* 1.9, 11.1, 15.1 Hz, H-4), 7.30 (1 H, dd, *J* 11.1, 15.3 Hz, H-3);

MS (ESI): 271 ($[MH]^+$);

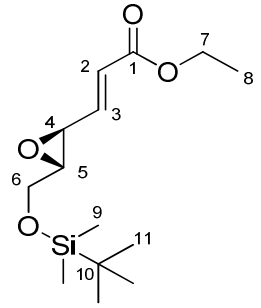
HRMS (ESI): Calculated for $C_{14}H_{27}O_3Si$, 271.1724. Found: $[MH^+]$, 271.1712 (4.5 ppm error)];

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2931, 2857, 1717, 1321, 1258, 1226, 1178, 1127, 1071, 1001, 837, 778.

Obtained data in accord with those reported in literature.[85]

Lab Notebook Reference: PC/4/52.

Ethyl (2*E*,4*S,5*S**)-6-(*tert*-butyldimethylsilyloxy)-2,4-dienoate-4,5-epoxide, *E*,*trans*-222**



To a stirred solution of diene *E*,*E*-**290** (780 mg, 2.88 mmol) in CH_2Cl_2 (10 mL) at rt was added *m*CPBA (70% purity, 1.07 g, 4.33 mmol). After 16 h, the reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq. solution, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The organic layer was washed with $NaHCO_3$ (sat. aq. solution, 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a white solid. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford epoxide *E*,*trans*-**222** (607 mg, 74%) as a clear, colourless oil.

R_f (SiO_2, 4:1 petrol:Et_2O): 0.50;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.07 (3 H, s, H-9), 0.08 (3 H, s, H-9), 0.89 (9 H, s, H-11),1.29 (3 H, t, *J* 7.1 Hz, H-8), 3.06 (1 H, ddd, *J* 2.0, 3.1, 4.0 Hz, H-5), 3.43 (1 H, dd, *J*

2.0, 7.2 Hz, H-4), 3.77 (1 H, dd, *J* 4.0, 12.1 Hz, H-6), 3.88 (1 H, dd, *J* 3.1, 12.1 Hz, H-6), 4.20 (2 H, q, *J* 7.1 Hz, H-7), 6.15 (1 H, d, *J* 15.7 Hz, H-2), 6.69 (1 H, dd, *J* 7.2, 15.7 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -3.0 (C-9), 14.2 (C-8), 18.3 (C-10), 25.8 (C-11), 53.6 (C-4), 60.6 (C-7), 61.0 (C-5), 62.2 (C-6), 124.0 (C-2), 144.1 (C-3), 165.6 (C-1);

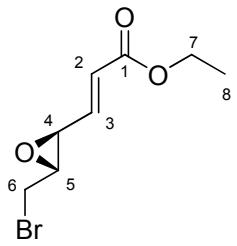
MS (ESI): 287 ($[MH]^+$), 309 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{14}H_{26}NaO_4Si$, 309.1498. Found: [MNa^+], 309.1498 (4.8 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3430, 2954, 2931, 2857, 1723, 1303, 1257, 1185, 1138, 1100, 1039, 837, 779.

Lab Notebook Reference: PC/4/54.

Ethyl (*E*,4*S,5*R**)-6-bromohexa-2,4-dienoate-4,5-epoxide, *E*,*trans*-223**



To a stirred solution of bromide *E*,*E*-**288** (843 mg, 3.85 mmol) in CH_2Cl_2 (10 mL) at rt was added *m*CPBA (70% purity, 1.42 g, 5.77 mmol). After 3 d, the reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq. solution, 10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. solution, 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a white solid. The crude material was purified by flash column chromatography (SiO_2, 4:1 petrol:Et_2O) to afford epoxide *E*,*trans*-**223** (452 mg, 50%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.29 (3 H, t, *J* 7.1 Hz, H-8), 3.25 (1 H, dd, *J* 1.9, 5.6, 6.0 Hz, H-5), 3.39 (1 H, dd, *J* 5.6, 10.8 Hz, H-6), 3.43 (1 H, ddd, *J* 0.8, 1.9, 7.0 Hz, H-4), 3.46 (1 H, dd, *J* 6.0, 10.8 Hz, H-6), 4.21 (2 H, q, *J* 7.1 Hz, H-7), 6.17 (1 H, dd, *J* 0.8, 15.7 Hz, H-2), 6.66 (1 H, dd, *J* 7.0, 15.7 Hz, H-3);

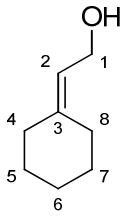
MS (ESI): 235 ($[MH]^+$), 257 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_8H_{12}{}^{79}BrO_3$, 234.9964. Found: $[MH^+]$, 234.9960 (2.6 ppm error).

Obtained data in accord with reported literature.[86]

Lab Notebook Reference: PC/4/42.

2-Cyclohexylideneethanol, 291



To a stirred solution of ethyl cyclohexylideneacetate (1.00 g, 5.94 mmol) in toluene (30 mL) at rt was added DIBALH (1.0 M in toluene, 11.9 mL, 11.9 mmol). After 2 h, the resulting solution was quenched with Rochelle's salt (sat. aq. solution, 30 mL). The resulting biphasic solution was stirred vigorously for 2 h and then the layers were separated. The aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic layers were dired ($MgSO_4$), filtered and concentrated *in vacuo* to afford impure alcohol **291** as a clear, colourless oil. The crude material was used immediately in the next reaction without further purification.

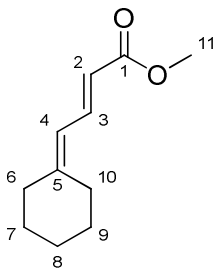
***R*$_f$ (SiO_2, 3:2 Et_2O:petrol):** 0.46;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.38 (1 H, br s, -OH), 1.48 – 1.60 (6 H, m, H-5, H-6 and H-7), 2.08 – 2.20 (4 H, m, H-4 and H-8), 4.14 (2 H, d, *J* 7.2 Hz, H-1), 5.36 (1 H, ttt, *J* 1.1, 1.2, 7.2 Hz, H-2).

Obtained data in accord with reported literature.[87]

Lab Notebook Reference: PC/9/32.

Methyl (2*E*)-4-cyclohexylidenebut-2-enoate, *E*,*E*-292



To a stirred solution of the impure alcohol **291** (5.94 mmol) in CH_2Cl_2 at rt was added MnO_2 (2.58 g, 29.7 mmol) and methyl (triphenylphosphoranylidene)acetate (3.97 g, 11.9 mmol). After 24 h, the resulting suspension was filtered through celite. The filtrate was concentrated *in vacuo* to deliver a brown oil. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford the desired diene *E*,*E*-**292** (725 mg, 68% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.35;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.55 – 1.67 (6 H, m, H-7, H-8 and H-9), 2.18 – 2.25 (2 H, m, H-6/10), 2.37 (2 H, m, H-6/10), 3.74 (3 H, s, H-11), 5.79 (1 H, d, *J* 15.1, H-2), 5.94 (1 H, d, *J* 11.6 Hz, H-4), 7.63 (1 H, dd, *J* 11.7, 15.1 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 26.5 (C-7/8/9), 27.9 (C-7/8/9), 28.5 (C-7/8/9), 29.8 (C-6/10), 37.7 (C-6/10), 51.4 (C-11), 118.2 (C-2), 120.5 (C-4), 140.6 (C-3), 154.6 (C-5), 168.2 (C-1);

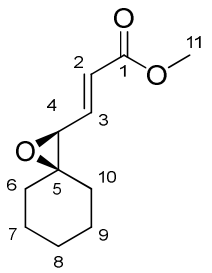
MS (ESI): 181 ($[MH]^+$), 203 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{11}H_{17}O_2$, 181.1223. Found: [MH^+], 181.1224 (0.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2888, 2812, 1693. 1612, 1414, 1288, 1253, 1196, 1150, 1123, 968.

Lab Notebook Reference: PC/9/36.

Methyl (2*E*)-3-[1-oxaspiro[2.5]oct-2-yl]acrylate, *E*,*trans*-224



To a stirred solution of diene *E*,*E*-**292** (661 mg, 3.67 mmol) in CH_2Cl_2 (14 mL) at rt was added *m*CPBA (70% purity, 1.36 g, 5.50 mmol). After 18 h, the reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq. solution, 10 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. solution, 30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a white solid. The crude material was purified by flash column chromatography (SiO_2, 5:1 petrol:Et_2O) to afford epoxide *E*,*trans*-**224** (704 mg, 98%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.29;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.40 – 1.82 (10 H, m, H-6, H-7, H-8, H-9 and H-10), 3.31 (1 H, dd, *J* 1.0, 6.4 Hz, H-4), 3.76 (3 H, s, H-11), 6.11 (1 H, dd, *J* 1.0, 15.7 Hz, H-2), 6.87 (1 H, dd, *J* 6.4, 15.7 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 24.8 (C-7/8/9), 25.1 (C-7/8/9), 25.4 (C-7/8/9), 29.2 (C-6/10), 35.4 (C-6/10), 51.7 (C-11), 62.2 (C-4), 66.5 (C-5), 124.3 (C-2), 142.9 (C-3), 166.2 (C-1);

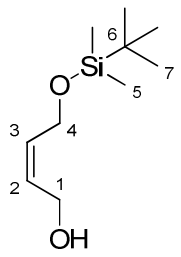
MS (ESI): 219 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{11}H_{16}NaO_3$, 219.0992. Found: [MNa^+], 219.0995 (1.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2891, 2817, 1700, 1631, 1425, 1293, 1275, 1244, 1174, 1152, 964, 887.

Lab Notebook Reference: PC/9/40.

(Z)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol, 226



To a stirred solution of *cis*-but-2-en-1,4-diol **225** (0.93 mL, 11.4 mmol) in THF (20 mL) at 0 °C was added NaH (60% w/w in mineral oil, 454 mg, 11.4 mmol). Once the effervescence had ceased, TBSCl (1.71 g, 11.4 mmol) was added in one portion. The suspension was then warmed slowly to rt. After 2 h, the reaction was quenched with NH_4Cl (sat. aq., 20 mL) and diluted with H_2O (20 mL) and Et_2O (20 mL) and the layers separated. The aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a clear, colourless oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petrol:Et_2O) to afford the desired alkene **226** (2.07 g, 90%) as a clear, colourless oil.

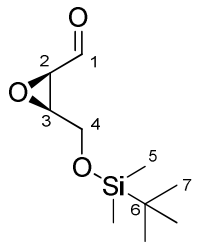
***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.32;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.08 (6 H, s, H-5), 0.90 (9 H, s, H-7), 2.02 (1 H, br s, -OH), 4.23 (4 H, m, H-1 and H-4), 5.61 – 5.75 (2 H, m, H-2 and H-3).

Obtained data in accord with those reported in literature.[69]

Lab Notebook Reference: PC/2/26.

(2*R,3*R**)-3-9{[*tert*-Butyl(dimethyl)silyl]oxy}methyl)oxirane-2-carbaldehyde, *cis*-228**



To a stirred solution of epoxide *cis*-**227** (3.68 g, 16.9 mmol) in CH_2Cl_2 (100 mL) at rt was added DMP (8.58 g, 20.2 mmol). After 3 d, the reaction mixture was filtered through a celite plug eluting with CH_2Cl_2. The filtrate was diluted with H_2O (100 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a colourless oil. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to afford aldehyde *cis*-**228** (2.96 g, 81%) as a clear, colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.45;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.07 (6 H, s, H-5), 0.88 (9 H, s, H-7), 3.39 (1 H, dd, *J* 4.5, 4.7 Hz, H-2), 3.43 (1 H, dddd, *J* 0.4, 2.9, 3.7, 4.7 Hz, H-3), 3.95 (1 H, dd, *J* 3.7, 12.4 Hz, H-4), 4.01 (1 H, dd, *J* 2.9, 12.4 Hz, H-4), 9.50 (1 H, dd, *J* 0.4, 4.5 Hz, H-1);

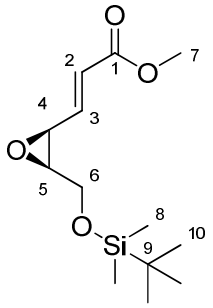
MS (ESI): 217 ($[MH]^+$), 239 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{10}H_{21}O_3Si$, 217.1254. Found: $[MH^+]$, 217.1254 (0.1 ppm error).

Obtained data in accord with those reported in literature.[88]

Lab Notebook Reference: PC/5/74.

Methyl (2*E*)-3-((2*S,3*R**)-3-((*tert*-butyldimethylsilyloxy)methyl)oxiran-2-yl)acrylate, *E*,*cis*-229**



To a stirred solution of aldehyde *cis*-**228** (2.96 g, 13.7 mmol) in CH_2Cl_2 at rt was added Ph_3PCHCO_2Me (4.31 g, 16.4 mmol). After 16 h, the reaction mixture was concentrated *in vacuo* to afford a yellow solid. The crude material was purified by flash column chromatography (SiO_2, 9:1 petrol:Et_2O) to afford epoxide *E*,*cis*-**229** (3.48 g, 93%) as a clear oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.22;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.08 (6 H, s, H-8), 0.89 (9 H, s, H-10), 3.35 (1 H, dd, *J* 5.2, 9.7 Hz, H-5), ddd (1 H, ddd, *J* 1.0, 4.4, 6.6 Hz, H-4), 3.71 – 3.76 (2 H, m, H-6), 3.76 (3 H, s, H-7), 6.15 (1 H, dd, *J* 1.0, 15.7 Hz, H-2), 6.82 (1 H, dd, *J* 6.6, 15.7 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.28 (C-8), 18.3 (C-9), 25.8 (C-10), 51.8 (C-7), 54.8 (C-4), 59.4 (C-5), 60.9 (C-6), 124.9 (C-2), 141.7 (C-3), 165.8 (C-1);

MS (ESI): 273 ($[MH]^+$), 295 ($[MNa]^+$);

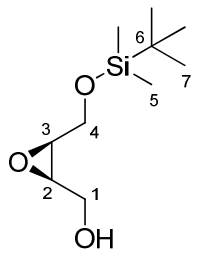
HRMS (ESI): Calculated for $C_{13}H_{24}O_4SiNa$, 295.1336. Found: [MNa^+], 295.1333 (1.0 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 778, 838, 978, 1035, 1099, 1156, 1196, 1259, 1311, 1438, 1472, 1659, 1727, 2857, 2930, 2953.

CHN analysis: Found C, 57.0; H, 8.72%. $C_{13}H_{24}O_4Si$ requires C, 57.3; H, 8.88%.

Lab Notebook Reference: PC/4/15.

[(2*R,3*S**)-3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)oxiran-2-yl]methanol, *cis*-227**



To a stirred solution of alkene **226** (1.44 g, 7.12 mmol) in CH_2Cl_2 (40 mL) at rt was added *m*CPBA (70% purity, 2.63 g, 10.7 mmol). After 20 h, the resulting suspension was quenched with $Na_2S_2O_3$ (sat. aq. solution, 40 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. solution, 75 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a colourless oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petrol:Et_2O) to afford epoxide *cis*-**227** (1.51 g, 97%) as a clear, colourless oil.

***R*_f (SiO_2, 1:1 petrol:Et_2O):** 0.31;

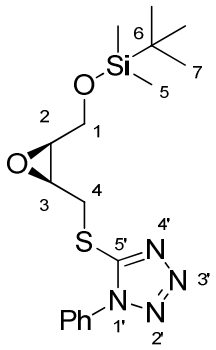
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.09 (3 H, s, H-5), 0.10 (3 H, s, H-5), 0.90 (9 H, s, H-7), 3.18 – 3.27 (2 H, m, H-2 and H-3), 3.73 (1 H, dd, *J* 5.5, 11.7 Hz, H-1 or H-4), 3.76 (1 H, dd, *J* 5.3, 12.3 Hz, H-1 or H-4), 3.82 (1 H, dd, *J* 6.0, 12.3 Hz, H-1 or H-4), 3.93 (1 H, *J* 5.5, 11.7 Hz, H-1 or H-4);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3406, 2930, 2857, 1471, 1256, 1099, 837, 778.

Obtained data in accord with those reported in literature.[70]

Lab Notebook Reference: PC/5/35.

(2*S,3*S**)-4-(1'-Phenyl-1'*H*-tetrazol-5'-yl-thio)-1-(*tert*-butyldimethylsilyloxy)but-2-ene epoxide, *cis*-230**



To a stirred solution of alcohol *cis*-**227** (3.78 g, 17.3 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (6.17 g, 34.6 mmol) in THF (60 mL) at rt was added PPh_3 (11.3 g, 43.3 mmol) followed by DIAD (6.81 mL, 34.6 mmol). After 2 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. solution, 100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a crude white solid. The crude material was passed through a silica plug eluting with 1:1 petrol:Et_2O to deliver a crude white solid. The crude material was purified by flash column chromatography (SiO_2, 1:1 petrol:Et_2O) to deliver epoxide *cis*-**230** (5.23 g, 80%) as clear, colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.53;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.08 (3 H, s, H-5), 0.09 (3 H, s, H-5), 0.90 (9 H, s, H-7), 3.22 (1 H, dt, *J* 4.1, 5.0 Hz, H-3), 3.47 – 3.54 (2 H, m, H-2 and H-1), 3.73 (1 H, dd, *J* 7.8, 16.7 Hz, H-1), 3.87 (2 H, d, *J* 5.0 Hz, H-4), 7.52 – 7.61 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.4 (C-5), 18.3 (C-6), 25.8 (C-7), 32.1 (C-1), 54.4 (C-2), 58.1 (C-3), 61.1 (C-4), 123.8 (C-Ph), 129.9 (C-Ph), 130.3 (C-Ph), 133.5 (C-Ph), 153.6 (C-5');

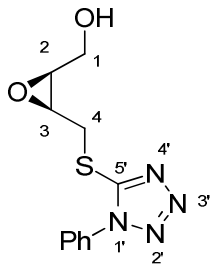
MS (ESI): 379 ($[MH]^+$), 401 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{17}H_{27}N_4O_2SSi$, 379.1618. Found: $[MH^+]$, 379.1605 (3.4 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2954, 2928, 2856, 1500, 1472, 1458, 1417, 1387, 1252, 1095, 839, 779.

Lab Notebook Reference: PC/5/36.

(2*S,3*S**)-4-(1'-Phenyl-1'*H*-tetrazol-5'-yl-thio)but-2-en-1-ol epoxide, *cis*-231**



A solution of epoxide *cis*-**230** (5.55g, 14.7 mmol) in AcOH:THF:H_2O (3:1:1, 100 mL) was stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (100 mL) and brine (100 mL). The organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered and evaporated to deliver alcohol *cis*-**231** (3.33g, 85%) as a clear, colourless oil.

***R*$_f$ (SiO$_2$, 7:3 Et$_2$O:petrol):** 0.13;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 3.29 – 3.33 (1 H, m, H-2 or H-3), 3.43 – 3.52 (2 H, m, H-4 and H-2 or H-3), 3.68 – 3.76 (1 H, m, H-4), 3.86 (1 H, dd, *J* 6.3, 12.6 Hz, H-1), 4.01 (1 H, dd, *J* 4.5, 12.6 Hz, H-1), 7.56 – 7.60 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 30.2 (C-4), 55.7 (C-2 or C-3), 57.4 (C-2 or C-3), 59.6 (C-1), 123.9 (C-Ph), 130.0 (C-Ph), 130.5 (C-Ph), 133.3 (C-Ph), 153.5 (C-5');

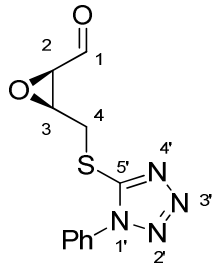
MS (ESI): 265 ($[MH]^+$), 287 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{11}H_{13}N_4O_2S$, 265.0754. Found: [MH^+], 265.0744 (3.4 ppm error)];

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3317, 2982, 2924, 1719, 1500, 1464, 1386, 1239, 1180, 1145, 1107, 1043.

Lab Notebook Reference: PC/5/37.

(2*S,3*R**)-4-(1'-Phenyl-1'H-tetrazol-5'-yl-thio)but-2-enal epoxide, *cis*-232**



To a stirred solution of alcohol *cis*-**231** (3.19 g, 12.1 mmol) in CH_2Cl_2 (70 mL) at rt was added DMP (6.14 g, 14.5 mmol). After 3 h, the reaction mixture was quenched with $Na_2S_2O_3$ (sat. aq. solution, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with $NaHCO_3$ (sat. aq. solution, 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver impure aldehyde *cis*-**232** a crude white solid. The crude material was used in the next reaction without purification.

***R*f (SiO2, 3:2 Et2O:petrol):** 0.21;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.51 (1 H, dd, *J* 6.4, 14.5 Hz, H-4), 3.65 (1 H, dd, *J* 3.4, 4.5 Hz, H-2), 3.64 (1 H, dd, *J* 5.7, 14.5 Hz, H-4), 3.84 (1 H, ddd, *J* 4.5, 5.7, 6.4 Hz, H-3), 7.46 – 7.56 (5 H, m, -Ph), 9.68 (1 H, d, *J* 3.4 Hz, H-1);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 30.6 (C-4), 57.1 (C-3), 58.4 (C-2), 123.7 (C-Ph), 130.0 (C-Ph), 130.5 (C-Ph), 133.3 (C-Ph), 153.6 (C-5'), 196.4 (C-1);

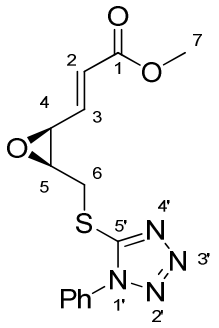
MS (ESI): 263 ($[MH]^+$), 285 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{11}H_{11}N_4NaO_2S$, 285.0417. Found: [MH^+], 285.0412 (1.2 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 692, 762, 1015, 1075, 1092, 1242, 1389, 1499, 1596, 1722.

Lab Notebook Reference: PC/5/39.

Methyl (2*E*,4*S,5*S**)-6-(1'-phenyl-1'H-tetrazol-5'-yl-thio)hex-2,4-dienoate-4,5-epoxide, *E*,*cis*-233**



To a stirred solution of impure aldehyde *cis*-**232** (12.1 mmol, assume 100% purity) in CH_2Cl_2 (70 mL) at rt was added Ph_3PCHCO_2Me (4.76 g, 18.2 mmol). After 2 h, the reaction mixture was concentrated *in vacuo* to deliver a crude yellow solid. The crude material was purified by flash column chromatography (SiO_2, 5:4:1 petrol:Et_2O:CH_2Cl_2) to afford epoxide *E*,*cis*-**233** (1.97 g, 51% over two steps) as a clear, colourless oil and the *Z*-isomer (850 mg, 22% over two steps) as a clear, colourless oil.

R_f (SiO_2, 1:1 petrol:Et_2O): 0.19;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.39 (1 H, dd, *J* 7.2, 14.2 Hz, H-6), 3.59 (1 H, dd, *J* 5.1, 14.2 Hz, H-6), 3.73 (1 H, ddd, *J* 1.1, 4.3, 5.6 Hz, H-5), 3.77 (3 H, s, H-7), 3.80 (1 H, ddd, *J* 4.3, 5.1, 7.2 Hz, H-4), 6.19 (1 H, dd, *J* 1.1, 15.7 Hz, H-2), 6.88 (1 H, dd, *J* 5.6, 15.7 Hz, H-3), 7.57 – 7.61 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 35.6 (C-6), 51.9 (C-7), 56.3 (C-4), 57.0 (C-5), 123.8 (C-Ph), 125.7 (C-2), 129.9 (C-Ph), 130.4 (C-Ph), 133.1 (C-Ph), 140.1 (C-3), 153.7 (C-5'), 165.3 (C-1);

MS (ESI): 319 ($[MH]^+$), 341 ($[MNa]^+$);

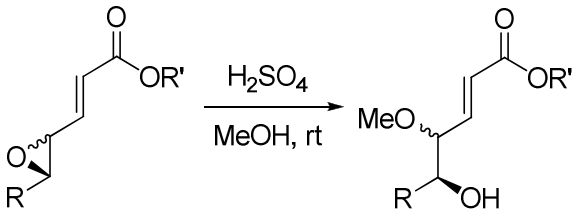
HRMS (ESI): Calculated for $C_{14}H_{15}N_4O_3S$, 319.0859. Found: [MH^+], 319.0845 (3.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 978, 1014, 1039, 1090, 1195, 1273, 1312, 1387, 1436, 1499, 1595, 1654, 1717, 2366.

Lab Notebook Reference: PC/5/40.

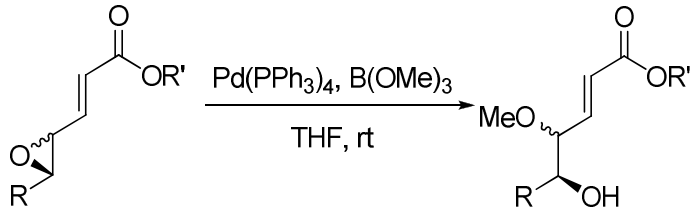
5.4.2. General Procedures for 4-methoxydienoate synthesis

General Procedure A – Acid-promoted Epoxide Opening of (*E*)-Methyl 3-(Oxiran-2-yl)acrylates



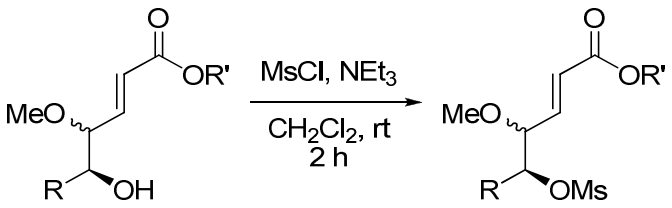
To a stirred solution of epoxide (1.00 mmol) in MeOH (10 mL) was added conc. H_2SO_4 (2 drops). The resulting solution was stirred at rt until complete as monitored by TLC, after which time, the reaction mixture was quenched with brine and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography to afford the desired alcohol.

General Procedure B – Palladium-catalysed Epoxide Opening of (*E*)-Methyl 3-(Oxiran-2-yl)acrylates



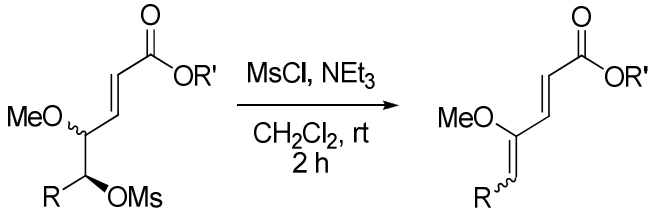
To a stirred solution of epoxide (1.00 mmol) and $B(OMe)_3$ (1.20 mmol) in THF (5 mL) at rt was added $Pd(PPh_3)_4$ (0.100 mmol). The resulting solution was stirred at rt until complete as monitored by TLC, after which time, the reaction mixture was quenched with $NaHCO_3$ (sat. aq. solution) and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 times). The combined organics were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography to afford the desired alcohol.

General Procedure C – Mesylation of 5-Hydroxy-4-methoxypent-2-enoates



To a stirred solution of alcohol (0.500 mmol) in CH_2Cl_2 (0.1 mL) at rt was added MsCl (0.750 mmol) followed by triethylamine (1.50 mmol). The resulting solution was stirred at rt for 2 h, after which time, the reaction mixture was diluted with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was used in the next reaction without purification.

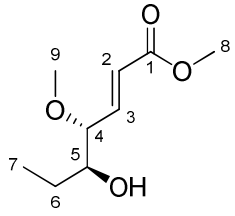
General Procedure D – DBU-promoted elimination of 4-methoxy-5-(methylsulfonyloxy)pent-2-enoates



To a stirred solution of impure mesylate (0.500 mmol) in CH_2Cl_2 (0.5 mL) was added DBU (0.600 mmol). The resulting solution was stirred at rt until complete as monitored by TLC, after which time, the reaction mixture was quenched with 10% HCl and diluted with H_2O and CH_2Cl_2 and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (twice). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography to afford the desired diene.

5.4.3. Experimental Procedures and Product Characterisation for Tables 12 and 13

Methyl (2*E*,4*R,5*S**)-5-hydroxy-4-methoxyhept-2-enoate, *E*,*anti*-214**



Procedure 1

Epoxide *E*,*trans*-**213** (442 mg, 2.83 mmol) was reacted as general procedure A for 2 h. Flash column chromatography (SiO_2, 3:2 Et_2O:petrol) afforded alcohol *E*,*anti*-**214** (353 mg, 66%) as a clear colourless oil.

Procedure 2

Epoxide *E*,*cis*-**213** (200 mg, 1.28 mmol) was reacted as general procedure B for 1 h. Flash column chromatography (SiO_2, 3:2 Et_2O:petrol) afforded alcohol *E*,*anti*-**214** (193 mg, 80%) as a clear colourless oil.

***R*$_f$ (SiO_2, 4:1 Et_2O:petrol):** 0.47;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.96 (3 H, t, *J* 7.5 Hz, H-7), 1.37 – 1.49 (2 H, m, H-6), 2.07 (1 H, br s, -OH), 3.34 (3 H, s, H-9), 3.64 – 3.70 (1 H, m, H-5), 3.71 – 3.76 (1 H, m, H-4), 3.75 (3 H, s, H-8), 6.03 (1 H, dd, *J* 1.1, 15.9 Hz, H-2), 6.86 (1 H, dd, *J* 6.8, 15.9 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 10.2 (C-7), 25.1 (C-6), 51.7 (C-8), 57.4 (C-9), 74.4 (C-5), 83.5 (C-4), 124.1 (C-2), 144.1 (C-3), 166.2 (C-1);

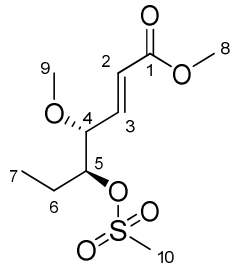
MS (ESI): 211 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_9H_{16}NaO_4$, 211.0941. Found: $[MNa^+]$, 211.0940 (0.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3459, 2938, 2881, 1725, 1660, 1438, 1304, 1278, 1194, 1172, 1105, 1039, 984.

Lab Notebook Reference: PC/1/91.

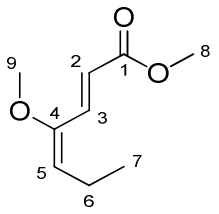
Methyl (2*E*,4*R,5*S**)-4-methoxy-5-(methylsulfonyloxy)hept-2-enoate, *E*,*anti*-215**



Alcohol *E*,*anti*-**214** (353 mg, 1.88 mmol) was reacted as general procedure C to afford impure mesylate *E*,*anti*-**215** as a clear yellow oil which was used immediately in the next reaction without further purification.

***R*$_f$ (SiO$_2$, 1:1 petrol:Et$_2$O):** 0.17;
^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 1.02 (3 H, t, *J* 7.3 Hz, H-7), 1.54 – 1.79 (2 H, m, H-6), 3.09 (3 H, s, H-10), 3.38 (3 H, s, H-9), 3.78 (3 H, s, H-8), 3.89 – 3.94 (1 H, m, H-4), 4.70 – 4.78 (1 H, m, H-5), 6.09 (1 H, dd, *J* 15.9, 1.2 Hz, H-2), 6.81 (1 H, dd, *J* 15.9, 6.7 Hz, H-3);
^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 9.8 (C-7), 23.9 (C-6), 38.7 (C-10), 51.8 (C-8), 57.5 (C-9), 81.5 (C-4), 84.9 (C-5), 125.0 (C-2), 141.9 (C-3), 165.8 (C-1);
MS (ESI): 267 ($[MH]^+$), 289 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_{10}H_{19}O_6S$, 267.0897. Found: [MH^+], 267.0900 (1.1 ppm error).
Lab Notebook Reference: PC/3/21.

Methyl (2*E*,4*E*)-4-methoxyhepta-2,4-dienoate, *E*,*E*-216



Mesylate *E*,*anti*-**215** (430 mg, 1.61 mmol) was reacted as general procedure D for 5 h. Flash column chromatography (SiO_2, 3:2 petrol:Et_2O) afforded diene *E*,*E*-**216** (241 mg, 76%) as a clear colourless gum.

***R*$_f$ (SiO$_2$, 4:1 petrol:Et$_2$O):** 0.43;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 1.03 (3 H, t, *J* 7.5 Hz, H-7), 2.20 – 2.28 (2 H, m, H-6), 3.57 (3 H, s, H-9), 3.74 (3 H, s, H-8), 4.98 (1 H, t, *J* 7.9 Hz, H-5), 6.21 (1 H, d, *J* 15.0 Hz, H-2), 7.45 (1 H, d, *J* 15.0 Hz, H-3);

^{13}C-NMR (100 MHz, CDCl$_3$): δ_C 15.2 (C-7), 19.7 (C-6), 54.3 (C-8/9), 59.8 (C-8/9), 111.9 (C-5), 117.6 (C-2), 135.0 (C-3), 150.0 (C-4), 167.4 (C-1);

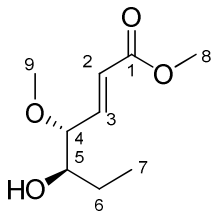
MS (ESI): 171 ([MH]$^+$), 193 ([MNa]$^+$);

HRMS (ESI): Calculated for $C_9H_{15}O_3$, 171.1016. Found: [MH$^+$], 171.1013 (1.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2936, 1712, 1645, 1446, 1368, 1324, 1267, 1193, 1108, 1063, 1043.

Lab Notebook Reference: PC/1/93.

Methyl (2*E*,4*R,5*R**)-5-hydroxy-4-methoxyhept-2enoate, *E*,*syn*-214**



Procedure 1

Epoxide *E*,*cis*-**213** (725 mg, 4.64 mmol) was reacted as general procedure A for 1 h. Flash column chromatography (SiO$_2$, 3:2 petrol:Et$_2$O) afforded alcohol *E*,*syn*-**214** (664 mg, 76%) as a clear, colourless oil.

Procedure 2

Epoxide *E*,*trans*-**213** (184 mg, 1.17 mmol) was reacted as general procedure B for 1 h. Flash column chromatography (SiO$_2$, 3:2 petrol:Et$_2$O) afforded alcohol *E*,*syn*-**214** (176 mg, 82%) as a clear, colourless oil.

***R*$_f$ (SiO$_2$, 1:1 petrol:Et$_2$O):** 0.19;

^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 0.97 (3 H, t, *J* 7.5 Hz, H-7), 1.33 -1.59 (2 H, m, H-6), 3.34 (3 H, s, H-9), 3.41 – 3.47 (1 H, m, H-5), 3.56 (1 H, m, H-4), 3.75 (3 H, s, H-8), 6.05 (2 H, dd, *J* 15.7, 1.1 Hz, H-2), 6.76 (1 H, dd, *J* 15.7, 7.2 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 9.7 (C-7), 25.4 (C-6), 51.7 (C-8), 57.5 (C-9), 74.5 (C-5), 84.2 (C-4), 124.0 (C-2), 144.5 (C-3), 166.2 (C-8);

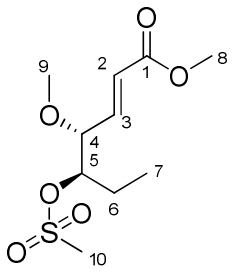
MS (ESI): 211 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_9H_{16}NaO_4$, 211.0941. Found: [MNa^+], 211.0941 (0.0 ppm error)];

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3434, 2937, 2254, 1720, 1656, 1463, 1439, 1383, 1346, 1284, 1175, 1136, 1092, 1050, 984.

Lab Notebook Reference: PC/2/4.

Methyl (2*E*,4*R,5*R**)-4-methoxy-5-(methylsulfonyloxy)hept-2-enoate, *E*,*syn*-215**



Alcohol *E*,*syn*-**214** (664 mg, 3.528 mmol) was reacted as general procedure C to afford impure mesylate *E*,*syn*-**215** as a yellow oil which was used in the next reaction without further purification.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.19;

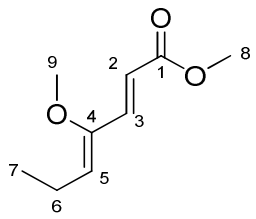
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.02 (3 H, t, *J* 7.3 Hz, H-7), 1.51 – 1.82 (2 H, m, H-6), 3.08 (3 H, s, H-10), 3.36 (3 H, s, H-9), 3.78 (3 H, s, H-8), 3.95 (1 H, dt, *J* 6.7, 1.3 Hz, H-4), 4.58 (1 H, ddd, *J* 8.5, 6.7, 3.7 Hz, H-5), 6.14 (1 H, dd, *J* 15.9, 1.3 Hz, H-2), 6.76 (1 H, dd, *J* 15.9, 6.7 Hz, H-3);

MS (ESI): 267 ($[MH]^+$), 289 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{10}H_{19}O_6S$, 267.0897. Found: [MH^+], 267.0900 (1.1 ppm error).

Lab Notebook Reference: PC/2/5.

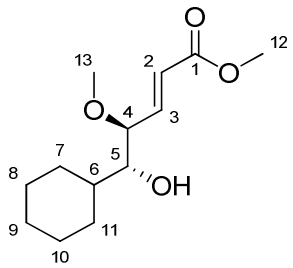
Methyl (2*E*,4*Z*)-4-methoxyhepta-2,4-dienoate, *E*,*Z*-216



Mesylate *E*,*syn*-**215** (3.53 mmol) was reacted as general procedure D for 2 h. Flash column chromatography (SiO_2, 4:1 petrol:Et_2O) afforded diene *E*,*Z*-**216** (364 mg, 61% over two steps) as a clear colourless gum.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.43;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.04 (3 H, t, *J* 7.6 Hz, H-7), 2.26 (2 H, quin, *J* 7.6 Hz, H-6), 3.62 (3 H, s, H-9), 3.76 (3 H, s, H-8), 5.39 (1 H, t, *J* 7.6 Hz, H-5), 6.02 (1 H, d, *J* 15.5 Hz, H-2), 7.03 (1 H, d, *J* 15.5 Hz, H-3);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 13.4 (C-7), 19.3 (C-6), 51.4 (C-8), 59.8 (C-9), 116.0 (C-2), 130.3 (C-5), 140.9 (C-3), 152.7 (C-4), 167.4 (C-1);
MS (ESI): 171 ($[MH]^+$), 193 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_9H_{15}O_3$, 171.1016. Found: $[MH^+]$, 171.1013 (1.5 ppm error).
Lab Notebook Reference: PC/2/5.

Methyl (2*E*,4*S,5*R**)-5-cyclohexyl-5-hydroxy-4-methoxypent-2-enolate, *E*,*anti*-234**



Epoxide *E*,*trans*-**220** (502 mg, 2.39 mmol) was reacted as general procedure A for 2 h. Flash column chromatography (SiO_2, 1:1 petrol:Et_2O) afforded alcohol *E*,*anti*-**234** (464 mg, 80%) as a clear colourless oil.

R_f (SiO_2, 1:1 petrol:Et_2O): 0.38;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.94 – 1.43 (5 H, m, -Cy), 1.53 – 1.78 (5 H, m, -Cy), 1.93 – 2.02 (1 H, m, -Cy), 3.33 (3 H, s, H-13), 3.53 (1 H, dd, *J* 4.0, 8.0 Hz, H-5), 3.76 (3 H, s, H-12), 3.82 (1 H, ddd, *J* 1.0, 4.0, 7.0 Hz, H-4), 6.06 (1 H, dd, *J* 1.0, 15.9 Hz, H-2), 6.90 (1 H, dd, *J* 7.0, 15.9 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 25.6 (C-Cy), 25.8 (C-Cy), 26.3 (C-Cy), 28.7 (C-Cy), 28.9 (C-Cy), 39.1 (C-6), 51.7 (C-12), 57.1 (C-13), 76.8 (C-5), 81.3 (C-4), 124.2 (C-2), 143.6 (C-3), 166.3 (C-1);

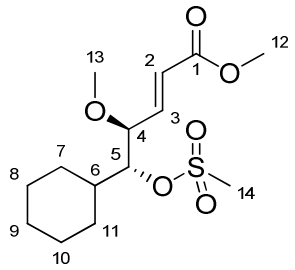
MS (ESI): 243 ($[MH]^+$), 265 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{13}H_{23}O_4$, 243.1591. Found: [MH^+], 243.1589 (0.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3451, 2880, 2808, 1697, 1630, 1417, 1254, 1174, 1150, 1092, 1021, 969.

Lab Notebook Reference: PC/9/59.

Methyl (2*E*,4*S,5*R**)-5-cyclohexyl-4-methoxy-5-[(methylsulfonyl)oxy]pent-2-enoate, *E*,*anti*-293**



Alcohol *E*,*anti*-**234** (449 mg, 1.85 mmol) was reacted as general procedure C to afford impure mesylate *E*,*anti*-**293** as a yellow oil which was used in the next reaction without purification.

R_f (SiO_2, 1:1 petrol:Et_2O): 0.38;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.02 – 1.30 (4 H, m, -Cy), 1.43 – 1.82 (6 H, m, -Cy), 1.92 – 2.02 (1 H, m, H-6), 3.10 (3 H, s, H-14), 3.35 (3 H, s, H-13), 3.78 (3 H, s, H-12),

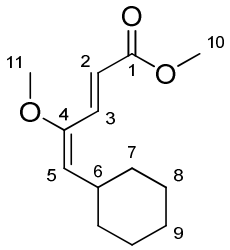
3.98 (1 H, ddd, *J* 1.2, 2.7, 6.8 Hz, H-4), 4.64 (1 H, dd, *J* 2.7, 9.2 Hz, H-5), 6.07 (1 H, dd, *J* 1.2, 15.8 Hz, H-2), 6.83 (1 H, dd, *J* 6.8, 15.8 Hz, H-3);

MS (ESI): 321 ($[MH]^+$), 343 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{14}H_{25}O_6S$, 321.1366. Found: $[MH^+]$, 321.1357 (2.1 ppm error).

Lab Notebook Reference: PC/9/64.

Methyl (2*E*,4*E*)-5-cyclohexyl-4-methoxypenta-2,4-dienoate, *E*,*E*-235



Mesylate *E*,*anti*-**293** (1.85 mmol, assume 100% purity) was reacted as general procedure D for 48 h. Flash column chromatography (SiO_2, 7:3 petrol:Et_2O) afforded enol ether *E*,*E*-**235** (232 mg, 56% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.67;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.01 – 1.37 (5 H, m, -Cy), 1.58 – 1.75 (5 H, m, -Cy), 2.29 – 2.43 (1 H, m, H-6), 3.54 (3 H, s, H-11), 3.74 (3 H, s, H-10), 4.80 (1 H, d, *J* 9.8 Hz, H-5), 6.20 (1 H, d, *J* 15.3 Hz, H-2), 7.44 (1 H, d, *J* 15.3 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 25.8 (C-Cy), 34.4 (C-Cy), 35.8 (C-6), 51.5 (C-10), 54.4 (C-11), 116.7 (C-5), 117.6 (C-2), 135.6 (C-3), 149.3 (C-4), 167.9 (C-1);

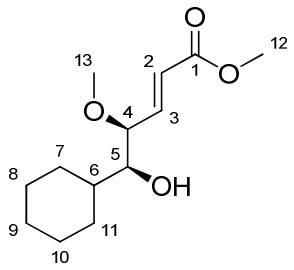
MS (ESI): 225 ($[MH]^+$), 247 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{13}H_{21}O_3$, 225.1485. Found: $[MH^+]$, 225.1483 (0.7 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2881, 2807, 1693, 1609, 1417, 1276, 1252, 1183, 1149, 1048, 958.

Lab Notebook Reference: PC/9/68.

Methyl (2*E*,4*S,5*S**)-5-cyclohexyl-5-hydroxy-4-methoxypent-2-enolate, *E*,*syn*-234**



Epoxide *E*,*trans*-**220** (516 mg, 2.45 mmol) was reacted as general procedure B for 3 h. Flash column chromatography (SiO_2, 1:1 petrol:Et_2O) afforded alcohol *E*,*syn*-**234** (295 mg, 72%) as a pale yellow oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.31;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.01 – 1.45 (6 H, m, -Cy), 1.53 – 1.81 (5 H, m, -Cy), 3.29 (1 H, dd, *J* 4.1, 6.5 Hz, H-5), 3.33 (3 H, s, H-13), 3.72 – 3.78 (1 H, m, H-4), 3.77 (3 H, s, H-12), 6.05 (1 H, dd, *J* 1.1, 15.8 Hz, H-2), 6.79 (1 H, dd, *J* 7.0, 15.8 Hz, H-3);

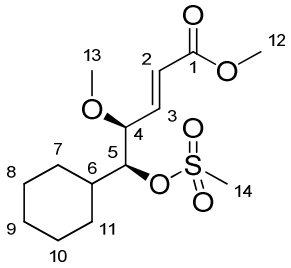
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 26.2 (C-Cy), 26.4 (C-Cy), 26.5 (C-Cy), 26.7 (C-Cy), 30.3 (C-Cy), 39.5 (C-6), 51.9 (C-12), 57.5 (C-13), 77.4 (C-5), 81.9 (C-4), 123.7 (C-2), 144.9 (C-3), 166.4 (C-1);

MS (ESI): 265 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{13}H_{22}NaO_4$, 265.1410. Found: $[MNa^+]$, 265.1411 (0.3 ppm error).

Lab Notebook Reference: PC/9/61.

Methyl (2*E*,4*S,5*S**)-5-cyclohexyl-4-methoxy-5-[(methylsulfonyl)oxy]pent-2-enoate, *E*,*syn*-293**



Alcohol *E*,*syn*-**234** (404 g, 1.67 mmol) was reacted as general procedure C to afford impure mesylate *E*,*syn*-**293** as a yellow oil which was used in the next reaction without purification.

***R*f (SiO2, 1:1 petrol:Et2O):** 0.31;

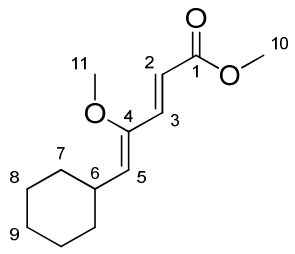
^{1}H-NMR (400 MHz, CDCl3): δ_H 1.05 – 1.34 (5 H, m, -Cy), 1.49 – 1.70 (5 H, m, -Cy), 1.74 – 1.80 (1 H, m, H-6), 3.08 (3 H, s, H-14), 3.32 (3 H, s, H-13), 3.79 (3 H, s, H-12), 3.98 (1 H, ddd, *J* 1.2, 6.8, 7.6 Hz, H-4), 4.46 (1 H, dd, *J* 3.5, 7.6 Hz, H-5), 6.13 (1 H, dd, *J* 1.2, 15.8 Hz, H-2), 6.73 (1 H, dd, *J* 6.8, 15.8 Hz, H-3);

MS (ESI): 321 ($[MH]^+$), 343 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{14}H_{25}O_6S$, 321.1366. Found: $[MH^+]$, 321.1380 (4.7 ppm error).

Lab Notebook Reference: PC/9/65.

Methyl (2*E*,4*Z*)-5-cyclohexyl-4-methoxypenta-2,4-dienoate, *E*,*Z*-235



Mesylate *E*,*syn*-**293** (1.67 mmol, assume 100% purity) was reacted as general procedure D for 16 h. Flash column chromatography (SiO_2, 4:1 petrol:Et_2O) afforded enol ether *E*,*Z*-**235** (232 mg, 62% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, 4:1 petrol:Et_2O):** 0.67;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.06 – 1.39 (5 H, m, -Cy), 1.61 – 1.78 (5 H, m, -Cy), 2.48 – 2.59 (1 H, m, H-6), 3.61 (3 H, s, H-11), 3.75 (3 H, s, H-10), 5.26 (1 H, d, *J* 10.0 Hz, H-5), 6.00 (1 H, d, *J* 15.5 Hz, H-2), 7.01 (1 H, d, *J* 15.5 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 25.5 (C-Cy), 32.6 (C-Cy), 35.2 (C-6), 51.4 (C-10), 60.2 (C-11), 116.1 (C-2), 134.6 (C-5), 141.2 (C-3), 151.7 (C-4), 167.4 (C-1);

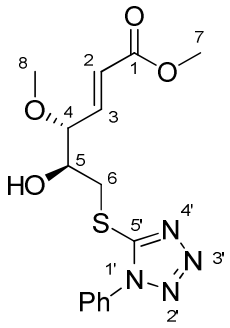
MS (ESI): 225 ($[MH]^+$), 247 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{13}H_{21}O_3$, 225.1485. Found: [MH^+], 225.1479 (2.5 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2881, 2806, 1693, 1606, 1415, 1281, 1244, 1175, 1147, 1025, 957.

Lab Notebook Reference: PC/9/69.

Methyl (2*E*,4*R,5*S**)-5-hydroxy-4-methoxy-6-(1'-phenyl-1'H-tetrazol-5'-ylthio)hex-2-enoate, *E*,*syn*-236**



Epoxide *E*,*cis*-**233** (372 mg, 1.17 mmol) was reacted as general procedure A for 1 h. Flash column chromatography (SiO_2, 6:2:1 Et_2O:petrol:CH_2Cl_2) afforded alcohol *E*,*syn*-**236** (295 mg, 72%) as a clear colourless oil.

***R*$_f$ (SiO_2, 7:3 Et_2O:petrol):** 0.20;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.39 (3 H, s, H-8), 3.42 (1 H, dd, *J* 8.2, 13.9 Hz, H-6), 3.62 (1 H, dd, *J* 3.4, 13.9 Hz, H-6), 3.77 (3 H, s, H-7), 3.91 (1 H, ddd, *J* 1.3, 5.1, 6.4 Hz, H-4), 4.06 (1 H, ddd, *J* 3.4, 5.1, 8.2 Hz, H-5), 6.13 (1 H, dd, *J* 1.3, 15.9 Hz, H-2), 6.91 (1 H, dd, *J* 6.5, 15.9 Hz, H-3), 7.54 – 7.60 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 36.0 (C-6), 51.6 (C-7), 57.6 (C-8), 71.6 (C-5), 82.0 (C-4), 123.7 (C-Ph), 124.1 (C-2), 129.7 (C-Ph), 130.1 (C-Ph), 133.3 (C-Ph), 143.5 (C-3), 154.3 (C-5'), 165.9 (C-1);

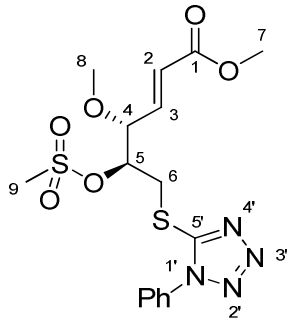
MS (ESI): 351 ($[MH]^+$), 373 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{15}H_{19}N_4O_4S$, 351.1122. Found: [MH^+], 351.1107 (3.1 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3415, 2994, 2950, 2832, 1720, 1661, 1597, 1500, 1389, 1280, 1247, 1172, 1097, 1016, 912, 732, 692, 647.

Lab Notebook Reference: PC/5/41.

Methyl (2*E*,4*R,5*S**)-4-methoxy-5-(methylsulfonyloxy)-6-(1'-phenyl-1'H-tetrazol-5'-ylthio)hex-2-enoate, *E*,*syn*-294**



Alcohol *E*,*syn*-**236** (295 mg, 0.842 mmol) was reacted as general procedure C to afford impure mesylate *E*,*syn*-**294** as a crude brown oil which was used in the next reaction without purification.

***R*f (SiO2, 7:3 Et2O:petrol):** 0.17;

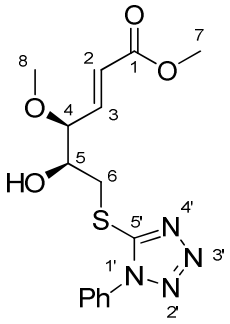
^{1}H-NMR (400 MHz, CDCl3): δ_H 3.05 (3 H, s, H-9), 3.38 (1 H, dd, *J* 8.8, 14.6 Hz, H-6), 3.43 (3 H, s, H-8), 3.78 (3 H, s, H-7), 3.86 (1 H, dd, *J* 3.5, 14.6 Hz, H-6), 4.19 (1 H, ddd, *J* 1.4, 5.2, 6.1 Hz, H-4), 5.15 (1 H, ddd, *J* 3.5, 5.2, 8.8 Hz, H-5), 6.20 (1 H, dd, *J* 1.4, 15.8 Hz, H-2), 6.87 (1 H, dd, *J* 6.1, 15.8 Hz, H-3), 7.55 – 7.60 (5 H, m, -Ph);

MS (ESI): 429 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{16}H_{21}N_4O_6S_2$, 429.0897. Found: $[MH^+]$, 429.0915 (4.1 ppm error).

Lab Notebook Reference: PC/5/42.

Methyl (2*E*,4*S,5*S**)-5-hydroxy-4-methoxy-6-(1'-phenyl-1'H-tetrazol-5'-ylthio)hex-2-enoate, *E*,*anti*-236**



Epoxide *E*,*cis*-**233** (317 mg, 0.996 mmol) was reacted as general procedure B for 2 h. Flash column chromatography (SiO_2, 6:3:1 Et_2O:petrol:CH_2Cl_2) afforded alcohol *E*,*anti*-**236** (180 mg, 52%) as a clear colourless oil.

***R*$_f$ (SiO_2, 7:3 Et_2O:petrol):** 0.22;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.35 (3 H, s, H-8), 3.42 (1 H, dd, *J* 8.1, 14.2 Hz, H-6), 3.62 (1 H, dd, *J* 3.0, 14.2 Hz, H-6), 3.74 (3 H, s, H-7), 3.90 (1 H, ddd, *J* 1.2, 5.5, 6.5 Hz, H-4), 4.08 (1 H, ddd, *J* 3.0, 5.5, 8.1 Hz, H-5), 6.10 (1 H, dd, *J* 1.2, 15.9 Hz, H-2), 6.90 (1 H, dd, *J* 6.5, 15.9 Hz, H-3), 7.48 – 7.62 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 36.1 (C-6), 51.7 (C-7), 57.7 (C-8), 72.4 (C-5), 82.5 (C-4), 123.7 (C-Ph), 124.3 (C-2), 129.8 (C-Ph), 130.2 (C-Ph), 133.4 (C-Ph), 143.9 (C-3), 154.6 (C-5'), 166.0 (C-1);

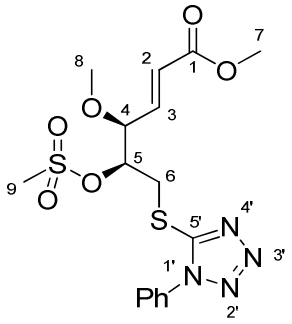
MS (ESI): 351 ($[MH]^+$), 373 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{15}H_{19}N_4O_4S$, 351.1122. Found: $[MH^+]$, 351.1131 (2.8 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3390, 2895, 1696, 1476, 1416, 1389, 1367, 1345, 1281, 1259, 1227, 1175, 1153, 1083, 1061, 1026, 999, 968.

Lab Notebook Reference: PC/9/71.

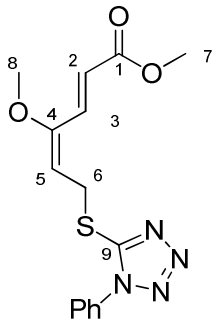
Methyl (2*E*,4*S,5*S**)-4-methoxy-5-(methylsulfonyloxy)-6-(1'-phenyl-1'H-tetrazol-5'-ylthio)hex-2-enoate, *E*,*anti*-294**



Alcohol *E*,*anti*-**236** (179 mg, 0.418 mmol) was reacted as general procedure C to afford mesylate *E*,*anti*-**294** as a crude yellow oil which was used in the next reaction without purification.

***R*f (SiO2, 7:3 Et2O:petrol):** 0.22;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.05 (3 H, s, H-9), 3.30 (1 H, dd, *J* 9.0, 14.7 Hz, H-6), 3.37 (3 H, s, H-8), 3.73 (3 H, s, H-7), 3.73 (1 H, dd, *J* 3.1, 14.7 Hz, H-6), 4.14 (1 H, ddd, *J* 1.0, 2.9, 6.7 Hz, H-4), 5.17 (1 H, ddd, *J* 2.9, 3.1, 9.0 Hz, H-5), 6.12 (1 H, dd, *J* 1.0, 15.8 Hz, H-2), 6.81 (1 H, dd, *J* 6.7, 15.8 Hz, H-3), 7.52 – 7.55 (5 H, m, -Ph);
MS (ESI): 429 ($[MH]^+$);
HRMS (ESI): Calculated for $C_{16}H_{21}N_4O_6S_2$, 429.0897. Found: $[MH^+]$, 429.0902 (1.2 ppm error).
Lab Notebook Reference: PC/9/72.

Methyl (2*E*,4*E*)-4-methoxy-6-(1'-phenyl-1'H-tetrazol-5'-ylthio)hexa-2,4-dienoate, *E*,*E*-236



Procedure 1

Mesylate *E*,*syn*-**294** (0.842 mmol, assume 100% purity) was reacted as general procedure D for 18 h. Flash column chromatography (SiO_2, 6:3:1 petrol:Et_2O:CH_2Cl_2) afforded enol ether *E*,*E*-**237** (235 mg, 84% over two steps) as a yellow oil.

Procedure 2

Mesylate *E*,*anti*-**294** (0.418 mmol, assume 100% purity) was reacted as general procedure D for 7 h. Flash column chromatography (SiO_2, 1:1 petrol:Et_2O) afforded enol ether *E*,*E*-**237** (117 mg, 84% over two steps) as a yellow oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.31;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.63 (3 H, s, H-8), 3.78 (3 H, s, H-7), 4.28 (2 H, d, *J* 8.7 Hz, H-6), 5.28 (1 H, t, *J* 8.7 Hz, H-5), 6.35 (1 H, d, *J* 15.2 Hz, H-2), 7.46 (1 H, d, *J* 15.2 Hz, H-3), 7.53 – 7.61 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 30.4 (C-6), 51.8 (C-7), 54.9 (C-8), 100.8 (C-5), 121.0 (C-2), 123.7 (C-Ph), 129.8 (C-Ph), 130.1 (C-Ph), 133.2 (C-3), 133.6 (C-Ph), 153.7 (C-9), 154.4 (C-4), 167.1 (C-1);

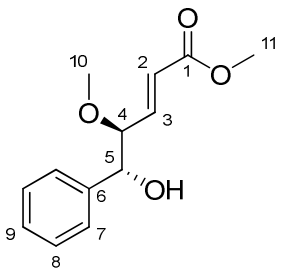
MS (ESI): 333 ($[MH]^+$);

HRMS (ESI): Calculated for $C_{15}H_{17}N_4O_3S$, 333.1016. Found: [MH^+], 333.1005 (3.1 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2953, 1730, 1714, 1644, 1598, 1501, 1455, 1435, 1415, 1386, 1308, 1278, 1195, 1171, 1091, 1050, 1015, 913, 762, 732, 693.

Lab Notebook Reference: PC/5/42.

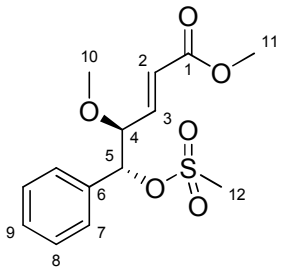
Methyl (2*E*,4*R,5*S**)-5-hydroxy-4-methoxy-5-phenylpent-2-enolate, *E*,*anti*-238**



Epoxide *E*,*trans*-**221** (250 mg, 1.22 mmol) was reacted as general procedure A for 1 h. Flash column chromatography (SiO_2, 3:2 petrol: Et_2O) afforded alcohol *E*,*anti*-**238** (171 mg, 59%) as a clear colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.38;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.45 (1 H, br s, -OH), 3.27 (3 H, s, H-10), 3.69 (3 H, s, H-11), 4.26 (1 H, d, *J* 5.4 Hz, H-5), 4.39 (1 H, ddd, *J* 1.9, 4.5, 5.4 Hz, H-4), 6.01 (1 H, dd, *J* 1.9, 15.7 Hz, H-2), 6.98 (1 H, dd, *J* 4.5, 15.7 Hz, H-3), 7.26 – 7.39 (5 H, m, -Ph);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 51.5 (C-11), 57.2 (C-10), 74.0 (C-4), 86.1 (C-5), 121.4 (C-2), 127.3 (C-Ph), 128.3 (C-Ph), 128.5 (C-Ph), 137.0 (C-6), 145.9 (C-3), 166.7 (C-1);
MS (ESI): 259 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_{13}H_{16}NaO_4$, 259.0941. Found: $[MNa^+]$, 259.0930 (3.6 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3397, 2903, 2840, 1696, 1634, 1416, 1291, 1254, 1177, 1153, 1086, 1034, 957, 908, 754, 719, 692.
Lab Notebook Reference: PC/8/31.

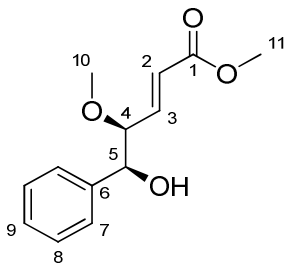
Methyl (2*E*,4*R,5*S**)-4-methoxy-5-[(methylsulfonyl)oxy]-5-phenylpent-2-enoate, *E*,*anti*-243**



Alcohol *E*,*anti*-**238** (66 mg, 0.278 mmol) was reacted as general procedure C to afford impure mesylate *E*,*anti*-**243** as a yellow oil which was used in the next reaction without purification.

***R*$_f$ (SiO$_2$, 1:1 petrol:Et$_2$O):** 0.38;
^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 2.57 (3 H, s, H-12), 3.25 (3 H, s, H-10), 3.70 (3 H, s, H-11), 4.33 (1 H, d, *J* 6.0 Hz, H-5), 5.19 (1 H, ddd, *J* 1.6, 5.4, 6.0 Hz, H-4), 6.05 (1 H, dd, *J* 1.6, 15.8 Hz, H-2), 6.98 (1 H, dd, *J* 5.4, 15.8 Hz, H-3), 7.27 – 7.39 (5 H, m, -Ph);
MS (ESI): 337 ([MNa]$^+$);
HRMS (ESI): Calculated for $C_{14}H_{18}NaO_6S$, 337.0716. Found: [MNa$^+$], 337.0701 (4.2 ppm error).
Lab Notebook Reference: PC/9/48.

Methyl (2*E*,4*S,5*S**)-5-hydroxy-4-methoxy-5-phenylpent-2-enolate, *E*,*syn*-238**



Epoxide *E*,*trans*-**221** (54 mg, 0.264 mmol) was reacted as general procedure B for 3 h. Flash column chromatography (SiO$_2$, 1:1petrol: Et$_2$O) afforded alcohol *E*,*syn*-**238** (52 mg, 84%) as a clear colourless oil.

***R*f (SiO2, 1:1 petrol:Et2O):** 0.25;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.39 (3 H, s, H-10), 3.70 (3 H, s, H-11), 3.83 (1 H, ddd, *J* 1.3, 6.3, 7.6 Hz, H-4), 4.51 (1 H, d, *J* 7.6 Hz, H-5), 5.87 (1 H, dd, *J* 1.3, 15.8 Hz, H-2), 6.60 (1 H, dd, *J* 6.3, 15.8 Hz, H-3), 7.27 – 7.37 (5 H, m, -Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 51.7 (C-11), 57.8 (C-10), 76.5 (C-5), 85.5 (C-4), 123.7 (C-2), 127.0 (C-Ph), 128.3 (C-Ph), 128.4 (C-Ph), 138.8 (C-6), 143.7 (C-3), 166.1 (C-1);

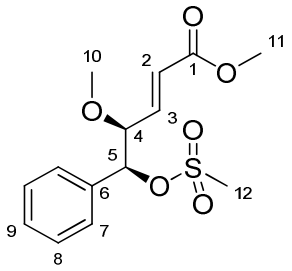
MS (ESI): 259 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{13}H_{16}NaO_4$, 259.0941. Found: $[MNa^+]$, 259.0933 (2.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3405, 2905, 1697, 1633, 1416, 1285, 1260, 1177, 1153, 1098, 1044, 969, 753, 720, 692.

Lab Notebook Reference: PC/9/26.

Methyl (2*E*,4*S,5*S**)-4-methoxy-5-[(methylsulfonyl)oxy]-5-phenylpent-2-enoate, *E*,*syn*-243**



Alcohol *E*,*syn*-**238** (66 mg, 0.278 mmol) was reacted as general procedure C to afford impure mesylate *E*,*syn*-**243** as a yellow oil which was used in the next reaction without purification.

***R*f (SiO2, 1:1 petrol:Et2O):** 0.25;

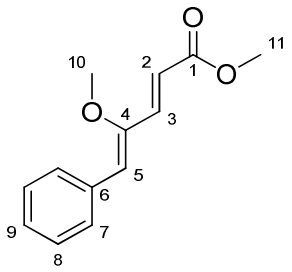
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 2.84 (3 H, s, H-12), 3.39 (3 H, s, H-10), 3.66 (3 H, s, H-11), 5.19 (1 H, ddd, *J* 1.4, 6.0, 7.5 Hz, H-4), 5.39 (1 H, d, *J* 7.5 Hz, H-5), 5.95 (1 H, dd, *J* 1.4, 15.8 Hz, H-2), 6.45 (1 H, dd, *J* 6.0, 15.8 Hz, H-3), 7.27 – 7.38 (5 H, m, -Ph);

MS (ESI): 337 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{14}H_{18}NaO_6S$, 337.0716. Found: [MNa^+], 337.0701 (4.2 ppm error).

Lab Notebook Reference: PC/9/48.

Methyl (2*E*,4*Z*)-4-methoxy-5-phenylpenta-2,4-dienoate, *E*,*Z*-252



Mesylate *E*,*syn*-**243** (0.278 mmol, assume 100% purity) was reacted as general procedure D for 2 h. Flash column chromatography (SiO_2, 7:3 petrol:Et_2O) afforded enol ether *E*,*Z*-**252** (44 mg, 72% over two steps) as a clear, colourless oil.

***R*$_f$ (SiO_2, 7:3 petrol:Et_2O):** 0.68;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.66 (3 H, s, H-10), 3.79 (3 H, s, H-11), 6.18 (1 H, d, *J* 15.4 Hz, H-2), 6.18 (1 H, s, H-5), 7.21 (1 H, d, *J* 15.4 Hz, H-3), 7.29 (1 H, dt, *J* 1.5, 7.4 Hz, H-9), 7.34 – 7.39 (2 H, m, H-Ph), 7.66 – 7.69 (2 H, m, H-Ph);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 51.7 (C-11), 58.7 (C-10), 117.8 (C-2), 124.8 (C-5), 128.3 (C-Ph), 128.6 (C-Ph), 129.5 (C-Ph), 134.3 (C-6), 141.7 (C-3), 153.9 (C-4), 167.4 (C-1);

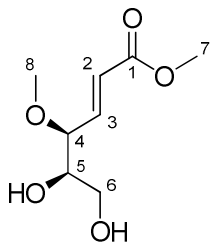
MS (ESI): 219 ([$MH]^+$);

HRMS (ESI): Calculated for $C_{13}H_{15}O_3$, 219.1016. Found: [MH^+], 219.1017 (0.6 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2907, 1707, 1597, 1415, 1340, 1285, 1248, 1181, 1152, 1100, 1017.

Lab Notebook Reference: PC/9/50.

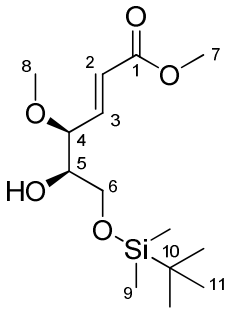
Methyl (2*E*,4*S,5*R**)-5,6-dihydroxy-4-methoxy-hexa-2,4-enoate, *E*,*syn*-239**



Epoxide *E*,*cis*-**229** (100 mg, 0.367 mmol) was reacted as general procedure A for 30 min to afford diol *E*,*syn*-**239** (23 mg, 33%) as a clear, colourless oil.

***R*f (SiO2, 7:3 Et2O:petrol):** 0.09;
^{1}H-NMR (400 MHz, CDCl3): δ_H 3.24 (3 H, s, H-8), 3.40 (1 H, dd, *J* 6.9, 12.3 Hz, H-6), 3.48 – 3.56 (1 H, m), 3.53 (1 H, dd, *J* 3.8, 12.3 Hz, H-6), 3.66 (3 H, s, H-7), 3.70 – 3.77 (1 H, m), 5.97 (1 H, d, *J* 15.8 Hz, H-2), 6.73 (1 H, dd, *J* 6.5, 15.8 Hz, H-3);
MS (ESI): 191 ($[MH]^+$), 213 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_8H_{14}NaO_5$, 213.0733. Found: [MNa^+], 213.0735 (-0.8 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3418, 2950, 1723, 1660, 1438, 1284, 1196, 1174, 1113, 1044, 987.
Lab Notebook Reference: PC/4/37.

Methyl (2*E*,4*S,5*R**)-6-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methoxyhexa-2-enoate, *E*,*anti*-253**



Epoxide *E*,*cis*-**229** (1 g, 3.67 mmol) was reacted as general procedure B for 2 h. Flash column chromatography (SiO_2, 1:1 petrol:Et_2O) afforded alcohol *E*,*anti*-**253** (914 mg, 82%) as a clear oil.

R_f (SiO_2, 1:1 petrol:Et_2O): 0.40;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.07 (3 H, s, H-9), 0.08 (3 H, s, H-9), 0.90 (9 H, s, H-11), 2.47 (1 H, d, *J* 5.3 Hz, -OH), 3.33 (3 H, s, H-8), 3.65 – 3.72 (3 H, m, H-5 and H-6), 3.75 (3 H, s, H-7), 3.80 (1 H, ddd, *J* 1.3, 5.7, 6.4, H-4), 6.06 (1 H, dd, *J* 1.3, 15.9 Hz, H-2), 6.93 (1 H, dd, *J* 6.4, 15.9 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.48 (C-9), -5.44 (C-9), 18.2 (C-10), 25.8 (C-11), 51.6 (C-7), 57.6 (C-8), 63.1 (C-6), 73.2 (C-5), 80.9 (C-4), 123.4 (C-2), 145.3 (C-3), 166.3 (C-1);

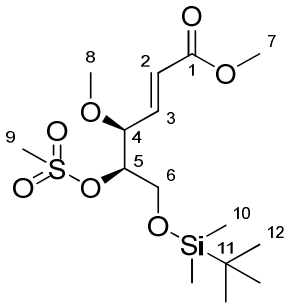
MS (ESI): 305 ($[MH]^+$), 327 ($[MNa]^+$)

HRMS (ESI): Calculated for $C_{14}H_{29}O_5Si$, 305.1779. Found: [MH^+], 305.1782 (-1.2 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3436, 2930, 2857, 1729, 1437, 1255, 1169, 1103, 837, 778.

Lab Notebook Reference: PC/4/35.

Methyl (2*E*,4*S,5*R**)-6-(*tert*-butyldimethylsilyloxy)-4-methoxy-5-(methylsulfonyloxy)hexa-2-enoate, *E*,*anti*-295**



Alcohol *E*,*anti*-**253** (1.03 g, 3.38 mmol) was reacted as general procedure C to afford impure mesylate *E*,*anti*-**295** as a yellow oil which was used in the next reaction without purification.

R_f (SiO_2, 1:1 petrol:Et_2O): 0.40;

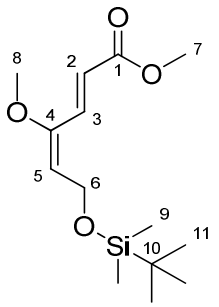
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.07 (6 H, s, H-10), 0.89 (9 H, s, H-12), 3.07 (3 H, s, H-9), 3.38 (3 H, s, H-8), 3.70 (1 H, dd, *J* 5.6, 11.2 Hz, H-6), 3.77 (3 H, s, H-7), 3.84 (1 H, dd, *J* 6.2, 11.2 Hz, H-6), 4.12 (1 H, ddd, *J* 1.3, 3.6, 6.6 Hz, H-4), 4.71 (1 H, ddd, *J* 3.6, 5.6, 6.2 Hz, H-5), 6.10 (1 H, dd, *J* 1.3, 15.8 Hz, H-2), 6.83 (1 H, dd, *J* 6.6, 15.8 Hz, H-3);

MS (ESI): 383 ($[MH]^+$), 405 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{15}H_{31}O_7SSi$, 383.1554. Found: [MH^+], 383.1549 (1.5 ppm error).

Lab Notebook Reference: PC/4/39.

Methyl (2*E*,4*E*)-6-(*tert*-butyldimethylsilyloxy)-4-methoxyhexa-2,4-dienoate, *E*,*E*-254



Mesylate *E*,*anti*-**295** (3.38 mmol, assumed 100% purity) was reacted as general procedure D for 16 h. Flash column chromatography (SiO_2, 9:1 petrol:Et_2O) afforded enol ether *E*,*E*-**254** (874 mg, 90% over two steps) as a clear oil.

***R*$_f$ (SiO_2, 3:2 petrol:Et_2O):** 0.67;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.09 (6 H, s, H-9), 0.90 (9 H, s, H-11), 3.62 (3 H, s, H-8), 3.76 (3 H, s, H-7), 4.38 (2 H, d, 7.3 Hz, H-6), 5.08 (1 H, t, *J* 7.3 Hz, H-5), 6.27 (1 H, d, *J* 15.3 Hz, H-2), 7.43 (1 H, d, *J* 15.3 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.0 (C-9), 18.3 (C-10), 25.9 (C-11), 51.7 (C-7), 54.6 (C-8), 58.7 (C-6), 108.0 (C-5), 119.2 (C-2), 134.9 (C-3), 151.7 (C-4), 167.5 (C-1);

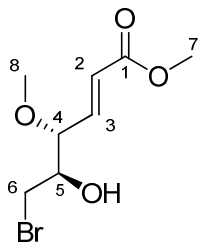
MS (ESI): 309 ([$MNa]^+$);

HRMS (ESI): Calculated for $C_{14}H_{26}NaO_4Si$, 309.1492. Found: [MNa^+], 309.1493 (0.1 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2954, 2931, 2857, 1723, 1644, 1608, 1464, 1436, 1307, 1271, 1221, 1193, 1169, 1114, 1067, 1049, 835, 777.

Lab Notebook Reference: PC/4/39.

Methyl (*E*,4*R,5*R**)-6-bromo-5-hydroxy-4-methoxyhex-2-enoate, *E*,*anti*-240**



Epoxide *E*,*trans*-**223** (432 mg, 1.84 mmol) was reacted as general procedure A for 15 h. Flash column chromatography (SiO_2, 1:1 petrol:Et_2O) afforded alcohol *E*,*anti*-**240** (393 mg, 80%) as a clear colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.36 (3 H, s, H-8), 3.52 (1 H, dd, *J* 4.2, 10.6 Hz, H-6), 3.57 (1 H, dd, *J* 6.0, 10.6 Hz, H-6), 3.76 (3 H, s, H-7), 3.80 – 3.84 (2 H, m, H-4 and H-5), 6.11 (1 H, dd, *J* 1.2, 15.8 Hz, H-2), 6.87 (1 H, dd, *J* 6.6, 15.8 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 35.6 (C-6), 51.8 (C-7), 57.8 (C-8), 72.6 (C-5), 81.6 (C-4), 124.5 (C-2), 143.8 (C-3), 166.1 (C-1);

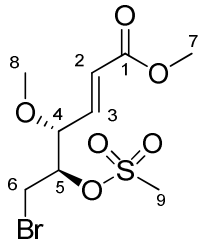
MS (ESI): 255 ($[MH]^+$), 277 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_8H_{13}{}^{81}BrO_4Na$, 276.9849. Found: [MNa^+], 276.9841 (2.8 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3444, 2951, 1724, 1660, 1437, 1282, 1193, 1171, 1103, 1039, 985.

Lab Notebook Reference: PC/4/79.

Methyl (*E*,4*R,5*R**)-6-bromo-4-methoxy-5-(methylsulfonyloxy)hex-2-enoate, *E*,*anti*-296**



Alcohol *E*,*anti*-**240** (120 mg, 0.449 mmol) was reacted as general procedure C to afford a yellow oil. The crude material was purified by flash column chromatography (SiO_2, 3:2 petrol:Et_2O) to afford mesylate *E*,*anti*-**296** (1:0.4, 122 mg, 79%) as an orange gum.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 3.12 (3 H, s, H-9), 3.41 (3 H, s, H-8), 3.47 (1 H, dd, *J* 5.6, 11.4 Hz, H-6), 3.64 (1 H, dd, *J* 6.3, 11.4 Hz, H-6), 3.78 (3 H, s, H-7), 4.21 – 4.25 (1 H, m, H-4), 4.79 – 4.85 (1 H, m, H-5), 6.16 (1 H, dd, *J* 1.3, 15.8 Hz, H-2), 6.79 (1 H, dd, *J* 6.6, 15.8 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 29.4 (C-6), 38.6 (C-9), 51.8 (C-7), 57.9 (C-8), 79.5 (C-4), 80.8 (C-5), 125.6 (C-2), 141.1 (C-3), 165.5 (C-1);

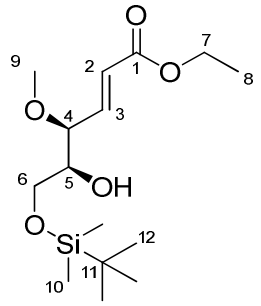
MS (ESI): 331 ($[MH]^+$), 353 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_9H_{16}{}^{79}BrO_6S$, 330.9851. Found: [MH^+], 330.9864 (3.9 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3102, 3002, 2949, 1724, 1660, 1439, 1358, 1313, 1260, 1173, 1117, 1039, 1010, 970, 922, 855, 795, 733.

Lab Notebook Reference: PC/4/82.

Ethyl (2*E*,4*S,5*S**)-6-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methoxy-hex-2-enoate, *E*,*syn*-235**



Epoxide *E*,*trans*-**222** (540 mg, 1.89 mmol) was reacted as general procedure B for 40 min. Flash column chromatography (SiO_2, 3:2 petrol:Et_2O) afforded alcohol *E*,*syn*-**235** (346 mg, 57%) as a yellow oil.

***R*$_f$ (SiO_2, 7:3 petrol:Et_2O):** 0.26;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.06 (3 H, s, H-10), 0.07 (3 H, s, H-10), 0.89 (9 H, s, H-12), 1.30 (3 H, t, *J* 7.1 Hz, H-8), 2.54 (1 H, d, *J* 5.0 Hz, -OH), 3.37 (3 H, s, H-9), 3.55 – 3.75 (3 H, m, H-4 and H-6), 3.90 (1 H, ddd, *J* 1.3, 5.0, 6.5 Hz, H-5), 4.21 (2 H, q, *J* 7.1 Hz, H-7), 6.06 (1 H, dd, *J* 1.3, 15.8 Hz, H-2), 6.86 (1 H, dd, *J* 6.5, 15.8 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.5 (C-10), 14.2 (C-8), 18.2 (C-11), 25.8 (C-12), 57.8 (C-9), 60.5 (C-7), 63.0 (C-6), 73.5 (C-4), 80.8 (C-5), 123.7 (C-2), 144.4 (C-3), 165.9 (C-1);

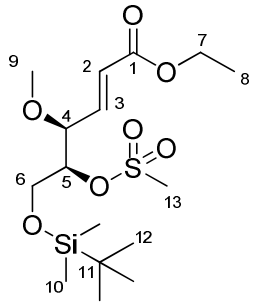
MS (ESI): 319 ($[MH]^+$), 341 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{15}H_{31}O_5Si$, 319.1941. Found: [MH^+], 319.1927 (4.3 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3428, 2954, 2929, 2855, 1722, 1301, 1256, 1174, 1115, 1041, 837, 778.

Lab Notebook Reference: PC/4/55.

Ethyl (2*E*,4*S,5*S**)-6-(*tert*-butyldimethylsilyloxy)-5-(methylsulfonyloxy)-4-methoxy-hex-2-enoate, *E*,*syn*-297**



Alcohol *E*,*syn*-**235** (1.03 mg, 3.23 mmol) was reacted a general procedure C to afford impure mesylate *E*,*syn*-**297** as a yellow oil which was used in the next reaction without purification.

***R*$_f$ (SiO$_2$, 7:3 petrol:Et$_2$O):** 0.26;

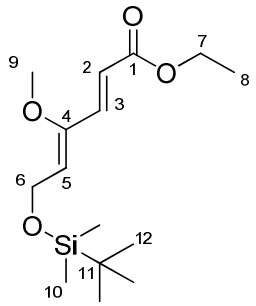
^{1}H-NMR (400 MHz, CDCl$_3$): δ_H 0.07 (3 H, s, H-10), 0.08 (3 H, s, H-10), 0.89 (9 H, s, H-12), 1.30 (3 H, t, *J* 7.1 Hz, H-8), 3.06 (3 H, s, H-13), 3.37 (3 H, s, H-9), 3.72 (1 H, dd, *J* 5.3, 11.7 Hz, H-6), 3.88 (1 H, dd, *J* 3.6, 11.7 Hz, H-6), 4.11 (1 H, ddd, *J* 1.4, 6.0, 6.1 Hz, H-4), 4.22 (2 H, q, *J* 7.1 Hz, H-7), 4.55 (1 H, ddd, *J* 3.6, 5.3, 6.1 Hz, H-5), 6.14 (1 H, dd, *J* 1.4, 15.8 Hz, H-2), 6.80 (1 H, dd, *J* 6.0, 15.8 Hz, H-3);

MS (ESI): 397 ([MH]$^+$), 419 ([MNa]$^+$);

HRMS (ESI): Calculated for $C_{16}H_{32}O_7NaSSi$, 419.1535. Found: [MNa$^+$], 419.1520 (3.5 ppm error).

Lab Notebook Reference: PC/4/86.

Ethyl (2*E*,4*Z*)-6-(*tert*-butyldimethylsilyloxy)-4-methoxyhexa-2,4-dienoate, *E*,*Z*-256



Mesylate *E*,*syn*-**297** (3.23 mmol, assumed 100% purity) was reacted as general procedure D. Flash column chromatography (SiO_2, 9:1 petrol:Et_2O) afforded enol ether *E*,*Z*-**256** (645 mg, 69% over two steps) as a clear oil.

***R*$_f$ (SiO_2, 9:1 petrol:Et_2O):** 0.34;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 0.78 (6 H, s, H-10), 0.90 (9 H, s, H-12), 1.30 (3 H, t, *J* 7.1 Hz, H-8), 3.63 (3 H, s, H-9), 4.22 (2 H, q, *J* 7.1 Hz, H-7), 4.39 (2 H, d, *J* 6.4 Hz, H-6), 5.49 (1 H, t, *J* 6.4 Hz, H-5), 6.06 (1 H, d, *J* 15.6 Hz, H-2), 7.02 (1 H, d, *J* 15.6 Hz, H-3);

^{13}C-NMR (100 MHz, $CDCl_3$): δ_C -5.2 (C-10), 14.3 (C-8), 18.3 (C-11), 25.9 (C-12), 57.9 (C-6), 60.2 (C-9), 60.5 (C-7), 118.6 (C-2), 126.3 (C-5), 139.9 (C-3), 152.9 (C-4), 166.8 (C-1);

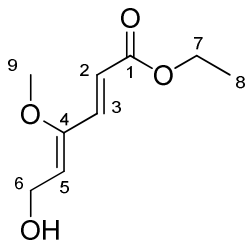
MS (ESI): 301 ($[MH]^+$), 323 ($[MNa]^+$);

HRMS (ESI): Calculated for $C_{15}H_{29}O_4Si$, 301.1830. Found: [MH^+], 301.1823 (1.8 ppm error);

IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 2931, 2857, 1716, 1621, 1464, 1365, 1290, 1259, 1165, 1099, 1046, 835, 777.

Lab Notebook Reference: PC/4/86.

(2*E*,4*Z*)-Ethyl 6-hydroxy-4-methoxyhexa-2,4-dienoate, *E*,*Z*-262



To a stirred solution of enol ether *E*,*Z*-**256** (188 mg, 0.656 mmol) in CH_2Cl_2 (10 mL) at rt was added TBAF (1.0 M in CH_2Cl_2). After 2 h, the reaction was concentrated *in vacuo* to deliver a brown gum. The crude material was purified by flash column chromatography (SiO_2, 4:1 Et_2O:petrol) to afford alcohol *E*,*Z*-**262** (95 mg, 78%) as a clear oil.

***R*$_f$ (SiO_2, 4:1 Et_2O:petrol):** 0.25;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H 1.27 (3 H, t, *J* 7.1 Hz, H-8), 2.58 (1 H, br s, -OH), 3.61 (3 H, s, H-9), 4.18 (2 H, q, *J* 7.1 Hz, H-7), 4.31 (2 H, d, *J* 6.6 Hz, H-6), 5.52 (1 H, dd, *J* 6.6 Hz, H-5), 6.05 (1 H, d, *J* 15.6 Hz, H-2), 6.98 (1 H, d, *J* 15.6 Hz, H-3);

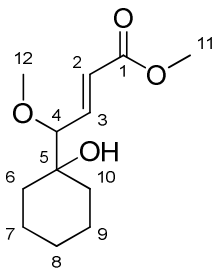
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 14.2 (C-8), 57.5 (C-6), 60.4 (C-9), 60.6 (C-7), 119.2 (C-2), 124.3 (C-5), 139.6 (C-3), 154.3 (C-4), 166.7 (C-1);

MS (ESI): 187 ($[MH]^+$);

HRMS (ESI): Calculated for $C_9H_{15}O_4$, 187.0965. Found: $[MH^+]$, 187.0961 (2.2 ppm error).

Lab Notebook Reference: PC/4/62.

Methyl (2*E*)-(1-hydroxycyclohexyl)-4-methoxybut-2-enoate, *E*-244



Epoxide *E*-**224** (109 mg, 0.555 mmol) was reacted as general procedure B for 2 h. Flash column chromatography (SiO_2, 1:1petrol: Et_2O) afforded alcohol *E*-**244** (90 mg, 71%) as a clear colourless oil.

***R*$_f$ (SiO_2, 1:1 petrol:Et_2O):** 0.29;
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H1.06 – 1.72 (10 H, m, H-6, H-7, H-8, H-9 and H-10), 2.11 (1 H, br s, -OH), 3.31 (3 H, s, H-12), 3.49 (1 H, dd, *J* 1.1, 7.2 Hz, H-4), 3.75 (3 H, s, H-11), 6.00 (1 H, dd, *J* 1.1, 15.9 Hz, H-2), 6.86 (1 H, dd, *J* 7.2, 15.9 Hz, H-3);
^{13}C-NMR (100 MHz, $CDCl_3$): δ_C 21.2 (C-Cy), 21.4 (C-Cy), 25.8 (C-Cy), 32.6 (C-Cy), 34.0 (C-Cy), 51.6 (C-12), 57.8 (C-11), 73.1 (C-5), 87.5 (C-4), 124.2 (C-2), 144.6 (C-3), 166.2 (C-1);
MS (ESI): 251 ($[MNa]^+$);
HRMS (ESI): Calculated for $C_{12}H_{20}NaO_4$, 251.1254. Found: $[MH^+]$, 251.1251 (3.9 ppm error);
IR $\bar{\nu}_{max}$ (film)/cm^{-1}: 3448, 2889, 2814, 1699, 1631, 1417, 1364, 1328, 1257, 1153, 1081, 1022, 961, 721.
Lab Notebook Reference: PC/9/18.

Appendix I. NMR spectra for synthetic cuevaene A (±)-15

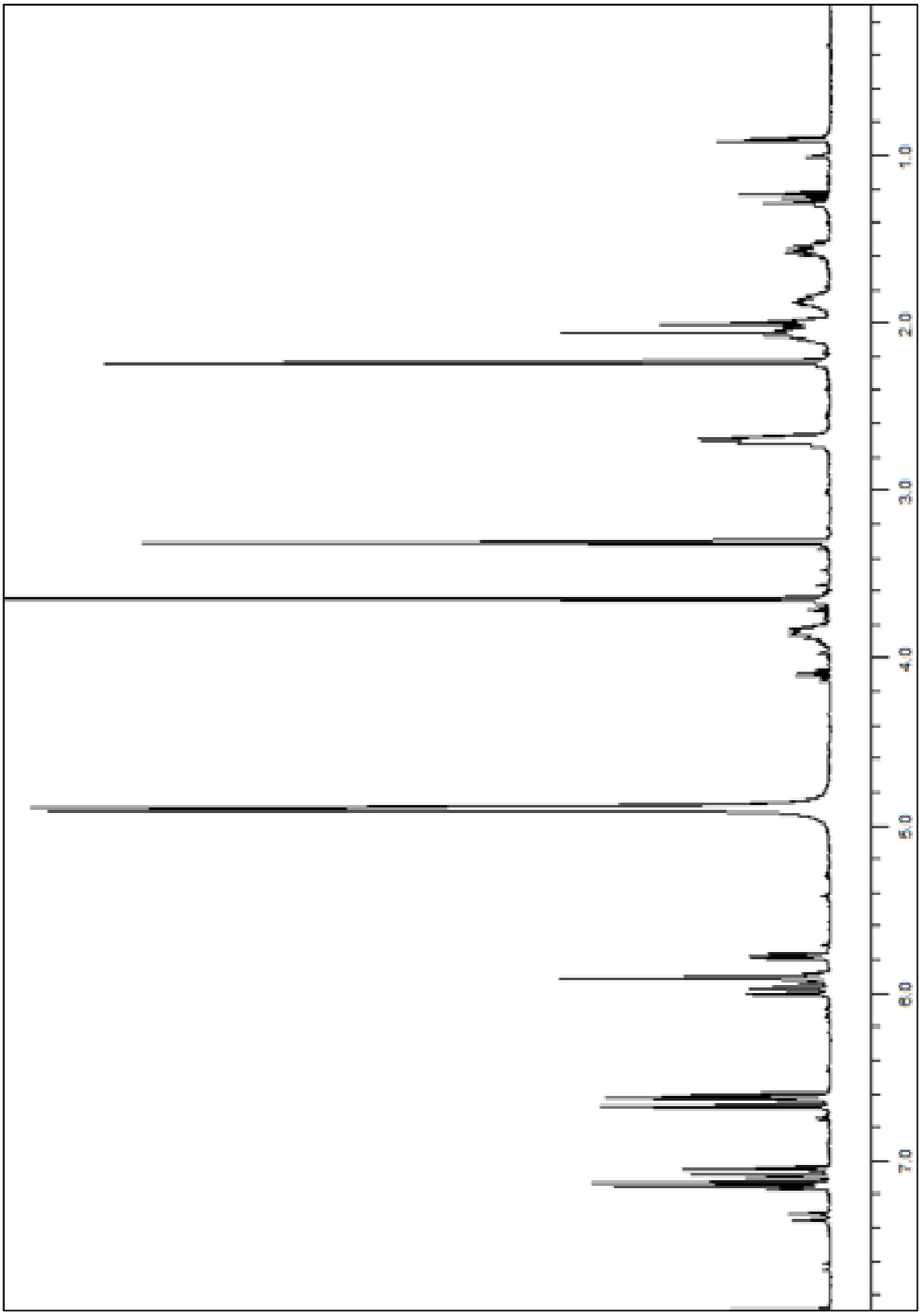


Figure 1. ^{1}H-NMR spectrum of synthetic (±)-**15** in CD_3OD

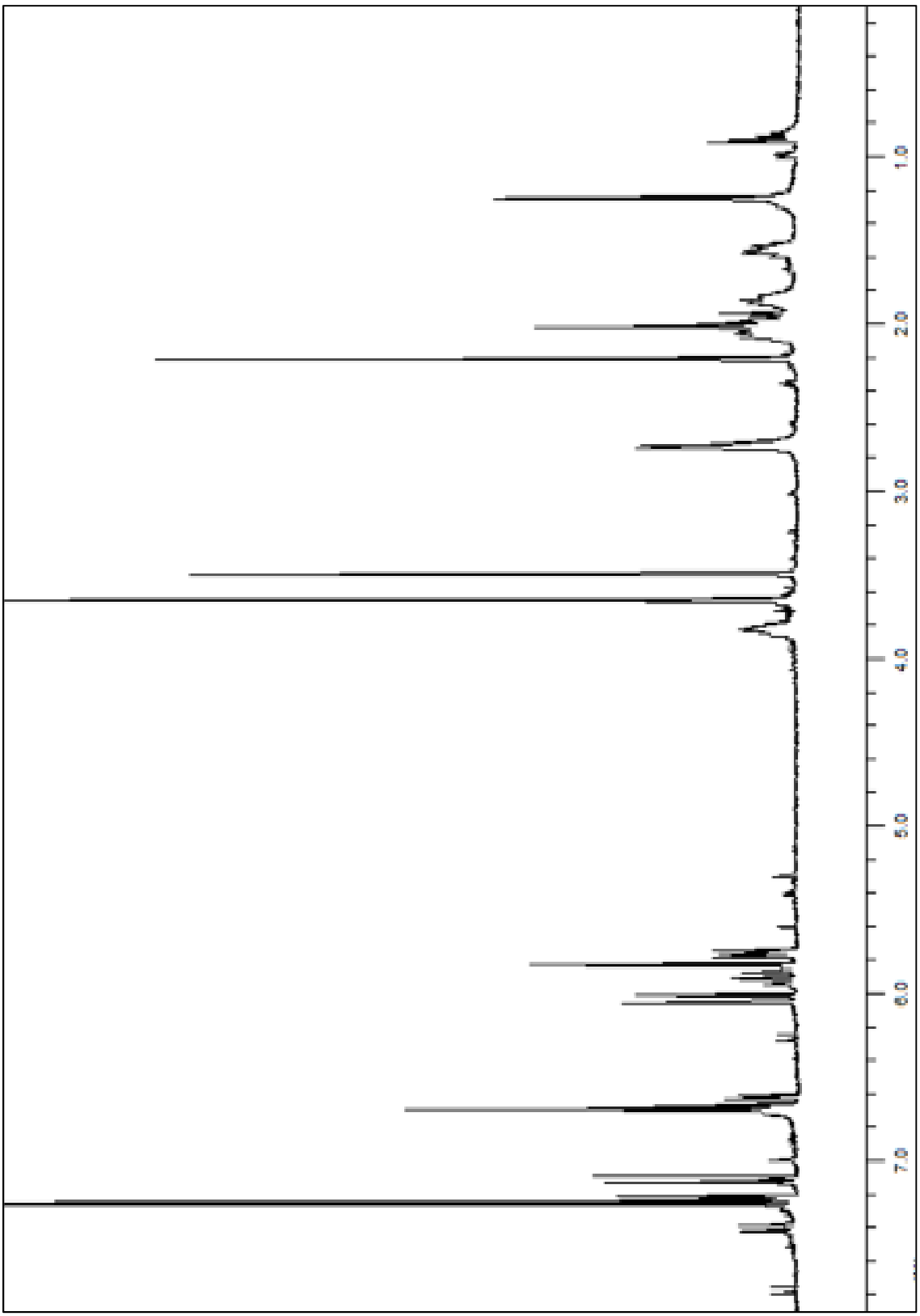


Figure 2. ^{1}H-NMR spectrum of synthetic (±)-**15** in $CDCl_3$

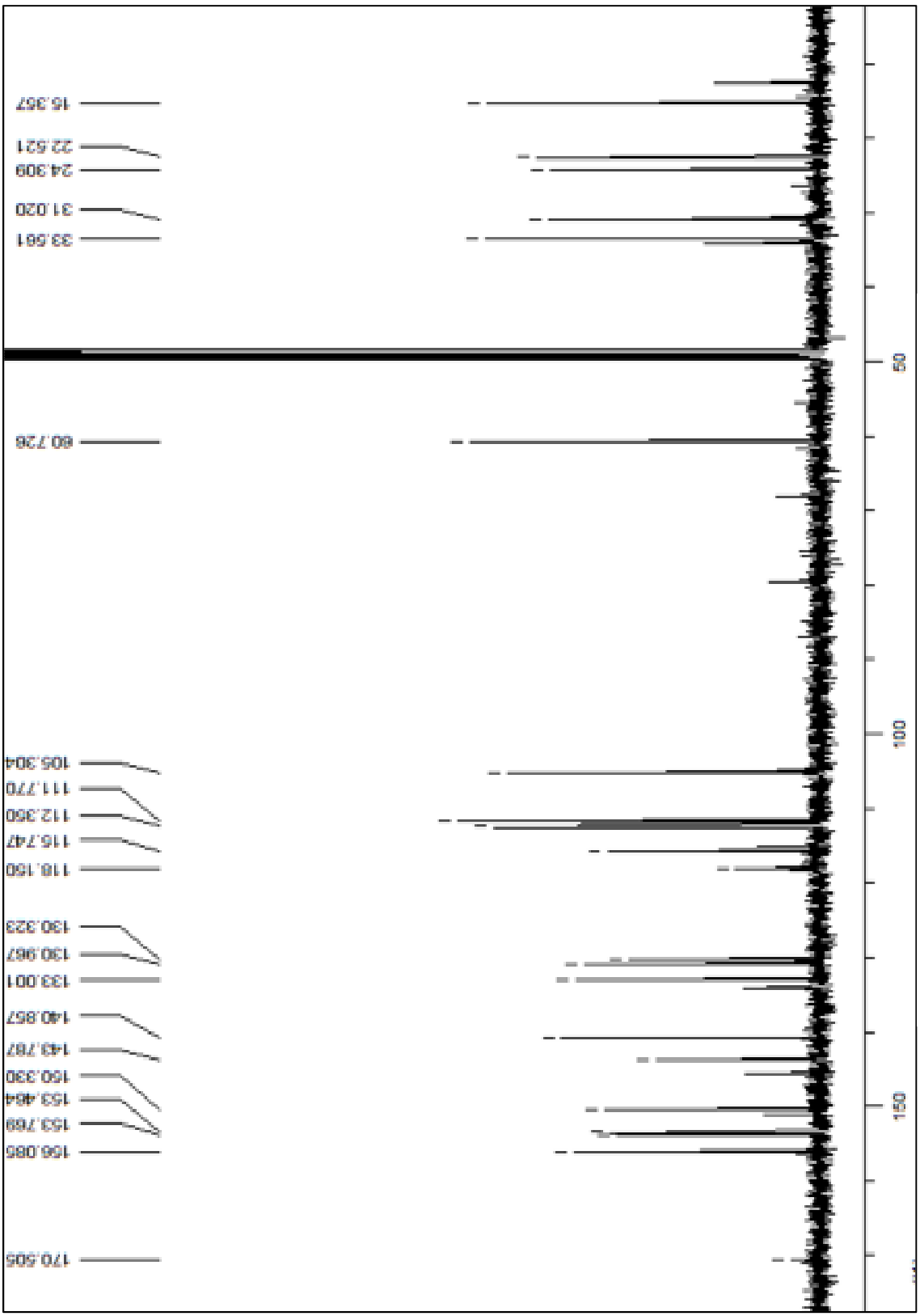


Figure 3. ^{13}C-NMR spectrum of synthetic (±)-**15** in CD_3OD

Appendix II. Isolation NMR-spectroscopic Data for Cuevaene A

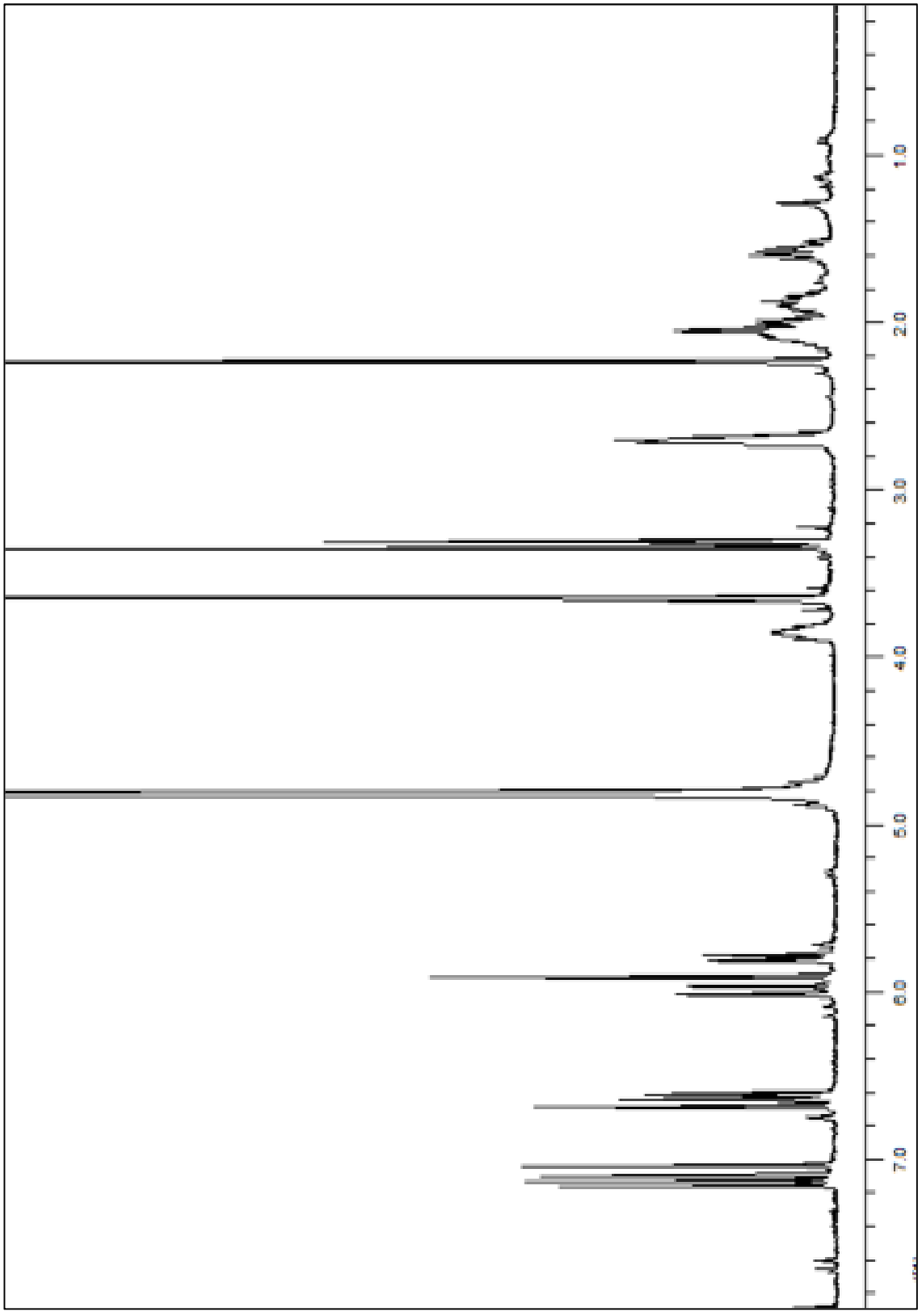


Figure 1. ^{1}H-NMR spectrum of cuevaene A in CD_3OD.
Data processed from raw fid provided by isolation authors

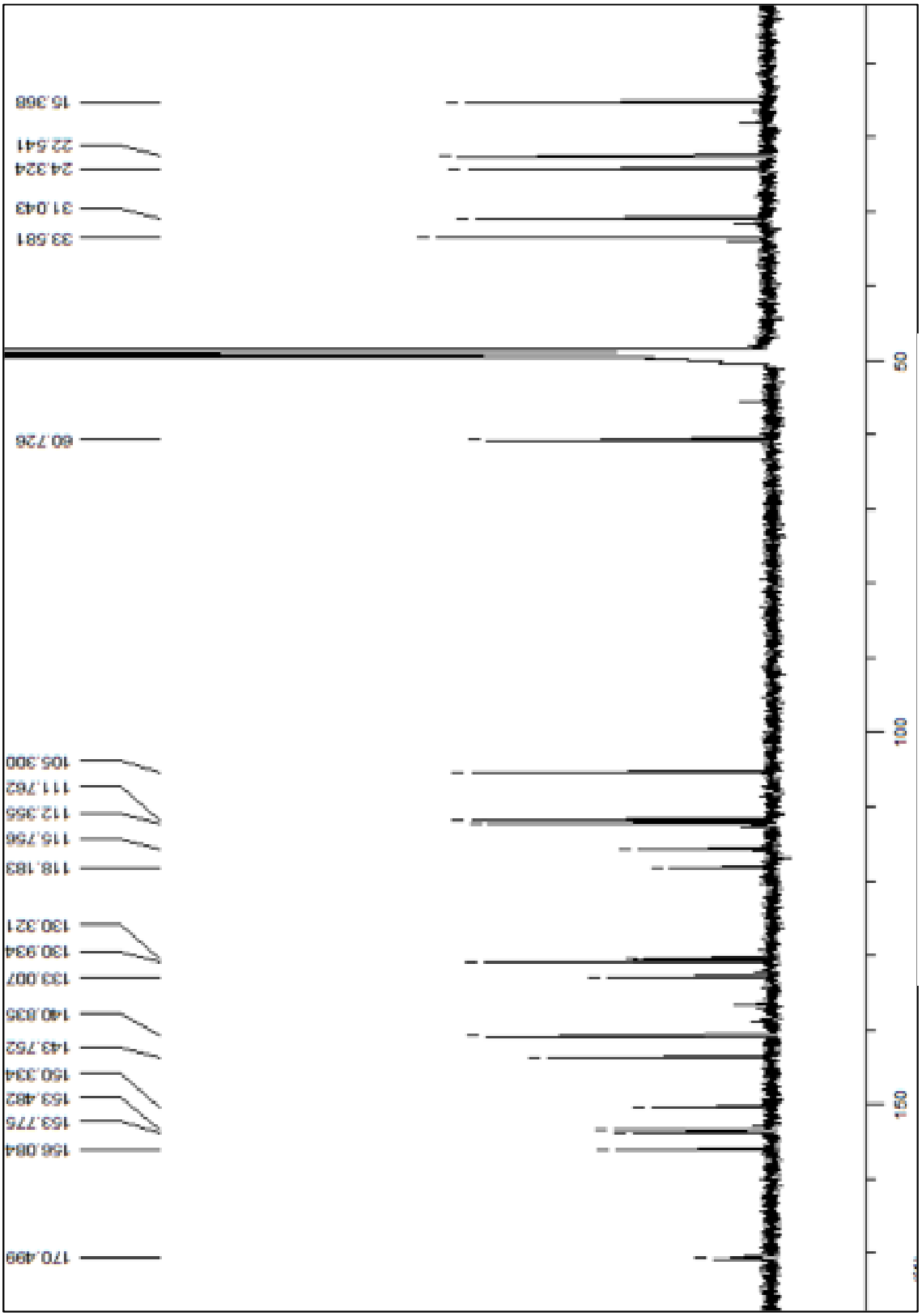
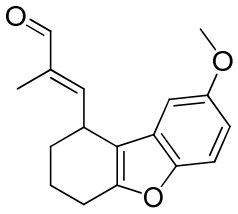


Figure 2. ^{13}C-NMR spectrum of cuevaene A in CD_3OD.
Data processed from raw fid provided by isolation authors

Appendix III. X-Ray Crystallographic Data for Aldehyde 124 (CCDC 914596)



124

Empirical Formula	$C_{17}H_{18}O_3$
Formula Weight	270.31
Temperature/K	110.0
Crystal System	Monoclinic
Space Group	$P2_1/c$
a/Å	8.8508(4)
b/Å	9.1144(4)
c/Å	18.0233(7)
α/°	90.00
β/°	103.855(4)
γ/°	90.00
Volume/Å^3	1411.63(11)
Z	4
ρ_{calc} mg/mm^3	1.272
m/mm^{-1}	0.086
F(000)	576.0
Crystal Size/mm^3	0.1475 x 0.0748 x 0.0726
2Θ range for data collection	5.8 to 52.1 °
Index Ranges	$-10 \leq h \leq 10$, $-10 \leq k \leq 11$, $-21 \leq l \leq 21$
Reflections Collected	5538
Independent Reflections	2750 [R(int) = 0.0380]
Data/Restraints/Parameters	2750/4/212
Goodness-of-fit on F^2	1.102
Final R indexes [I>=2σ (I)]	$R_1 = 0.0718$, $wR_2 = 0.1307$
Final R indexes [all data]	$R_1 = 0.1156$, $wR_2 = 0.1488$
Largest diff. peak/hole/eÅ^{-3}	0.29/-0.24

Appendix IV. Craven, P. G. E.; Taylor, R. J. K. *Tetrahedron Lett.* 2012, *53*, 5422 – 5425.[49]

Tetrahedron Letters 53 (2012) 5422–5425

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Total synthesis and structural confirmation of (±)-cuevaene A

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ABSTRACT

The total synthesis and structural reassignment of cuevaene A have been completed. The key synthetic steps in the total synthesis included a base-promoted double conjugate addition and further elaboration to generate the tricyclic core structure, followed by construction of the trienoic acid side chain. Detailed comparison of proton and carbon NMR data with published values enabled the connectivity of the natural product, which had been debated in earlier publications, to be confirmed.

Cuevaenes A and B are triene natural products isolated from *Streptomyces* sp. HKI 0180 in 2000 by Gräfe et al.[1] and shown to possess moderate antibacterial activity against Gram-positive bacteria (Fig. 1). Using a combination of mass spectrometry and 1D and 2D NMR spectroscopy, Gräfe's group assigned structures **1** and **2**, respectively, to cuevaenes A and B.

In 2009, two structurally related natural products, JBIR-23 (**3**) and 24 (**4**), were isolated from the same species of bacteria by Shin-ya and co-workers.[2] Trienes **3** and **4** show extremely promising activity against an asbestos-caused lung cancer, malignant pleural mesothelioma.[3] Natural products **1**–**4** all share the same 4-methoxy-6-methylheptatrienoic acid side chain, which appears to be a previously undescribed natural product structural motif. Given the similarity of the tricyclic core system in cuevaene A, JBIR-23 (**3**) and 24 (**4**), and the fact that all of the compounds were isolated from the same strain of bacteria, Shin-ya's group suggested that these four natural products may share the same biosynthetic pathway. Moreover, they proposed that, if this was indeed the case, the structures of **1** and **2**, initially proposed by Gräfe et al., may be incorrect and the alternative structures **5** and **6**, in which the positioning of the side chains on the tricyclic core system matches that seen in **3** and **4**, are more likely to be correct (Fig. 1).

To confirm the Shin-ya hypothesis, in 2010, Liu et al. synthesised both **1** and **5** in an attempt to confirm the structure of cuevaene A but, surprisingly, they found that the proton and carbon NMR spec-

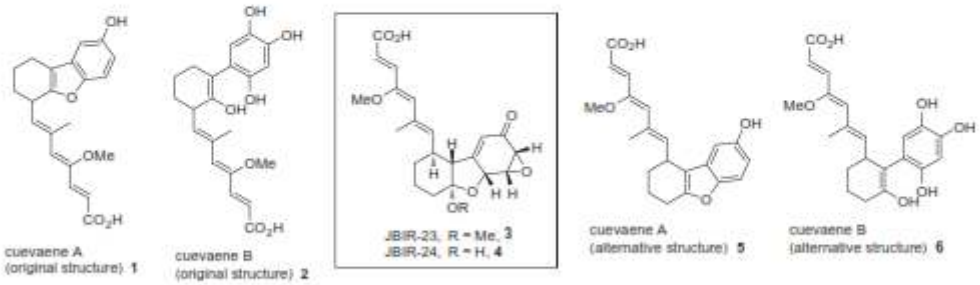

Figure 1. Structures of cuevaenes and JBIR compounds.

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E-mail address: richard.taylor@york.ac.uk (R.J.K. Taylor).

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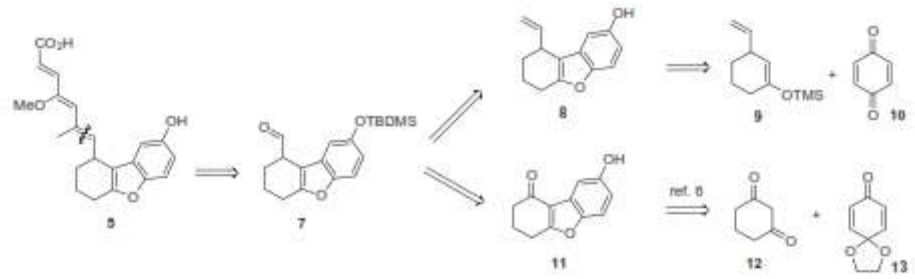


Scheme 1.

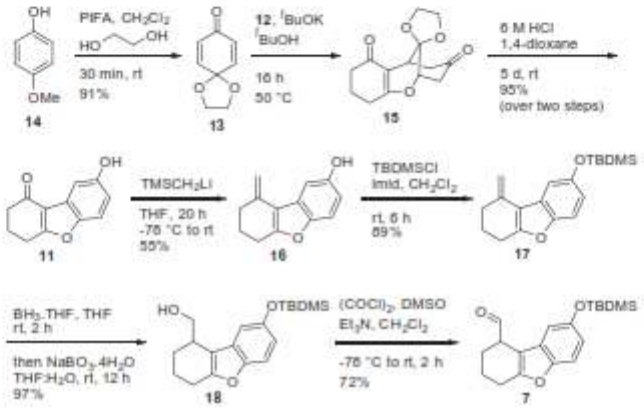
troscopic data of both their synthetic samples failed to match those reported for the natural product.[4] Having an interest in the preparation of JBIR analogues, we decided to first solve the ambiguity concerning the structure of cuevaene A. For reasons outlined later, we felt that structure **5** proposed by Shin-ya was most likely to be correct and therefore embarked on its re-synthesis (Scheme 1).

Liu's synthetic route utilised the tricyclic aldehyde **7** as the cornerstone synthetic intermediate then elaborating the trienoic acid side chain using sequential olefination reactions (Scheme 1). Aldehyde **7** was accessed from alkene **8**, itself prepared from the known[5] Lewis acid promoted condensation between silyl enol ether **9** and *p*-benzoquinone (**10**). Our synthetic plan utilised the same aldehyde intermediate **7** and a similar, but more streamlined, end-game to that described by Liu et al. However, we envisioned that aldehyde **7** could be accessed via a homologation reaction of known ketone **11** (Scheme 1).[6] Ketone **11** is readily accessed from commercially-available cyclohexa-1,3-dione (**12**) and quinone monoketal **13** via a double conjugate addition process followed by acidic rearrangement.[6]

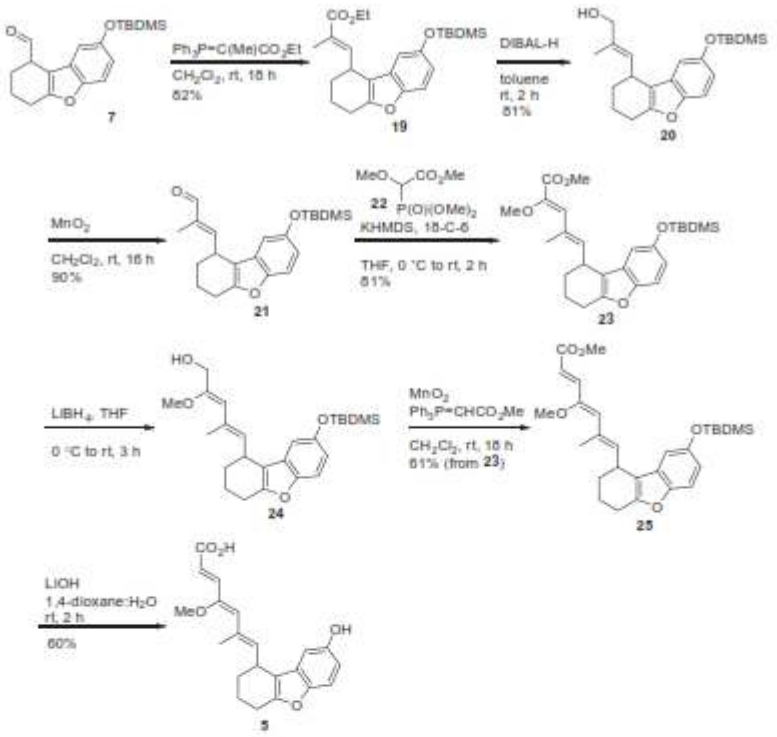
Quinone monoketal **13** was readily prepared by dearomatisation of 4-methoxyphenol (**14**) using phenyliodonium trifluoroacetate (PIFA), by modification of a known procedure.[7] The published procedure[7] uses CH_2Cl_2 as the solvent but, on a larger scale, significant amounts of *p*-benzoquinone were formed. However, we found that switching the solvent to ethylene glycol, with a minimum amount of dichloromethane to aid dissolution of phenol **14**, enabled the reaction to be carried out efficiently on a larger scale (30 mmol) (Scheme 2). Following literature procedures,[6] compound **13** was then converted into ketone **11** in excellent yield via a ^{t}BuOK-catalysed double conjugate addition followed by an acidic rearrangement of intermediate **15** using 6 M hydrochloric acid.

We next planned to homologate ketone **11** by an olefination/hydroboration/oxidation sequence. Unfortunately, standard Wittig chemistry (e.g. $Ph_3PCH_3^+Br^-$, ^{n}BuLi) was unsuccessful, but eventually methylenation was accomplished using the commercially available Peterson reagent, trimethylsilylmethyllithium, albeit in a moderate yield. It should be noted that silylation of compound **11** prior to olefination could not be achieved, whereas the analogous protection of phenol **16** to give the TBDMS silyl ether **17** was carried out in good yield. Subsequent hydroboration using BH_3.THF followed by treatment with sodium perborate[8] gave alcohol **18** in a good yield (traditional work-up conditions, such as $NaOH/H_2O_2$, caused deprotection of the silyl ether; direct oxidation of the intermediate borane to aldehyde **7** was unsuccessful). Subsequent oxidation of compound **18** using the Swern procedure gave the desired aldehyde **7** in 39% yield over 7 steps from phenol **14**. Compound **7**, prepared by a different route, was also employed in the study by Liu and co-workers[4]

The completion of the synthesis employed a sequential olefination sequence similar to that developed by Liu's group,[4] although a number of improvements were introduced (Scheme 3). Firstly, aldehyde **7** was treated with ethyl 2-(triphenylphosphoranylidene)propanoate to yield the desired unsaturated ester **19** in good yield and exclusively as the *E*-isomer (the NMR data corresponded closely to those reported by Liu and co-workers[4]). While Liu's

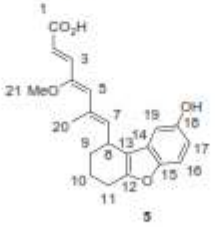


Scheme 2.



Scheme 3.

Table 1
Comparison of NMR spectroscopic data of cuevaene A (**5**) (all values are in ppm with respect to TMS)



	Cuevaene A[1,11]	Liu's synthetic **5**[9]	Our synthetic **5**	
Proton	CD_3OD (300 MHz)	$CDCl_3$ (400 MHz)	CD_3OD (400 MHz)	$CDCl_3$ (400 MHz)
16	7.15 (d, 8.7)	7.23 (d, 8.0)	7.15 (d, 8.7)	7.22 (d, 8.3)
3	7.07 (d, 15.4)	7.12 (d, 15.2)	7.07 (d, 15.4)	7.11 (d, 15.4)
19	6.69 (d, 2.4)	6.69 (s)	6.69 (d, 2.4)	6.70 (d, 2.0)
17	6.63 (dd, 2.4, 8.7)	6.68 (d, 8.4)	6.63 (dd, 2.4, 8.7)	6.68 (dd, 2.0, 8.3)
2	5.99 (d, 15.4)	6.04 (d, 15.6)	5.99 (d, 15.4)	6.03 (d, 15.4)
5	5.91 (s)	5.84 (s)	5.91 (s)	5.83 (s)
7	5.80 (d, 10.0)	5.77 (d, 10.0)	5.79 (d, 10.1)	5.76 (d, 9.9)
8	3.80–3.91 (m)	3.82–3.83 (m)	3.84 (ddd, 5.7, 7.7, 10.1)	3.78–3.87 (m)
21	3.65 (s)	3.66 (s)	3.65 (s)	3.65 (s)
11	2.66–2.74 (m)	2.72–2.73 (m)	2.67–2.74 (m)	2.68–2.76 (m)
20	2.24 (s)	2.22 (s)	2.24 (s)	2.21 (s)
9,10	1.96–2.15 (m)	1.98–2.11 (m)	1.96–2.14 (m)	1.95–2.11 (m)
	1.81–1.95 (m)	1.82–1.89 (m)	1.81–1.93 (m)	1.80–1.92 (m)
	1.50–1.66 (m)	1.52–1.60 (m)	1.50–1.63 (m)	1.50–1.61 (m)

group used $LiBH_4$ to carry out the reduction of ester **19**, we achieved better yields using DIBAL-H as the reducing agent. Subsequent oxidation of the resulting alcohol **20** to aldehyde **21** was then effected, in a good yield, using MnO_2. A Horner–Wadsworth–Emmons reaction with phosphonate **22**[9] afforded the desired diene **23** in a good yield, again with complete stereoselectivity. Liu et al. found it necessary to reprotect the phenol after this step, but we found that by using only one equivalent of base, the need for reprotection could be avoided while maintaining the yield. $LiBH_4$ reduction of methyl ester **23** gave the desired alcohol **24** in essentially quantitative yield, although it proved to be unstable as a solution in chloroform. The final alkene was then installed using a tandem oxidation process (TOP),[10] using manganese dioxide in the presence of methyl (triphenylphosphoranylidene)acetate, to afford the desired triene **25** as a single stereoisomer and in good yield. The final deprotection and hydrolysis were carried out using Liu's LiOH procedure (60%) giving Shin-ya's proposed structure of cuevaene A, (**5**). Our overall yield of cuevaene A (**5**) from phenol **14** is 7% over 14 steps (as compared to Liu's route which gave 5% yield over 13 steps).[4]

Having prepared the alternative structure **5** for cuevaene A as proposed by Shin-ya et al.,[2] we were in a position to clarify the correct structural assignment. At this point, we contacted Professor Gräfe's group and they kindly sent us the original data from the isolated natural products.[11] However, on inspection of the original data, we realised that an error had been made in reporting the ^1H NMR data for cuevaene A in the original publication;[1] the original ^1H NMR data was actually collected in CD_3OD, but in the publication the solvent was reported to be $CDCl_3$. We therefore collected the ^1H NMR data for compound **5** in both CD_3OD and $CDCl_3$ and compared these with the data reported by Gräfe[1,11] and Liu[4] (Table 1).

As can be seen, the ^1H NMR data of our synthetic compound **5** corresponded extremely well to those reported by Gräfe's group in deuterated methanol,[1,11] and by Liu and co-workers in $CDCl_3$.[4] The doubt as to the correct structure of cuevaene A (**5**) expressed by Liu et al. was obviously due to the original misreporting of the NMR solvent. This conclusion is also supported by a comparison of the ^{13}C NMR spectroscopic data of **5** with that of the natural product which show a very close match, {e.g. (CD_3OD, 100 MHz) 170.5 (C-1; Lit.[1] 170.5), 153.5 (C-4; Lit.[1] 153.4) and 33.6 (C-8; Lit.[1] 33.5)}.[12] The side-chain positioning was further confirmed by observed HMBC interactions between C-12 and H-11 and C-13 and H-7. In addition, NOE interactions between H-3 and H-5, and H-5 and H-7, confirmed the geometries of the two trisubstituted alkenes.

In conclusion, we have successfully synthesised Shin-ya's proposed structure of cuevaene A (**5**)[2] from 4-methoxyphenol (**14**) in 14 steps and 7% overall yield. In addition, we have confirmed the true structure of cuevaene A (**5**), correcting the initial misassignment[1] and subsequent structural uncertainty.[4] Furthermore, by extrapolation, cuevaene B should be reassigned as structure **6**,[2] to match the connectivity of cuevaene A (**5**). We are currently applying this methodology to prepare structurally related natural products, JBIR-23 (**3**) and 24 (**4**).

Acknowledgements

We are grateful to the University of York and Elsevier for postgraduate support (P.G.E.C.) and to the Society of Chemical Industry for additional Scholarship funding.

Supplementary data

Supplementary data (general procedures and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.121.

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11. Original unprocessed NMR spectroscopic data was supplied courtesy of Dr. Michael Ramm, Leibniz Institute for Natural Product Research and Infection Biology, and was processed using MestReC software, to be consistent with the spectroscopic data for our synthetic compounds. The data shown for cuevaene A in this paper therefore differs slightly from the published data (Ref.[1]).
12. The full ^{13}C NMR data is given in the Supplementary data section.

Appendix V. Craven, P. G. E.; Taylor, R. J. K. *Synlett.* 2013, *24*, 363 – 368.[89]

Stereocontrolled Routes to 4-Methoxypentadienoates for Use in Natural Product Synthesis

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Abstract: Mild and efficient routes to (*E*,*E*)- and (*E*,*Z*)-4-methoxypentadienoic acid esters from readily accessible γ,δ-epoxydienoates are described. The crucial epoxide methanolysis can be carried out in stereocomplementary ways by the use of either acid-mediated or palladium-catalysed procedures, the latter procedure proving preferable in most cases.

Key words: epoxides, stereoselective synthesis, palladium catalysis, acid catalysis, diene synthesis

JBIR-23 (**1**) and JBIR-24 (**2**) are two novel natural products which were isolated in 2009 from *Streptomyces* sp. AK-AB27 and shown to possess promising anticancer activity against an aggressive form of lung cancer, malignant pleural mesothelioma (Figure 1).[1] The only structurally related natural products are cuevaene A (**3**) and B (**4**) which were reported in 2000 by Gräfe et al.[2] also having been isolated from *Streptomyces* and shown to possess moderate activity against Gram-positive bacteria. Compounds **1**–**4** all contain the same (*E*,*Z*,*E*)-4-methoxy-6-methylheptatrienoic acid side chain which, to the best of our knowledge, is unique to this small group of natural products.

(±)-Cuevaene A (**3**) has recently been synthesised by Liu et al.[3] and by our own group[4] with both synthetic routes employing a conventional Wittig-based procedure to install the alkenes in a stepwise manner. Whilst successful, this linear strategy was rather lengthy and the Horner–Wadsworth–Emmons reaction using methyl(dimethoxyphosphoryl)(methoxy)acetate employed to install the key methoxy enol ether proved rather capricious.

As part of our ongoing interest in the total synthesis of natural products **1**–**4**, we have investigated alternative, more efficient procedures to prepare building blocks for the construction of methoxylated polyene side chains. Herein we report two complementary and straightforward procedures for the stereocontrolled conversion of dienoates **5** into a range of (*E*,*E*)- and (*E*,*Z*)-4-methoxypentadienoates (*E*,*E*)-**6** or (*E*,*Z*)-**6** (Scheme 1).

The starting point for this investigation was a report by Watt et al.[5] in 1983 in which they converted γ,δ-epoxydienoate **7** into ethoxy dienoate **9** (Scheme 2).

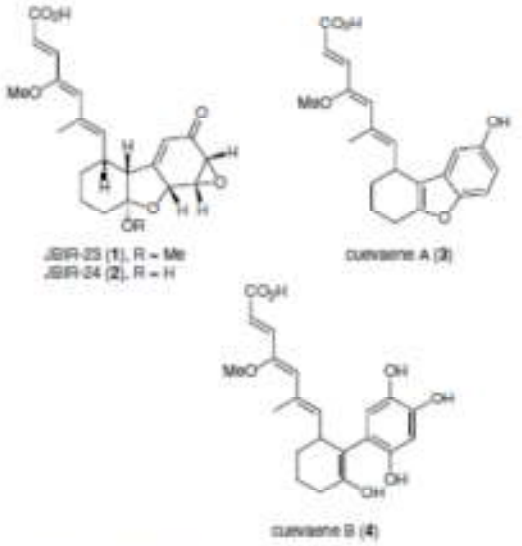
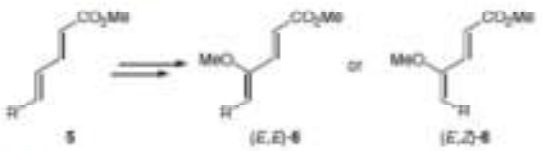


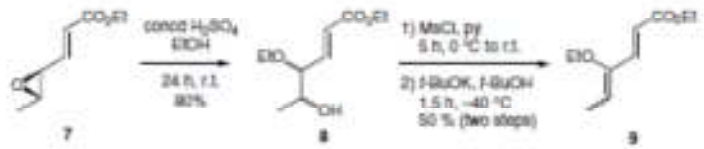
Figure 1 Natural products containing (*E*,*Z*,*E*)-4-methoxy-6-methylheptatrienoic acid side chains

The acid-promoted ring opening of epoxide **7** with ethanol afforded ethoxy alcohol **8** (stereochemistry not defined) in good yield. Treatment of alcohol **8** with mesyl chloride and subsequent elimination of the intermediate mesylate with *t*-BuOK delivered, in moderate yield, the desired 4-ethoxy-diene **9**. Watt et al.[5] did not comment on the stereoselectivity of this process, but the reported data indicates that only one product was formed, suggesting that the process was diastereoselective. Given these results, we envisioned that the analogous epoxide ring opening using methanol, rather than ethanol, should deliver the methoxydienes required for our natural product studies. In this publication, we describe the successful implementation of this strategy.



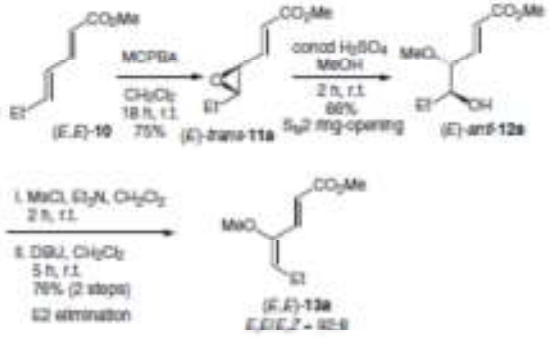
Scheme 1

SYNLETT 2013, 24, 0363–0368
Advanced online publication: 23.01.2013
DOI: 10.1055/s-0032-1318130; Art ID: ST-2012-D1095-L



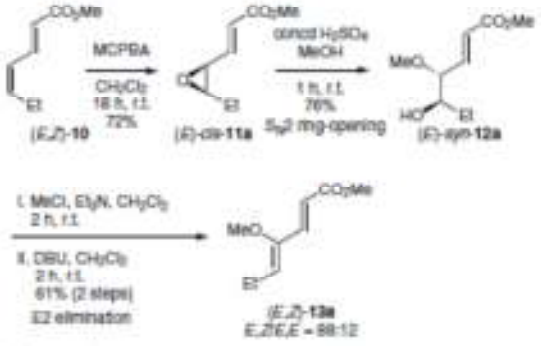
Scheme 2

The initial studies were carried out using (*E*)-*trans*-**11a**, readily obtained by modification of a literature procedure[6a] from methyl hepta-(2*E*,4*E*)-dienoate (*E*,*E*)-**10**[6b] (Scheme 3). Treatment of the epoxide (*E*)-*trans*-**11a** with methanol and concentrated sulfuric acid, delivered the expected methoxy alcohol as a single diastereomer, believed to be (*E*)-*anti*-**12a** based on S_N2 ring opening. Subsequent mesylation under standard conditions and elimination using DBU, which in our hands proved to be more efficient than *t*-BuOK, delivered the desired (*E*,*E*)-methoxy-diene (*E*,*E*)-**13a** (containing at most 8% of the *E*,*Z* isomer) in good yield. The stereochemistry of (*E*,*E*)-**13a** was confirmed by NOE NMR spectroscopic experiments (see later) and is consistent with S_N2 epoxide ring opening followed by a DBU-promoted E2 elimination as shown in Scheme 3.



Scheme 3

Of course, the main targets for the natural product study were 4-methoxyhepta-(2*E*,4*Z*)-dienoates and therefore it was important to establish the stereoselectivity of this sequence (Scheme 4). Therefore, methyl hepta-(2*E*,4*Z*)-dienoate (*E*,*Z*)-**10**[6a] was converted into epoxide (*E*)-*cis*-**11a** by treatment with MCPBA.[6b] Subsequent acid-catalysed methanolysis to give (*E*)-*syn*-**12a** followed by mesylation and treatment with DBU delivered predominantly the expected product diene (*E*,*Z*)-**13a** (*E*,*Z*/*E*,*E* = 88:12). We attribute the stereochemical leakage to a competing E1cb pathway; in all cases the *E*/*Z*-mixtures were inseparable using conventional chromatography.



Scheme 4

NMR spectroscopy and NOE experiments were employed to confirm the structures of dienes (*E*,*E*)- and (*E*,*Z*)-**13a** (Figure 2) as shown in Scheme 5 and Table 1.

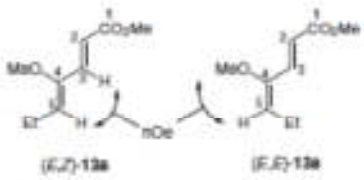


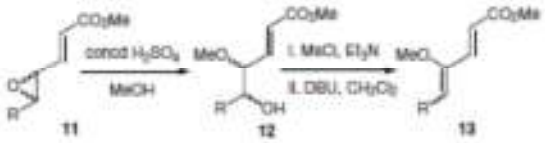
Figure 2

Table 1 Selected NMR Spectroscopic Data for (*E*,*E*)-**13a** and (*E*,*Z*)-**13a**[a]

Position	δ_H (*E*,*E*)-**13a**	δ_C (*E*,*E*)-**13a**	δ_H (*E*,*Z*)-**13a**	δ_C (*E*,*Z*)-**13a**
2	6.02 (d, *J* = 15.5 Hz)	116.0	6.21 (d, *J* = 15.0 Hz)	117.6
3	7.03 (d, *J* = 15.5 Hz)	140.9	7.45 (d, *J* = 15.0 Hz)	135.0
5	5.39 (t, *J* = 7.6 Hz)	130.3	4.98 (t, *J* = 7.9 Hz)	11.9
OMe	3.62	59.8	3.57	59.8
CO_2Me	3.76	51.4	3.74	54.3

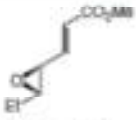
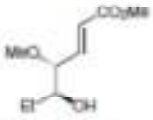
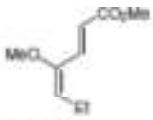
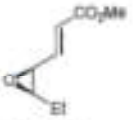
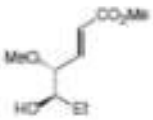
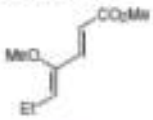
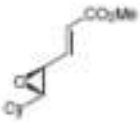
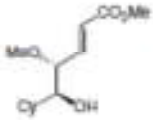
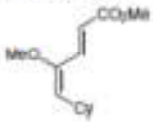
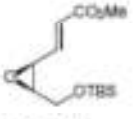
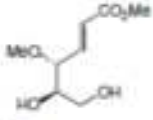
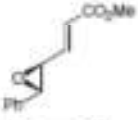
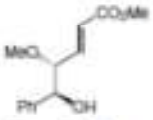
[a] All data collected at 400 MHz in $CDCl_3$ and reported as their shifts in ppm with their multiplicities and *J* values.

Having established successful conditions for the formation of dienes (*E,E*)-**13a** and (*E,Z*)-**13a**, we went on to investigate the scope of the process in terms of the terminal substituent (Scheme 5 and Table 2).



Scheme 5

Table 2 Acid-Mediated Epoxide Ring-Opening Sequence Leading to 4-Methoxypentadienoates **13**[a–c]

Entry	Epoxide	Alcohol	Diene
1	 (*E*)-*trans*-**11a**	 (*E*)-*anti*-**12a** 66%, 2 h	 (*E,E*)-**13a** 76%, 5 h *E,E*:*E,Z* = 92:8
2	 (*E*)-*cis*-**11a**	 (*E*)-*syn*-**12a** 70%, 1 h	 (*E,Z*)-**13a** 61%, 2 h *E,Z*:*E,E* = 88:12
3	 (*E,trans*-**11b**	 (*E*)-*anti*-**12b** 80%, 2 h	 (*E,E*)-**13b** 56%, 48 h *E,E*:*E,Z* = 72:28
4	 (*E*)-*cis*-**11c**	 **14** 33%, 0.5 h	not attempted
5	 (*E*)-*trans*-**11d**	 (*E*)-*anti*-**12d** 63%, 16 h	failed

[a] Epoxide-opening reactions were performed with concd H_2SO_4 in 0.1 M MeOH at r.t. for the indicated time.
[b] Mesylation reactions were performed with MsCl (1.5 equiv) and Et_3N (3.0 equiv) in 0.1 M CH_2Cl_2 at r.t. for 2 h.
[c] Elimination reactions were performed with DBU (1.2 equiv) in 0.1 M CH_2Cl_2 at r.t. for the indicated time.

However, although it proved possible to vary the type of terminal aliphatic substituent [from ethyl (Table 2, entries 1 and 2) to cyclohexyl (Table 2, entry 3), for example], this sequence became problematic with functionalised aliphatic and aromatic substrates (Table 2, entries 4 and 5). Thus, unsurprisingly, acid-sensitive groups are not well-tolerated in the acid-catalysed ring-opening process; epoxide (*E,cis*)-**11c** containing a TBS-protected primary alcohol underwent deprotection and further degradation in addition to the expected methanolysis (Table 2, entry 4). A different problem was encountered with the phenyl analogue (*E,trans*)-**11d**; in this case, the desired epoxide ring opening proceeded smoothly to deliver alcohol (*E,anti*)-**12d** in good yield, but on treatment with MsCl/DBU no elimination was observed (Table 2, entry 5), possibly for steric reasons.

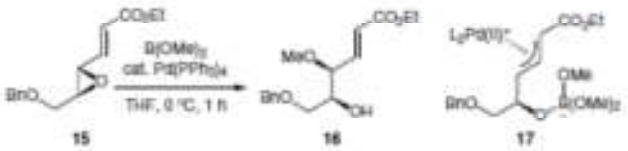
In order to overcome the above problems, particularly with acid-sensitive substrates, alternative, milder procedures were considered for the epoxide ring-opening step. In fact, such a procedure was readily available, as in 2008 Miyashita's group reported that treatment of γ,δ-epoxydienoate epoxides with $B(OR)_3$ and catalytic $Pd(PPh_3)_4$ produced alkoxy alcohols stereoselectively and in excellent yield; thus, reaction of epoxide **15** with $B(OMe)_3$ gave methoxy alcohol **16** stereoselectively and in excellent yield, presumably via the intermediacy of the π-allyl palladium(II) species **17** (Scheme 6).[7]

We therefore decided to investigate this palladium-catalysed epoxide-opening procedure in combination with the DBU-mediated elimination in order to expand the range of 4-methoxypentadienoates that could be accessed. This study was successful, and the results are summarised in Table 3.

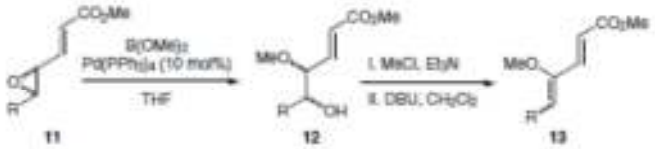
The first point to note is that the Miyashita palladium-catalysed sequence has the opposite stereoselectivity to the acid-mediated variant. Thus, under acid-mediated conditions, epoxide (*E*)-*trans*-**11a** gives diene (*E,E*)-**13a** and (*E*)-*cis*-**11a** gives diene (*E,Z*)-**13a** (Table 2, entries 1 and 2) whereas under palladium-catalysed conditions, epoxide (*E*)-*trans*-**11a** gives diene (*E,Z*)-**13a** and (*E*)-*cis*-**11a** gives diene (*E,E*)-**13a** (Scheme 7, Table 3, entries 1 and 2). The rationale for this stereocomplementarity is straightforward – with acid catalysis, epoxide ring opening by methanol occurs by an S_N2 mechanism whereas with palladium catalysis a 'double inversion' takes place via a π-allyl palladium(II) intermediate giving the opposite diastereomer of the methoxy alcohol.

This stereocomplementarity is valuable where only one diastereomeric epoxide is readily available; for example, the cyclohexyl system (*E*)-*trans*-**11b** gives (*E,E*)-**13b** with the acid-mediated route (Table 2, entry 3) and (*E,Z*)-**13b** with the palladium-mediated route (Table 3, entry 3). Again, we attribute the stereochemical leakage to a competing E1cb pathway.

It should also be noted that, when comparisons can be made (Table 3, entries 1–3), the combined yields for the palladium-catalysed sequence are comparable or slightly higher than those for the acid-mediated sequence. The



Scheme 6



Scheme 7

main advantage of the palladium-catalysed route, however, is that the mild nature of the procedure leads to a considerable expansion of its scope being applicable to several acid-sensitive substrates (Table 3, entries 4 and 5). A further point of interest is that (*E*)-*syn*-**12d** undergoes the expected E2 elimination to give diene (*E*,*Z*)-**13d** (Table 3, entry 7) whereas the diastereomeric alcohol (*E*)-*anti*-**12d** proved resistant to elimination (Table 2, entry 5). This slightly surprising observation presumably reflects the enhanced steric hindrance in the latter case (antiperiplanar elimination positions the bulky acrylate group gauche to both the mesylate and phenyl substituents).

Table 3 Pd(0)-Catalysed Epoxide Ring-Opening Sequence Leading to 4-Methoxypentadienoates **13**[a–c]

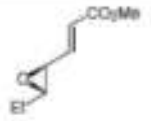
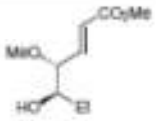
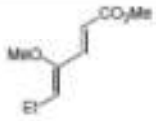
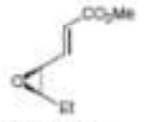
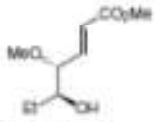
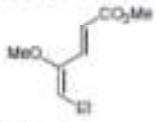
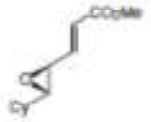
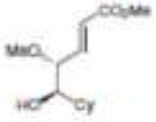
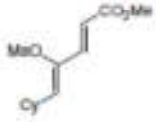
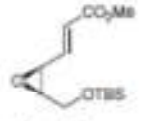
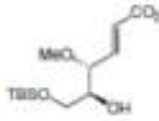
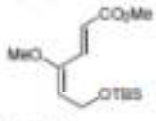
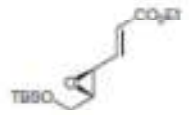
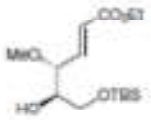
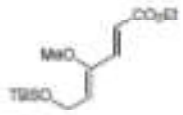
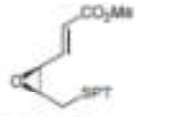
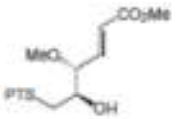
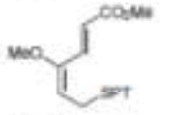
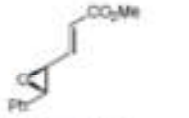
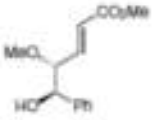
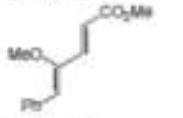
Entry	Epoxide	Alcohol	Diene
1	 (*E*)-*trans*-**11a**	 (*E*)-*syn*-**12a** 82%, 1 h	 (*E*,*Z*)-**13a** 61%, 2 h *E*,*Z*:*E*,*E* = 92:8
2	 (*E*)-*cis*-**11a**	 (*E*)-*anti*-**12a** 80%, 1 h	 (*E*,*E*)-**13a** 76%, 2 h *E*,*E*:*E*,*Z* = 88:12
3	 (*E*)-*trans*-**11b**	 (*E*)-*syn*-**12b** 80%, 2 h	 (*E*,*Z*)-**13b** 62%, 2 h *E*,*Z*:*E*,*E* = 83:17
4	 (*E*)-*cis*-**11c**	 (*E*)-*anti*-**12c** 82%, 1 h	 (*E*,*E*)-**13c** 90%, 2 h *E*,*E*:*E*,*Z* = >95:<5

Table 3 Pd(0)-Catalysed Epoxide Ring-Opening Sequence Leading to 4-Methoxypentadienoates **13**[a,c] (continued)

Entry	Epoxide	Alcohol	Diene
5	 (*E*)-*trans*-**11c**	 (*E*)-*syn*-**12c** 57%, 1 h	 (*E*,*Z*)-**13c** 69%, 2 h *E*,*Z*:*E*,*E* = >95:<5
6	 (*E*)-*cis*-**11e**	 (*E*)-*anti*-**12e** 52%, 2 h	 (*E*,*E*)-**13e** 84%, 7 h *E*,*E*:*E*,*Z* = >95:<5
7	 (*E*)-*trans*-**11d**	 (*E*)-*syn*-**12d** 84%, 1 h	 (*E*,*Z*)-**13d** 72%, 2 h *E*,*Z*:*E*,*E* = >95:<5

[a] Epoxide-opening reactions were performed with $Pd(PPh_3)_4$ (10 mol%) and $B(OMe)_3$ (1.2 equiv) in 0.2 M THF at r.t. for the indicated time.
[b] Mesylation reactions were performed with MsCl (1.5 equiv) and Et_3N (3.0 equiv) in 0.1 M CH_2Cl_2 at r.t. for 2 h.
[c] Elimination reactions were performed with DBU (1.2 equiv) in 0.1 M CH_2Cl_2 at r.t. for the indicated time. PT = 1-phenyl-1*H*-tetrazo-5-yl.

In conclusion, we developed two methods, one acid-mediated and the other palladium-catalysed, for the synthesis of 4-methoxypentadienoic esters from readily available epoxide starting materials. The two methods exhibit complementary stereoselectivity to deliver the resulting dienes predominantly as single isomers.[9–12] We are currently exploiting the methodology described herein in natural product synthesis.

Acknowledgment

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(8) **General Procedure for the Acid-Promoted Epoxide Ring Opening**
To a stirred solution of epoxide (1.0 equiv) in MeOH (0.1 M) was added a catalytic amount of concd H_2SO_4. The resulting solution was stirred at r.t. until complete as monitored by TLC. After this time, the reaction mixture was quenched with brine and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified by flash column chromatography to afford the desired alcohol.
(9) **General Procedure for the Pd(0)-Mediated Epoxide Ring Opening**
To a stirred solution of epoxide (1.0 equiv) and $B(OMe)_3$ (1.2 equiv) in THF (0.2 M) at r.t. was added $Pd(PPh_3)_4$ (10 mol%). The resulting solution was stirred at r.t. until complete as monitored by TLC. After this time, the reaction mixture was quenched with $NaHCO_3$ (sat. aq solution) and diluted with EtOAc. The aqueous layer was extracted with EtOAc (3 ×). The combined organics were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified by flash column chromatography to afford the desired alcohol.
(10) **General Procedure for the Mesylation and Elimination Sequence**
To a stirred solution of alcohol (1.0 equiv) in CH_2Cl_2 (0.15 M) at r.t. was added MsCl (1.5 equiv) followed by Et_3N (3.0 equiv). The resulting solution was stirred at r.t. for 2 h. After this time, the reaction mixture was diluted with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried ($MgSO_4$), filtered,

and concentrated in vacuo. The resulting crude mesylate (1.0 equiv) was redissolved in CH_2Cl_2 (0.1 M), and DBU (1.2 equiv) was added at r.t. The resulting solution was stirred at r.t. until complete as monitored by TLC. After this time, the reaction mixture was quenched with 10% HCl and diluted with H_2O and CH_2Cl_2, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting crude material was purified by flash column chromatography to afford the desired diene.

(11) **Methyl (2*E*,4*E*)-4-Methoxyhepta-2,4-dienoate [(*E*,*E*)-13a]**

IR (film): ν_{max} = 1712 (C=O), 1645 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (3 H, t, *J* = 7.5 Hz), 2.20–2.28 (2 H, m), 3.57 (3 H, s), 3.74 (3 H, s), 4.98 (1 H, t, *J* = 7.9 Hz), 6.21 (1 H, d, *J* = 15.0 Hz), 7.45 (1 H, d, *J* = 15.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.2, 19.7, 54.3, 59.8, 111.9, 117.6, 135.0, 150.0, 167.4 ppm. MS: *m*/*z* = 171 [MH]$^+$, 193 [MNa]$^+$. ESI-HRMS: *m*/*z* calcd for $C_9H_{15}O_3$: 171.1016; found [MH$^+$]: 171.1013 (1.5 ppm error).

(12) **Methyl (2*E*,4*Z*)-4-Methoxyhepta-2,4-dienoate [(*E*,*Z*)-13a]**

IR (film): ν_{max} = 1715 (C=O), 1639 (C=C) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (3 H, t, *J* = 7.6 Hz), 2.26 (2 H, q, *J* = 7.6 Hz), 3.62 (3 H, s), 3.76 (3 H, s), 5.39 (1 H, t, *J* = 7.6 Hz), 6.02 (1 H, d, *J* = 15.5 Hz), 7.03 (1 H, d, *J* = 15.5 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 19.3, 51.4, 59.8, 116.0, 130.3, 140.9, 152.7, 167.4 ppm. MS: *m*/*z* = 171 [MH]$^+$, 193 [MNa]$^+$. ESI-HRMS: *m*/*z* calcd for $C_9H_{15}O_3$: 171.1016; found [MH$^+$]: 171.1013 (1.5 ppm error).

Abbreviations

18-c-6	18-crown-6
Ac	Acetate
Alloc	Allyloxycarbonyl
aq	Aqueous
Bn	Benzyl
br	Broad
BRSM	Based on recovered starting material
Bu	Butyl
Bz	Benzoyl
cm	Centimetre
conc.	concentrated
COSY	Correlation spectroscopy
d	Doublet
d	Day
δ	Chemical shift
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DIAD	Di-*iso*-propyl azodicarboxylate
DIBAL-H	Di-*iso*-butylaluminium hydride
DIPA	Di-*iso*-propylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	Dimethyl formamide
DMP	Dess–Martin Periodinane
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
E1	Unimolecular elimination
E1cB	Unimolecular conjugate base elimination
E2	Bimolecular elimination
eq.	Equivalent

ESI	Electrospray ionisation
Et	Ethyl
FGI	Functional group interconversion
g	grams
h	Hour
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
i	*iso*
imid	imidazole
IC_{50}	Half maximal inhibitory concentration
IR	Infra-red
K	Kelvin
LDA	Lithium di-*iso*-propylamide
L-DIPT	Diisopropyl L-tartrate
Lit.	literature
m	Multiplet
m	*meta*
M	Molarity
***m*CPBA**	*meta*-Chloroperbenzoic acid
Me	Methyl
mg	Milligrams
min	Minute
mL	Millilitre
mmol	Millimoles
MOM	Methoxymethyl ether
mp	Melting point
MPM	Malignant pleural mesothelioma
Ms	Mesyl
MS	Mass spectrometry
m/z	Mass to charge ratio

n	normal
NBS	*N*-Bromo succinimide
NMR	Nuclear magnetic resonance
nOe	Nuclear overhauser effect
oct	octanoate
p	*para*
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PMB	*para*-Methoxy benzyl
ppm	Parts per million
Pr	Propyl
PT	Phenyltetrazole
TSA	Toulenesulfonic acid
Py	Pyridine
R_f	Retention factor
ROE	Rotating-frame overhauser enhancement
RSM	Recovered starting material
rt	Room temperature
s	Singlet
sat	Saturated
S_N1	Unimolecular nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
t	Triplet
t	*tert*
TBAF	Tributylammonium fluoride
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Triflate
TFA	Trifluoroacetic acid
TFDO	3-methyl-3-(trifluoromethyl)dioxirane

THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TOP	Tandem oxidation processes
Ts	Tosyl
Tr	Trityl
UV	Ultraviolet
w/w	Weight per weight

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