New Metal-Mediated Cyclisation Methods And Their Strategic Application In Novel Steroidal Natural Product Synthesis

Thesis submitted to the University of Strathclyde in fulfilment of the requirements for the degree of Doctor of Philosophy

By

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Declaration of Copyright

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Abstract

A programme of work towards the total synthesis of the natural product, agariblazeispirol C, has been performed, with significant advances towards the realisation of this overall goal having been achieved. Within the overall strategy for gaining access to the desired natural target, a number of individual preparative pathways have been taken. Optimisation studies on many of the individual reaction steps have been performed to enhance synthetic efficiencies within the formulated routes towards agariblazeispirol C. In particular, key metal-mediated cyclisation steps, an intramolecular Heck reaction and a selective cobalt-meditated Pauson-Khand annulation, are central to the established approach to the natural product system. With regards the Heck process, microwave technology has been utilised to enable the reaction time to be reduced from days to minutes and has also allowed a significant reduction in catalyst loading to be achieved. A more traditional approach towards the establishment of a successful intramolecular Pauson-Khand reaction has delivered some interesting results, as well as a cyclisation process which can be performed with good levels of efficiency. These synthetic advances have allowed the construction of the angularly-fused tetracyclic central core of the natural product system in an overall yield of 25% over 14 synthetic steps, when the most effective preparative pathway is considered. In addition to the many successes achieved during this body of work and despite advanced synthetic intermediates having been prepared, efforts towards the completion of the total synthesis of agariblazeispirol C and, more specifically, methods for the attachment of the oxygenated five carbon side-chain, have yet to be successful.

Abbreviations

AIBN	Azobisisobutyronitrile
Ar	Aromatic/Arene
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BRSM	Based on recovered starting material
Bu	Butyl
COD	Cyclooctadiene
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone
DMSO	Dimethylsulfoxide
Dod	Dodecyl
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPP	1,2-Bis(diphenylphosphino)propane
Et	Ethyl
eq	Equivalents
FTIR	Fourier transform infrared
g	Grammes
h	Hours
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons
Hz	Hertz

IBX	2-Iodoxybenzoic acid
LDA	Lithium di-*iso*-propylamide
M	Molar
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligrammes
MHz	Megahertz
Mins	Minutes
ml	Millilitres
mmol	Millimoles
mol	Moles
MS	Molecular sieves
MWI	Microwave irradiation
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance spectra; s – singlet d – doublet t – triplet q – quartet m -multiplet
o	Ortho
OTf	Triflate
PDC	Pyridinium dichromate
PMP	2,2,6,6,*N*-Pentamethyl piperidine
ppm	Parts per million
Pr	Propyl
r.t.	Room temperature

SM	Starting material
TBAF	Tetrabutylammonium fluoride
TBS	*Tert*-butyldimethylsilyl
Temp.	Temperature
TEMPO	2,2,6,6-Tetramethylpiperidinyloxy
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer chromatography
TMANO	Trimethylamine *N*-oxide
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate

Contents

1 Introduction

1.1 Agariblazeispirol C

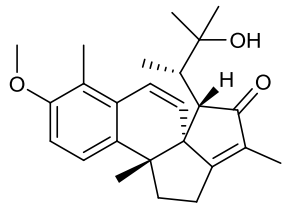
1.1.1 Agariblazeispirol C

Traditional medicine has been used for many thousands of years, and even today in some Asian and African countries, 80% of the people rely on this approach as their primary source of health care.[1] In many developed countries it is also reported that between 70% and 80% of the population have used some form of traditional medicine. Amongst the many forms of traditional medicine, herbal medicines are the most lucrative, generating sales of US$ 14 billion in China alone in 2005. A popular source of herbal medicine is the precious fungus A*garicus blazei* Murill. 100,000 – 300,000 Kg of the dried body of this fungus is produced in Japan every year and up to 500,000 people use this medicine to prevent cancer or as an adjuvant with cancer chemotherapy drugs.[2] A*garicus blazei* Murill originates from the Atlantic Forest in the highland area near São Paulo, Brazil (**Figure 1**).[3] In addition to cancer related treatments, this precious fungus has been used in traditional medicines in Brazil for the prevention of a range of diseases including diabetes, hyperlipidemia, arteriosclerosis, and chronic hepatitis.[2]

Figure 1

In addition to the extensive use of this precious fungus in traditional medicines, extensive research has been dedicated towards identifying the pharmacological effects of specific compounds contained within the mushroom. In particular, polysaccharides contained within the fungus have been shown to possess immuno-stimulating activity,[4-7] ergosterol derivatives display cytotoxicity,[8] and linoleic acid derived species have provided anti-mutagenic and bactericidal effects.[9]

Of the many compounds isolated from *Agaricus blazei* Murill, agariblazeispirol C **1**, reported in 2005,[10] is of particular interest to our research group (**Figure 2**). In contrast to many of the compounds isolated from this mushroom, the biological activity of **1** remains unknown, as biological screening has yet to be undertaken on this particular compound. In addition, the aforementioned molecule has an intriguing structure and to date there have been no reports in the chemical literature involving its synthesis. Therefore, the potential biological activity of agariblazeispirol C along with its interesting structure make this compound an ideal candidate as a target within a total synthesis programme.

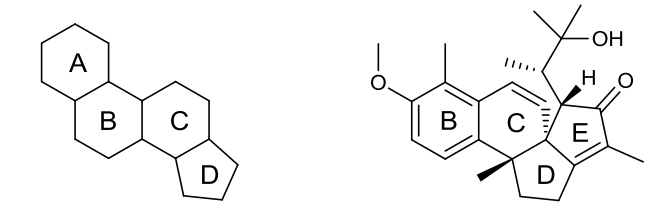


1

Figure 2

The molecular structure of agariblazeispirol C possesses characteristic features that are of interest to organic chemists, as well as biochemists. Of particular interest to the organic chemist are the four contiguous stereocentres running through the main body of the molecule and the exploration of methods by which such an array could be installed during a total synthesis. In addition to this, two of these stereocentres are contiguous, all-

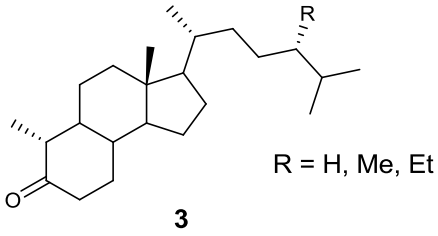
carbon, quaternary stereocentres, which elevates the challenge of installing this moiety. Furthermore, of particular interest to our research group is the presence of the cyclopentenone core in ring E. Significant research has been carried out within our laboratories towards the installation of the cyclopentenone core within complex molecules.



conventional steroid **2** agariblazeispirol C **1**

Figure 3

From a biological perspective, the core ring-structure of this molecule is an interesting and unusual type of steroid. Conventional steroids have a core ring-structure made up of 17 carbon atoms in the form of three six-membered rings and one five-membered ring fused together in the form shown **2** (**Figure 3**). Agariblazeispirol C **1** has only three of the rings commonly associated with a steroidal structure. Rings B, C, and D of the steroidal core are present, however, ring A is absent. Compounds of this type, referred to as des-A-ergostanes, have been reported before in the literature. The identification of compounds of the type **3**, which were isolated from a Cretaceous black shale in Italy, were the first sedimentary des-A-ergostanes to be discovered (**Figure 4**).[11]



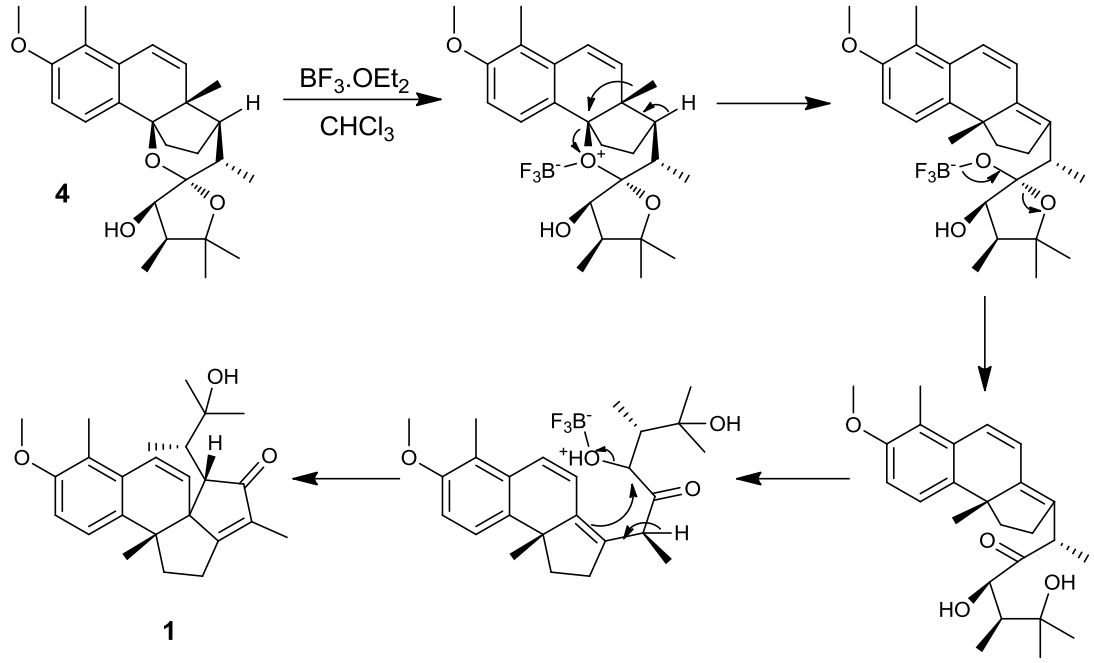
3

Figure 4

In such sedimentary deposits, it is understood that the A-ring is lost as a result of diagenesis.[12,13,11] However, compounds isolated from the cultured mycelia of *Agaricus blazei*, including agariblazeispirol C, were the first des-A-ergostanes to be isolated from living organisms. As a result, research has been carried out to determine the biosynthetic pathway through which this type of unusual steroid is constructed.

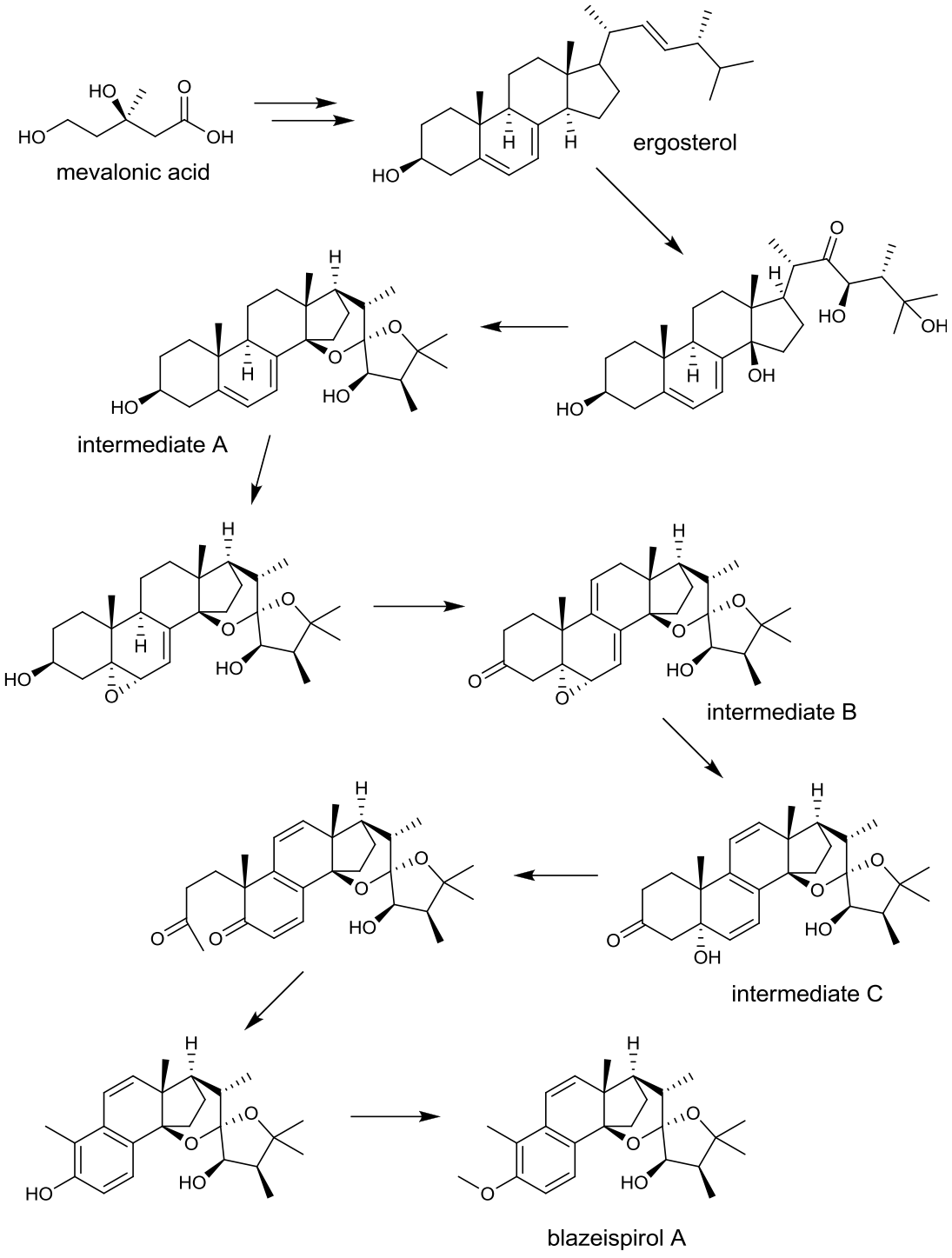
1.1.2 Biosynthetic Pathway

In the original publication reporting the isolation of agariblazeispirol C, the authors suggested that the biosynthesis could be initiated from blazeispirol A. In order to clarify this proposal, blazeispirol A **4** was treated under Lewis acidic conditions in an attempt to mimic the natural pathway and deliver agariblazeispirol C **1**. Under these conditions this transformation did proceed as predicted resulting in the formation of agariclazeispirol C, presumably *via* the pathway shown in **Scheme 1**.[10] Of particular note within the proposed mechanism is the 1,2-migration of the allylic methyl group in compound **4** to the benzylic position following complexation of the Lewis acidic boron reagent. The methyl group, positioned on the top face of the molecule, is shown to attack the leaving oxonium ion, also on the top face, in an S_N2 fashion. With the C-O anti-bonding sigma orbital positioned within the pocket between the 6.5-ring system, a direct substitution, *via* an S_N2 process, is unlikely. It is suggested that, following coordination of the Lewis acid, the oxinium ion leaves resulting in a planer benzylic carbocationic species. Finally, a 1,2-migration pathway would deliver the tricyclic product.



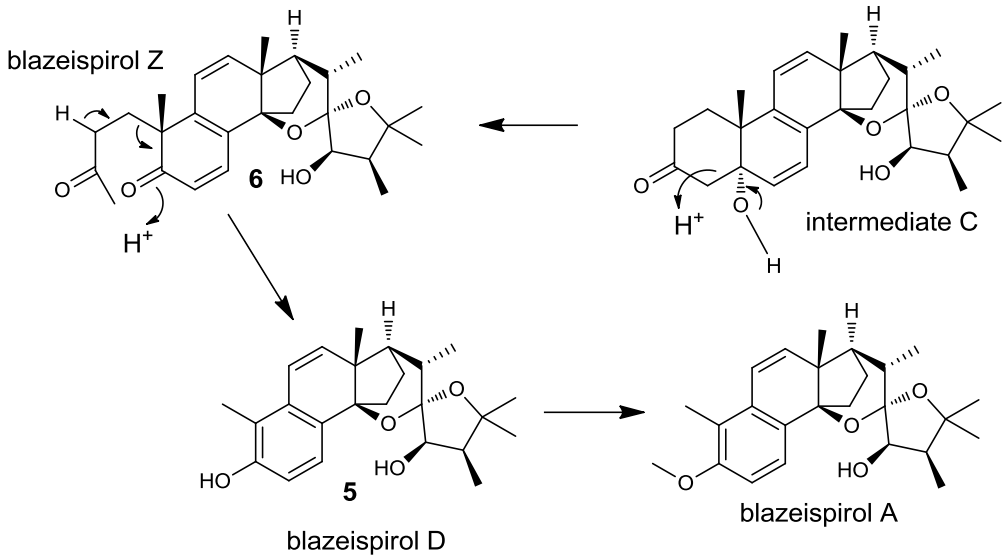
Scheme 1

The biosynthetic origin of agariblazeispirol C can be traced back even further as the origin of the precursor, blazeispirol A, has been studied in far greater detail *via* extensive ^{13}C-labeling studies. It has been shown that blazeispirol A is prepared through the biosynthetic pathway shown in **Scheme 2**.[14] Ergosterol, which is biosynthesised from mevalonic acid, is firstly oxidised and the product undergoes a subsequent intramolecular acetalisation process, involving the two tertiary alcohols and the ketone moiety, leading to intermediate A. A stereoselective-epoxidation/oxidation sequence then delivers intermediate B, which undergoes an elimination process that opens the newly installed epoxide and results in the formation of intermediate C. As a result of the ^{13}C-labelling studies, it was proposed that intermediate C was then converted in blazeispirol A *via* a process which resulted in the destruction of the A-ring.


mevalonic acid
ergosterol
intermediate A
intermediate B
intermediate C
blazeispirol A

Scheme 2

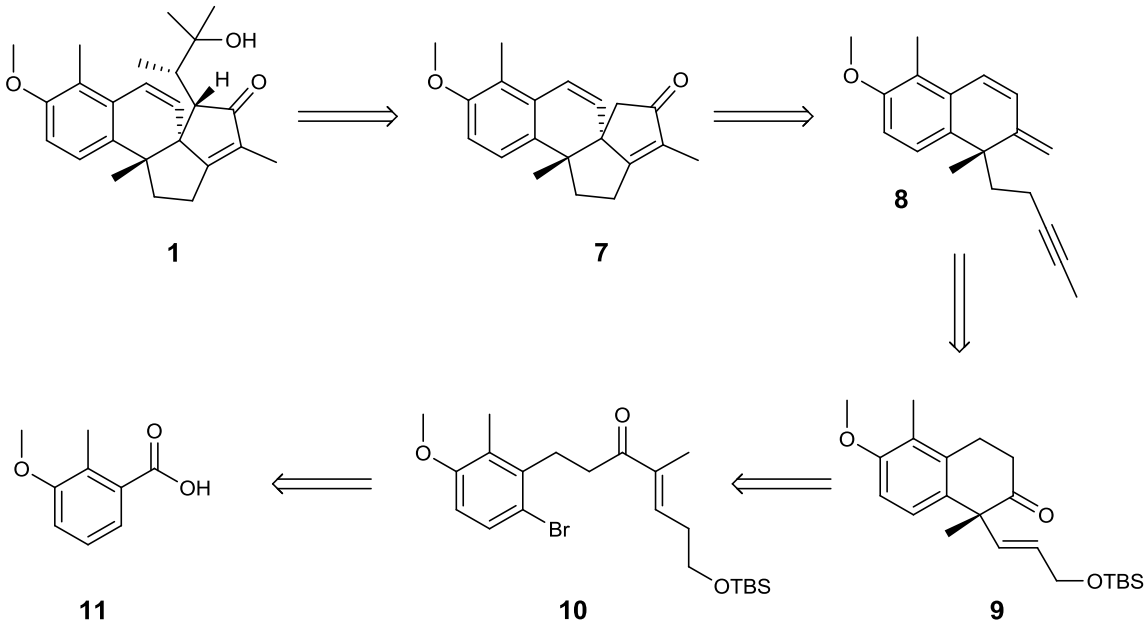
Further support for this proposed biosynthetic pathway was reported the following year by the isolation of key intermediates from the cultured mycelia of the fungus.[15] The isolation of blazeispirol D **5** and blazeispirol Z **6** supported the biosynthetic pathway shown in **Scheme 2** and allowed, for the first time, rationalisations to be made in relation to the pathway taken for the removal of the A-ring in living organisms. **Scheme 3** shows part of the proposed biosynthetic pathway and the mechanism through which the loss of the A-ring is believed to proceed. Firstly, a retro-aldol condensation is believed to occur from intermediate C leading to the ring opened product **6**, blazeispirol Z. Subsequently, a retro-Michael addition takes place to deliver the des-A-ergostane core of compound **5**, blazeispirol D. The isolation and characterisation of both **5** and **6** strongly support such a mechanistic pathway.



Scheme 3

1.1.3 Retrosynthetic Analysis

Within our research group, work is mainly centred on the development of metal-mediated processes and the use of such methodology within target molecule synthesis projects. In particular, transition metal chemistry has been thoroughly researched for many years within our laboratories using a range of metals including cobalt, chromium, iridium, and palladium. The retrosynthetic analysis of agariblazeispirol C **1** has two transition metal-mediated cyclisation methods at its core, more specifically, involving palladium and cobalt. The first step in the retrosynthetic proposal is removal of the oxygenated side chain to furnish the tetracyclic intermediate **7**. It is envisaged that the cyclopentenone motif within this tetracyclic core could be accessed *via* the second of the key metal-mediated cyclisations in the form of an intramolecular Pauson-Khand reaction. Preparation of the Pauson-Khand precursor **8** could be achieved from bicycle **9**, which we propose to set up through the first key cyclisation step, an intramolecular Heck reaction from compound **10**. Finally, this fragment could be accessed from the commercially available, and relatively inexpensive, benzoic acid derivative **11** (**Scheme 4**). This synthetic strategy is at the core of the research conducted as part of this programme and is presented here. As such, a review of the key synthetic methods which are central to our preparative approaches will now be presented.



Scheme 4

1.2 The Mizoroki-Heck Reaction

1.2.1 The Mizoroki-Heck Reaction

The formation of carbon-carbon bonds in organic synthesis can still present challenges for the synthetic organic chemist to face, especially when steric demands and wide functional group compatibility need to be surmounted. In this regard, extensive research has been dedicated towards the development of suitable and efficient methods that will satisfy increasingly complex requirements. Undoubtedly, the most effective advancements within this area have came from the creation and development of organometallic methods to carry out such transformations. In particular, palladium-catalysed chemistry has been at the forefront of this preparative progress due to the versatility of this metal, coupled with its tolerance of many functional groups and reagents. One of the most successful types of palladium-catalysed carbon-carbon bond forming processes has been the Mizoroki-Heck (Heck) reaction, following independent reports by Mizoroki[16] and Heck[17] in the early 1970's. In general, the process involves the coupling of two reaction partners, an organohalide or *pseudo*halide, and an olefin, under palladium conditions to deliver the coupled product as depicted in **Figure 5**. The halide or *pseudo*halide is generally connected to an sp^2 carbon in the form of either an aryl or vinyl halide. For the purpose of this introduction, this will generally be referred to as an aryl halide, whilst being representative of both aryl and vinyl compounds, as well as halides and *pseudo*halides.

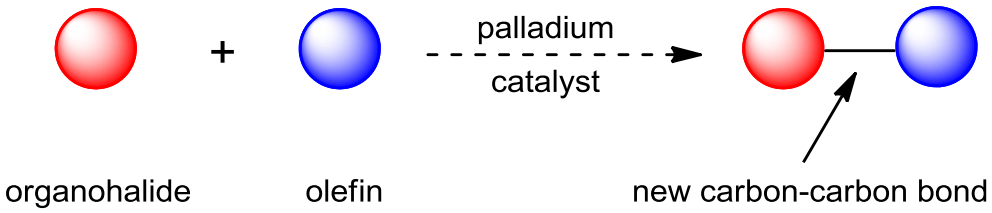
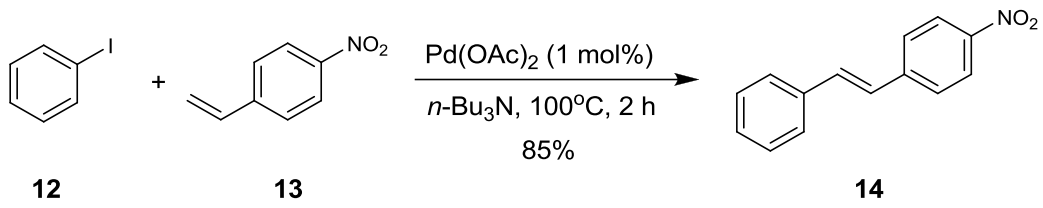


Figure 5

An example of a Heck reaction, from the seminal work by Heck, shows the carbon-carbon bond forming process between iodobenzene **12** and electron-deficient styrene **13**, which delivered the biaryl product **14** in an excellent 85% isolated yield (**Scheme 5**).[17]

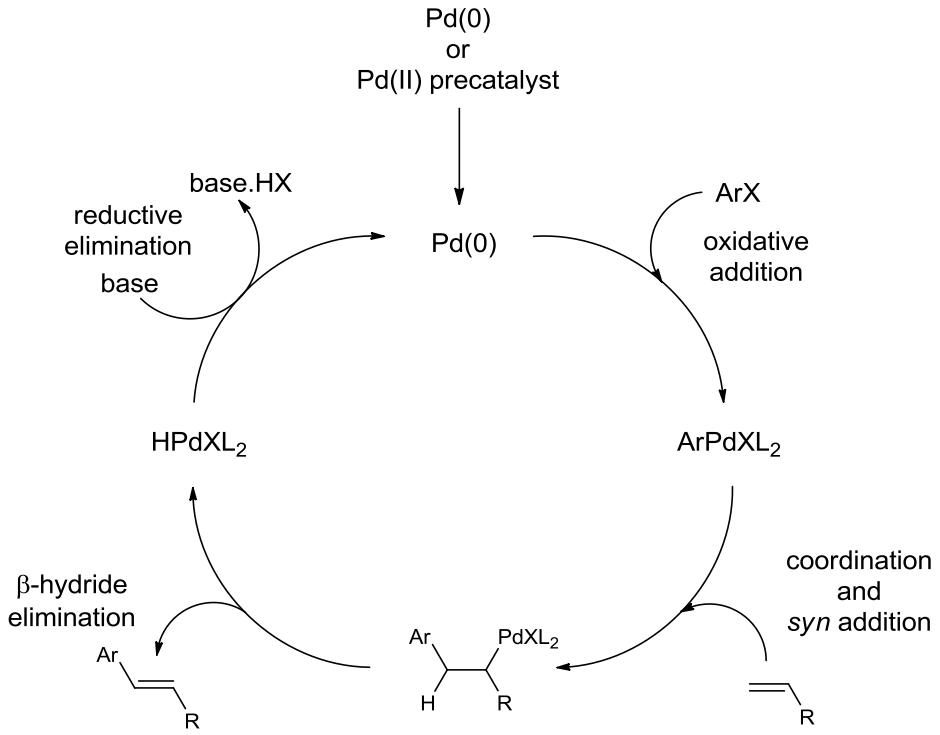


12 **13** **14**

Scheme 5

1.2.2 Reaction Mechanism

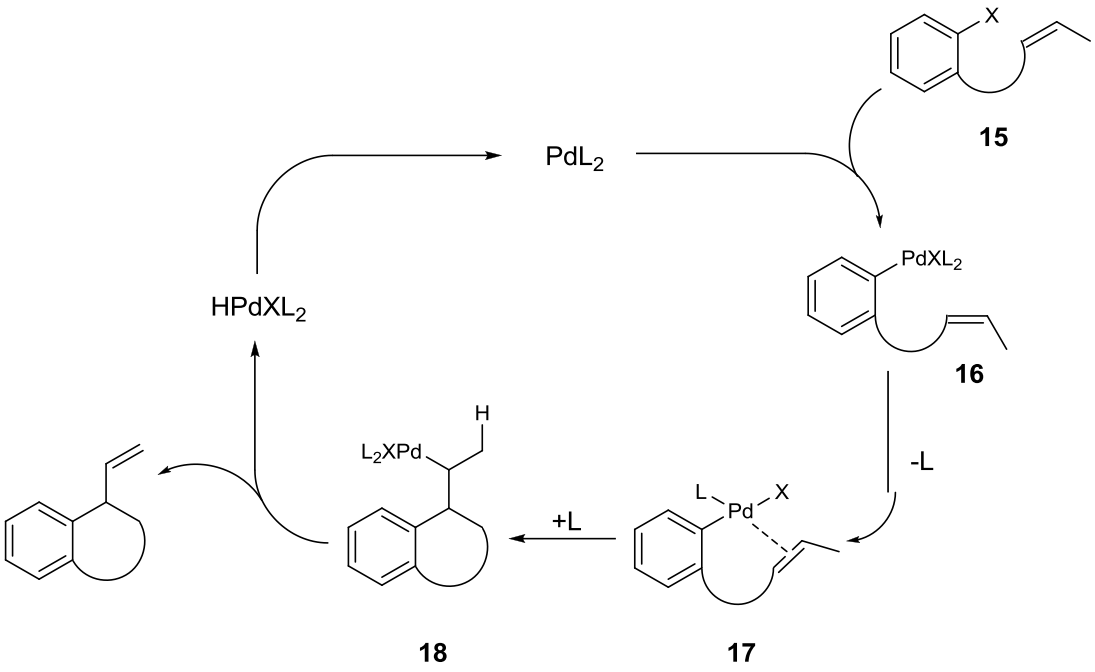
The mechanism through which the Heck reaction proceeds has been the focus of much research and debate for many years. The general mechanism that appears in many text books, which was widely accepted for many years, is now believed to be a very simplistic view of the actual reaction pathway (**Scheme 6**).[18] It is proposed that the catalytic cycle starts with the oxidative addition of Pd(0), either from a Pd(0) source or formed *in situ* from a Pd(II) precatalyst, into the aryl halide bond. The olefinic coupling partner then coordinates to the Pd(II) organopalladium halide species, which is followed by addition of this organometallic compound across the π-system of the olefin in a *syn*-fashion. β-Hydride elimination then generates the Heck product and liberates a hydridopalladium (II) species, which regenerates the Pd(0) catalyst following a reductive elimination process mediated by a stoichiometric amount of base.



Scheme 6

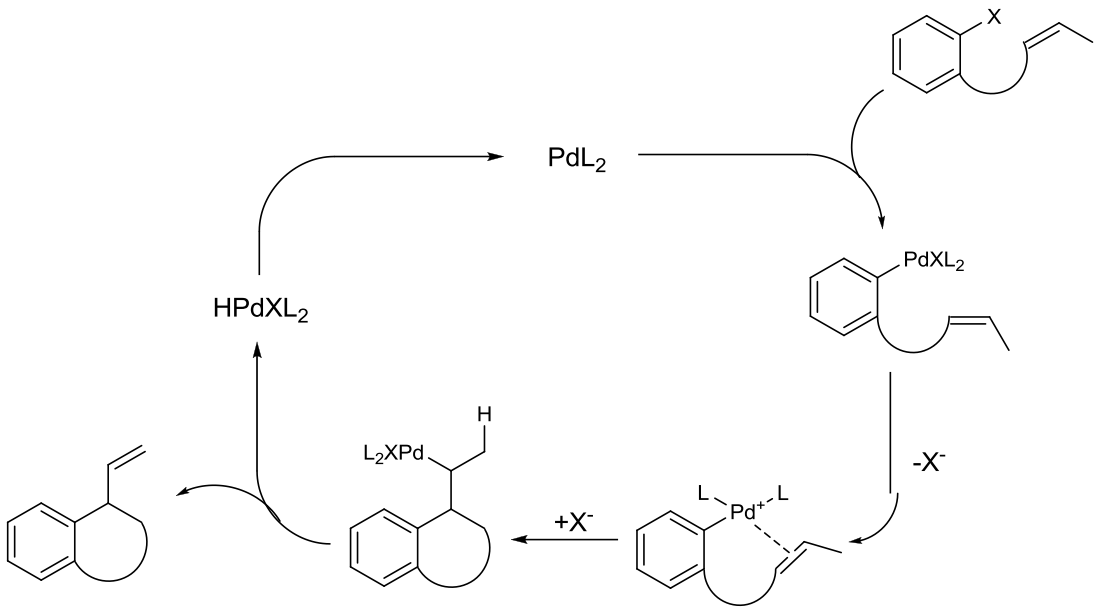
There are two major variants of the general Heck mechanism that is shown in **Scheme 6**. Firstly, there is the 'Neutral Pathway' which is the route that alkenyl and aryl halides are believed to react *via*, under normal Heck reaction conditions. A model intramolecular Heck reaction process can be used to outline the salient features of this mechanism (**Scheme 7**).[19] As discussed above, the catalytically active palladium (0) species undergoes oxidative addition with the aryl halide **15** resulting in the formation of palladium (II) complex **16**. Decomplexation of a phosphine ligand from the palladium centre then creates a vacant site for the pendant alkene to coordinate, delivering complex **17**. The σ-arylpalladium species then adds across the coordinated alkene and the phosphine ligand re-enters the coordination sphere of the metal. This process is named the 'Neutral Pathway' because the palladium remains neutral during the ligand exchange process between complex **16** and complex **18**. The resulting complex **18** then follows the

pathway described above to deliver the coupled product and regenerate the catalytically active palladium (0) complex.



Scheme 7

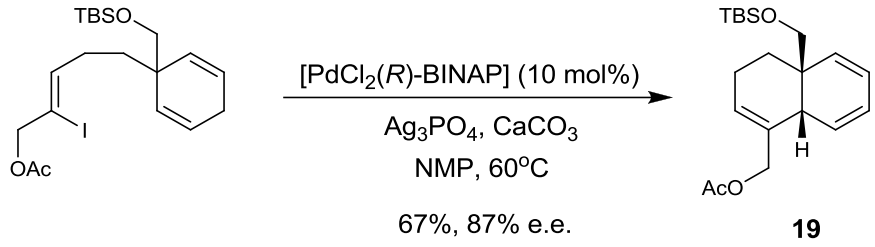
The second pathway through which the Heck reaction can proceed is *via* the 'Cationic Pathway' (**Scheme 8**).[19] In contrast to the 'Neutral Pathway' outlined before, it is the halide or *pseudo*halide that dissociates, creating a vacant site in the coordination sphere of the palladium centre to enable the alkene to coordinate prior to the insertion step. As a result, there is a cationic palladium species created during the catalytic cycle.



Scheme 8

This 'Cationic Pathway' is generally followed by perfluorosulfonates, as these *pseudo*halides tend to dissociate more readily from the metal centre. However, alternative reaction conditions can also be employed that divert vinyl and aryl halides through a cationic pathway. This becomes extremely important in the asymmetric variant of the Heck reaction. Bidentate ligands, such as BINAP, are commonly used to impart enantioselectivity during Heck reactions. However, following a 'Neutral Pathway' one of the phosphines has to dissociate to allow coordination of the olefin and hence the chiral information around the metal centre is diluted. As it is the coordination/insertion process that produces the enantioselectivity, it is important to have the key chiral ligand coordinated in a bidentate fashion during this particular part of the reaction process. Consequently, silver salts are commonly added to the reaction mixture to abstract the halide from the palladium centre and force the reaction through a 'Cationic Pathway'. This allows the ligand to remain coordinated and enhances the enantiomeric excess of the overall reaction. An example of the use of silver salts during

an asymmetric Heck process can be seen from the inclusion of Ag_3PO_4 in the intramolecular reaction to form the *cis*-decalin derivative **19** (**Scheme 9**).[20]



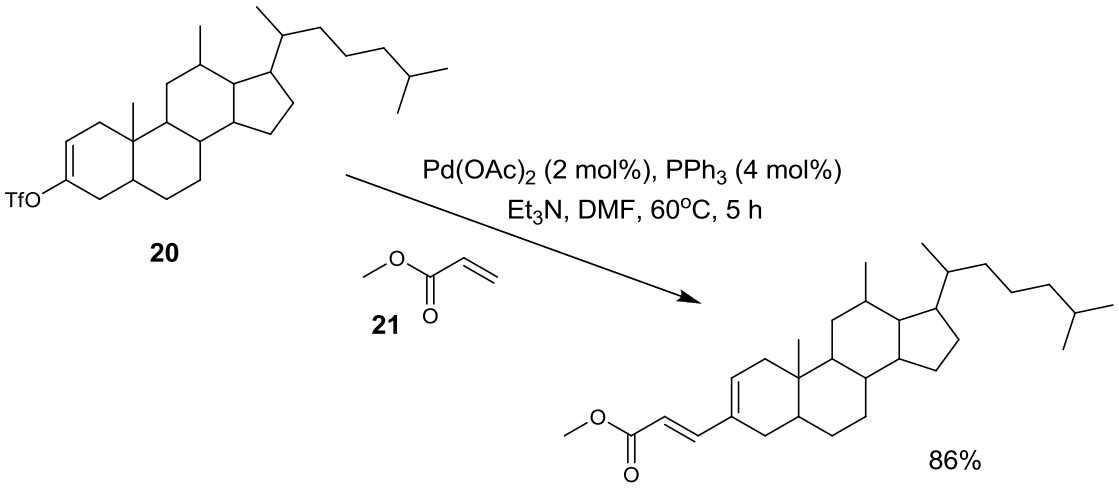
Scheme 9

There is a third pathway, the 'Anionic Pathway', that is believed to be followed during Heck reaction.[19] This mechanistic route will not be discussed further within this review.

1.2.3 Coupling partners

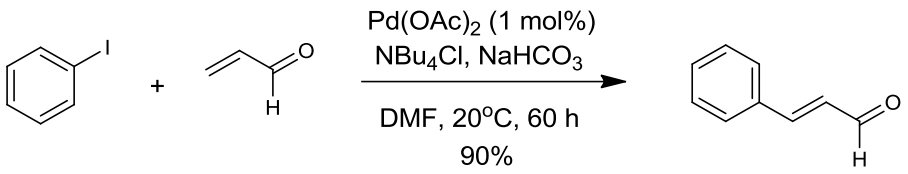
1.2.3.1 Organohalide Derivatives

Early reports of the Heck reaction involved the use of iodides and bromides as effective coupling partners within the emerging palladium-catalysed coupling process. Further research introduced the use of aryltriflates as suitable reactants for this process.[21] In the mid-80's Ortar reported the efficient cross-coupling of enol triflates with a range of olefinic coupling partners.[22] An example of the success of such a process, under relatively mild reaction conditions, can be seen from the coupling of enol triflate **20** with methyl acrylate **21**, delivering the coupled product in an excellent 86% isolated yield (**Scheme 10**).



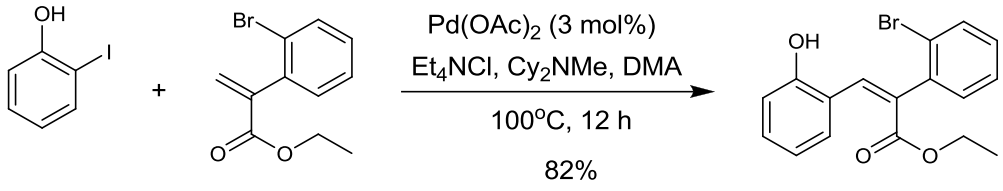
Scheme 10

With conditions developed for the Heck reaction to incorporate a wide range of organohalide coupling partners, there was a drive towards the development of conditions to allow the reaction to be performed under milder reaction conditions. Milder reaction conditions would allow sensitive substrates to be used within the reaction manifold and also enable the process to be scaled up efficiently, in particular, for employment on an industrial scale. In this regard, conditions reported by Jeffery, incorporating a solid-liquid phase transfer catalyst, were shown to be capable of coupling aryl iodides at room temperature.[23] Under the conditions, now known as 'Jeffrey's conditions', iodobenzene was coupled effectively with acrolein at room temperature to the deliver the substituted olefinic product in an excellent 90% yield, albeit over an extended 60 hour reaction time (**Scheme 11**).



Scheme 11

With respect to the organohalide derivative, the rate of the Heck reaction is inversely proportional to the bond strength of the carbon-halogen bond to be broken. Therefore, the reactivity of substrates with respect to the halide is generally I > OTf > Br >> Cl. The reason for this general trend is the subject of much debate. Originally it was suggested that the oxidative addition of Pd(0) into the organohalide species was the rate-determining step of the catalytic cycle and the rate of the reaction was dependant on the strength of carbon-halide bond to be broken in this step. However, several mechanistic studies have been performed to investigate this phenomenon further and have shown that the rate determining step is not always the oxidative addition.[24,25] It has been shown that in many instances it is in fact the insertion of the olefin into the carbon-metal bond that is the rate-determining step within the reaction sequence. This explanation rationalises why reactions that follow the cationic pathway are more facile than processes that follow a neutral pathway. The olefin will coordinate and insert faster into the more electron-deficient palladium complex. Additionally, the general trend in reactivity with respect to the organohalide derivative can be explained by considering the olefin insertion step within the cationic pathway. In order for the cationic species to be generated, to allow olefin coordination and insertion, the halide must dissociate from the metal. The ability of the halide to dissociate, and enable coordination of the olefin, will be directly related to the stability of the halide in its anionic form. Whatever the reason for this difference in reactivity, it has been elegantly exploited by Guy during the cross-coupling of aryl iodide **22** and α,β-unsaturated ester derivative **23**.[26] The potential for homo-coupling of the α,β-unsaturated ester derivative **23** was suppressed by the subtle choice of halide present on the aryl ring of each of the coupling partners. The aryl iodide **22** undergoes oxidative addition much faster than the aryl bromide compound leading to excellent chemoselectivity and the cross-coupled product in an 82% yield (**Scheme 12**).

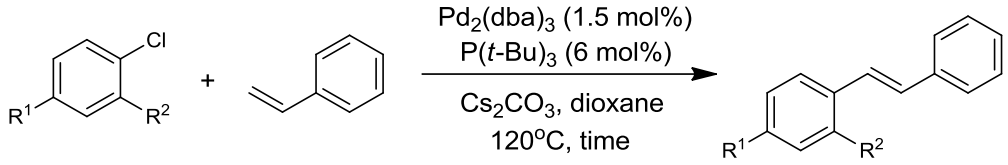


22 **23**

Scheme 12

As mentioned, aryl halides with weaker C-X bonds are much more effective substrates for the Heck reaction due to a faster oxidative addition step. However, due to the price and ease of accessing aryl chlorides, relative to aryl iodides and bromides, as well as the broader commercial availability of aryl chlorides, significant effort has been focused towards developing conditions that allow the chlorinated substrates to be used within the Heck reaction. By the end of the 1990's, many research groups had published conditions that allowed aryl chlorides to be used as coupling partners in the Heck reaction.[27-35] The ability to incorporate less reactive aryl chlorides within the Heck reaction was a major breakthrough, however, the reported conditions generally required elevated reaction temperatures (>100°C) and were limited in substrate scope. Having stated this, conditions reported by Fu did allow the coupling of sterically demanding and electron-rich aryl chlorides.[36] In relation to this, the specific employment of the electron-rich and sterically hindered ligands delivered reactivity that was previously unattainable. It is believed that the electron-donating phosphine produces a more electron-rich palladium complex which can undergo the oxidative addition process more efficiently. In addition, it has been shown that the steric bulk of the ligand promotes the formation of a monoligated $Pd(PR_3)$ species prior to oxidative addition.[37] Through computational studies it has been shown that oxidative addition of organohalides to monoligated species is a very energetically favourable process when compared to bisphosphine complexes.[38] However, not all palladium bisphosphine complexes favour dissociation to the monoligated complex and the equilibrium is dependent on the nature of the phosphine ligand. It is the ability of the $P(t\text{-}Bu)_3$ ligand to promote the formation of this

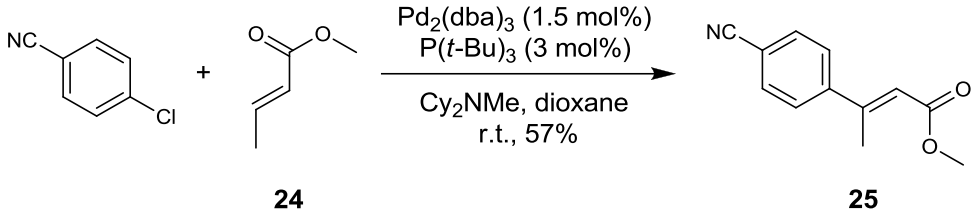
monoligated metallic species that makes it so effective in Heck reactions involving organochlorides. Furthermore, the increased steric bulk around the palladium centre, due to the more encumbered phosphine ligands, promotes a faster reductive elimination step within the catalytic cycle. For instance, use of the P(*t*-Bu)$_3$ ligand with $Pd_2(dba)_3$ catalyst in the presence of Cs_2CO_3 enabled the coupling of both sterically encumbered and 'less reactive' electron-rich aryl chlorides with styrene (**Scheme 13**).[36]



	time	yield
R^1 = H, R^2 = Me	30 h	84%
R^1 = OMe, R^2 = H	114 h	70%

Scheme 13

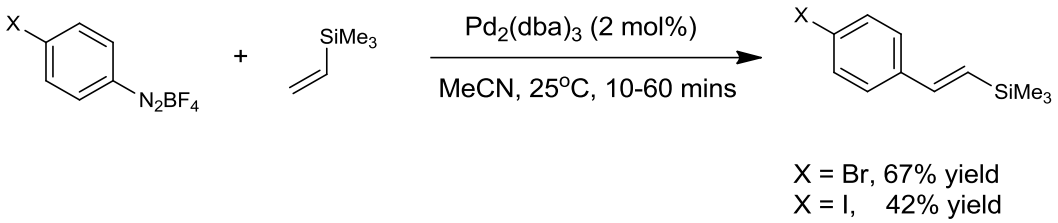
Further advancements in this area in the following years introduced conditions that allowed the coupling of aryl bromides and even aryl chlorides at room temperature. The replacement of the base (Cs_2CO_3) within Fu's previous conditions, with Cy_2NMe, enabled these reactions to be carried out efficiently at ambient temperature.[39] Incorporation of Cy_2NMe as the base allowed even trisubstituted olefins to be prepared from aryl chlorides under relatively accessible conditions (**Scheme 14**). An important feature to note at this point is the inversion of stereochemistry around the disubstituted olefin **24**. The substituents within the 1,2-disubstituted alkene are in an *E*-configuration in the starting compound but are inverted during the reaction procedure and have a *Z* relationship in the trisubstituted product **25**.



24 **25**

Scheme 14

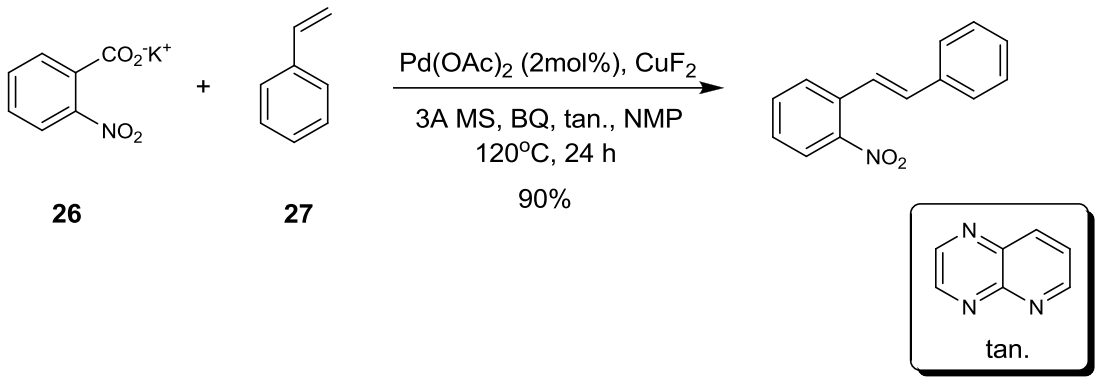
In addition to halides and triflates, there have been Heck reactions reported that utilise a range of alternative coupling partners for this transformation. Diazonium salts have been shown to be effective coupling partners in the Heck reaction. In fact, they have been shown to have a far superior reactivity towards Heck conditions than aryl bromides and even aryl iodides. A report by Kikukawa elegantly demonstrates this enhanced reactivity by coupling diazonium salts, that also possess halides, in a chemoselective manner to deliver the desired product in good yields (**Scheme 15**).[40] In addition to the selectivity obtained in the presence of the aryl halide moiety, it must be noted that the reactions were completed in less than 1 hour at room temperature.



Scheme 15

As well as diazonium salts, the Heck reaction has also been shown to be attainable with aryl sulfonyl halides,[41] aroyl chlorides,[42] and vinyl phosphates.[43] More recent developments within the arena of Heck chemistry have seen a numbers of reports involving the efficient decarboxylative Heck process. This approach, which is experiencing ever increasing attention, involves the use of benzoic acid derivatives as

the reaction substrates that, following loss of CO_2, couple effectively with alkenes. An example of such a process is the coupling of potassium carboxylate **26** with styrene **27** to deliver the desired olefinic product in 90% yield (**Scheme 16**).[44]

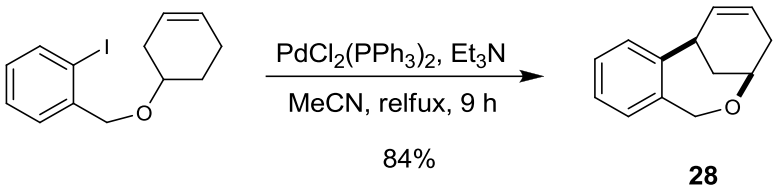


26 **27**

Scheme 16

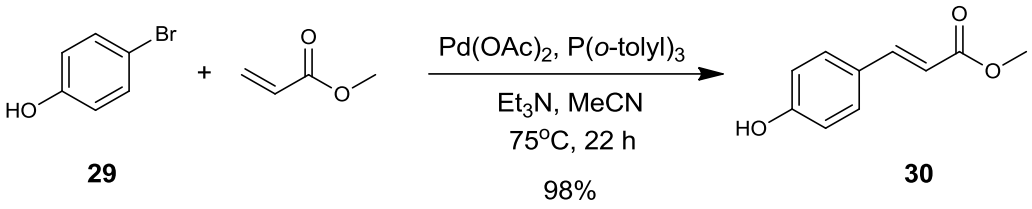
1.2.3.2 Alkene Partners

Since the discovery of the Heck reaction in the early 1970's, a wide range of alkenes have been shown to be effective within both intra- and intermolecular reactions. Electronically neutral substrates undergo Heck cyclisations and can result in excellent yields of the desired product. An example of such a process is the 7-*exo*-intramolecular cyclisation to furnish bicycle **28**, which was obtained in 84% yield (**Scheme 17**).[45]



Scheme 17

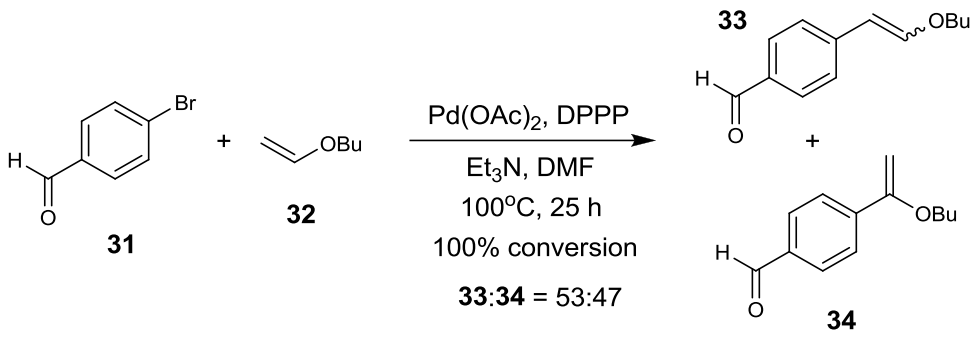
Electron-deficient alkenes, such as methyl acrylate undergo Heck reactions efficiently and are capable of delivering the reaction product in high yields. An example of methyl acrylate in an intermolecular process with aryl bromide **29** furnishes the disubstituted olefin **30** in an excellent yield (**Scheme 18**).[46] Moreover, the reaction progressed with the expected regioselectivity, i.e. with the electron-rich carbon of the organometallic intermediate bonding to the electron-deficient β-position of the α,β-unsaturated acrylate derivative. This is commonly the case for Heck reactions involving electron-deficient alkenes.[21,19]



Scheme 18

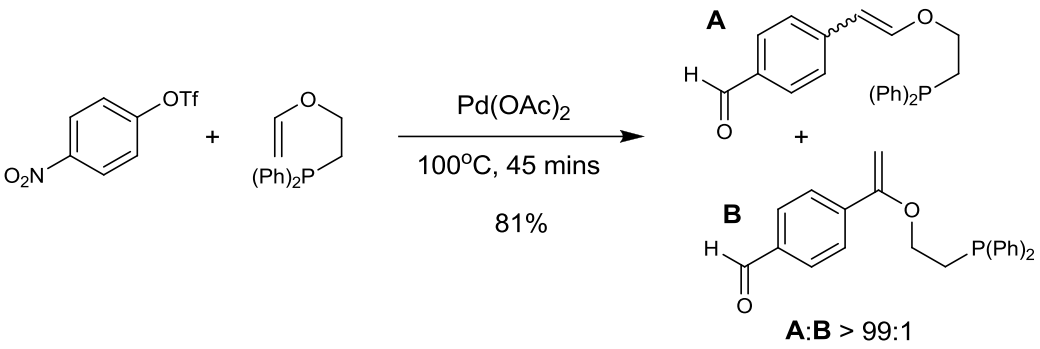
Electron-rich alkenes also participate well in the Heck reaction and deliver coupled products in high yields. However, Heck reactions involving electron-rich alkenes are generally not as regioselective as their electron-deficient counterparts. An example of this diminished regioselectivity can be seen from the cross-coupling reaction involving aryl bromide **31** and enol ether **32** (**Scheme 19**).[47] Under the reaction conditions, a 100% conversion to the desired products was obtained, however there was no real regioselectivity obtained during the reaction process, delivering disubstituted olefins **33**

and **34** in a 53:47 ratio, respectively. The linear product **33** was obtained as an 80:20 mixture of *E*- and *Z*-isomers, respectively.



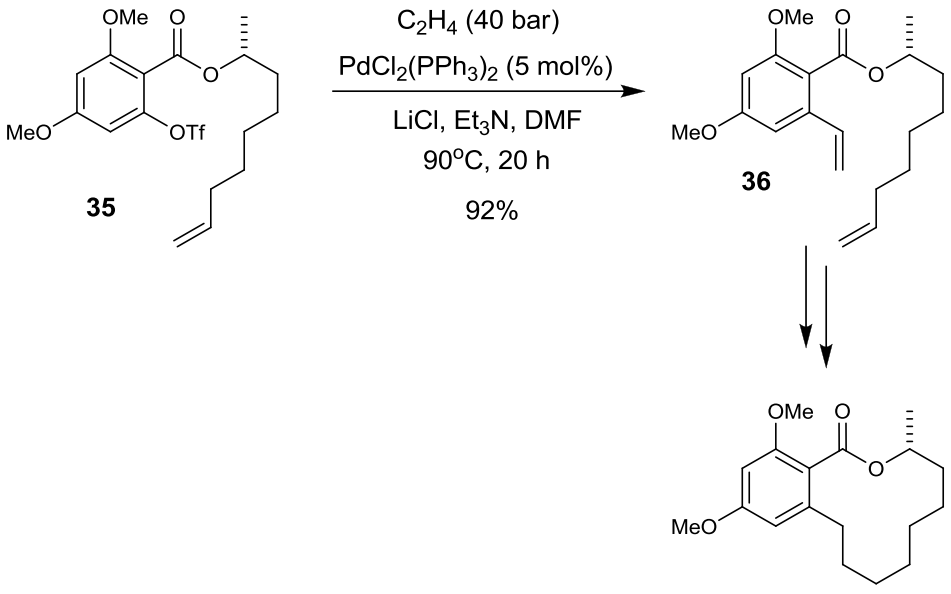
Scheme 19

As a result of the poor regioselectivity generally obtained from intermolecular Heck reactions involving electron-rich olefins, significant research has been focused towards the development of reactions conditions that enable high regioselectivity to obtained with such substrates.[21] In this regard, conditions have been developed to enable either the linear or the branched products to be obtained selectively from Heck reactions involving vinyl ether. An example of this methodology being adopted to deliver the linear product in high selectivity is shown in **Scheme 20**.[48] The Lewis basic phosphorus tether acts as a ligand and coordinates to the palladium centre, influencing the regiochemical outcome of the reaction.



Scheme 20

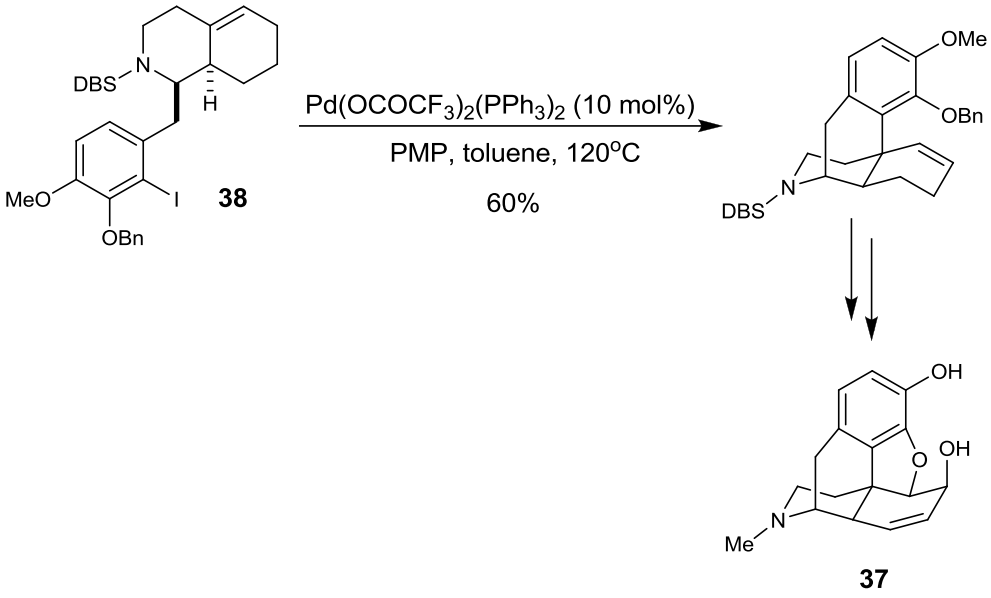
Development work on the Heck reaction has also enabled the use of gaseous alkenes as coupling partners. An example of the use of gaseous alkenes within the arena of total synthesis can be seen from Fürstner's synthesis of Lasiodiplodin. Fürstner reported the intermolecular Heck reaction between aryl triflate **35** and gaseous ethylene, delivering the coupled product **36** in an excellent 92% yield (**Scheme 21**).[49]



Scheme 21

1.2.3.3 Construction of Quaternary Stereocentres

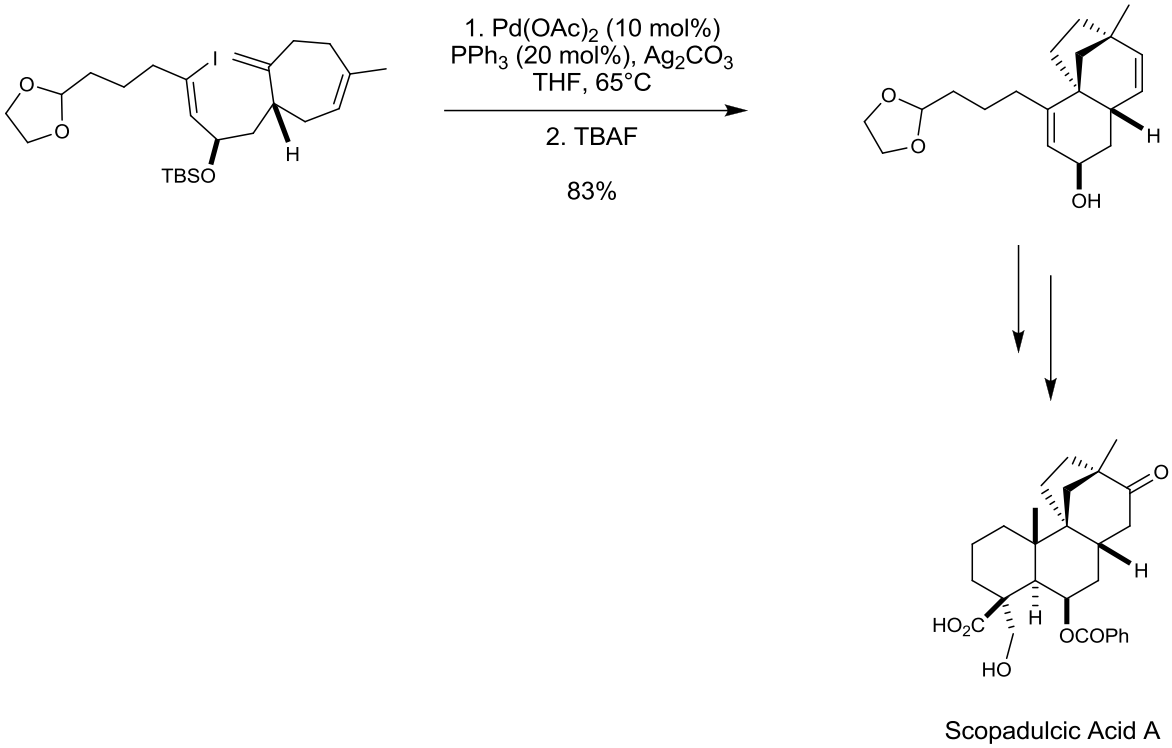
The formation of all-carbon quaternary stereocentres remains one of the major challenges for the organic chemist. Indeed, many naturally occurring compounds possess such a motif and, consequently, there is a drive for the scientific community to overcome this challenge. In this regard, the intramolecular Heck reaction has been shown to be a powerful tool for the construction of quaternary carbon centres. An example of the ability of the palladium-mediated cyclisation to construct quaternary stereocentres within complex natural product synthesis can be seen from the synthesis of (-)-morphine **37**, reported by Overmann (**Scheme 22**).[50] The key step in the overall route was the palladium-mediated cyclisation of aryl iodide **38** to install the all-carbon stereocentre in a 60% yield.



Scheme 22

A further example of the intramolecular Heck methodology being employed to access quaternary carbon stereocentres was displayed during Overmann's reported synthesis of scopadulcic acid A. In fact, this very elegant approach towards the natural target utilised

a tandem Heck process to install two adjacent all-carbon quaternary stereocentres, as outlined in **Scheme 23**, in an excellent 83% yield.[50]

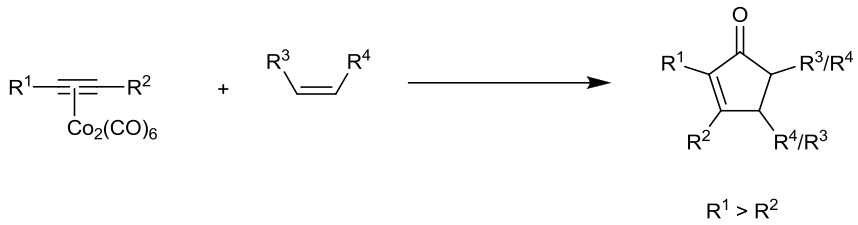


Scheme 23

1.3 The Pauson-Khand Reaction

1.3.1 The Pauson-Khand Reaction

Transition metal-mediated cyclisations have become an invaluable method for the preparation of highly functionalised carbocyclic targets. In particular, the Pauson-Khand reaction (PKR), discovered in the early 1970's at the University of Strathclyde,[51-53] has evolved into an irreplaceable synthetic tool for the preparation of cyclopentenones.[54-58] The PKR is a formal, three component, [2+2+1] cycloaddition which incorporates an alkene, an alkyne, and a molecule of carbon monoxide to furnish a substituted cyclopentenone framework (**Scheme 24**).

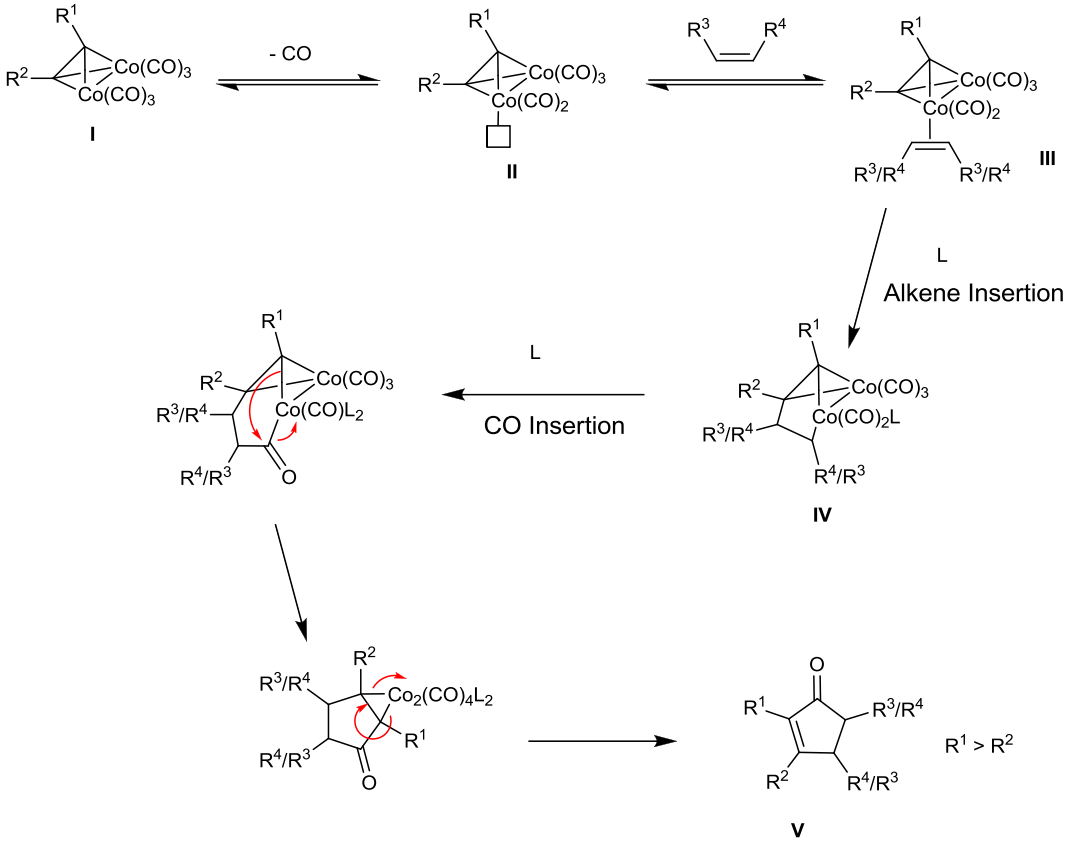


Scheme 24

The original PKR reported by Pauson and Khand was an intermolecular process incorporating an alkene and an alkyne from separate molecular units. However, in 1981 Schore reported the first intramolecular variant of this method.[59] Since this discovery it has been the intramolecular reaction which has become the most successful in terms of reactivity and stereoselectivity.

1.3.2 Reaction Mechanism

The mechanism for the stoichiometric PKR was first postulated by Magnus in the mid-1980's and was based purely on observations over a number of individual Pauson-Khand annulation processes (**Scheme 25**).[60] The now widely accepted mechanism starts from tetrahedral dicobalt complex **I**. The first step, believed to be rate-determining, involves the reversible loss of a CO ligand from one of the cobalt centres to produce coordinatively unsaturated cobalt complex **II**. Coordination of the alkene moiety to the vacant site on the cobalt produces **III**, which, by insertion into the cobalt-carbon bond furnishes cobaltacycle **IV**. It is this insertion step that is believed to be responsible for the regio- and stereochemical outcome of the process. Migratory insertion of a cobalt-bound CO ligand, followed by two reductive elimination steps furnishes the final cyclopentenone **V**.



Scheme 25

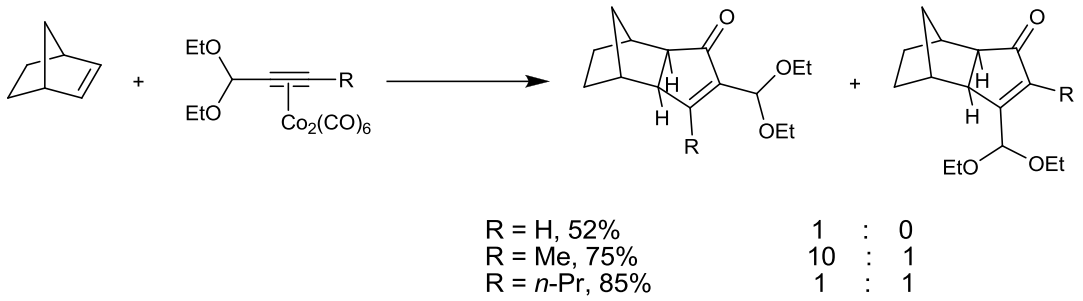
Other than from preparative cyclisation outcomes, evidence to support the mechanism proposed by Magnus has been limited due to the difficulty met in observing any of the proposed reaction intermediates. Gas phase mass spectrometry results reported by Gimbert did however provide support for the Magnus' mechanism.[61] Further support was provided by an earlier photo-induced IR experiment performed by Gordon, which identified the existence of the initial decarbonylated intermediate.[62]

1.3.3 Intermolecular Pauson-Khand Reactions

The intermolecular PKR can be viewed as an expedient means of preparing highly complex structures, however, there are two main drawbacks which have limited the scope of this reaction. Firstly, the intermolecular version of the PKR suffers from isuues of regioselectivity associated with the positions of the alkene and alkyne fragments in the cyclopentenone products. Secondly, the reaction suffers from a distinct lack of reactivity when unstrained alkenes are involved. Each of these issues will now be discussed further.

1.3.4 Regioselectivity

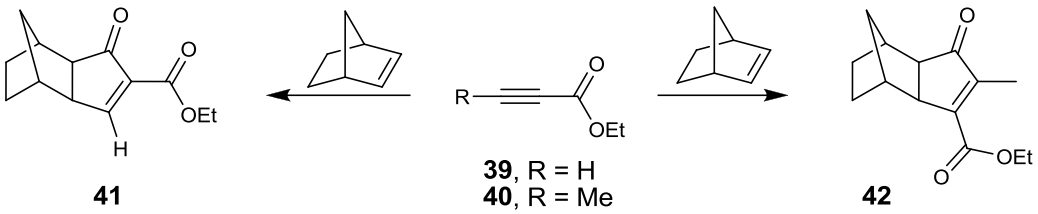
In terms of regioselectivity, the larger of the alkyne substituents is generally incorporated α to the carbonyl unit in the cyclopentenone product. This selectivity arises from insertion of the coordinated alkene, present in intermediate **III**, into the less sterically encumbered cobalt-carbon bond. The alkyne regioselectivity tends to diminish as the size of the groups at each of the alkyne termini become similar (**Scheme 26**).[63]



R = H, 52%	1	:	0
R = Me, 75%	10	:	1
R = *n*-Pr, 85%	1	:	1

Scheme 26

There are however certain experimental results which cannot be explained by the hypothesis based on steric arguements. One particular example of this unorthodox regioselectivity is displayed in the PKR's involving ethyl propiolate **39** and ethyl butynoate **40**. Results have shown that the reaction involving ethyl propiolate[63] **39** results in an α-carbethoxy-substituted cyclopentenone **41**, as expected according to sterics. However, the reaction involving ethyl butynoate[64] results in a β-carbethoxy-substituted cyclopentenone **42** (**Scheme 27**).



41

39, R = H
40, R = Me

42

Scheme 27

Results from a theoretical study reported by Gimbert and Greene suggest that this unexpected selectivity is the result of a *trans*-effect exerted by the alkyne.[65] It is proposed that the electron-withdrawing groups on the alkyne instil electron density differences within the acetylenic carbons. As a result one of the CO ligands becomes more labile and this in effect dictates the regioselectivity observed within the reaction. This hypothesis can be seen more explicitly in **Figure 5**. As depicted in **A**, the electron-

deficient acetylenic carbon renders the *trans*-CO ligand, as shown in the figure, the most labile on the cobalt centre. The vacant coordination site in **B**, resulting from dissociation of this ligand, is situated *trans* to the electron deficient carbon. The olefin will then coordinate to the metal centre to produce **C**, and will subsequently insert into the carbon-cobalt bond as shown, leading to **D**. Insertion of the olefinic species into this specific carbon-cobalt bond would lead to the cyclopentenone product with R^1 in the β-position (see **Scheme 27**).

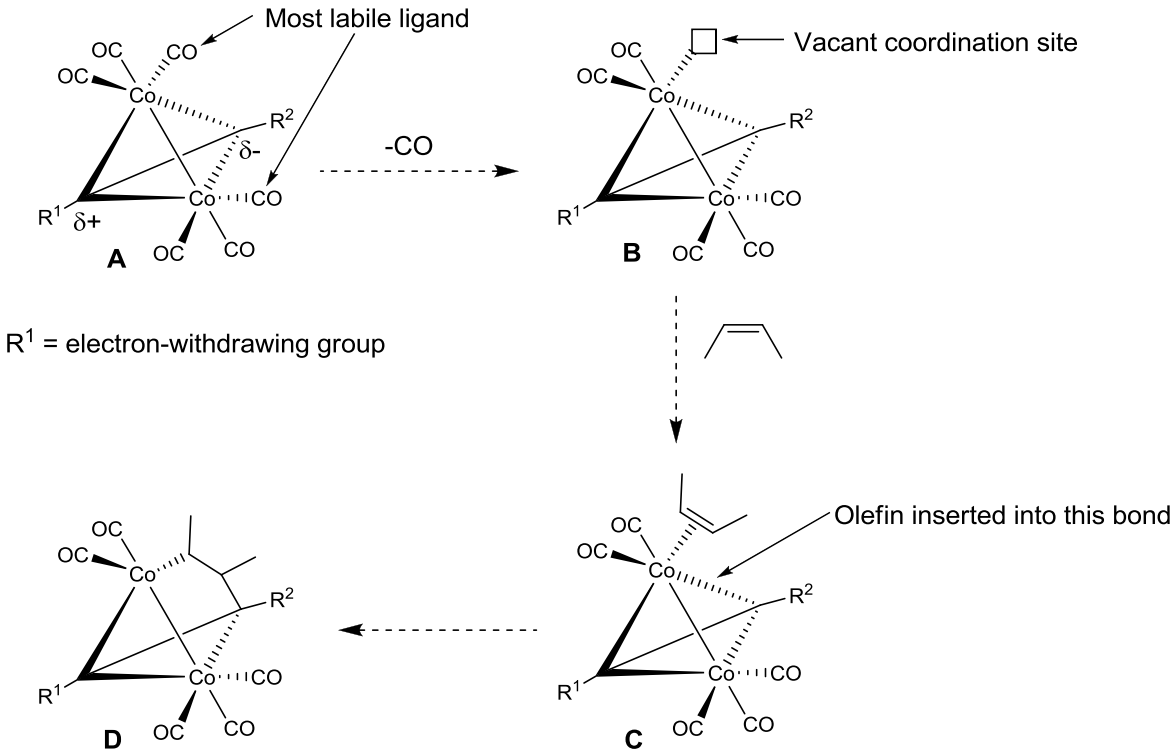
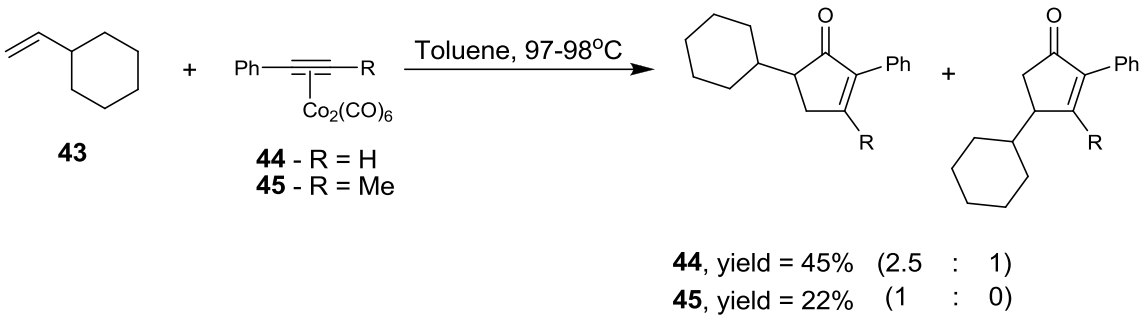


Figure 5

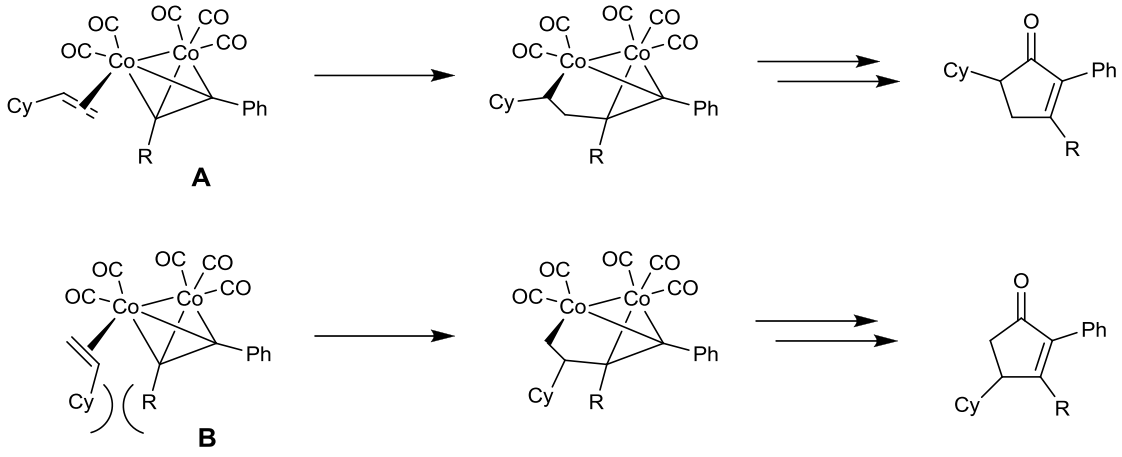
The regioselectivity associated with the alkene insertion is believed to be created by the alkyne substituents. Reactions involving internal alkynes generally give cyclopentenones with a high level of regiocontrol in the olefin insertion. However, analogous reactions involving terminal alkynes produce regioisomeric mixtures of products. This is demonstrated in the PKR's involving olefin **43**. The reaction with terminal acetylene **44**

produces a 2.5 to 1 mixture of regioisomers, whereas, the reaction with internal acetylene **45** produces only the 5-substituted product exclusively (**Scheme 28**).[66]



Scheme 28

Consideration of the two possible olefin rotamers, **A** and **B**, provides a mechanistic rationale (**Scheme 29**).



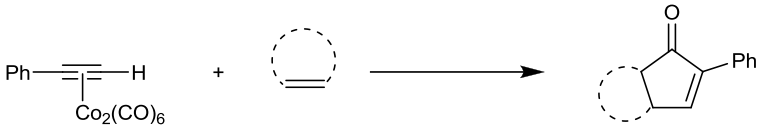
Scheme 29

In the case of acetylene **44** (R = H) there is little steric hindrance between the proton (R = H) and the olefinic substituent. This leads to poor selectivity between rotamers **A** and **B** and, in turn, results in poor olefin regioselectivity. However, reactions involving

internal alkynes, like acetylene **45** (R = Me), produce higher selectivity due to the greater steric interactions present within reaction intermediate **B**. This increased interaction results in the smaller olefinic substituent being incorporated adjacent to the acetylenic carbon.

1.3.5 Alkene Reactivity

Amongst the many trends observed within PKR's over the past four decades, an apparent lack of reactivity has been evident in reactions involving unstrained olefins. Due to this, the majority of intermolecular PKR's have been carried out with strained olefins such as norbornene and norbornadiene. A distinct correlation between olefin strain and reactivity can be seen by comparing the intermolecular reactions involving norbornene, cyclopentene, and cyclohexene (**Table 1**). Reactions involving the most highly strained olefin, norbornene, can be performed under relatively mild reaction conditions producing good yields of the desired product (**Table 1**, entry 1).[53] Moving to the less strained olefin, cyclopentene, considerably harsher conditions are required to produce even moderate yields of the corresponding cyclopentenone (**Table 1**, entry 2).[67] Finally, reactions involving the relatively unstrained cyclohexene return vastly reduced yields of the desired product (**Table 1**, entry 3).[67] Interestingly, the authors reported that, performing this reaction under the forcing conditions utilised in **Table 1**, entry 2 did not result in an improved yield of desired product with cyclohexene.

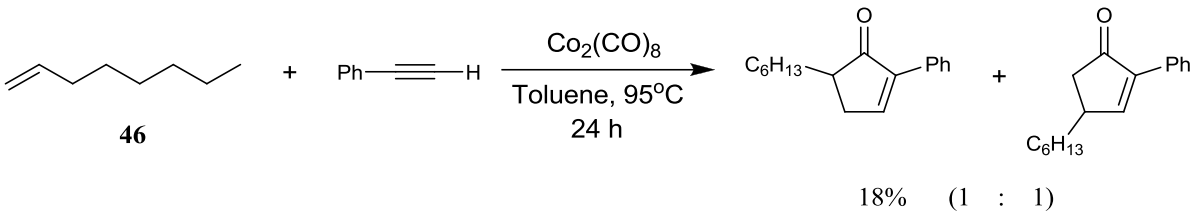


Entry	*Olefin*	*Conditions*	*Yield (%)*
1	Norbornene	Mesitylene, 60-70°C, 4 h	59
2	Cyclopentene	Toluene, 160°C, 80 atm, 7 h	47
3	Cyclohexene	Toluene, reflux, 6 h	3

Table 1

1.3.6 Directed Pauson-Khand Reactions

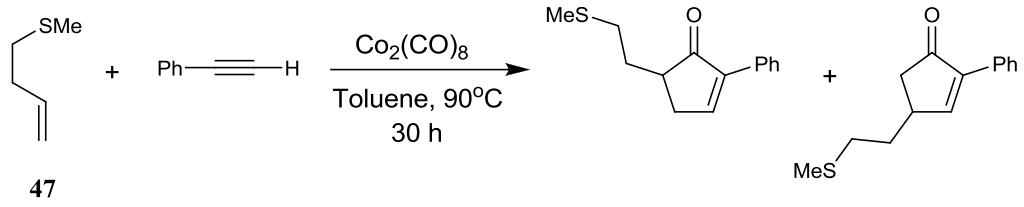
As discussed above, the two main disadvantages associated with intermolecular PKR's is the poor regioselectivity and lack of alkene reactivity obtained during these reactions. The effect of these limiting factors is illustrated in the intermolecular reaction involving the, unstrained, terminal olefin **46** which produces a 50:50 mixture of regioisomeric products in a poor 18% yield (**Scheme 30**).[68]



Scheme 30

The first major breakthrough in combating these limiting factors was the development of the directed PKR by Krafft,[68] where the use of Lewis basic ligands, tethered to the alkene *via* an alkyl chain, to direct the alkene insertion step was reported. The use of both nitrogen and sulfur ligands provided excellent levels of regiocontrol within

intermolecular reactions. Additionally, the use of a directing ligand resulted in increased levels of reaction efficiency. An example of these beneficial effects can be seen in the PKR involving terminal olefin **47** (**Scheme 31**). An excellent yield of 61% was obtained, as well as very good levels of regioselectivity of 18:1 being observed.

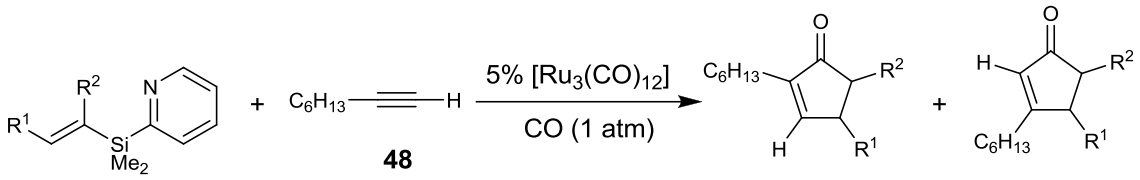


47

61% (18 : 1)

Scheme 31

An improvement to the directed PKR was reported by Itami and Yoshida.[69] They demonstrated the use of a pyridylsilyl directing group, attached to the olefin, in a catalytic version of the intermolecular PKR. The authors reported the use of this group as a means of gaining control of the olefin regioselectivity and also enabling reactions to be carried out with simple, unreactive, olefins. This technique allows the regioselective incorporation of the desired substituent at either the 4- or 5-position in the cyclopentenone, made possible by selecting the appropriate starting alkenylsilane. The major advantage this method has over Krafft's ligand directed methodology is the ease with which the directing group is removed as part of the overall cycloaddition process. An example of the possible control over olefin regioselectivity can be seen in the reactions involving alkyne **48** (**Scheme 32**).

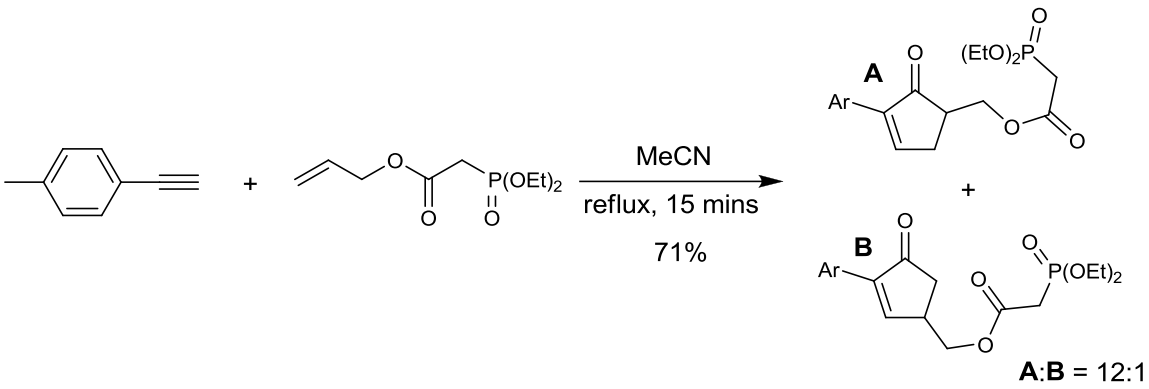


$R^1 = C_4H_9$, $R^2 = H$ 55% (89 : 11)

$R^1 = H$, $R^2 = CH_3$ 40% (62 : 38)

Scheme 32

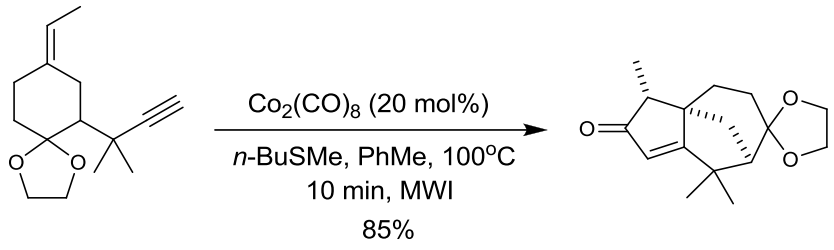
Work within our own laboratories has developed methodology to enable regioselective Pauson-Khand reactions to be perfomed using allylphosphonates as coupling partners.[70] In addition to this earlier work, more recent efforts have been focused towards the use of extended derivates within regioselective Pauson-Khand reactions. An example from this recent study illustrates the high regioselectivty that is attainable by incorporating a phosphorus tether / ligand to the olefinic coupling partner (**Scheme 33**).[71]



Scheme 33

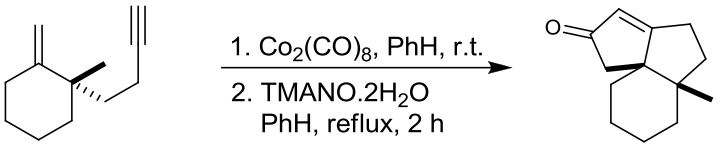
1.3.7 Intramolecular Pauson-Khand Reactions

As stated above, the first example of an intramolecular PKR was reported by Schore in the early 1980's.[59] Since its discovery, the intramolecular variant of this metal-mediated cycloaddition has become the most successful. A significant advantage that this reaction holds over its intermolecular counterpart is the elimination of issues regarding regioselectivity. An example of its potential was demonstrated during a recent natural product synthesis undertaken within our own laboratories. The key step in the total synthesis of 2-*epi*-α-cedren-3-one was carried out under new and improved, microwave-assisted,[72-75] catalytic PKR conditions. As shown below, an excellent 85% yield was obtained for this very efficient key cyclisation step (**Scheme 34**).[76]



Scheme 34

A further example of a highly successful intramolecular PKR was reported by Hoshino and Ishizaki.[77,78] The authors reported the formation of an angular fused tricyclic system **49**, which bears similarities to intermediate **7** within our current natural product synthesis route as part of the research performed within this PhD programme (**Scheme 35**).

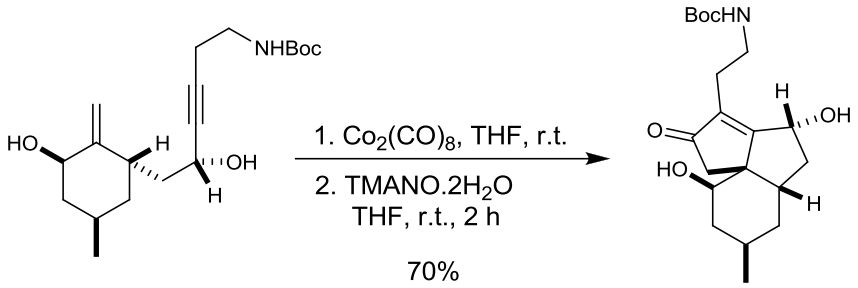


49

Scheme 35

Among the pertinent features when comparing the preparation of enone **49** and the proposed intermediate target **7** is the formation of two contiguous quaternary stereocentres. However, it is noted that the enyne required to form intermediate **7** possesses an internal alkyne and a conjugated olefin. Both of these features have the potential to make the formation of intermediate **7** more synthetically challenging.[58]

Encouragingly, a second example reported from the same group demonstrates an intramolecular PKR utilising an internal alkyne in the highly efficient key step towards the formal total synthesis of Magellanine (**Scheme 36**).[79]

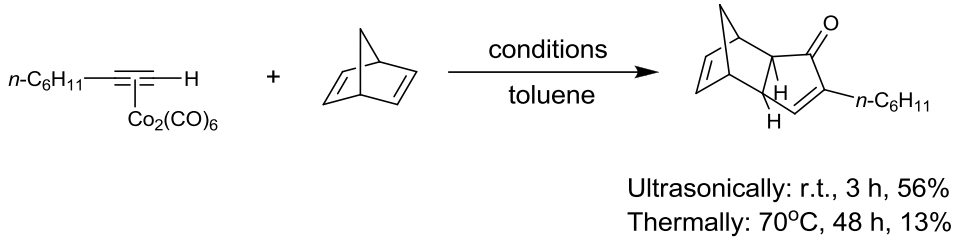


Scheme 36

1.3.8 Pauson-Khand Reaction Promoters

Despite their versatility and tolerance towards a number of functional groups, traditional PKR's have some limitations due to the relatively harsh reaction conditions, high temperature (usually 60-120°C) and long reaction times (6 h - 4 days), required.[55] Therefore, much research has been focused towards developing promoters for this annulation process.

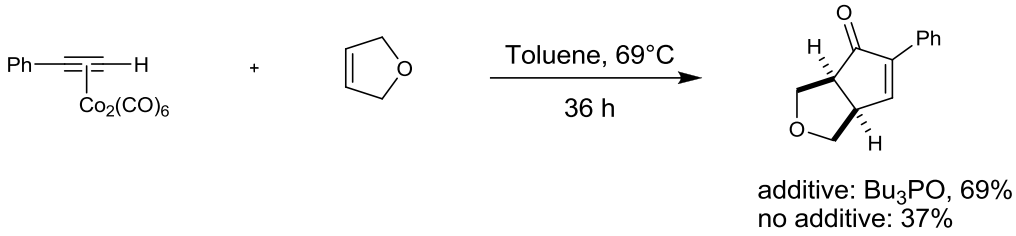
Work by Pauson developed conditions for the promotion of PKR's using ultrasound.[80] The authors reported significant rate enhancements could be achieved at lower temperatures compared to traditional thermal conditions. An example of this can be seen in (**Scheme 37**). The intermolecular PKR between norbornadiene and the terminal alkyne yields 13% of product under thermal conditions compared to 56% under the ultrasonication conditions.



Scheme 37

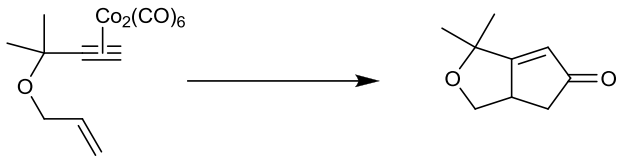
A second method of promotion, reported by Pauson in the same publication, was the addition of phosphine oxides to the reaction mixtures.[80] The addition of tributylphosphine oxide to the intermolecular PKR involving 2,5-dihydrofuran resulted in an enhancement of yield from 37%, with no additive, to 69% from the reaction with the phosphine oxide additive (**Scheme 38**). However, with both the ultrasonication process (*vide infra*) and the methods incorporating phosphine oxides, the outcome over a

series of examples were inconsistent, leading to a lack of general or widespread applicability.



Scheme 38

Smit and Caple reported an efficient method for the promotion of PKR's using dry-state conditions.[81] Their serendipitous discovery involved adsorbing the cobalt-complexed starting material onto silica or alumina and removing the solvent. The resulting dry powder was then gently heated to facilitate the reaction. The example reported by these authors involved the intramolecular PKR of cobalt-complexed enyne **50** (**Table 2**). A significant increase in yield of the desired product was observed over the previously reported result under thermal conditions.

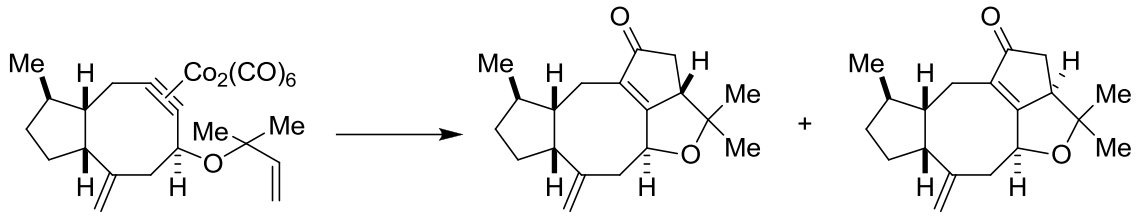


50

Conditions	*Yield (%)*
SiO_2, 45°C, 30 min[81]	75
isooctane, 60°C, 24 h[82]	29

Table 2

In 1990 Schreiber described the first use of amine *N*-oxides to promote the PKR.[83] In particular, the use of *N*-methylmorpholine *N*-oxide (NMO) was reported to promote intramolecular PKR's at room temperature. Amine *N*-oxide promoted reactions have also been shown to be more stereoselective than thermally or ultrasonically promoted reactions, due to the mild conditions under which they are performed. An example of this increased stereoselectivity is given in (**Table 3**).[84] Within such processes it is believed that the amine *N*-oxide oxidises one of the CO ligands to CO_2, which, through loss of this ligand, provides a coordination site for the olefin and also renders the first step irreversible.

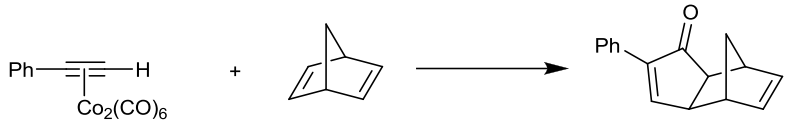


a **b**

Conditions	*Yield (%)*	*Selectivity (**a**:**b**)*
NMO, DCM, r.t.	68	11 : 1
CH_3CN, 82°C	75	4 : 1
CH_3CN, 45°C	45	3 : 1

Table 3

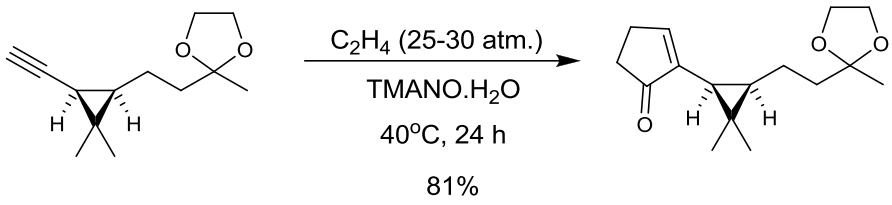
Almost simultaneous with the reports from the Schreiber laboratories, Jeong and Chung reported the use of trimethylamine *N*-oxide (TMANO) as a promoter for the PKR.[85] The TMANO promoted intermolecular reaction involving phenylacetylene returned a significant yield enhancement over the analogous reaction performed under thermal conditions (**Table 4**).[53] There was however a significant drop in stereoselectivity, even at 0°C.



Conditions	*Yield (%)*	*Selectivity (exo:endo)*
TMANO, DCM, 0°C, 2 h[85]	80	83 : 17
benzene, 60-70°C, 4 h[53]	45	1 : 0

Table 4

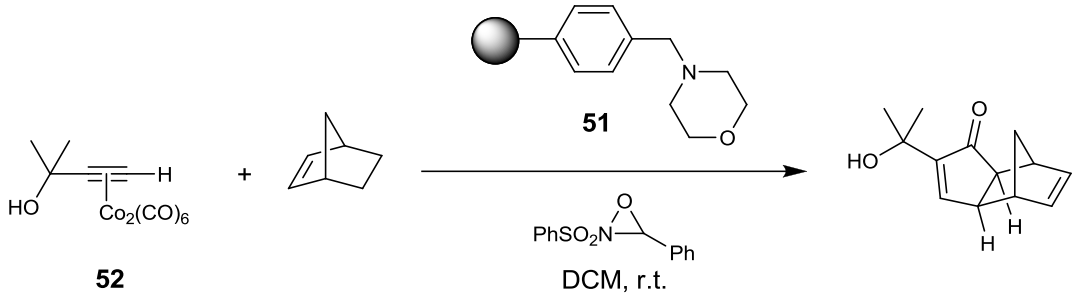
Further research within our laboratories utilising amine *N*-oxides as promoters led to the development of highly effective conditions for the use of gaseous olefins within the Pauson-Khand reaction. This methodology was incorporated during the key-step towards the total synthesis of (+)-taylorione, which was an intermolecular Pauson-Khand cyclisation involving ethylene (**Scheme 39**).[86,87]



Scheme 39

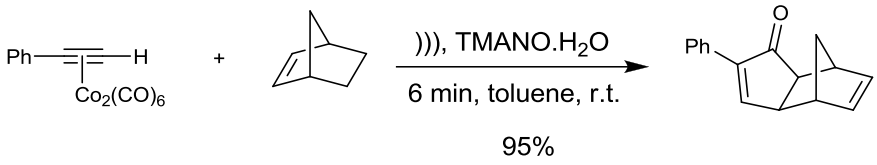
In a modification to the classical, solution phase, *N*-oxide promoted chemistry, Kerr reported an efficient polymer-supported NMO protocol.[88,89] This polymer supported promoter not only allowed efficient recycling of the amine but also aided the simplification of the work-up procedure. It was also shown that the *N*-oxide promoter could by prepared in situ by treatment of the commercially available, polymer supported, amine **51** with Davis' reagent. The efficiency of this methodology can be

seen from the intermolecular PKR between norbornene and cobalt complex **52** (**Scheme 40**).



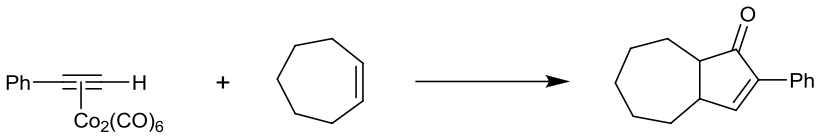
Scheme 40

The use of high powered ultrasound in conjunction with amine *N*-oxide promoters has also been reported. This methodology allows the preparation of cyclopentenone products with significantly reduced reaction times being required compared to previously reported results. An example of this rapid reaction rate can be seen in **Scheme 41**, where the desired product was delivered in excellent yield after only a six minute reaction period.[90]



Scheme 41

In an extension to Krafft's ligand-directed PKR methodology which utilised sulfur to increase reaction efficacy, Sugihara and Yamaguchi demonstrated the use of alkyl methyl sulfides as promoters for the PKR.[91] Sulfide-promoted reaction conditions allow intermolecular reactions involving simple, unstrained, olefins to be performed resulting in high yields of the desired product (**Table 5**). In the example shown, analogous reactions under NMO promotion (0%) and thermal promotion (23%) were also performed. It is worth noting that, despite the success of the sulfide-promoted procedure, in contest to the *N*-oxide mediated methods, elevated temperatures are required to drive the reaction to successful completion.

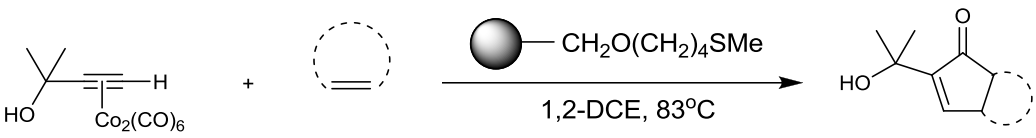


Conditions	*Yield (%)*
NMO, DCM, 23°C, 10 min	decomplexation of SM
toluene, reflux, 3 days	23
n-BuSMe, 1,2-DCE, 83°C, 90 min	85

Table 5

This sulfide-promoted methodology was proven to be highly successful, especially in its ability to promote reactions which proceeded very poorly under alternative conditions. However, there are a few drawbacks associated with this procedure. In addition to the more elevated temperatures required, this volatile sulfide possesses a very unpleasant odour and also imparts a lachrymatory effect. In addition to this, the sulfide itself is relatively expensive and this existing protocol doesn't allow for it to be readily recycled. In light of this, Kerr developed a polymer-supported version of this sulfide promoter.[92] Attachment of the promoter to a Merrifield resin enabled both promotion of the reaction and also simple and efficient recycling of the promoter. As reported previously, the

promoter-assisted inter- and intramolecular PKR's were shown to be successful even in reactions involving unstrained olefins. Examples of this methodology with individual olefin substrates are shown in **Table 6**.



Alkene	*Time (min)*	*Yield (%)*
Norbornene	30	92
2,5-Dihydrofuran	30	47
Cyclopentenone	90	50

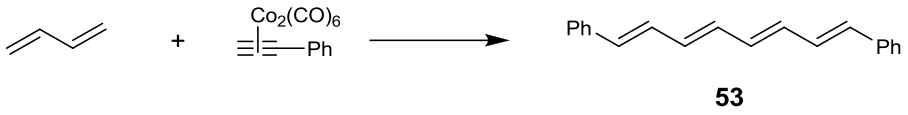
Table 6

Further work by Kerr developed conditions for the use of a non-volatile replacement for the sulfide reported by Sugihara and Yamaguchi. In relation to the Pauson-Khand reaction, it was reported that DodSMe could be used to promote such annulations and, in some instances, an increased efficiency was observed compared to annulations performed using *n*-BuSMe (**Scheme 42**).[93]

Scheme 42

1.3.9 Conjugated Alkenes

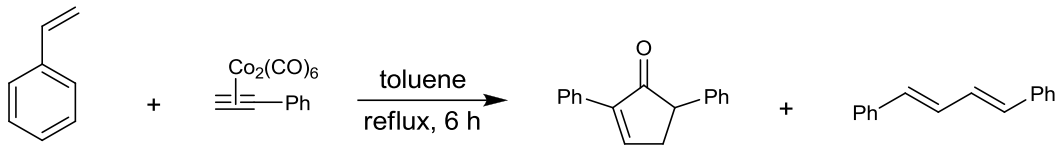
Since the inception of the Pauson-Khand reaction, conjugated alkenes have proved to be one of the more challenging types of coupling partner. This challenge arises from the tendency of such alkenes to undergo side reactions when subjected to Pauson-Khand conditions. The most common problem associated with these reactions is the competing hydrogen migration pathway which results in a conjugated product without the insertion of carbon monoxide. This is illustrated by the reaction of butadiene with phenyl acetylene cobalt complex, which results in the formation of the linear tetraene **53** (**Scheme 43**).[58]



53

Scheme 43

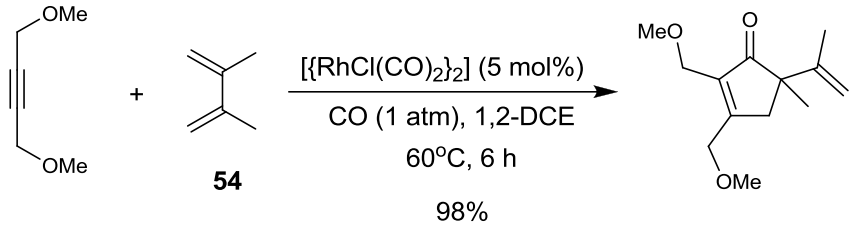
This tendency to form side products is not limited to dienes; styrene also leads to the formation of products that are formed as conjugated dienes without the insertion of a carbon monoxide ligand (**Scheme 44**).[58]



Scheme 44

Due to the rather unpredictable nature of reactions involving conjugated dienes under classical cobalt-mediated conditions, reaction conditions based around alternative

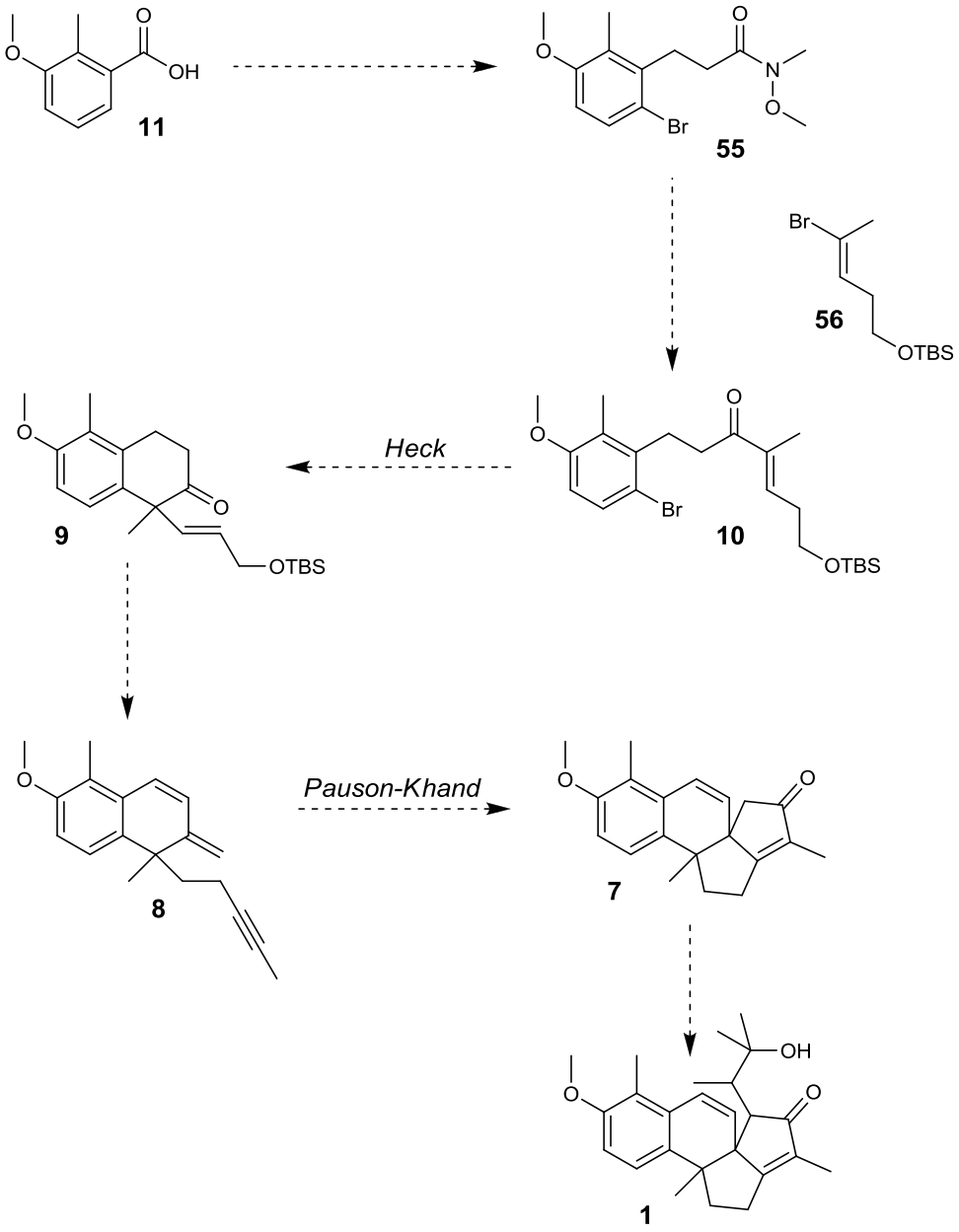
transition metals have been investigated. In particular, rhodium-based methods have been shown to be reasonably effective at producing cyclopentenones from conjugated alkenes. In relation to this, conditions reported by Wender were shown to produce the desired cyclopentenone product in excellent yield from diene **54** (**Scheme 45**).[94,95]



Scheme 45

1.4 Strategy Towards the Synthesis of Agariblazeispirol C

Following a review of the literature concerning both the Heck and the Pauson-Khand reactions, the main challenges within this natural product synthesis project must be readdressed. The proposed approach towards agariblazeispirol C **1** begins with the commercially available benzoic acid derivative **11** (**Scheme 46**). Initial work will be focused towards the preparation of two key intermediates, Weinreb amide **55**, prepared from benzoic acid **11**, and vinyl bromide **56**. Intermediates **55** and **56** will then be used to prepare enone **10**, which is the starting material for the first of the key metal-mediated cyclisation processes. Following the Heck reaction, preparation of the precursor for the second of the key metal-mediated cyclisations will be investigated. The synthesis of enyne **8** in sufficient quantities will allow conditions for this cyclisation reaction to be fully investigated. Following a review of the literature concerning these processes, it is believed that conditions can be developed that will allow each of these key metal-mediated cyclisation processes to be performed efficiently. Finally, research towards the completion of this natural product target will be investigated.

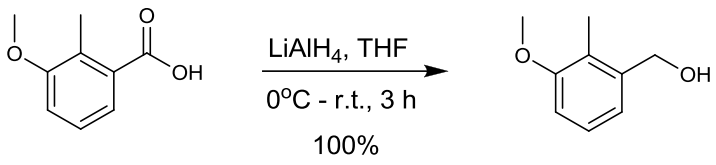


Scheme 46

2 Results and Discussion

2.1 Preparation of the Heck Precursor

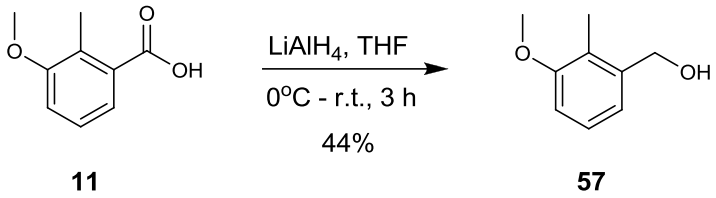
At the outset of this project, efforts were focused towards the preparation of multi-gramme quantities of the Heck precursor **10**. In order to prepare this intermediate it was first essential to synthesise Weinreb intermediate **55**. It should be noted that preliminary studies towards this key intermediate had taken place during an earlier short programme within our laboratory.[96] Accordingly, the initial approach taken followed the previously utilised synthetic pathway from the commercially available benzoic acid **11**. Lihium aluminium hydride reduction of this substrate delivered the corresponding alcohol **57** in quantitative yield (**Scheme 47**).



11 **57**

Scheme 47

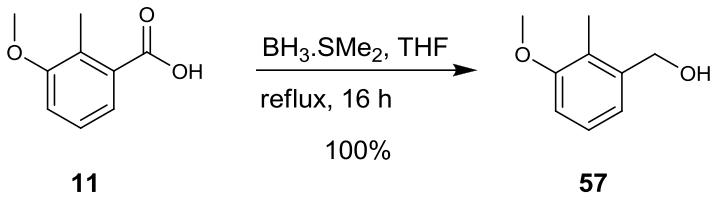
It was noted during subsequent repetition of this process that the quality of the lithium aluminium hydride was key to the success of this reaction. In one instance, a very poor 44% yield of the desired alcohol **57** was obtained (**Scheme 48**). The diminished yield was attributed to the formation of a dense brown emulsion during the work-up procedure, presumably caused by the aluminium residues. Separation of the desired product from this emulsion proved difficult and concurrent loss of product occurred.



11 **57**

Scheme 48

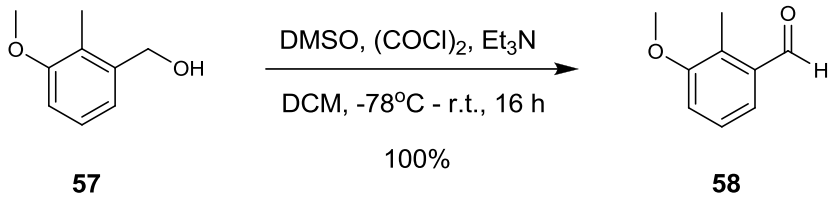
As a result of the problems encountered during the lithium aluminium hydride-mediated reduction process, a more efficient and reproducible method was investigated. It has been shown in the literature that the incorporation of borane-based reagents is highly effective for the reduction of carboxylic acids. In this respect, a borane-mediated reduction of acid **11** was carried out, which pleasingly delivered the desired alcohol **57** in quantitative yield (**Scheme 49**), with no emerging practical issues, even on more elevated scales.



11 **57**

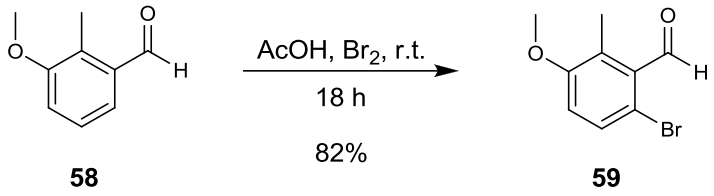
Scheme 49

Following the successful reduction of the benzoic acid derivative, the next step in the synthesis was an oxidation of benzyl alcohol **57** to produce the benzaldehyde derivative **58**. This transformation was performed under standard Swern[97] conditions to deliver the desired aldehyde in quantitative yield (**Scheme 49**).



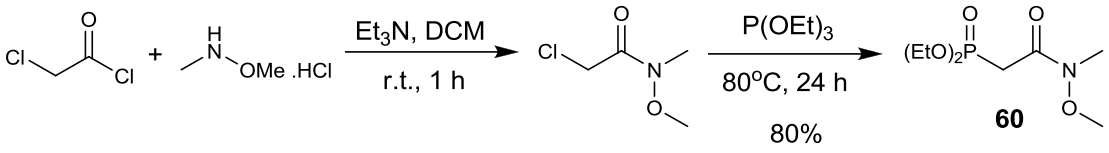
Scheme 49

The following step in the synthetic sequence involved the regioselective bromination of the freshly prepared benzaldehyde derivative **58**, as reported by Kende.[98] This transformation was carried out under relatively mild reaction conditions with only the desired product detectable by ^{1}H NMR. Pleasingly, the brominated product **59** was obtained in excellent yield following purification by recrystallisation (**Scheme 50**).



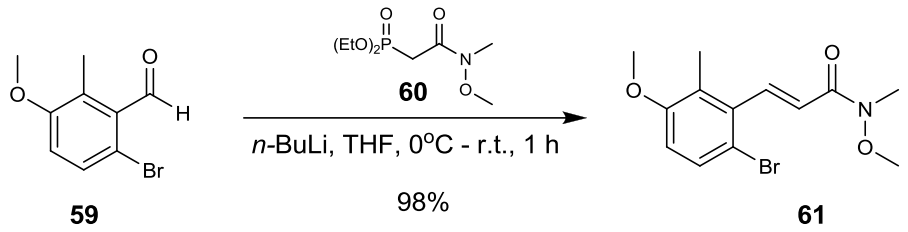
Scheme 50

The penultimate step towards the required Weinreb amide **55** required an olefination of aldehyde **59**, which was carried out using Horner-Wadsworth-Emmons (HWE) methodology.[99,100] However, before the olefination could be carried out, it was first essential to prepare the required functionalised phosphonate ester **60**. This was performed using a literature procedure which can easily be carried out on a multi-gramme scale.[101] Pleasingly, an excellent 80% yield of the desired product was obtained following purification *via* Kugelrohr distillation (**Scheme 51**).



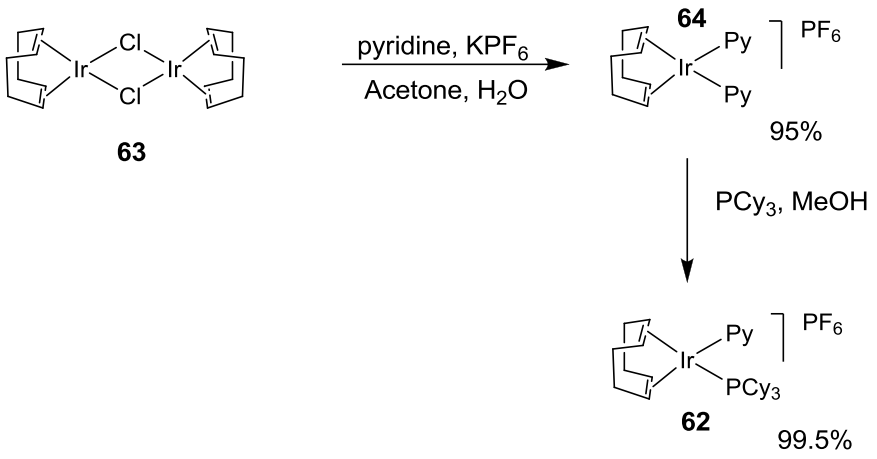
Scheme 51

Following the preparation of both partners that were required for the HWE reaction, attention focused on the olefination process. Phosphonate ester **60** was treated with *n*-BuLi before the addition of bromoaldehyde **59**. The reaction proceded with complete *E*-selectivity and enamide **61** was isolated in an excellent 98% yield (**Scheme 52**).



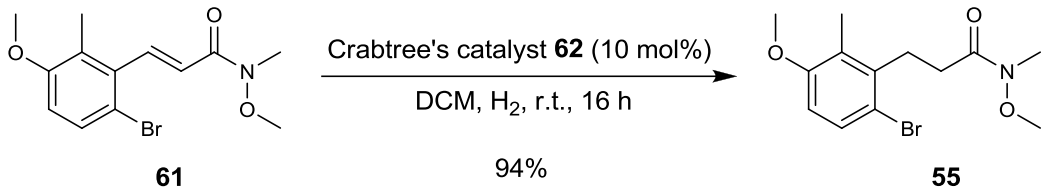
Scheme 52

With enamide **61** in hand, the final step towards the preparation of Weinreb amide **55** was hydrogenation of the newly installed olefin. Due to the sensitivity of the labile aryl halide towards heterogeneous hydrogenation catalysis conditions,[96] reduction of the olefin moiety was performed under milder homogeneous conditions using Crabtree's catalyst. Before the hydrogenation could be carried out, it was first necessary to prepare the catalyst **62** from the commercially available iridium dimer **63** (**Scheme 53**).[102] This was achieved in almost quantitative yield *via* intermediate **64**, which, due to the expense of the starting material, was extremely gratifying.



Scheme 53

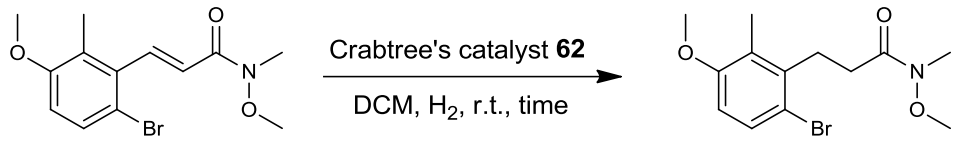
Employment of the newly prepared catalyst **62** under an atmosphere of hydrogen gas resulted in an excellent yield of the saturated Weinreb amide product **55** (**Scheme 54**), with no concomitant hydridodebromination.



Scheme 54

Due to the expensive nature of the chosen catalyst, especially in larger scale reactions, efforts were made to enhance the efficiency of this hydrogenation procedure. In this regard, the catalyst loading used in the reaction was investigated to ascertain whether 10 mol% of the catalyst was required to achieve complete conversion of the unsaturated amide. Initially, the catalyst loading was lowered to 7.5 mol%, which pleasingly resulted in complete conversion after 16 hours and delivered a 99% yield of the desired product (**Table 7**, **entry 1**). Following this initial reaction, it was noted during a subsequent

repetition of this process that the reaction was in fact complete after 8 hours employing only 7.5 mol% of the catalyst (**Table 7**, **entry 2**). In a final attempt to improve the efficiency of the hydrogenation process using Crabtree's catalyst, the catalyst loading was reduced to 4 mol%. Pleasingly, the reaction did run to completion, albeit in a slightly extended reaction time of 24 hours (**Table 7**, **entry 3**).

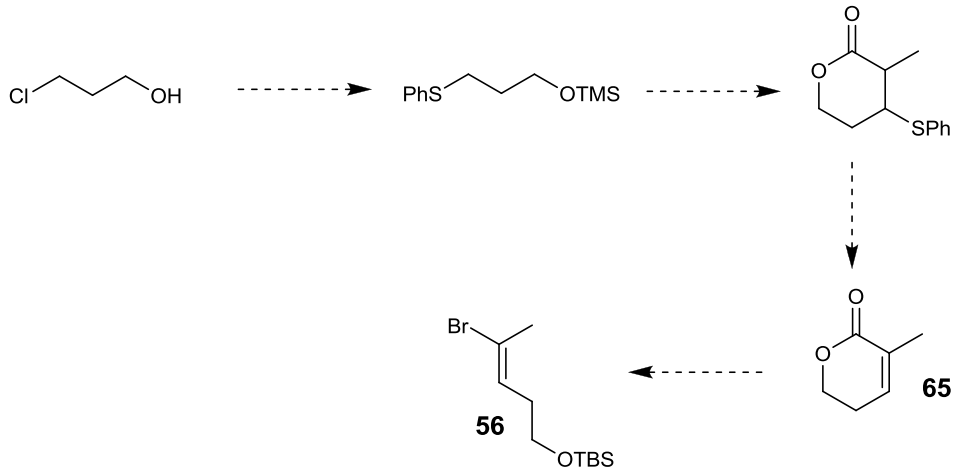


61 **55**

Entry	mol% of **62**	Reaction time (h)	Yield (%)
1	7.5	16	99
2	7.5	8	89
3	4	24	88

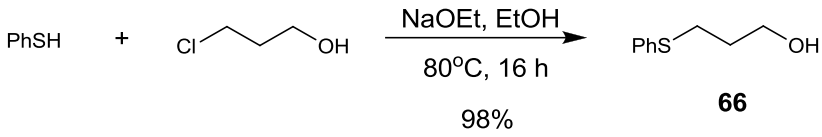
Table 7

With multi-gramme quantities of the required Weinreb amide **55** produced, coupling of this material with the appropriate Grignard reagent would deliver the desired Heck precursor **10**. In this regard, it was essential to prepare the required vinyl bromide **56**. In this regard, the proposed synthesis towards the preparation of vinyl bromide **56** is shown in **Scheme 55**.



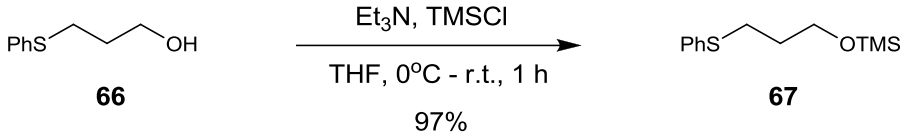
Scheme 55

To access vinyl bromide **56**, it was first necessary to synthesise the key intermediate **65** following a literature procedure reported by Paterson.[103] The first step towards this goal was the preparation of phenyl sulfide **66**, which was achieved *via* the alkylation of thiophenol with 3-chloropropanol. As shown in **Scheme 56**, the reaction was heated for 16 hours and the desired product was obtained in an excellent 98% yield.



Scheme 56

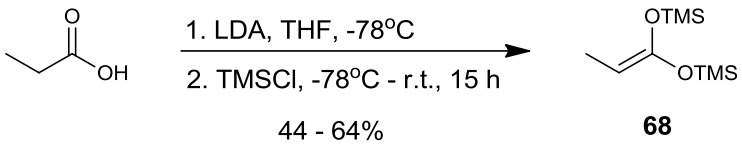
Preparation of sulfide **66** was followed by protection of the alcohol functionality with trimethylsilyl chloride. This was carried out without incident delivering the protected alcohol **67** in near quantitative yield (**Scheme 57**).



66 **67**

Scheme 57

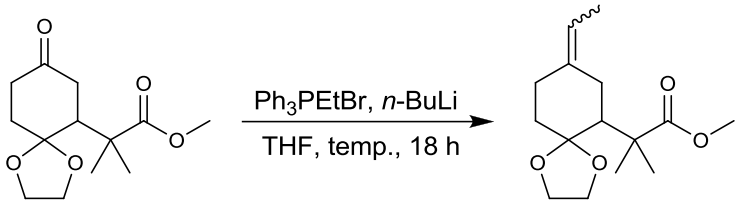
Following the preparation of the TMS-protected alcohol **67**, it was necessary to prepare *bis*-silylketene acetal **68** before the formation of the key lactone **65** could be undertaken. This was carried out by the double deprotonation of propionic acid followed by the addition of two equivalents of TMSCl.[104] During the addition of the external electrophilic quench, it was essential to maintain a low temperature (below -65°C) in order to minimise the amount of *C*-silated byproduct formed during the reaction. The results obtained during this reaction were quite variable, which was believed to be a direct result of slight variations in the reaction temperature during the addition of the TMSCl (**Scheme 58**).



68

Scheme 58

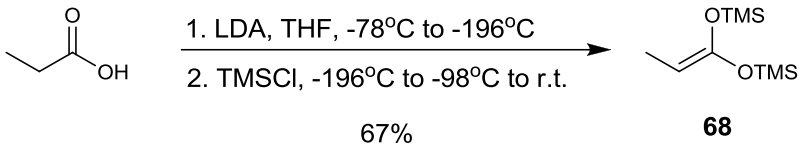
In order to overcome the unpredictable nature of this reaction, alternative reaction conditions were sought. Previous low temperature work carried out within our laboratory involved freezing a reaction mixture in liquid nitrogen and allowing the reaction to warm to -90°C in an effort to obtain enhanced stereoselectivity during a total synthesis project.[76] As can be seen from **Table 8**, the selectivity of the desired *Z*-isomer was increased from 2:1 at room temperature to 9.2:1 using the extremely low temperature reaction conditions.



Entry	Temperature	Yield (%)	*Z*:*E* ratio
1	r.t.	92	2.0:1
2	-78°C	99	4.0:1
3	-196°C to -90°C	95	9.2:1

Table 8

It was proposed that applying such a strategy to the preparation of **68** would allow more consistent results to be obtained. Therefore, the reaction mixture was cooled to -196°C prior to the addition of TMSCl. Warming of the reaction mixture to -98°C, in a methanol/liquid nitrogen bath, was then carried out before finally allowing the reaction mixture to warm to room temperature overnight (**Scheme 59**). Pleasingly, a 67% yield of the desired product was obtained in what proved to be a more simple and less laborious practical procedure.



Scheme 59

With both TMS-protected alcohol **67** and *bis*-silylketene acetal **68** prepared, formation of the key lactone **65** was undertaken. As shown in **Scheme 60**, chlorination of **67** with NCS was followed by reaction with the previously prepared *bis*-silylketene acetal **68** in the presence of $ZnBr_2$.[105,106] Work-up of the reaction mixture under acidic conditions

mediated removal of the silicon groups and facilitated lactonisation of the corresponding product to deliver lactone **69**. Finally, oxidation of the sulfide using *m*-CPBA was followed by DBU-mediated elimination to deliver the desired α,β-unsaturated δ-lactone **65** in a good 62% yield over all of the steps described.

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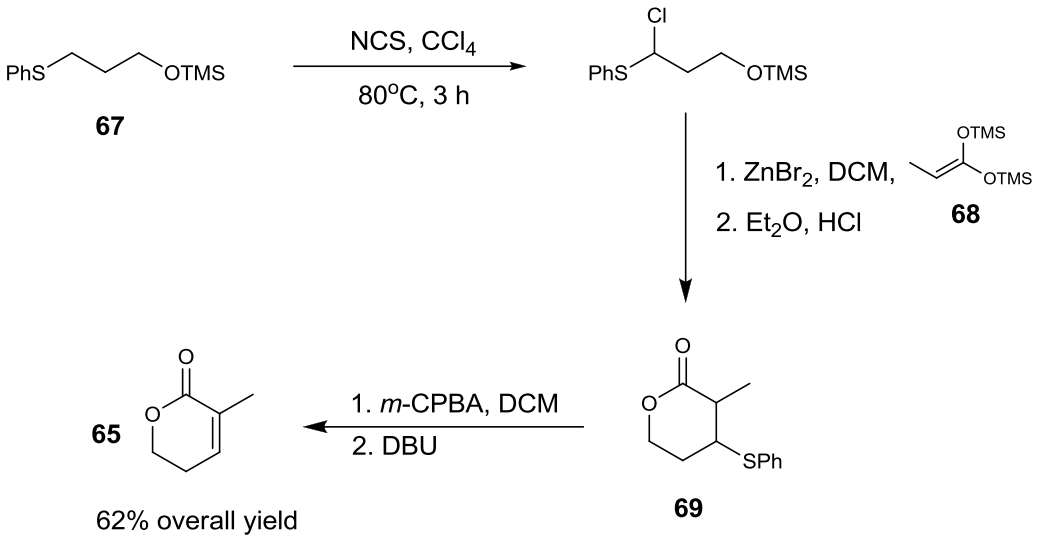
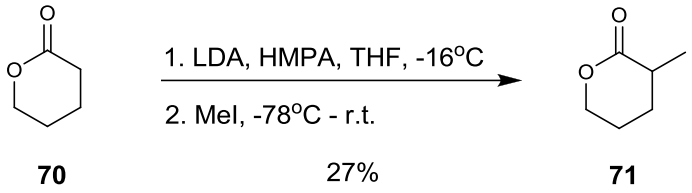


Scheme 60

Following the preparation of unsaturated lactone **65** it was noted that the current multi-step synthetic route towards this target was rather cumbersome and also required the preparation of *bis*-silylketene acetal **68**, which, due to its sensitive nature, required to be freshly prepared on each occasion. Consequently, a more effective and direct route towards this target was investigated. In this regard, it was proposed that methylation of commercially available lactone **70** followed by introduction of the enone functionality would deliver the α,β-unsaturated lactone in a more concise fashion.

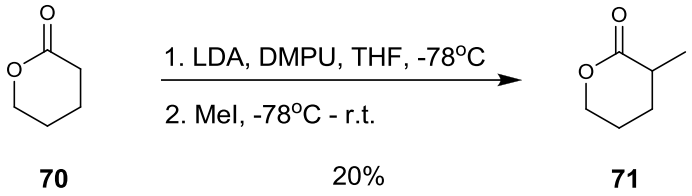
The first step towards developing this procedure was methylation of lactone **70**, for which literature precedent was available.[107] The authors reported the use of HMPA as an additive to increase the reactivity of the initially formed enolate. Unfortunately, on

applying these conditions, a poor 27% yield was obtained for the formation of lactone **71** (**Scheme 61**).



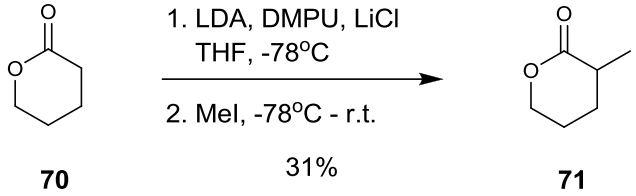
Scheme 61

An analogous reaction was carried out with DMPU as the additive, as a replacement for HMPA, but this did not result in an improved yield (**Scheme 62**).



Scheme 62

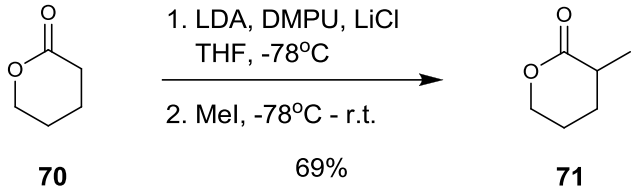
It was proposed that the low reactivity of the lithium enolate towards the electrophile was due to the solution aggregation state of this intermediate. In this regard, it has been well documented in the literature that inorganic halide salts can be employed in order to break-up such complex solution aggregates. In particular, lithium chloride has been shown to be highly effective[108-112] and has been used extensively as an additive in magnesium-enolate chemistry within our laboratory.[113] With this in mind, the reaction was repeated with both DMPU and lithium chloride as additives (**Scheme 63**).



70 **71**

Scheme 63

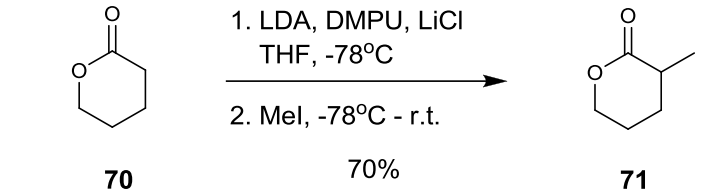
The moderate 31% yield obtained was encouraging, however a further enhancement in yield would be beneficial in order to prepare large quantities of this early-stage intermediate in an efficient manner. During this optimisation study it was observed that, on addition of saturated sodium bicarbonate solution, a dense white emulsion formed which proved problematic during the work-up procedure. It was proposed that the extent of the emulsion formation was elevated by shaking the reaction mixture in the separating funnel during the work-up procedure. Therefore, on repetition of this reaction, it was found that stirring the biphasic solution in a round-bottom flask, followed by separation of the organic layer, led to enhanced yields of the methylated product **71**. Following this protocol, an enhanced yield of 69% was obtained (**Scheme 64**).



70 **71**

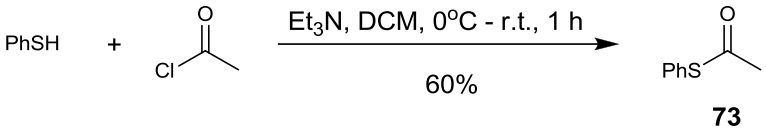
Scheme 64

A further simplification of the work-up procedure involved direct distillation of the reaction mixture following removal of the reaction solvent *in vacuo*. This approach avoided the potential formation of any emulsion and the need for column chromatography. Pleasingly, this procedure resulted in a 70% yield of the desired product (**Scheme 65**).



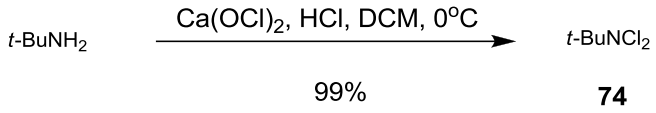
Scheme 65

With an efficient procedure in place for the methylation reaction, attention turned to the introduction of the enone functionality. It was decided to install the enone functionality following a procedure reported by Mukiyama,[114,115] which has also been extended within our own laboratory.[116] For this, it was necessary to prepare the required sulphur-based reagent **72**. The first step towards this reagent was the preparation of thioacetate **73** (**Scheme 66**). This reaction was carried out on a one mole scale and the crude product was purified by reduced pressure distillation to yield the desired product in a 60% yield.



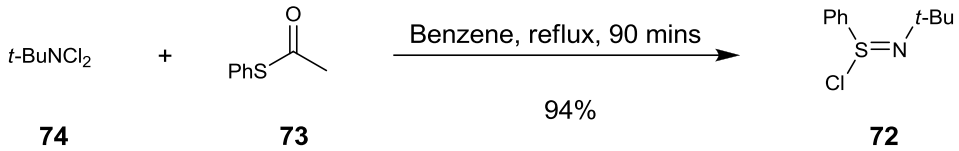
Scheme 66

Next, the dichloroamine **74** was prepared from commercially available starting materials. As shown in **Scheme 67**, the reaction of *tert*-butylamine with calcium hypochlorite under acidic conditions delivered the desired compound **74** in excellent yield.



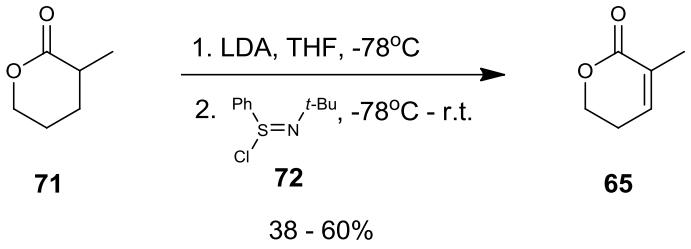
Scheme 67

With both precursors prepared, formation of the sulfur reagent, *N-tert*-butylbenzenesulfinimidoyl chloride, **72** was carried out. As shown in **Scheme 68**, this reagent was prepared in 94% yield.



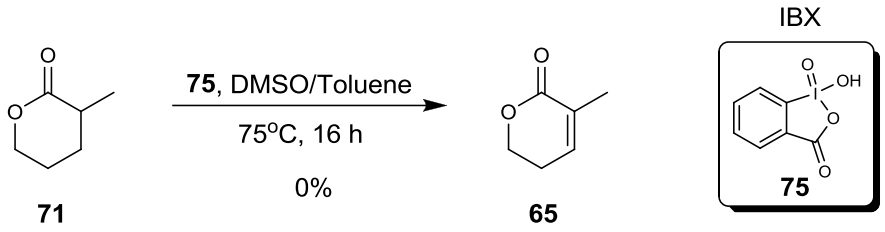
Scheme 68

Introduction of the enoate functionality was then carried out using the freshly prepared sulfur reagent **72**. However, results were variable due to the difficulty met in removing the sulfur by-products from the desired unsaturated lactone product. Column chromatography was initially used as the method of purification, however, obtaining clean material proved difficult. Following chromatography, the unsaturated lactone **65** was recovered in around a 60% yield. Due to the problems associated with purification of this material, an alternative purification strategy was investigated. The crude material was first purified by distillation and then further purified by column chromatography, which provided clean material, albeit in a somewhat compromised 38% yield (**Scheme 69**).



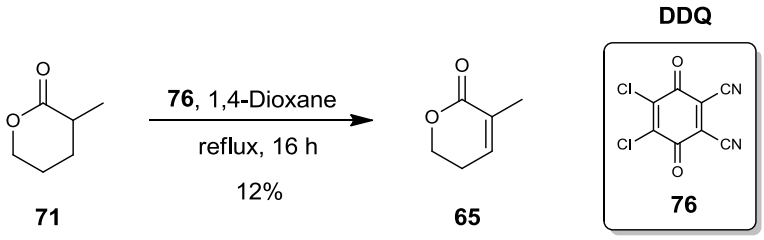
Scheme 69

Due to the difficulties met in purifying lactone **65** following the oxidation by sulfur reagent **72**, alternative methods under which to facilitate this oxidation process were investigated. The first protocol to be investigated involved the use of conditions reported by Nicoloau.[117,118] This method employed the IBX reagent **75**, as shown in **Scheme 70**. Unfortunately, no reaction occurred and the starting material was recovered.



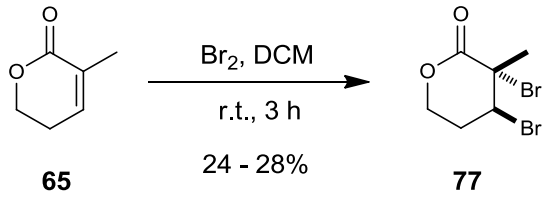
Scheme 70

Further conditions that were investigated to facilitate this oxidation process involved DDQ **76** in refluxing 1,4-dioxane.[119] After 16 hours, TLC analysis showed that there was a new product spot, however starting material still remained. The reaction was worked-up and purified resulting in a 12% yield of the desired unsaturated product. The unreacted starting material was recovered from the reaction mixture (**Scheme 71**). Whilst this method of oxidation did produce the desired product in a clean reaction, due to the slow nature of this transformation under these conditions this approach was abandoned.



Scheme 71

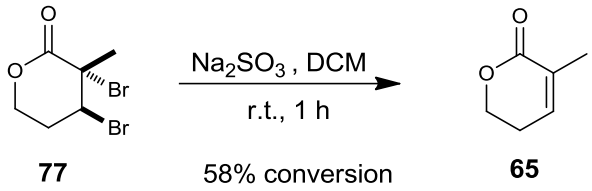
Although an efficient route towards the key α,β-unsaturated lactone **65** was not fully developed, sufficient quantities of this intermediate had been prepared in order to continue the synthesis towards the required vinyl bromide **56**. The first step towards this goal was bromination of the enone functionality with molecular bromine to furnish **77** (**Scheme 72**). Frustratingly, the yields obtained for this process were somewhat disappointing.



Scheme 72

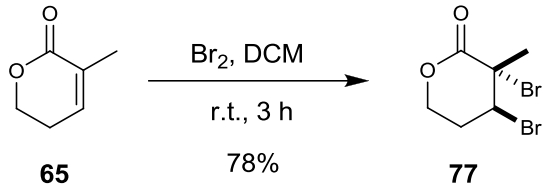
Results from TLC analysis on the reaction mixture, as the process had progressed, had indicated that no starting material remained. However, following the work-up procedure previously reported, TLC analysis then indicated that there was in fact starting material present. As a result, it was decided to repeat the reaction and follow progress by IR. Since the reaction was performed in DCM, a solution cell IR experiment was carried. Interestingly, the IR experiment showed that no starting material remained after 16 hours. The reaction mixture was then subjected to the same work-up procedure as previously reported. Surprisingly, analysis of the product by IR prior to column

chromatography indicated a significant amount of starting material. From this observation it was proposed that the sodium sulfite used in the work-up procedure was responsible for converting the product back to the starting material. To further investigate this proposal, saturated sodium sulfite solution was added to a solution of pure product **77** in DCM (**Scheme 73**). ^{1}H NMR of the reaction mixture after 1 hour at room temperature showed a 58% conversion of the brominated product **77** back to the unsaturated material **65**.



Scheme 73

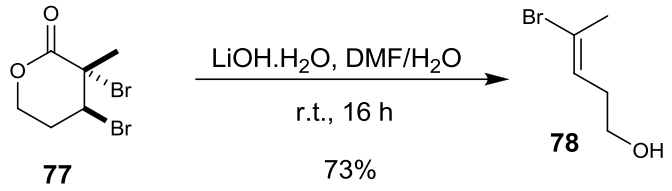
With a better understanding of this reaction process, it was then decided to eliminate the work-up procedure and simply remove the reaction solvent *in vacuo* and perform column chromatography on the crude reaction product. Encouragingly, this resulted in an excellent 78% yield of the desired product (**Scheme 74**).



Scheme 74

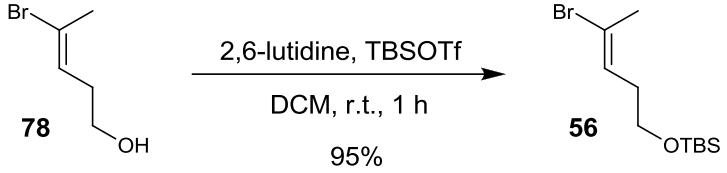
With conditions now in place for a successful bromination, attention turned to the next step in the synthesis. Saponification of the lactone in the presence of lithium hydroxide, followed by decarboxylation and elimination of bromide, resulted in vinyl bromide **78**

(**Scheme 75**). Furthermore, only one isomer, the *E*-isomer, was obtained after column chromatography.



Scheme 75

The final step towards the preparation of the required vinyl bromide **56** was protection of the hydroxyl group using silicon chemistry. In this regard, a TBS group was introduced under standard conditions (**Scheme 76**).

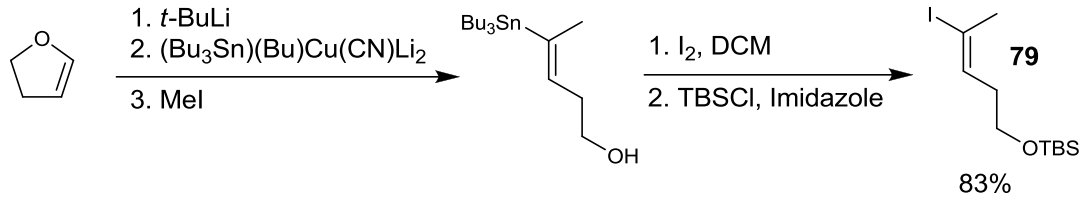


Scheme 76

With the required vinyl bromide in hand, attention could then be focused towards the preparation of the Heck precursor **10** for the first of the key metal-mediated cyclisation processes. However, the multi-step procedure required for the preparation of vinyl bromide **56** was still rather cumbersome and time consuming for the synthesis of large quantities of this material.

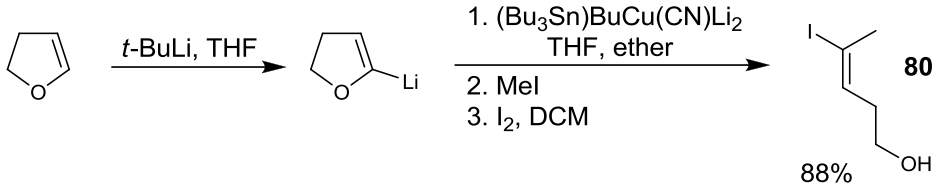
As a consequence of the lengthy route to access **64**, focus turned towards the preparation of the key vinyl bromide in a more facile manner. A more thorough literature search

revealed a publication by Sulikowski reporting a concise two-pot procedure for the preparation of the iodo-derivative **79**, from commercially available 2,3-dihydrofuran (**Scheme 77**).[120]



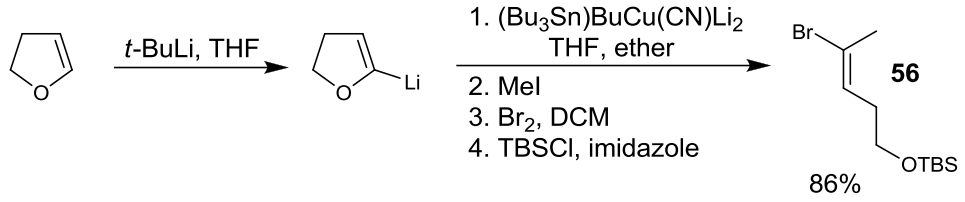
Scheme 77

In an initial attempt to recreate this literature procedure it was decided to simplify the process slightly and eliminate the *in situ* protection step. As shown in **Scheme 78**, the vinyl iodide **80**, possessing the free hydroxyl group, was obtained in an excellent 88% yield from the cheap and commercially available starting material, 2,3-dihydrofuran.



Scheme 78

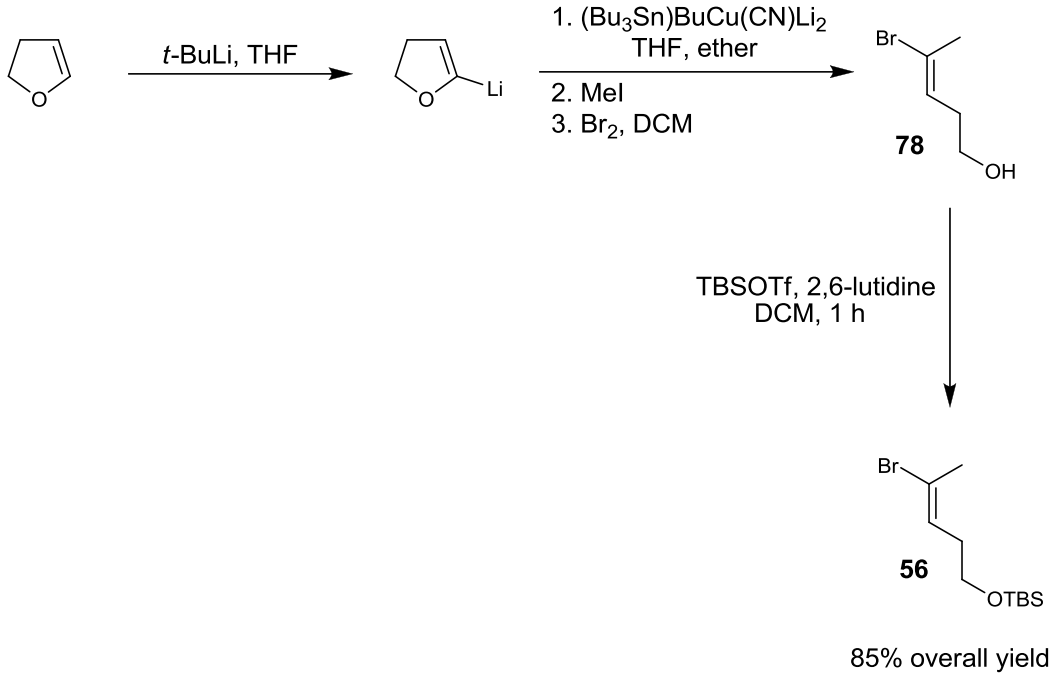
Following the success in accessing the alcohol **80** it was decided to repeat the process and to incorporate the *in situ* protection of the alcohol. A second alteration to the reported procedure was to replace the iodination step with a bromination step in order to deliver the desired vinyl bromide **56**. As shown in **Scheme 79**, this approach successfully and rapidly delivered the desired protected vinyl bromide **56** in an 86% yield.



Scheme 79

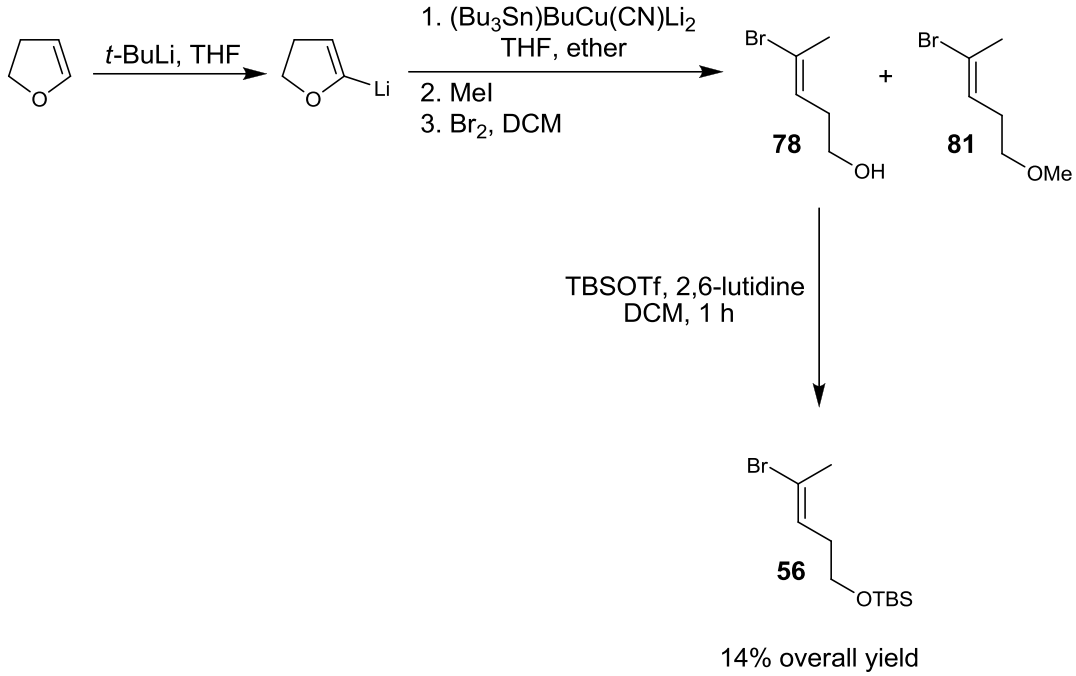
Following this process it was found that removal of the tin residues from the desired product by column chromatography was somewhat more difficult on the protected material than it was during the purification of alcohol **78**. In fact, it was necessary to further purify the protected alcohol **56** *via* distillation in order to remove the residual tin entities. In spite of the difficulties met in purifying the desired material, this route to the vinyl bromide **56** proved to be a rapid and efficient method for the preparation of large quantities of this product, and certainly when compared to the multi-step procedures that had been employed to this stage in the overall study.

Correspondingly, in subsequent reactions towards the protected product **56** it was decided to employ a two-step procedure due to the ease of purification of the alcohol **78** from the residual tin by-products (**Scheme 80**).



Scheme 80

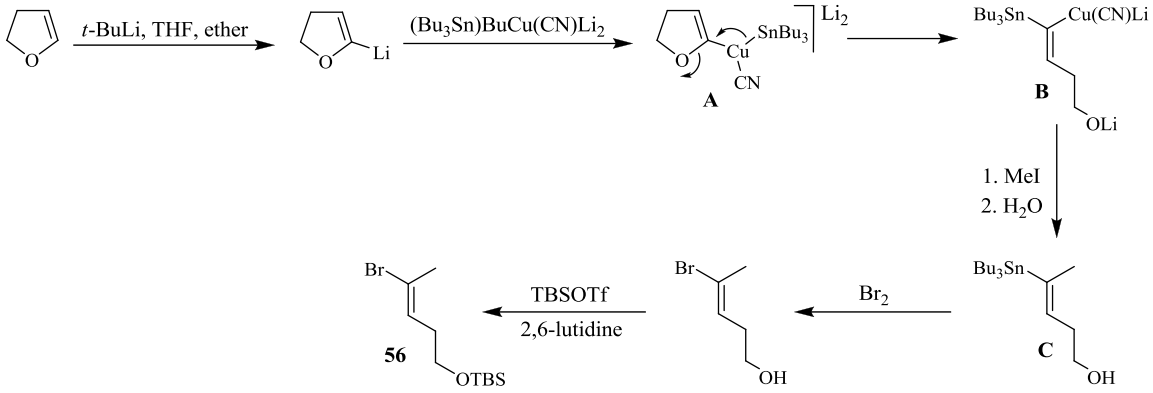
Satisfyingly, this two-step procedure was suitable for the preparation of large quantities of the required material. The reaction was performed on an 85 mmol scale resulting in an excellent 85% yield, as shown in **Scheme 80**. However, it was noted during this body of research that it is essential to follow the developed procedure carefully and strictly. On one occasion, the reaction mixture was allowed to stir for 16 hours, instead of 3 hours, following the addition of methyl iodide, before being quenched. This resulted in a very poor 14% yield of the desired product. The majority of the mass balance of this reaction was made up by the methyl ether **81**, as shown in **Scheme 81**. Presumably, the extended reaction time enables the less reactive alkoxide to react with the excess methyl iodide present to form this undesired by-product.



Scheme 81

According to the chemical literature,[121-123] there are two proposed pathways by which this transformation is believed to take place. Firstly, preparation of a higher order cuprate **A**, which is a common intermediate in both of the proposed mechanisms, is carried out from the starting dihydrofuran (**Scheme 82**). The first of the proposed pathways then proceeds *via* a 1,2-migration to give vinyl cuprate **B**, which is quenched with methyl iodide to deliver vinyl stannane **C**. Reaction with bromine followed by protection of the alcohol results in the vinyl bromide product **56**.

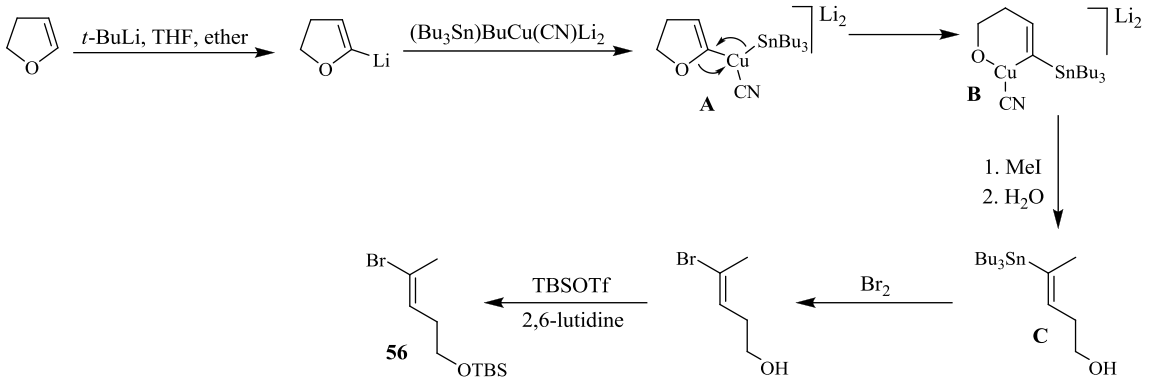
1,2-Migration mechanism



Scheme 82

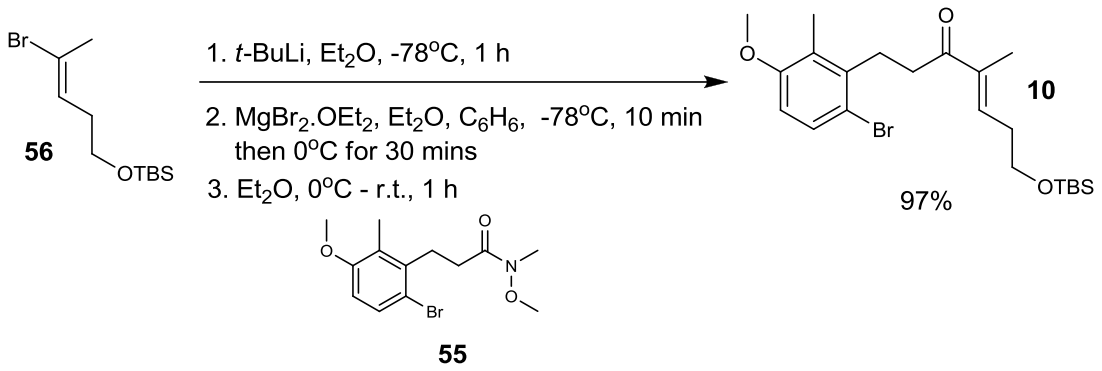
The second of the proposed mechanisms is believed to proceed *via* a dyotropic rearrangement of intermediate **A**, resulting in metallocycle **B** (**Scheme 83**). Intermediate **B** is then quenched with methyl iodide to deliver intermediate **C**. The reaction subsequently proceeds through an identical pathway as the migration mechanism shown in **Scheme 82**.

Dyotropic rearrangement mechanism



Scheme 83

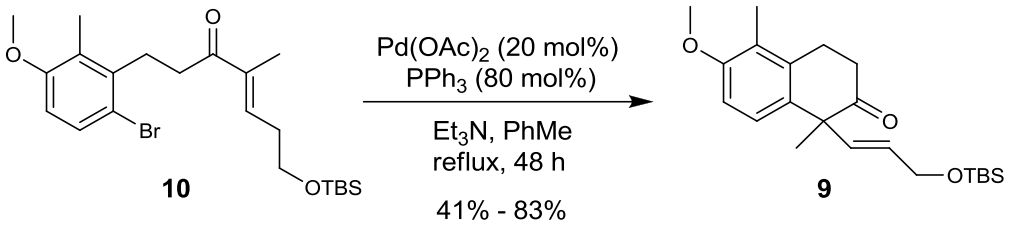
With a high yielding and highly efficient route into both of the required fragments developed, attention turned to the preparation of the precursor for the first of the key metal-mediated cyclisation steps. This reaction was facilitated *via* lithiation of the vinyl bromide, followed by transmetallation with freshly prepared $MgBr_2.OEt_2$, resulting in the preparation of the corresponding Grignard reagent. Treatment of the Weinreb amide **55** with the Grignard reagent resulted in the desired enone **10** in an excellent 97% isolated yield (**Scheme 84**).



Scheme 84

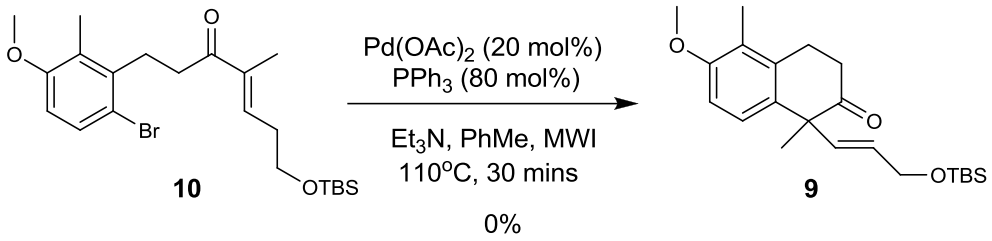
2.2 The Heck Reaction

With enone **10** now in hand, the first of the key metal-mediated transformations could be attempted. This Heck reaction was first attempted using the previously employed conditions from the initial preliminary study.[96] Encouragingly, the dersired product was isolated in an 83% yield (**Scheme 85**). However, on repetition of this process only moderate yields of 58% and 41% were achieved.



Scheme 85

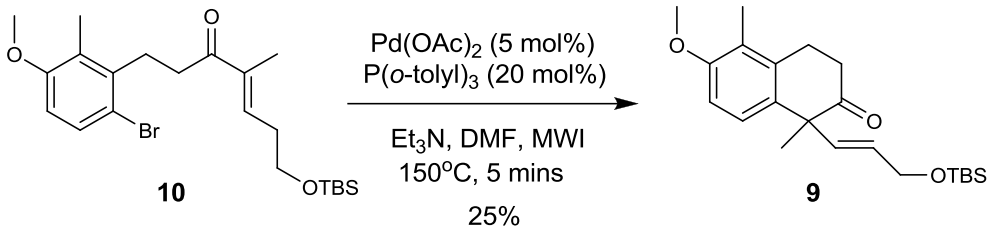
As a result of the unpredictable nature of this process, in addition to the high catalyst loading and long reaction time required, it was decided to investigate more efficient and reproducible conditions for this transformation. In this regard, due to the ability of microwave technology to accelerate such reactions,[124] it was decided to attempt this Heck reaction under microwave irradiation (**Scheme 86**). The reaction was performed under microwave irradiation in toluene at 110°C for 30 minutes. Unfortunately, this resulted in no conversion of the starting material into the desired product.



Scheme 86

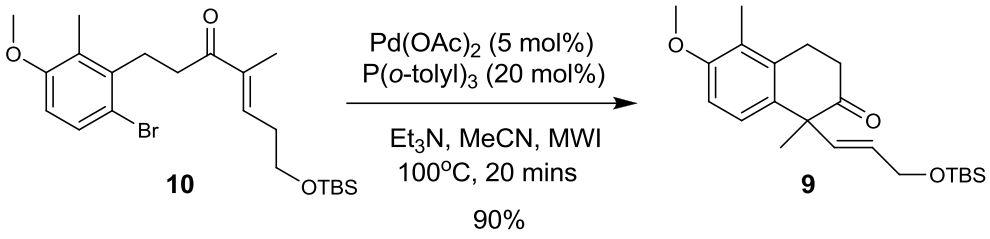
As a result of this poor initial reaction outcome, alternative reaction conditions were sought. Firstly, it was decided to change the reaction solvent. As the ability of a solvent to respond to microwave-assisted heating is directly proportional to the dielectric constant of that particular solvent, a solvent with a higher dielectric constant was employed.[124] Due to the abundance of literature showing DMF to be successful in microwave-assisted processes, this was chosen as the solvent and 150°C was selected as the reaction temperature. In addition, a more electron-rich and sterically encumbered

phosphine ligand was also sourced. In this regard, triphenylphosphine was replaced with tri-*o*-tolylphosphine. Finally, as palladium-mediated cross-coupling reactions have been shown to be generally more efficient under microwave heating than reactions carried out under thermal promotion, the catalyst loading was reduced to 5 mol%.[124] In accordance with the previously reported conditions, the ligand to catalyst ratio was kept constant at 4:1. Encouragingly, under the newly developed, microwave-assisted, low catalyst loading, conditions a 25% yield of the desired product was obtained after 5 minutes (**Scheme 87**).



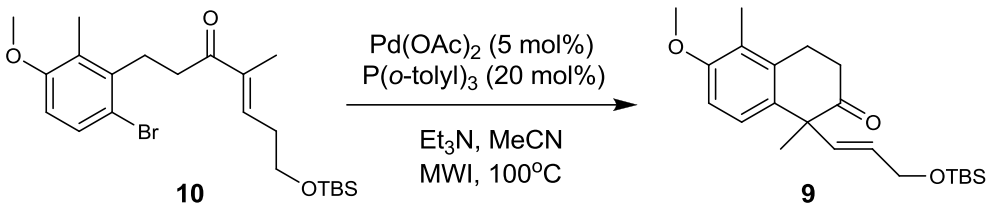
Scheme 87

It was observed, however, that there was no starting material remaining in the reaction mixture. The mass balance was made up of degradation products as a result of the forcing conditions employed in this process. Therefore, it was decided to reduce the reaction temperature to 100°C. In this regard, the reaction solvent was also replaced as a lower boiling solvent would be sufficient. Acetonitrile was selected as this solvent possesses what could be an effective dielectric constant, but is much easier to remove from the reaction mixture that the higher boiling DMF. The reaction, performed on a 1.49 mmol scale, was monitored by ^{1}H NMR, and pleasingly showed no remaining starting material after 20 minutes and delivered an excellent yield of 90% of olefinic product **9** (**Scheme 88**).



Scheme 88

Considering that under the previously optimised thermal reaction conditions between 48 and 72 hours were required to generate a comparable yield with 20 mol% of the palladium catalyst, this outcome is a demonstration of the potential enhancement of sluggish reactions that is attainable under microwave-assisted conditions. This reaction was repeated on a larger scale and an equally impressive 91% yield was obtained after 20 minutes (**Table 9, entry 1**). However, a drop-off in the reaction rate was observed when the reaction scale was further increased. When the reaction was carried out on a 13.37 mmol scale, incomplete conversion was obtained after 20 minutes (**Table 9**, **entry 2**). In this instance, 50 minutes of heating at 100°C was required to push the reaction to completion. However, an 87% yield was still obtained for this process over the extended reaction time.

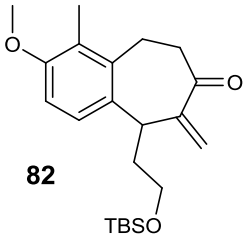


Entry	Scale (mmol)	Time (mins)	Yield (%)
1	7.03	20	91
2	13.37	50	87

Table 9

It is believed that drop-off in rate (**Table 9**, **entry 2**) was caused by inefficiencies in the cooling of the reaction mixture during the reaction, which we believe is a result of the larger-reaction-volume to surface-area ratio of the vessel. As a result, the microwave attenuator is switched off for periods during the reaction.

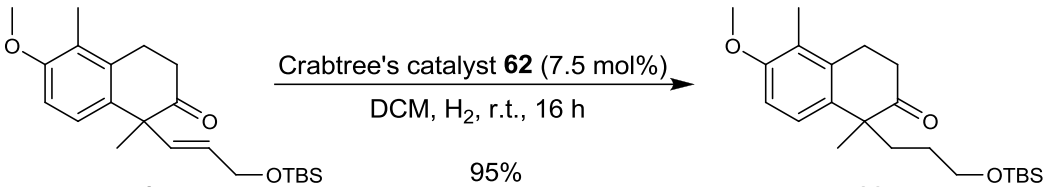
Furthermore, during the investigations into an improved method for the intramolecular Heck reaction, it was observed that the 7-*endo* product **82** was also being formed in around an 8:92 ratio to the desired product. Interestingly, this product was not observed in any reaction that was carried out under thermal promotion.



82

2.3 Preparation of the Pauson-Khand Precursor

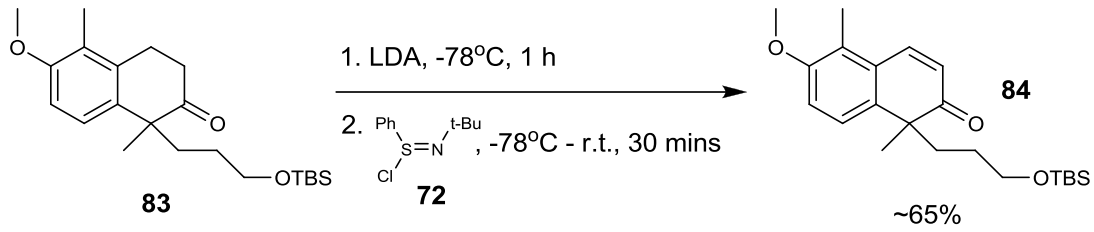
Following the successful optimisation of an efficient intramolecular Heck process, preparation of the Pauson-Khand precursor **8** was initiated. The first step towards this target was reduction of the newly installed double bond. This was affected using the previously prepared catalyst **62** to deliver the saturated product **83** in an excellent yield (**Scheme 89**).



9 **83**

Scheme 89

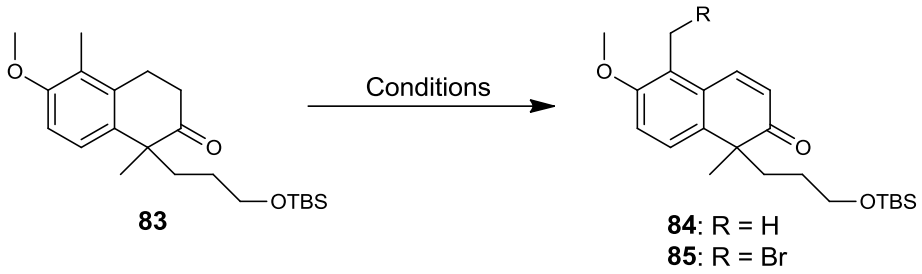
The next step in the synthesis was the attempted oxidation of ketone **83** to introduce the enone motif. The previously prepared sulfur reagent **72** (**Scheme 68**) was again employed to facilitate this transformation. Following the reaction, as summarised in **Scheme 90**, the crude product from this transformation was purified by column chromatography but, as in two previous cases where this reagent had been employed, it was found to be difficult to remove the sulfur impurities, and isolation of clean material proved to be demanding. During work within our own laboratory it has become common practice to remove these by-products by flushing the column with toluene prior to chromatography with the desired eluent. However, due to the relatively non-polar nature of the enone product **84**, this was not possible in this instance. The difficulties associated with purification following this reaction, coupled with the modest yield obtained, led us to investigate further methods for the required introduction of the enone functionality.



Scheme 90

One idea that was pursued was to brominate at the benzylic position under radical conditions, which we believed would lead to elimination of HBr, and ultimately result in the formation of the desired enone. This reaction was carried out using NBS, with AIBN as the radical initiator. Initially, 1 equivalent of NBS was used as we were aware of the potential of halogenating undesirably on the benzylic methyl group. Frustratingly, this reaction gave a mixture of products. A mixture of starting material **83**, desired product **84**, and by-product **85** were obtained in a 16:65:19 ratio (**Table 10**, **entry 1**). The desired product **84** and the undesired compound **85** were obtained as an inseparable 3:1 mixture (**84**:**85**) in a 55% yield following column chromatography. The reaction was

then repeated with 1.3 equivalents of NBS in an effort to completely consume the starting material and isolate the desired product in a more elevated yield (**Table 10**, **entry 2**). Unfortunately, this led to an inseparable complex mixture of products, probably a result of dibromination at the benzylic methyl unit, as well as the products observed under the previous reaction conditions. This transformation was also attempted using the procedure reported by Nicolaou.[117] The starting material was heated with IBX in a mixture of DMSO and toluene, however mass degradation occurred and no product or starting material was isolated from the reaction mixture (**Table 10**, **entry 3**).



83

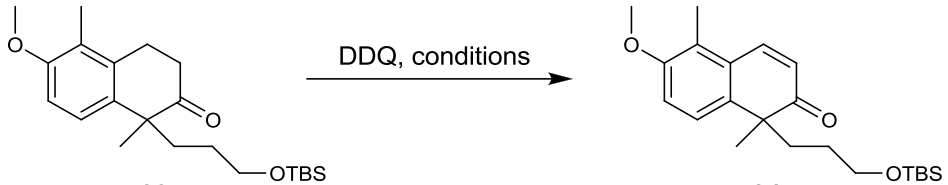
84: R = H
85: R = Br

Entry	Conditions	Outcome
1	NBS (1 eq), AIBN, CCl_4, reflux, 3 h	55% of **84**:**85** (3:1)
2	NBS (1.3 eq), AIBN, CCl_4, reflux, 3 h	inseparable mixture
3	IBX, DMSO, Toluene, reflux	mass degradation

Table 10

A further method of incorporating the enone functionality into the ring was attempted using DDQ. It was thought that exposure of the ketone to DDQ would result in oxidation to the enone as transformations similar to this have been reported on numerous occasions within the literature.[125] Initially, 1.5 equivalents of the reagent were used, which resulted in incomplete conversion of the starting material and a 36% isolated yield (**Table 11**, **entry 1**). As there was incomplete conversion in the first attempt, the reaction was repeated using 3 equivalents of DDQ (**Table 11**, **entry 2**). Complete

consumption of the starting material was obtained, however, only 12% of the desired product was isolated. Due to the low yield and degradation that was observed, the reaction was repeated under milder reaction conditions at 70°C (**Table 11**, **entry 3**). Under these milder conditions, which required an extended reaction time of 48 hours to consume all of the starting material, a poor 12% of the desired product was again obtained. In a final attempt to enhance the efficiency of this process, the reaction was carried out in benzene (**Table 11**, **entry 4**). Disappointingly, this failed to furnish the product in a more elevated yield and incomplete conversion was once again observed.

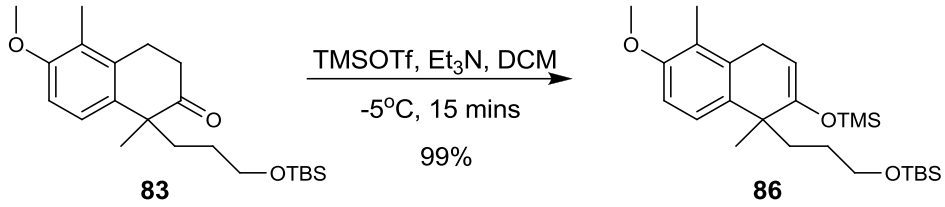


83 **84**

Entry	DDQ (eq)	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	1.5	1,4-dioxane	Reflux	24	36 (70 BRSM)
2	3	1,4-dioxane	Reflux	24	12
3	3	1,4-dioxane	70	48	12
4	3	Benzene	70	48	20 (65 BRSM)

Table 11

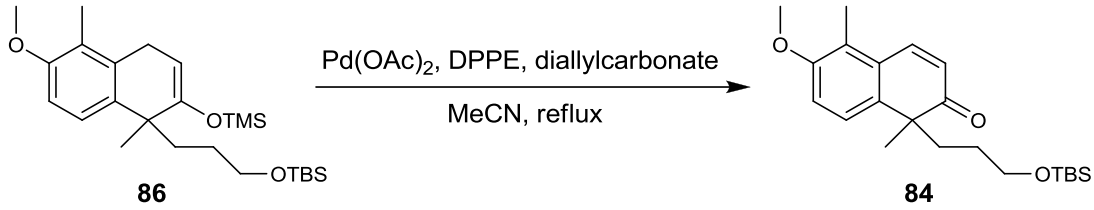
Undeterred by the poor results achieved to this point, further reaction conditions to transform the ketone to the enone were investigated. It was decided to attempt this transformation under catalytic Saegusa conditions.[126] Before the Saegusa reaction could be carried out, it was necessary to prepare the required trimethylsilyl enol ether **86** (**Scheme 91**).



83 **86**

Scheme 91

With the enol ether in hand, catalytic Saegusa conditions could be investigated. At the outset, conditions that had previously been shown to be successful within our laboratory (on a separate synthesis programme) were investigated,[127] when 10 mol% of palladium acetate was employed as well as 9 mol% of bis(diphenylphosphino)ethylene. The reaction mixture was refluxed in acetonitrile, with diallylcarbonate as the terminal oxidant, for 42 hours. Following this time, a 25% conversion to product was observed (**Table 12**, **entry 1**). In an attempt to drive this reaction towards completion, one further portion of the diallycarbonate was added and the reaction mixture was refluxed for a further 24 hours. However, no further conversion was observed. It was then decided to increase the catalyst loading to 20 mol% in an attempt to obtain a higher level of conversion (**Table 12**, **entry 2**). In this instance, a 40% yield of product was obtained after a reaction time of 114 hours.

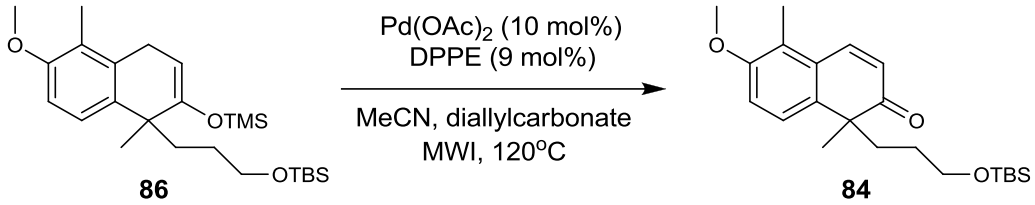


86 **84**

Entry	$Pd(OAc)_2$ (mol%)	DPPE (mol%)	Time (h)	Outcome
1	10	9	42 + 24	25% conv
2	20	18	114	40% yield

Table 12

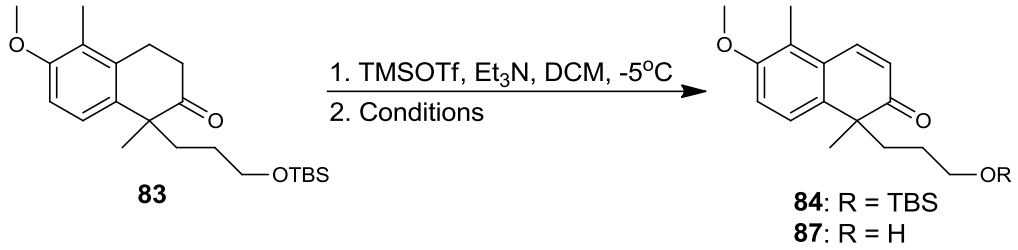
As a result of the sluggish nature of this reaction, alternative reaction conditions were investigated. Due to the exceptional acceleration of the previous palladium-catalysed process in this synthesis under microwave promotion (**Scheme 88**), it was decided to apply this technology in an effort to enhance the efficiency of this catalytic Saegusa process. The reaction was carried out at 120^{o}C for 10 minutes resulting in a 21% conversion of starting material into product (**Table 13**, **entry 1**). In an attempt to enhance this conversion, the reaction was repeated for an increased reaction time of 120 minutes (**Table 13**, **entry 2**). Unfortunately, this resulted in mass degradation and hydrolysis of the starting material.



Entry	Time (mins)	Outcome
1	10	21% conversion
2	120	mass degradation and hydrolysis of SM

Table 13

Due to the poor turnover in the catalytic reaction, it was decided to form the silyl enol ether and then perform the required oxidation process using stoichiometric amounts of palladium acetate (**Table 14**, **entry 1**). Pleasingly this resulted in an excellent 70% overall yield of the desired enone over the two reaction steps. Due to the long reaction time required, on repetition of this process the reaction mixture was gently warmed to 50°C during the oxidation step. This increase in reaction temperature resulted in a reduced reaction time of 48 hours and an elevated yield of 86% being obtained (**Table 14**, **entry 2**). Following the successful development of Saegusa oxidation conditions facilitated by stoichiometric amounts of palladium acetate, conditions for an efficient process mediated by catalytic amounts of the catalyst were again investigated. Following a literature procedure, conditions using 10 mol% of palladium acetate with oxygen as the terminal oxidant were examined (**Table 14**, **entry 3**).

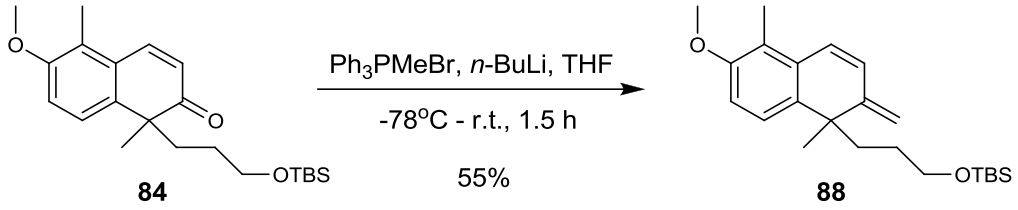


Entry	Conditions	Yield (Product)
1	$Pd(OAc)_2$, MeCN, r.t., 72 h	70% (**84**)
2	$Pd(OAc)_2$, MeCN, 50°C, 48 h	86% (**84**)
3	$Pd(OAc)_2$ (10 mol%), DMSO, O_2, 80°C, 16 h	66% (**87**)

Table 14

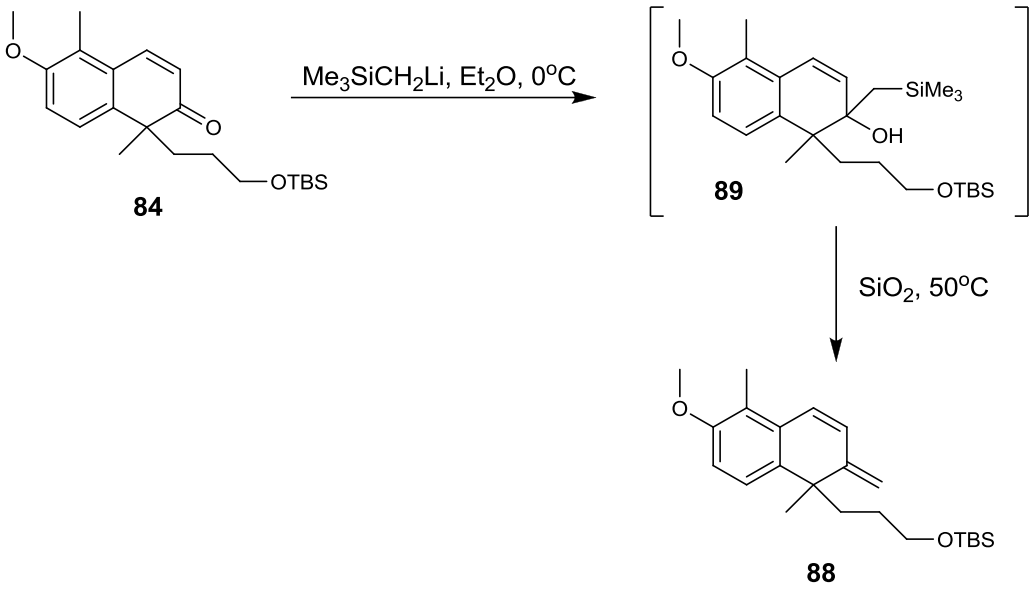
Pleasingly, the catalytic turnover in this case was efficient and there was complete conversion of the starting material after 16 hours. However, concomitant removal of the silicon-based protecting group was also observed, delivering enone **87** in 66% yield. This process became extremely efficient in the preparation of enone **87** as this species was required later in the synthesis (*vide infra*, **Scheme 108**).

With an efficient set of conditions in place to prepare the enone, attention focused towards the olefination reaction. Following standard Wittig conditions, the desired diene **88** was delivered in a moderate 55% yield (**Scheme 92**).



Scheme 92

The moderate yield obtained for this transformation dictated that alternative and more efficient reaction conditions had to be found. In relation to this, attention turned towards the use of conditions first reported by Peterson.[128] Following a literature procedure,[129] the enone **84** was treated with trimethylsilylmethyllithium (**Table 15**). Initially, the reaction was performed with 1.2 equivalents of this Peterson reagent but only 59% conversion of the starting material into β-hydroxysilane **89** was obtained (**Table 15**, **entry 1**). The reaction was therefore repeated with 2 equivalents of the reagent and an increased conversion of 88% was obtained (**Table 15**, **entry 2**). On moving to 3 equivalents of the reagent, no starting material remained after 1 hour at 0°C (**Table 15**, **entry 3**). The β-hydroxysilane intermediate **89**, produced from 1,2-addition of the Peterson reagent into enone **84**, was isolated and stirred on dry silica at 50°C to facilitate degradation to the methylenated product. After 2 hours, TLC analysis showed that quantities of the intermediate **89** still remained. It was decided to isolate the product from the intermediate and investigate alternative conditions to facilitate the transformation into the desired product.

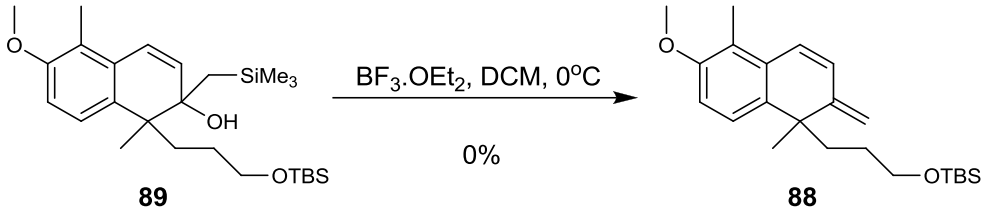


Entry	Time (h)	Me_3SiCH_2Li (eq)	Outcome[a]
1	6	1.2	59% conversion
2	6	2	88% conversion
3	1	3	28% yield of **88** (+ 45% of **89**)

[a] conversions quoted correspond to the conversion of **84** to **89** observed.

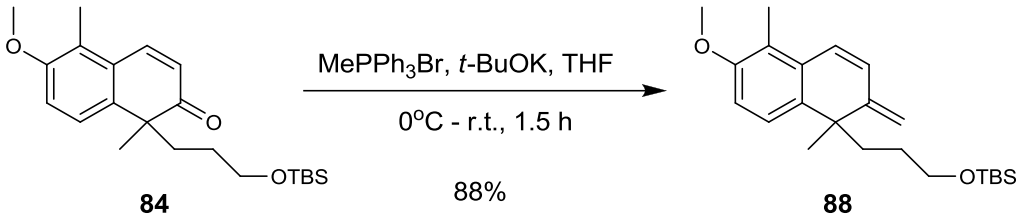
Table 15

The intermediate that was recovered was treated with boron trifluoride diethyl etherate. It was anticipated that the strong Lewis acid would transform the intermediate into the desired product[130] and also facilitate the deprotection of the alcohol,[131] which is the next proposed step in the synthetic sequence. However, upon treatment with the Lewis acid, the reaction mixture turned black very quickly and no identifiable product was isolated from the reaction mixture (**Scheme 93**). Due to the disappointing results obtained from this study involving the Peterson methodology, alternative olefination conditions were investigated.



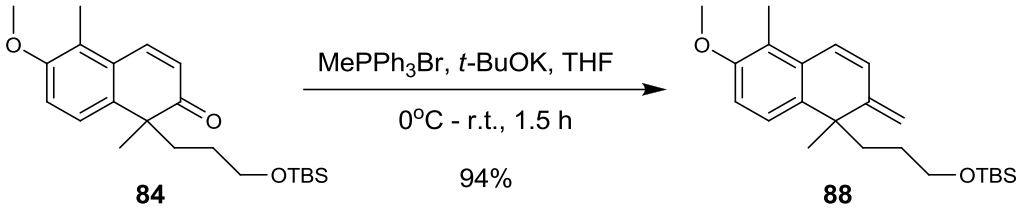
Scheme 93

Re-assessing the chemical literature regarding Wittig chemistry, the importance that the counter-ion of the base has on the outcome of the reaction was noted.[132] In relation to this, it was found that higher yields were often obtained from reactions with potassium counter-ions. This was investigated further and the desired olefination reaction was repeated with *t*-BuOK as the base (**Scheme 94**). Satisfyingly this resulted in an excellent yield of 88% for the desired diene **88** being obtained.



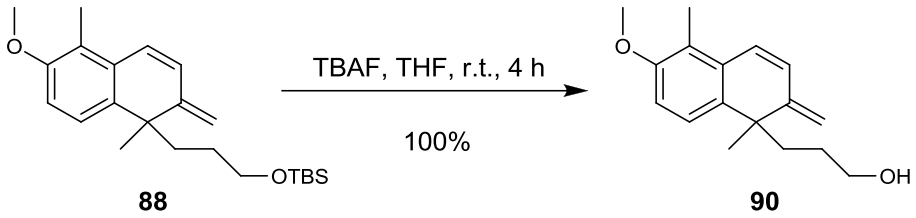
Scheme 94

A further increase in the isolated yield of this olefination process was realised by employing Barbier reaction conditions. Previously, the ylide had been performed before the addition of the enone to the reaction mixture. Following the Barbier methodology, the phosphonium salt was then stirred in THF with the enone starting material **84**. The base was then added to the reaction mixture and an immediate bright yellow colour appeared. As a result of this alteration to the reaction procedure, an elevated yield of 94% was obtained (**Scheme 95**).



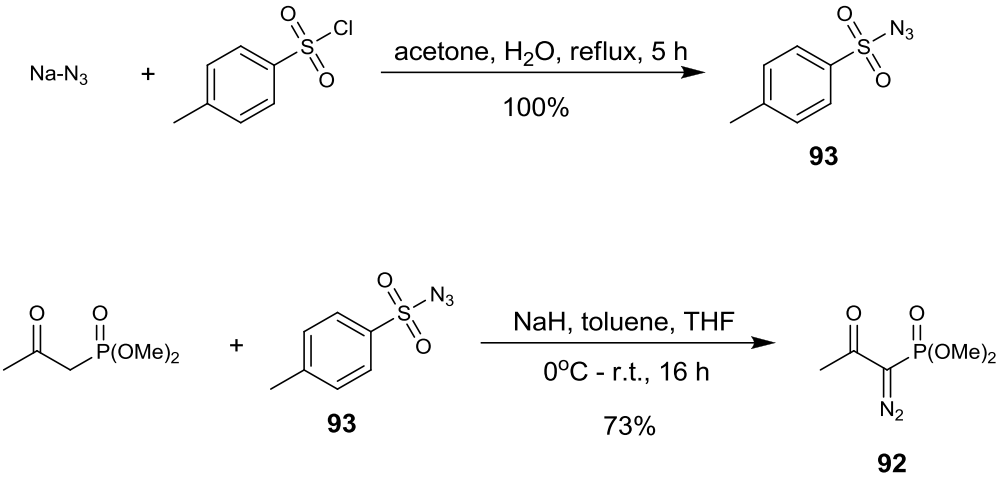
Scheme 95

With excellent conditions for the Wittig reaction successfully developed, attention turned towards the continued route for preparation of the Pauson-Khand precursor **8**. The next step towards this goal was a fluoride-mediated removal of the silicon-based protecting group (**Scheme 96**). As anticipated, the desired alcohol **90** was delivered in excellent yield.



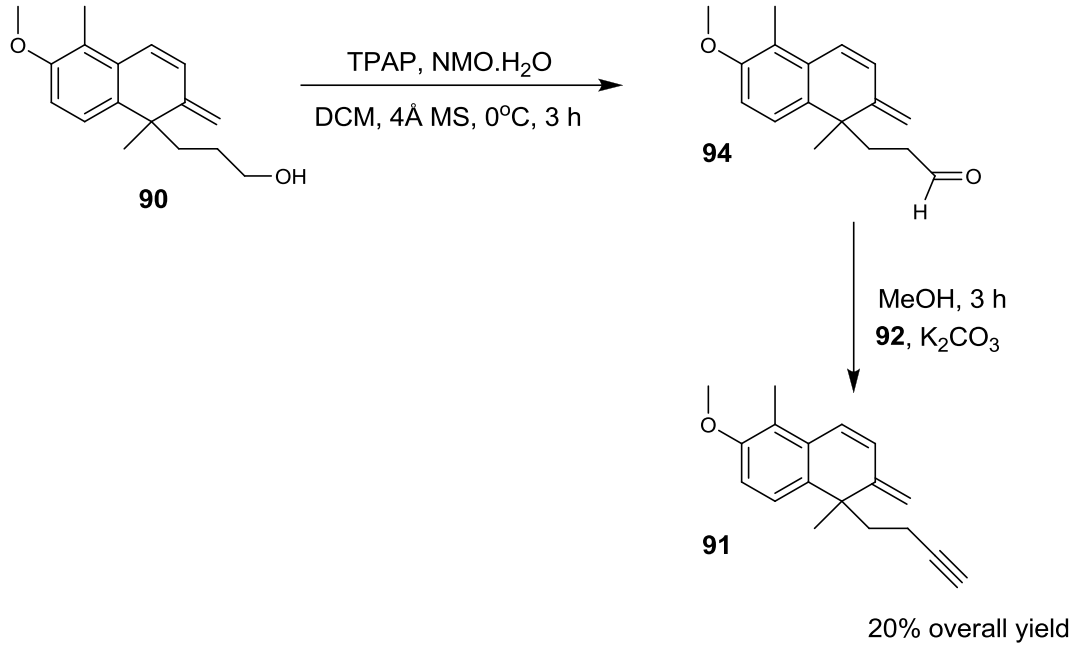
Scheme 96

Next, the alcohol **90** was transformed into alkyne **91** in a two step process. Before this chemistry could be carried out, it was essential to prepare the Ohira-Bestmann reagent **92**. This reagent was prepared according to a literature procedure (**Scheme 97**).[133] Tosyl azide **93** was prepared from sodium azide and tosyl chloride in one step and in excellent yield. The Ohira-Bestmann reagent **92** was then synthesised in 73% yield using the freshly prepared tosyl azide.



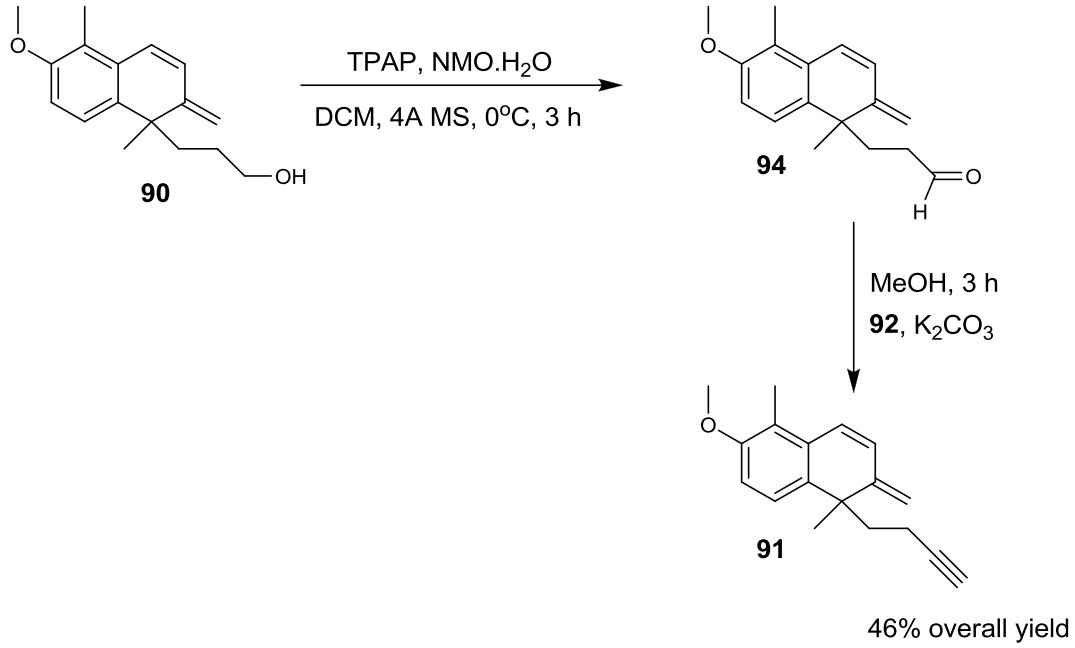
Scheme 97

With the required reagent prepared, conversion of the alcohol **90** into the terminal alkyne **91** could be performed. The primary alcohol was first subjected to mild oxidation conditions to furnish the aldehyde **94**. Unfortunately, the batch of TPAP that was used was sub-standard, which was later confirmed by Sigma-Aldrich, and the oxidation reaction proved to be very inefficient. However, as the aldehyde is believed to be very unstable, any material available was salvaged and transformed into the terminal alkyne under conditions reported by Ohira and Bestmann (**Scheme 98**).[134,135] Unfortunately, due to the problems experienced during the oxidation reaction, a poor 20% yield of the desired alkyne **91** was obtained. In addition, only a small amount of the starting alcohol was recovered from the reaction mixture.



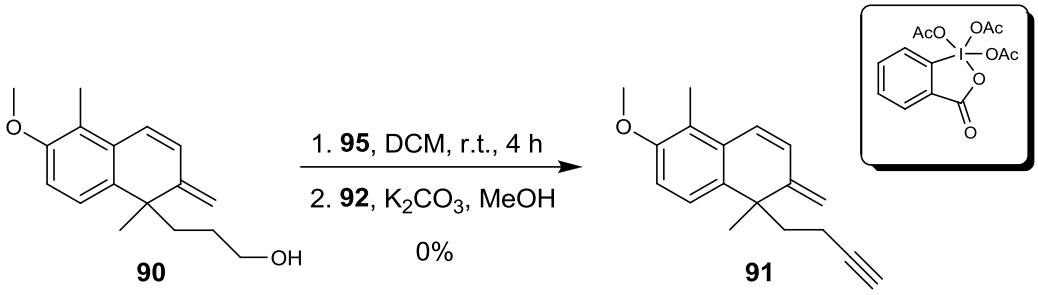
Scheme 98

Due to the poor result obtained with the TPAP sourced from Sigma-Aldrich, an alternative supplier was sought. In this regard, new material was purchased from Alfa Aesar and the reaction sequence was repeated. Pleasingly, with the new batch of oxidising agent, a 46% yield of the desired alkyne **91** was obtained (**Scheme 99**).



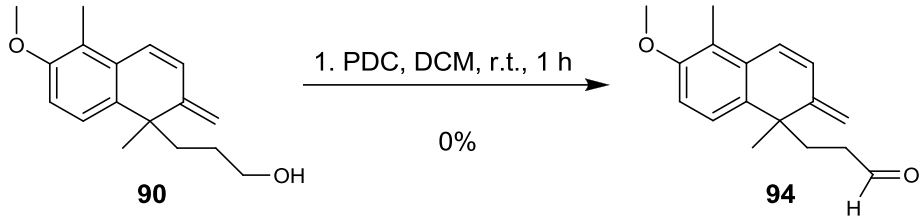
Scheme 99

As a result of the moderate yield obtained during the alkyne formation, it was decided to investigate alternative oxidation conditions. Therefore, the reaction sequence was repeated with the Dess-Martin reagent being employed as the oxidant (**Scheme 100**). Unfortunately, the reaction mixture was very messy and no identifiable material could be recovered from the reaction.



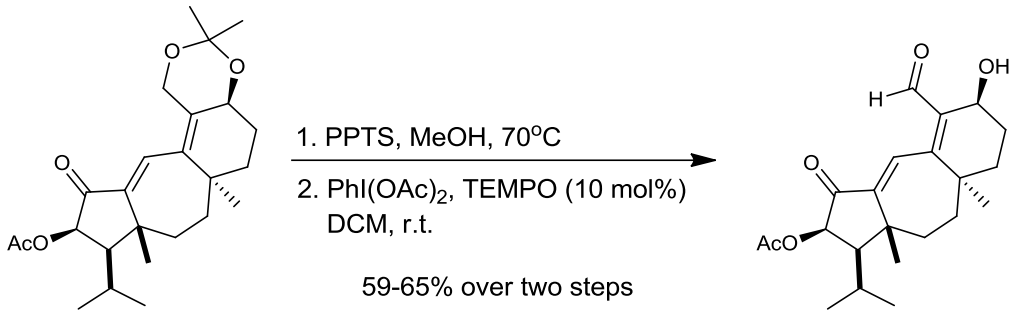
Scheme 100

Due to the poor result obtained using the Dess-Martin reagent, alternative conditions were investigated. PDC was the next oxidant of choice for this process. However, in common with the result obtained in the previous reaction, none of the desired product was obtained. In this instance, the TLC showed multiple spots following the oxidation process and the crude NMR showed mass degradation. The reaction was abandoned following this first oxidation step (**Scheme 101**).



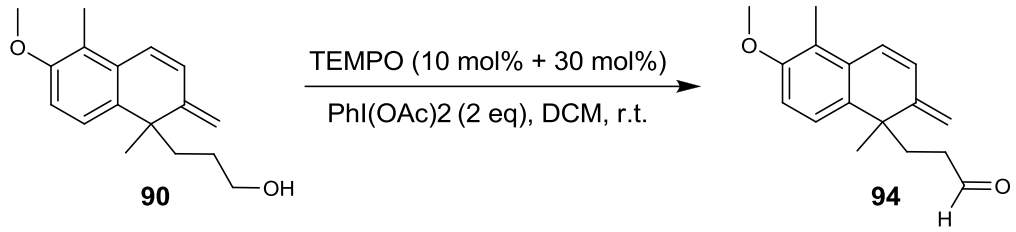
Scheme 101

Due to the rather disappointing results obtained under several oxidation conditions, alternative conditions were investigated. Whilst searching the literature, an interesting report by Danishefsky on the total synthesis of guanacastepene A was discovered. The final step in the reported synthesis was the oxidation of a primary alcohol to produce an aldehyde, which is reported to be extremely unstable. Firstly the diol was deprotected under acidic conditions to liberate the primary alcohol functionality. The alcohol was then oxidised under very mild TEMPO conditions at room temperature to deliver the target compound in up to 65% yield over the two steps (**Scheme 102**).[136]



Scheme 102

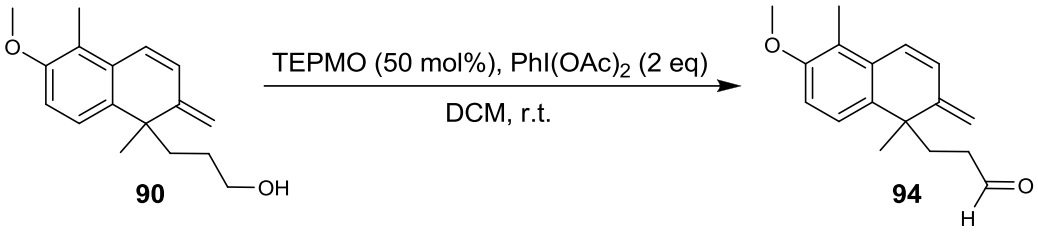
Due to the sensitive nature of aldehyde **94** in the current synthesis, it was decided to attempt the preparation of this compound under the mild TEMPO conditions used by Danishefsky. In accordance with Danishefsky's conditions, 10 mol% of the oxidant was employed along with 2 equivalents of diacetoxyiodo benzene as the terminal oxidant. Initially the reaction mixture was stirred for 16 hours, however TLC analysis showed that starting material was still present. Therefore, a further 30 mol% of TEMPO was added and the reaction mixture was stirred for an additional 16 hours. Following the prolonged reaction time, the crude product was very messy, presumably as a result of the sensitive nature of the aldehyde. The reaction mixture was purified by column chromatography but none of the desired product was isolated (**Scheme 103**).



Scheme 103

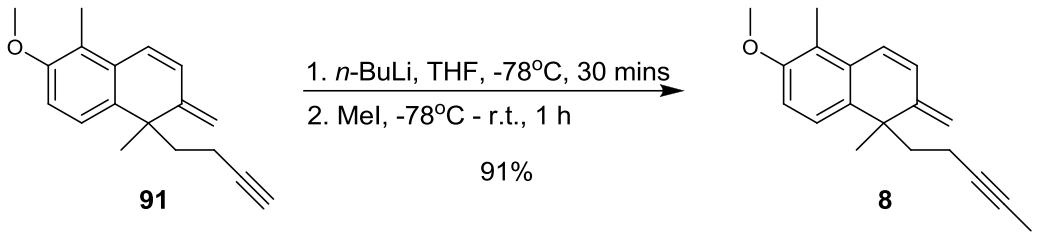
Following the slow nature of the transformation under catalytic TEMPO conditions, the reaction was repeated with an increased level of the oxidant present. 50 mol% of

TEMPO was added and the reaction mixture was stirred at room temperature. After 8 hours, ^{1}H NMR analysis of the crude reaction mixture showed a 50% conversion of the starting material into product. With this in mind, a further 50 mol% of TEMPO was added and the reaction mixture was stirred for a further 30 minutes. However, TLC analysis after this time showed no starting material or product to be present (**Scheme 104**). Further work towards successful oxidation on this alcohol under TEMPO conditions could investigate the use of quantitative amounts of the oxidant being employed from the start of the reaction.



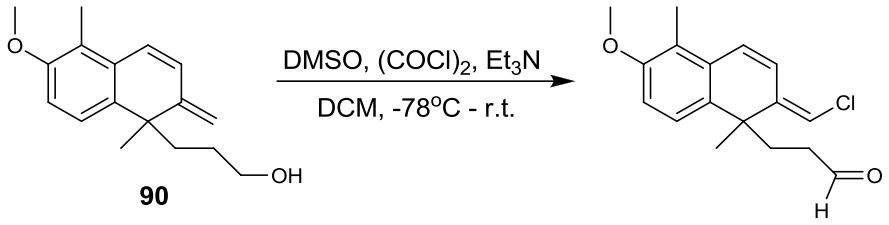
Scheme 104

During the investigations into alternative oxidation conditions, work towards the completion of the natural product synthesis was continued. The final step towards the preparation of the Pauson-Khand precursor **8** was methylation of the terminal alkyne **91**. Following the procedure summarised in **Scheme 105**, the desired enyne **8** was isolated in 91% yield.



Scheme 105

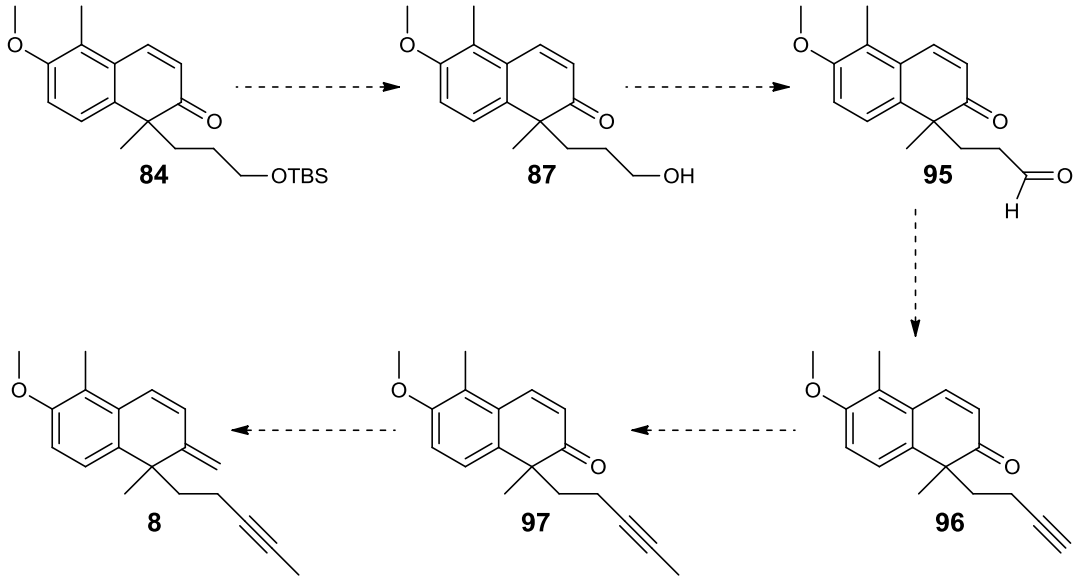
With enyne **8** in hand, the second of the key metal-mediated cyclisation processes could be investigated. Despite this, an alternative route for the synthesis of alkyne **8** from enone **84** was investigated, in an attempt to develop larger quantities of this advanced intermediate in a more facile manner. In this regard, it has previously been shown that diene **90** is susceptible to electrophilic halide sources, such as those present within the Swern reaction mixture, resulting in substitution of a halide on the terminal carbon of the diene (**Scheme 106**).[96]



90

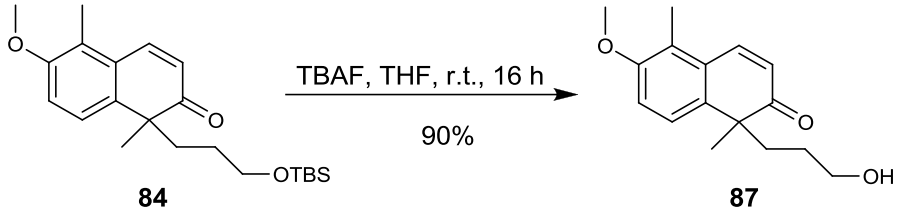
Scheme 106

Clearly, this outcome limits the reagents available to carry out some of the key transformations. In particular, this prohibits the use of Swern conditions in the preparation of the desired aldehyde **94**. Having stated this, an alternative approach towards enyne **8** would allow the use of the Swern conditions, which would potentially deliver the aldehyde in an elevated yield. An outline of the proposed alternative route is shown in **Scheme 107**. Firstly, removal of the silicon protecting group would liberate the alcohol functionality to deliver **87** and enable oxidation to the aldehyde **95**. It is proposed that this transformation could be performed under Swern conditions as, in contrast to the diene **90**, the enone functionality in **87** should be resistant to electrophilic halide sources. Following oxidation, the internal alkyne in **96** could be installed in a similar fashion to that used in the previous synthetic pathway. Finally, introduction of the *exo*-methylene group would deliver the desired enyne **97** required for the key intramolecular Pauson-Khand cyclisation.



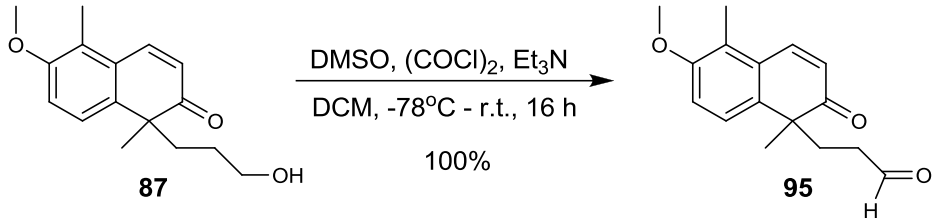
Scheme 107

The first step in this revised sequence was removal of the TBS group to yield alcohol **87** (**Scheme 108**). This process was carried out under fluoride-mediated conditions and a moderate 90% yield of the required alcohol **87** was obtained.



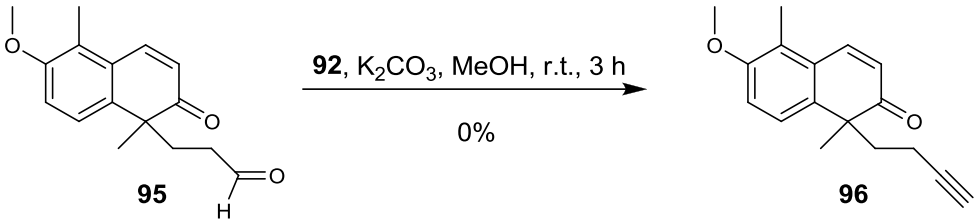
Scheme 108

The second step in this alternative sequence was the oxidation of primary alcohol **87** into aldehyde **95**. It was envisaged that this reaction would result in a high yield. If this was the case, this alternative pathway could then be seriously considered for full adoption within this total synthesis programme. Pleasingly, an excellent yield of the desired product **95** was obtained (**Scheme 109**).



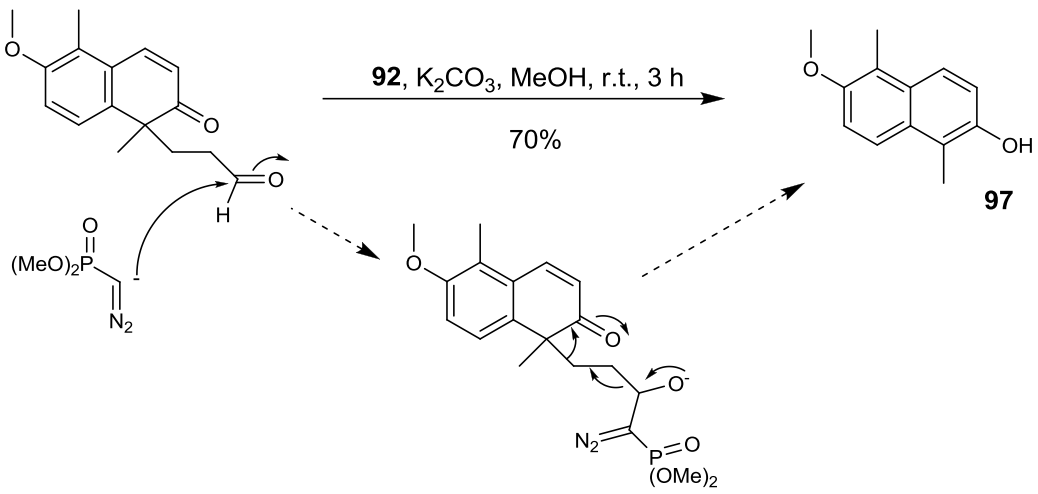
Scheme 109

Following a successful oxidation to prepare aldehyde **95**, attention turned towards the installation of the terminal alkyne functionality. It was decided to carry out this transformation under Ohira-Bestmann conditions using the previously prepared reagent **92** (**Scheme 110**).



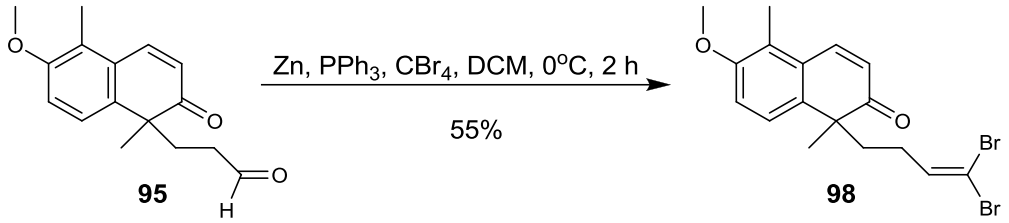
Scheme 110

Frustratingly, none of the desired product was isolated from the reaction mixture. A yellow solid was isolated by column chromatography which was later identified to be naphthol **97**. This by-product was isolated in 70% yield, with a possible mechanism being proposed for the formation of this species, as outlined in **Scheme 111**. Attack on the carbonyl group from the anionic olefination reagent could deliver the alkoxide intermediate as expected. However, instead of this intermediate collapsing as anticipated to the desired product, it is conceivable that it could collapse with loss of ethylene and aromatisation to yield the naphthol derivative **97**.



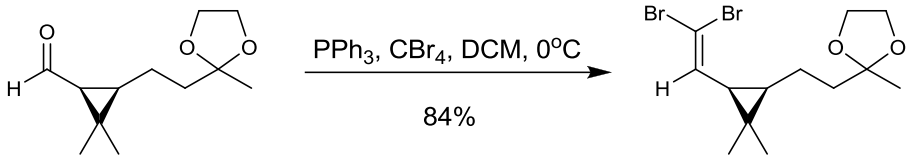
Scheme 111

As a consequence of this unforeseen side reaction, an alternative method of forming the alkyne **96** was investigated. It was decided to attempt this transformation under Ramirez-Corey-Fuchs conditions.[137,138] Initially, the dibromide intermediate **98** was prepared according to literature conditions (**Scheme 112**).



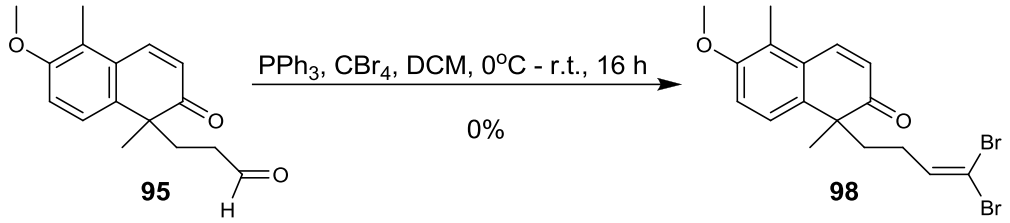
Scheme 112

Pleasingly, the desired material was obtained from this reaction. However, it was thought that 55% was a relatively moderate yield for such a transformation and alternative conditions were investigated. During the synthesis of (+)-taylorione within our own laboratory, a similar dibromoolefination process was performed in an 84% yield (**Scheme 113**).[139,140]



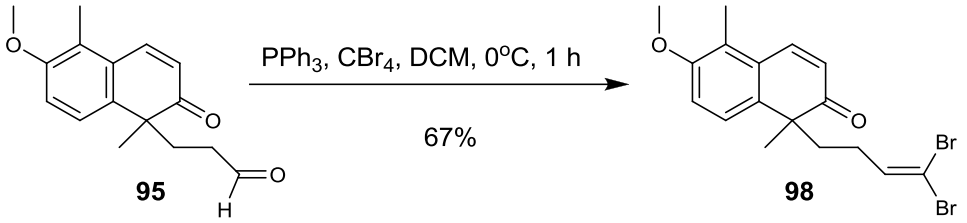
Scheme 113

Due to the success of this reported procedure, these reaction conditions were adopted for the synthesis of dibromide **98** (**Scheme 114**). Triphenylphosphine was added to a stirred solution of aldehyde **95** in DCM at 0°C. Carbon tetrabromide was then added to the reaction mixture, however, in contrast to the reported conditions,[87] there was no colour change was observed. TLC analysis showed only starting material to be present after 1 hour. As a result, the reaction mixture was warmed to room temperature and was stirred overnight. However, TLC analysis again only showed starting material to be present. The reaction was abandoned at this point and the aldehyde was recovered from the reaction mixture in good yield (99%).



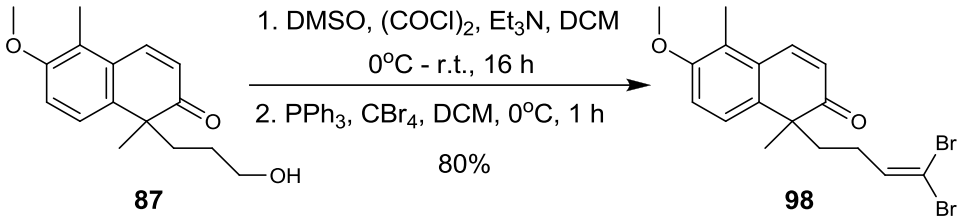
Scheme 114

As a result of this, rather surprising, lack of reactivity being observed, a further set of reaction conditions were investigated. In this regard, the reaction was repeated according to conditions reported by Bestmann (**Scheme 115**).[141] Following the conditions reported, carbon tetrabromide and triphenylphosphine were reacted together to form a bright yellow solution before the introduction of the aldehyde **95**. Pleasingly, this resulted in a good yield of 67% being obtained for this process.



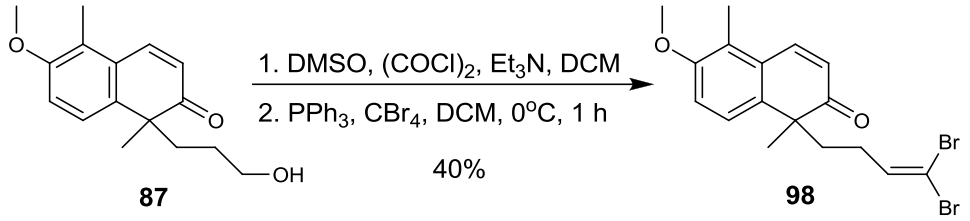
Scheme 115

Due to the potentially sensitive nature of aldehyde **95**, the preparation of the dibromo olefin **98** was repeated, starting from alcohol **87**. More specifically, following the Swern oxidation process the aldehyde **95** was retained as a solution in DCM and was not concentrated following the work-up procedure. Dibromoolefination was then conducted and, as a result, an elevated yield of 80% was obtained for this two-step transformation to the desired **98** (**Scheme 116**).



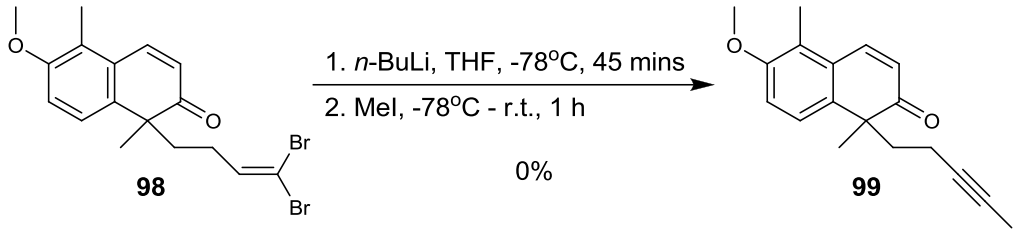
Scheme 116

It must be noted at this point that, on scaling up this reaction from a 2.08 mmol scale to a 10.8 mmol scale, a reduced yield of 40% was obtained over two steps from alcohol **87** to dibromide **97** (**Scheme 117**). During the investigation into the cause of this disappointing recovery, no other identifiable material was recovered from the reaction mixture.



Scheme 117

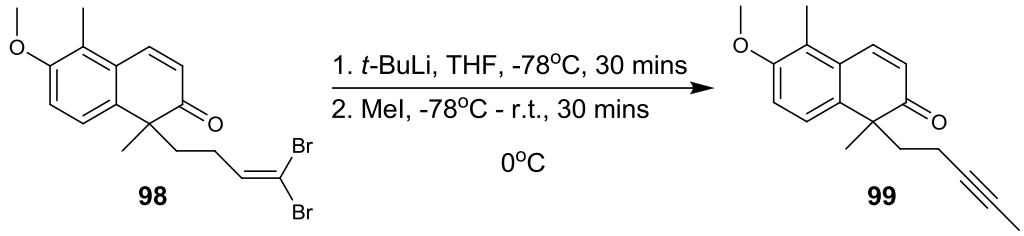
Following the optimisation study towards the formation of the dibromide **98**, enough material was in hand to attempt the subsequent step of the synthetic pathway. The dibromide was treated with *n*-BuLi and quenched with methyl iodide in an effort to generate the methylated alkyne in a one pot procedure (**Scheme 118**). However, in this initial approach, none of the desired product was isolated. ^{1}H NMR of the crude reaction mixture showed a plethora of products; none of these materials contained the characteristic signal of the olefinic enone protons. In this instance, and amongst other outcomes, it is thought that the *n*-BuLi may have nucleophilically attacked the enone moiety in preference to reacting with the dibromo olefin. These results were disappointing, however, it was believed that with a small amount of optimisation, this approach could still lead to a high yielding route to the Pauson-Khand precursor **8**.



Scheme 118

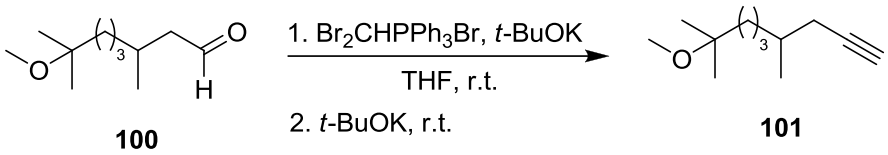
Following the disappointing results obtained using *n*-butyllithium, the reaction was repeated using a non-nucleophilic base, *t*-butyllithium (**Scheme 119**). However, ^{1}H

NMR analysis of the crude reaction showed a multicomponent solution and none of the distinctive enone peaks were present.



Scheme 119

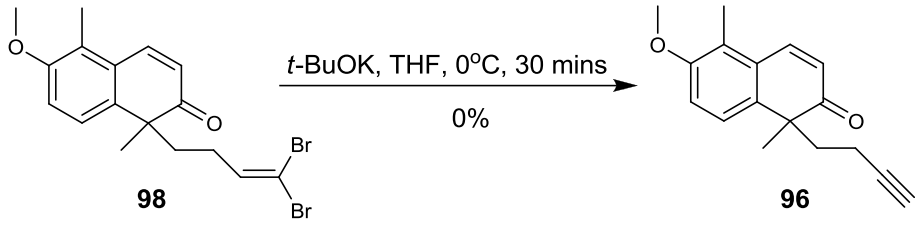
It has been shown in the literature that dibromo olefinic species can be transformed into terminal alkynes using potassium *t*-butoxide at room temperature. A report by Michel and Rassat showed the conversion of a series of aldehydes into terminal alkynes in excellent yield.[142] The authors reported the conversion of alkyl aldehyde **100** into alkyne **101** in a 97% yield in a two-step procedure (**Scheme 120**).



Scheme 120

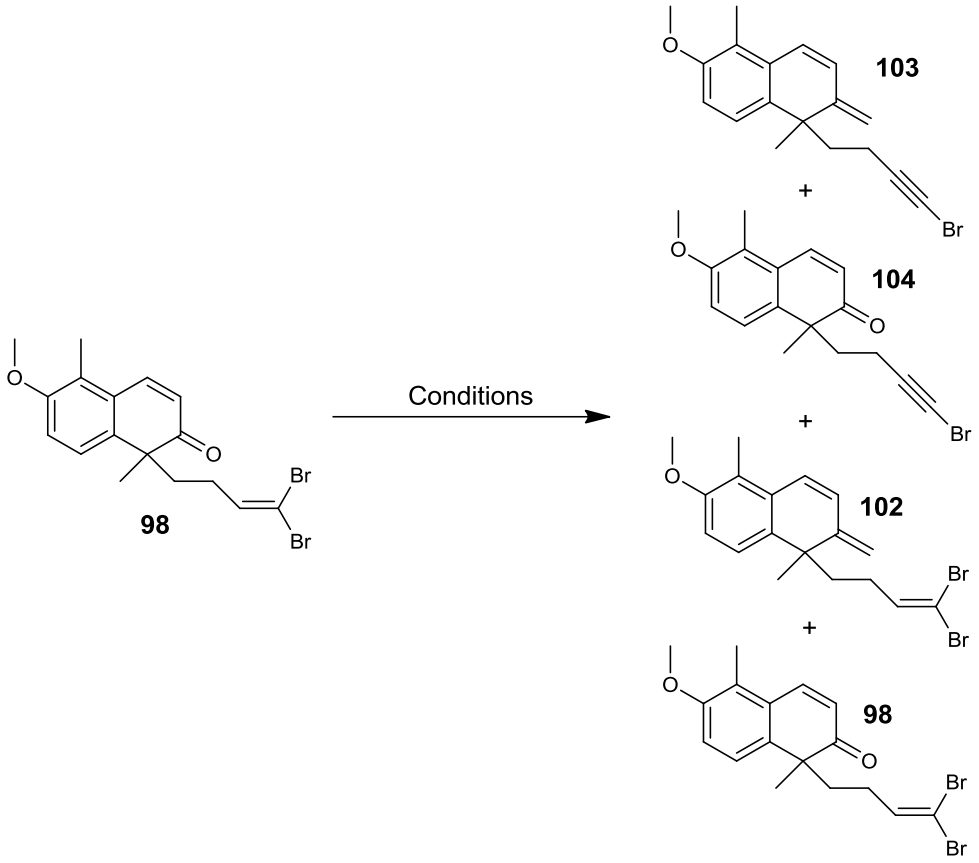
The conditions reported for the second step shown in **Scheme 120** were employed in the attempted transformation of dibromide **98** into terminal alkyne **96** (**Scheme 121**). It was also decided to perform the reaction at a slightly lower temperature than the conditions reported, with the intention of warming the reaction to room temperature if required. However, on addition of the base to the reaction mixture, a brown slurry formed and

following the work-up procedure, nothing identifiable was recovered from the reaction mixture.



Scheme 121

With the enone functionality seemingly incompatable with the base-mediated reaction conditions required to install the alkyne moiety, it was decided to alter the strategy towards the formation of the Pauson-Khand precursor **8** from dibromide **98**. In this regard, it was decided to olefinate the problematic enone before attempting to manipulate the dibromo olefin. The reaction conditions employed for the previous olefination within this synthesis (**Scheme 95**) were adopted here (**Table 16**, **entry 1**). A mixture of the desired diene **102** and by-product **103** were recovered from the reaction mixture as an inseperable 50:50 mixture in a combined yield of 56%. By-product **103** was believed to have formed *via* an HBr elimination process, as a result of the excess base employed in the olefination reaction. Therefore, the reaction was repeated with only 1.5 equivalents of the base added (**Table 16**, **entry 2**). The major product isolated from this attempted olefination procedure was in fact enone **104**, formed *via* HBr elimination from the parent enone **98**, and not diene **102** as anticipated. From the result obtained in these attempted olefination reactions, it was clear that the elimination process was in competition with the *in situ* ylide formation. Therefore, it was decided to pre-form the ylide before the addition of enone **98** (**Table 16**, **entry 3**).



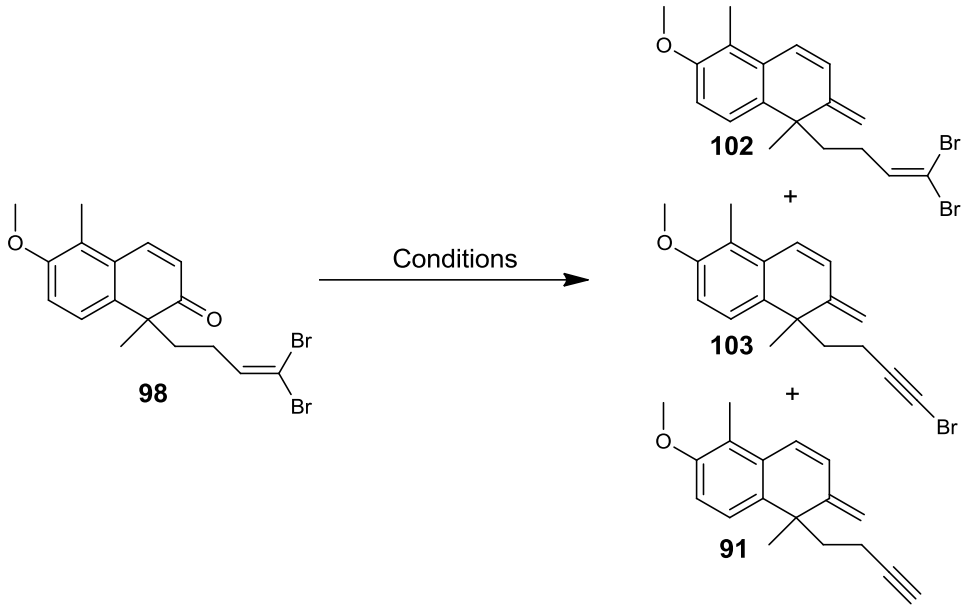
Entry	Conditions	Combined Yield	Product Distribution **103**:**104**:**102**:**98**
1	Ph_3PMeBr (3 eq), *t*-BuOK (2.5 eq), THF, 0°C, - r.t., 16 h	56%	1:0:1:0
2	Ph_3PMeBr (2 eq), *t*-BuOK (1.5 eq), THF, 0°C, - r.t., 16 h	60%	0:1:0:0
3	Ph_3PMeBr (2 eq), *t*-BuOK (1.5 eq), THF, 0°C, - r.t., 16 h	51%	0.16:0.43:0.18:0.23

Table 16

When the process summarised in **Table 16**, **entry 3** was attempted, a complex mixture of products was isolated from the reaction mixture. Compounds **103**, **104**, **102**, and **98**

were isolated in 8%, 22%, 9%, and 12% yields, respectively. Following this mixture of products being obtained and the presence of unreacted enone functionality within this mixture, the reaction was repeated with 3 equivalents of the ylide (**Table 17**, **entry 1**). In addition, in an effort to drive the reaction towards the formation of a single product, extra base was also added following the olefination process to transform any unreacted dibromo olefin into the bromo-alkyne. Surprisingly, a mixture of bromo-alkyne **103** and terminal-alkyne **91** was obtained in a 55% yield and a 1:3.65 mixture. However, with complete conversion of the enone functionality and an obvious pathway from the product mixture to the Pauson-Khand precursor **8**, efforts were made towards increasing the yield of the process. The initial attempt to enhance the efficiency of this interconversion was to reduce the reaction temperature. Consequently, the reaction was repeated at -78°C (**Table 17**, **entry 2**). Following the reaction at -78°C, a 46% yield was obtained of a 1:1 mixture of bromo-alkyne **103** and terminal alkyne **91**. So far, the products from these attempted olefination processes were being delivered in moderate yields at best. It seemed apparent that there were too many unwanted side-reactions taking place under uncontrolled conditions. It seems that the HBr elimination from the dibromo olefin is unavoidable as the ylide is sufficiently basic to mediate this process. However, the removal of the second bromide should be preventable be carefully selecting the base. As it has been shown that alkoxide-based reagents are capable of removing alkynyl halides,[143] an alternative base was investigated for the olefination. Previously it has been shown that the potassium counter-ion has a beneficial effect on the yield of the olefination reaction. Therefore, the base selected should posses such a potassium counter-ion. In addition, the base should also be non-nuceophilic and also be sufficiently strong to form the ylide. As a result, potassium hexamethyldisilazide was selected and the attempted olefination reaction was repeated (**Table 17**, **entry 3**). Satisfyingly, a 1:0.38 mixture of **102**:**103** was obtained in a 72% yield, with both products possessing the desired *exo*-cyclic alkene and with no loss of the alkynyl bromide. As a result of this encouraging result, the reaction was repeated but this time two equivalents of base were added following the olefination step in an attempt to transform the mixture into one single product (**Table 17**, **entry 4**). However, this

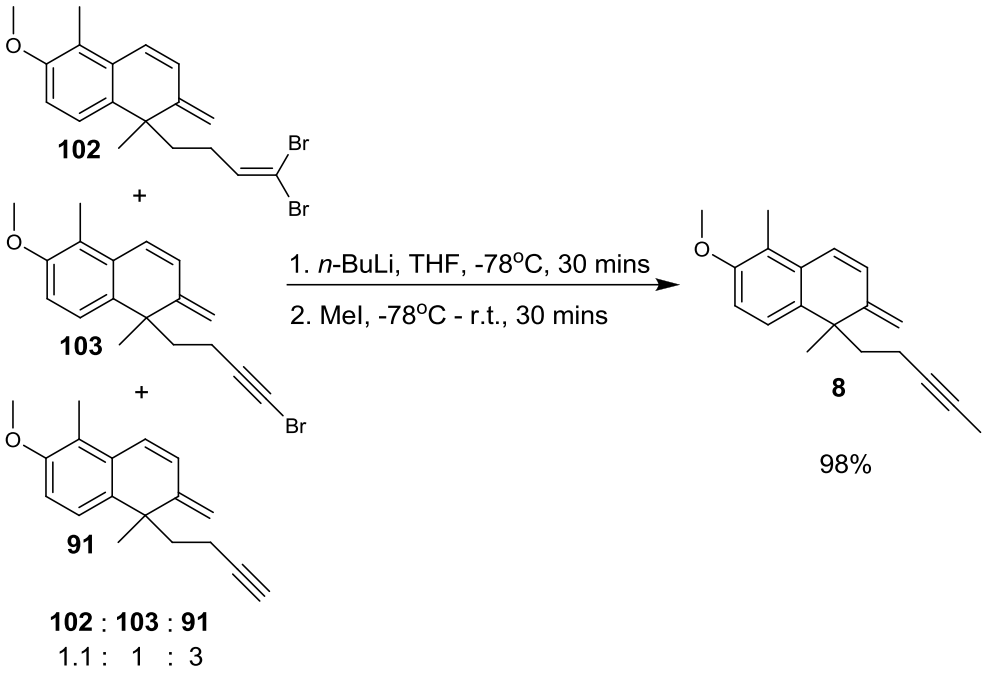
resulted in a mixture of products, which contained the terminal alkyne as the major product (36%), in a combined yield of 61%.



Entry	Conditions	Combined Yield	Product Distribution **102**:**103**:**91**
1	1. Ph_3PMeBr (3.125 eq), *t*-BuOK (3 eq), THF, 0°C, 1 h 2. *t*-BuOK (3 eq), 0°C, 30 mins	55%	0:1:3.65
2	1. Ph_3PMeBr (3.5 eq), *t*-BuOK (3 eq), THF, -78°C, 1 h 2. *t*-BuOK (3 eq), -78°C, 30 mins	46%	0:1:1
3	Ph_3PMeBr (4 eq), KHMDS (3.5 eq), THF, -78°C - r.t.	72%	2.6:1:0
4	1. Ph_3PMeBr (3.5 eq), KHMDS (4 eq), THF, -78°C, 1 h 2. KHMDS (2 eq), -78°C – r.t., 16 h	61%	1.1:1:3

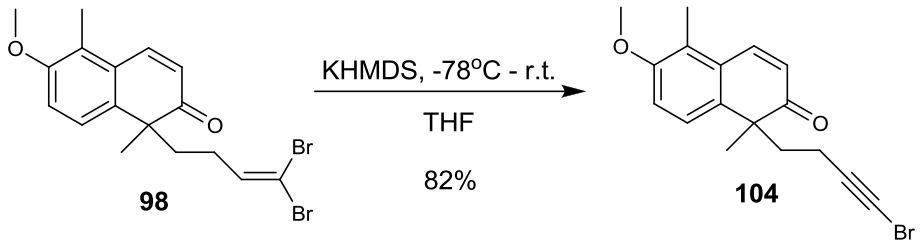
Table 17

Despite this result, the mixture obtained was treated with *n*-butyllithium and methyl iodide to deliver the desired Pauson-Khand precursor in an excellent 98% yield (**Scheme 122**).



Scheme 122

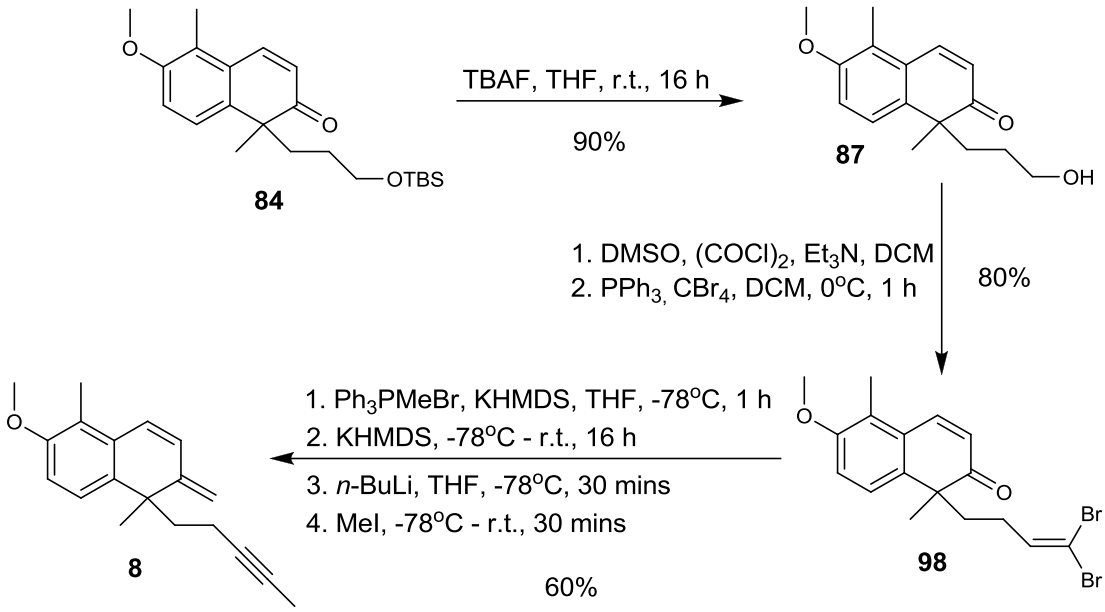
Due to the obvious compatibility of KHMDS with the starting material, it was decided to investigate the potential of this base in carrying out the HBr elimination from dibromide **98** in the presence of the enone functionality. As can be seen from **Scheme 123**, an 82% yield was obtained for this process.



Scheme 123

With effective conditions in hand to deliver bromo alkyne **104**, further work within this project could investigate the potential of transforming this intermediate into the Pauson-Khand precursor **8**. It could be envisaged that alkoxide-mediated removal of the halide would deliver the terminal alkyne, which could be compatible under olefination conditions to install the diene moiety. Alternatively, a non-nucleophilic base, such as sodium hydride, could be used to methylate the resulting terminal alkyne prior to the olefination procedure.

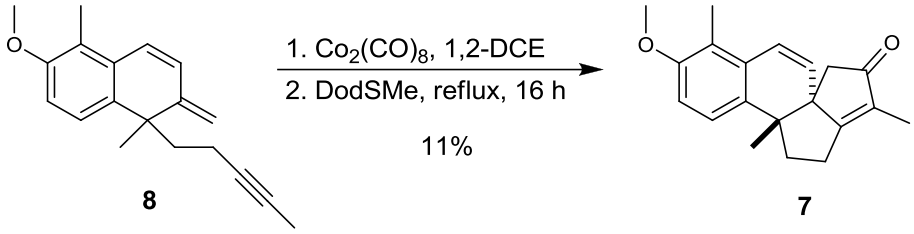
From the preparative studies conducted to this stage on various dibromoolefination, alkynylation, and methylenation strategies, the optimum approach is worth summarising. As shown in **Scheme 124**, enone **84** can be transformed into the desired Pauson-Khand precursor **8** in a 43% overall yield.



Scheme 124

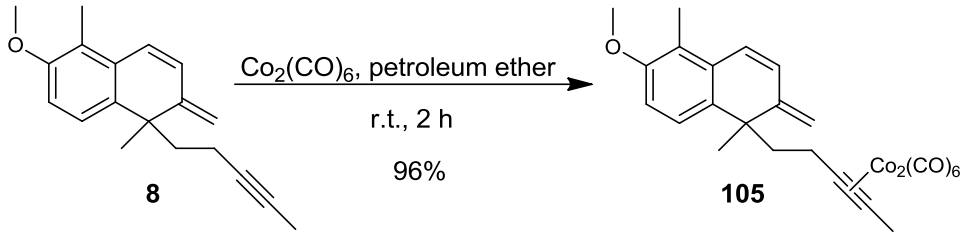
At this point in time, with several avenues investigated to access the Pauson-Khand precursor **8**, work towards the optimisation of the second of the key metal-mediated steps within this overall programme was initiated.

With sufficient amounts of the Pauson-Khand precursor **8** prepared, a thorough study on the second of the key metal-mediated cyclisations could be carried out. Within the preliminary studies from our laboratory and in a single unoptimised attempt, the key intramolecular Pauson-Khand reaction had been shown to deliver the desired product, albeit in a rather low yield (**Scheme 125**).[96] *In-situ* formation of the cobalt-alkyne complex followed by cyclisation under sulfide promoted Pauson-Khand conditions[93] delivered the tetracyclic product **7** in 11% yield. It had also been demonstrated that performing this cyclisation under *N*-oxide promoted conditions was unsuccessful and led to decomplexation of the cobalt-alkyne complex.



Scheme 125

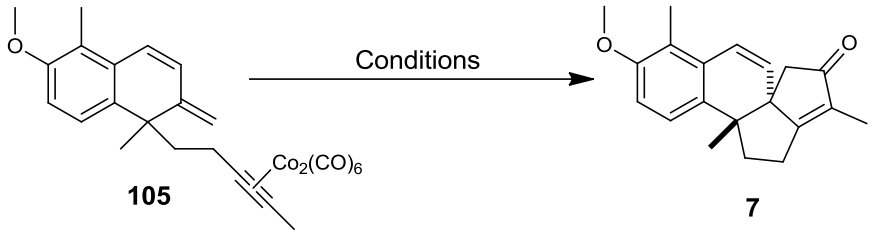
Due to the promising result obtained under sulfide promotion, further optimisation of this Pauson-Khand reaction was performed using this additive. Initially, it was decided to attempt this transformation using a two-step strategy, allowing purification of the cobalt-alkyne complex before subjecting it to cyclisation conditions. The cobalt-alkyne complex **105** was prepared by stirring the alkyne **8** with dicobalt octacarbonyl in petroleum ether at room temperature. The desired complex **105** was isolated in 96% yield following column chromatography (**Scheme 126**).



Scheme 126

With clean cobalt complex **105** in hand, the Pauson-Khand reaction was performed under sulfide-promoted conditions using dodecyl methyl sulfide in 1,2-DCE. The reaction mixture was refluxed for 48 hours resulting in a 36% isolated yield of the desired product **7** (**Table 18**, **entry 1**). It must be noted at this point that the dodecyl methyl sulfide used during this reaction was purchased from Sigma-Aldrich and was purified by distillation before use. Despite this successful cyclisation outcome, it was observed that cobalt-alkyne complex **105** remained, as shown by TLC analysis, following the 48 hours reaction period in refluxing 1,2-DCE. In an attempt to improve on the 36% yield obtained, the reaction was repeated and run until TLC analysis showed no remaining starting material. Based on this, a 45% yield of the tetracyclic product **7** was obtained after 5 days in refluxing solvent (**Table 18**, **entry 2**). Again, the dodecylmethyl sulfide used in this reaction was purchased from Sigma-Aldrich and was purified by distillation prior to use. In a further attempt to increase to isolated yield of the Pauson-Khand reaction, an alternative sulfide promoter was investigated. *n*-BuSMe, as developed by Sugihara,[91] was employed and the reaction was run for 5 days until no starting material remained. Unfortunately, a slightly reduced yield of 28% was obtained (**Table 18**, **entry 3**). With conditions in hand to deliver the Pauson-Khand product in a good 45% yield (**Table 18**, **entry 2**), it was decided that this was satisfactory in order to prepare material to work towards completion of the synthesis and future reactions would be performed under these developed conditions. However, on repeating this process it was noted that there was no cobalt complex **105** remaining in the reaction mixture after 48 hours. The reaction was stopped at this point and the product was isolated in only a

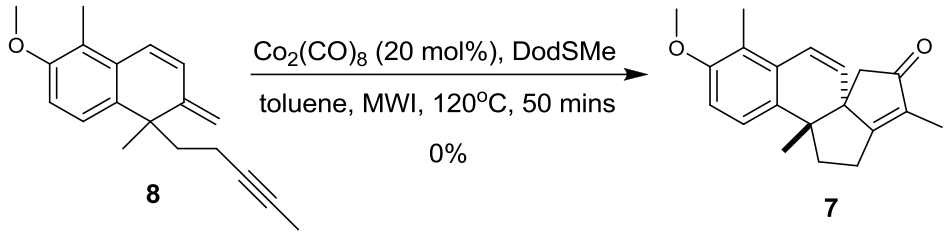
28% yield (**Table 18**, **entry 4**). Disappointingly, in the reaction discussed in **Table 18**, **entry 4**, no starting material was recovered from the reaction mixture. Following the reaction it was noted that the dodecylmethyl sulfide, which was purchased from Alfa Aesar and purified before use, had a pungent odour, which is not commonly associated with this reagent.[144] This result indicated that this Pauson-Khand process was particularly sensitive to the nature of the sulfide promoter and impurities within this reagent were causing degradation of the starting material or product. Therefore, the reaction was repeated with dodecylmethyl sulfide that had been freshly synthesised within our laboratory[145] (**Table 18**, **entry 5**). An excellent 61% yield was obtained for this key metal-mediated process after only 60 hours reaction time. In an attempt to enhance the efficiency of this reaction further, it was decided to attempt the cyclisation under microwave promotion, as this technique had proved to be very successful in the optimisation of the intramolecular Heck process. As shown in **Table 18**, **entry 6**, the cobalt complex **105** was heated to 90°C under microwave conditions in the presence of DodSMe for 10 minutes, however no conversion was observed and the complex was recovered. In an attempt to obtain some reactivity, the reaction was repeated under more forcing conditions (**Table 18**, **entry 7**). Following 10 minutes at 150°C, complete decomplexation of the starting material was observed.



Entry	Conditions	Yield
1	1,2-DCE, DodSMe (3.5 eq), reflux, 48 h	36%
2	1,2-DCE, DodSMe (3.5 eq), reflux, 120 h	45%
3	1,2-DCE, *n*-BuSMe (3.5 eq), reflux, 120 h	28%
4	1,2-DCE, DodSMe (3.5 eq), reflux, 48 h	28%
5	1,2-DCE, DodSMe (3.5 eq), reflux, 60 h	61%
6	1,2-DCE, DodSMe (3.5 eq), MWI, 90°C, 10 mins	0%
7	1,2-DCE, DodSMe (3.5 eq), MWI, 150°C, 10 mins	0%

Table 18

As with any transition-metal-mediated reaction, there is always a drive towards developing efficient reaction conditions that are catalytic in nature. In this regard, the reaction was repeated under catalytic Pauson-Khand conditions that were previously developed within our laboratory.[76] Enyne **8** was reacted with 20 mol% of dicobalt octacarbonyl in the presence of DodSMe as a promoter under microwave irradiation at 120°C. The reaction was performed in toluene as this was previously shown to be the most effective solvent for developing catalytic Pauson-Khand processes. The reaction mixture was heated for 50 minutes but none of the desired cyclopentenone **7** was obtained with only starting alkyne being recovered (**Scheme 127**).



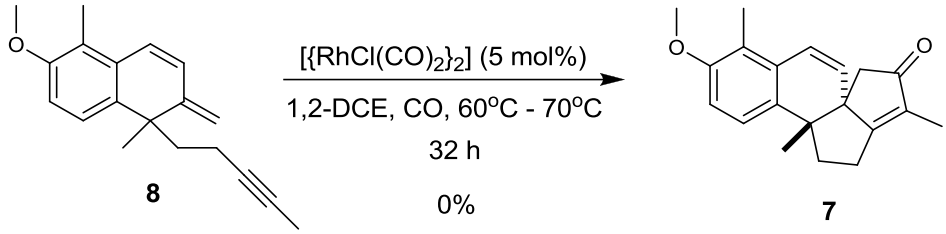
Scheme 127

Following this optimisation study on the intramolecular Pauson-Khand reaction of cobalt complex **105**, a very satisfying 61% yield of the desired product has been obtained. Notably, this cyclisation is considered to be particularly challenging due to: (i) the requirement to form two contiguous quaternary carbon centres, (ii) the use of a normally less reactive conjugated diene, and (iii) the internal alkyne substrate. During this study it has also been shown that the reaction process is more efficient under DodSMe promotion compared to *n*-BuSMe promotion. Interestingly, the reaction time was reduced from 120 hours to 60 hours by using freshly prepared sulfide promoter; the practical modification also increased the overall yield. Further efforts to enhance this process, either under catalytic conditions or under microwave promotion, did not result in any increased efficiency being obtained.

In a final attempt to improve on the isolated yield of the cyclisation reaction, an alternative transition-metal was investigated. In this regard, it been shown in the literature that rhodium-based systems are particularly effective for Pauson-Khand reactions where the olefinic part of the enyne is part of a conjugated diene system, as is the case in enyne **8**.[95,94]

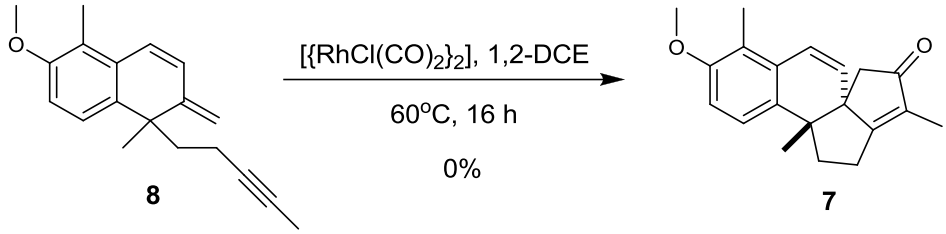
Initially, reaction conditions employing a catalytic amount of dichlorotetracarbonyldirhodium(I) were adopted (**Scheme 128**). The reaction was carried out in 1,2-DCE under an atmosphere of carbon monoxide The reaction mixture was heated to 60°C for 16 hours but TLC analysis showed only starting material to be

present. In an attempt to facilitate the desired annulation process, the reaction temperature was increased to 70°C and the mixture was stirred for a further 16 hours. At this point, TLC analysis showed multiple spots and none of the desired product was isolated.



Scheme 128

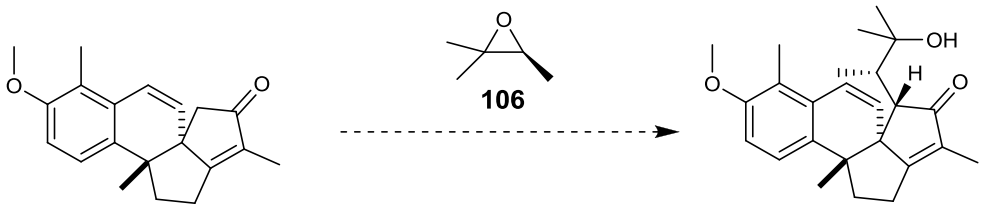
As a result of the poor result obtained under the catalytic rhodium conditions, a less challenging approach was adopted and the reaction was repeated with a stoichiometric amount of the rhodium dimer (**Scheme 129**). Complete degradation of the starting material was obtained after heating the reaction mixture in 1,2-DCE at 60°C for 16 hours.



Scheme 129

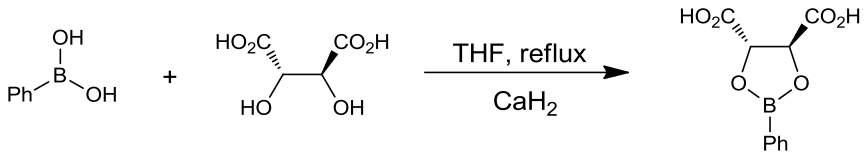
2.5 Towards the Total Synthesis of Agariblazeispirol C

Following the preparation of enone **7**, efforts towards the completion of the synthesis of agariblazeispirol C **1** were initiated. Due to the structure of the side-chain required on the α-position of the enone, it was envisaged that the most direct route to install such a motif would be *via* an epoxide (**Scheme 130**).



Scheme 130

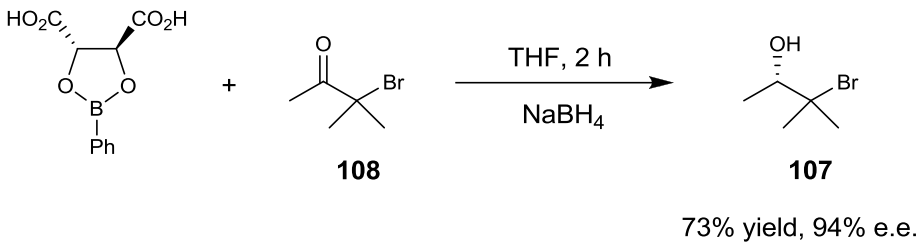
Although the current synthesis is racemic in nature at this point, any asymmetric synthesis of the natural product target would require the use of a chiral epoxide. Therefore, a route towards the required chiral epoxide **106** was developed. The first step towards the preparation of the chiral alcohol **107** was the synthesis of the chiral ligand required for the asymmetric reduction. This material was prepared from phenyl boronic acid and tartaric acid. The dehydration process, facilitated by calcium hydride, delivered the chiral ligand as a 0.2 M solution in THF (**Scheme 131**).[146,147]



Scheme 131

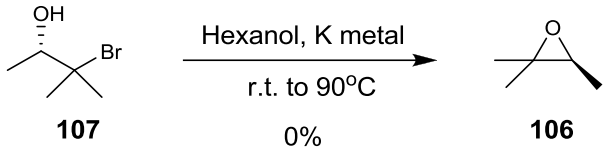
With the chiral ligand in hand, the asymmetric reduction of ketone **108** could be undertaken. Following the sodium borohydride-mediated conditions reported in the

literature, the desired chiral alcohol **107** was isolated in a 73% yield and with a 94% e.e. (**Scheme 132**).



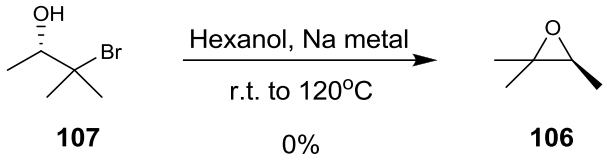
Scheme 132

The final step towards the preparation of the chiral epoxide **106** was attempted under the conditions reported in the literature (**Scheme 133**). Potassium metal was dissolved in dry hexanol to prepare an alcoholic solution of potassium hexoxide. The chiral alcohol **107** was then added to this mixture to form the desired epoxide **106**. As reported in the literature, isolation of the product was attempted *via* direct distillation of the reaction mixture, however none of the desired product was isolated.



Scheme 133

It was observed during the formation of the alkoxide base that the reaction mixture became very viscous and there was residual solid material remaining when the starting material was added. As a result, the process was repeated with sodium metal in an attempt to recover some of the desired epoxide **106** (**Scheme 134**).

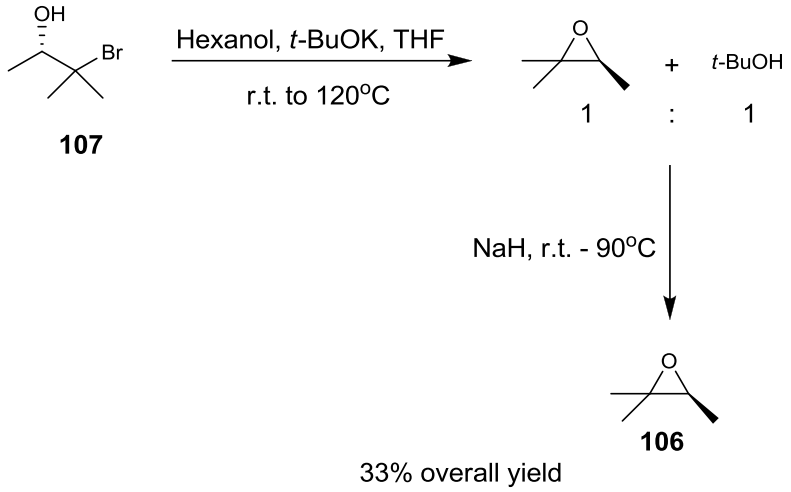


107 0% **106**

Scheme 134

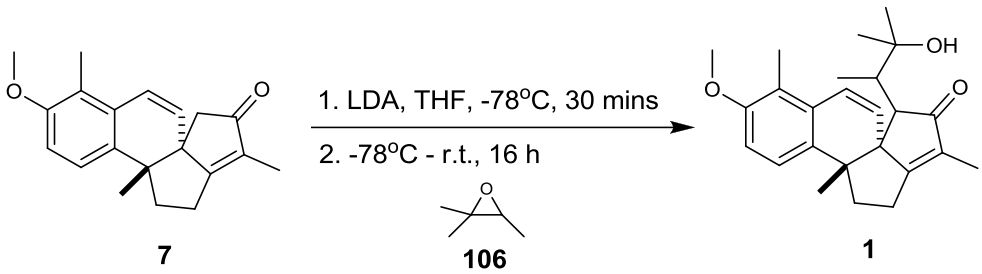
The procedure was carried out as summarised in **Scheme 134** but, again, no epoxide was isolated. In an attempt to distil some of the epoxide out of the reaction mixture the temperature was raised to 100°C for 30 minutes and then to 120°C for 1 hour, but isolation of the desired epoxide remained elusive.

Due to the highly viscous hexoxide mixtures, an alternative alkoxide base was investigated. As the original report had employed a potassium-based reagent, it was decided to attempt the reaction again using potassium *tert*-butoxide as the base. The reaction was once again performed in hexanol as a relatively high boiling solvent was required. In addition, a quantity of THF was also added to reduce the viscosity of the solution and also to aide azeotropic distillation of the product. Pleasingly, following distillation of the reaction mixture, the desired epoxide **106** was obtained as a 1:1 mixture with *tert*-butanol, a by-product formed during the reaction, in THF (**Scheme 135**). In order to remove the protic by-product, *tert*-butanol, from the desired epoxide **106**, the mixture was treated with excess sodium hydride. The epoxide was then separated from the non-volatile alkoxide salt *via* distillation, which delivered the epoxide, as a solution in THF, in a 33% overall yield.



Scheme 135

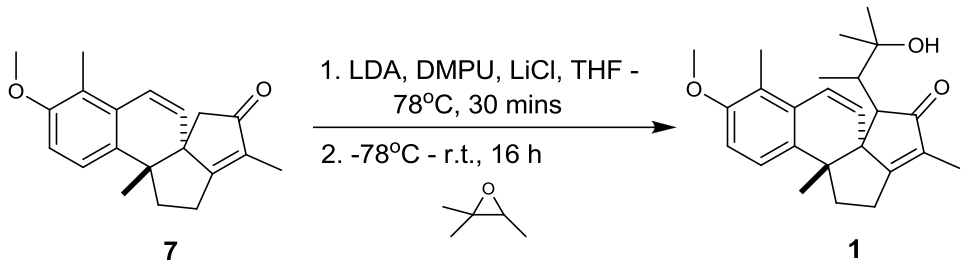
Due to the time spent in preparing the chiral epoxide **106**, it was decided to perform the initial investigation towards the completion of the total synthesis using the racemic form of this material, which is cheap and commercially available. In this regard, the enone was treated with LDA at -78°C followed by the addition of the racemic epoxide (**Scheme 136**). Frustratingly, TLC analysis showed only starting material to be present and none of the desired product **1** was isolated.



Scheme 136

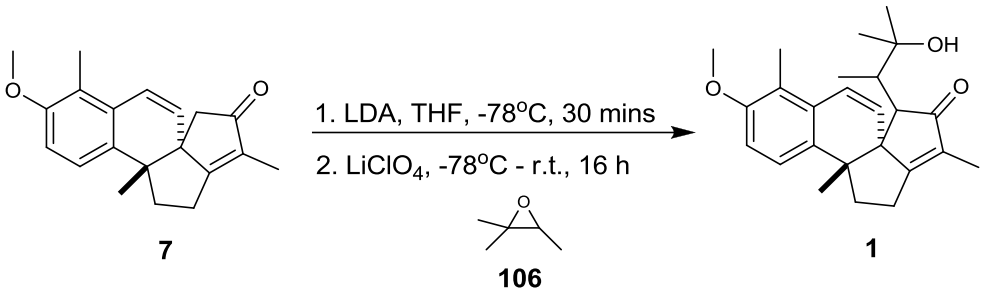
It was proposed that the observed lack of reactivity was a result of the aggregation state of the lithium enolate species. As a result, the reaction was repeated with the inclusion of

lithium chloride and DMPU as had proved to be successful earlier in the synthesis (**Scheme 60**). The reaction was carried out in the presence of these additives, however only starting material was isolated from the reaction mixture (**Scheme 137**).



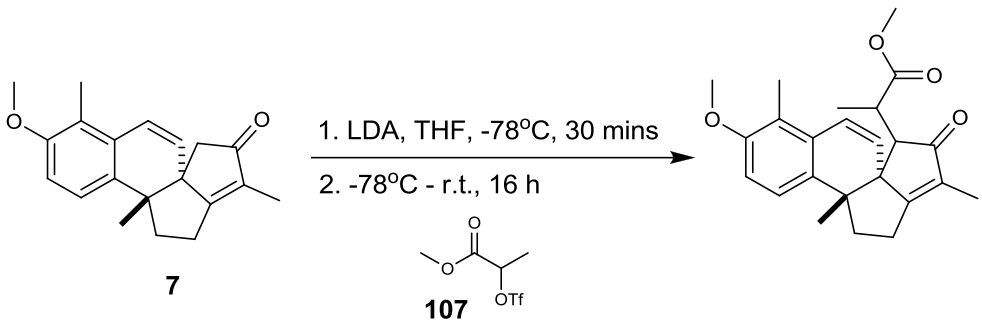
Scheme 137

Following the poor result achieved, further additives were considered in attempts to increase the reactivity of the electrophile. In this regard, strong Lewis acids such as $BF_3.OEt_2$ are commonly employed in epoxide chemistry to activate the epoxide towards nucleophilic attack. However, in unsymmetrical epoxides, such additives deliver the product *via* substitution at most heavily substituted side of the epoxide. In the case of epoxide **106** this would lead to the opposite regioisomer than is required within this total synthesis. However, it has been shown that mild Lewis acids, such as lithium perchlorate, can be used to activate the epoxide but not to alter the regioselectivity of the reaction.[148] Therefore, the reaction was repeated in the presence of anhydrous lithium perchlorate (**Scheme 138**). However, as observed previously, only starting material was recovered from this reaction.



Scheme 138

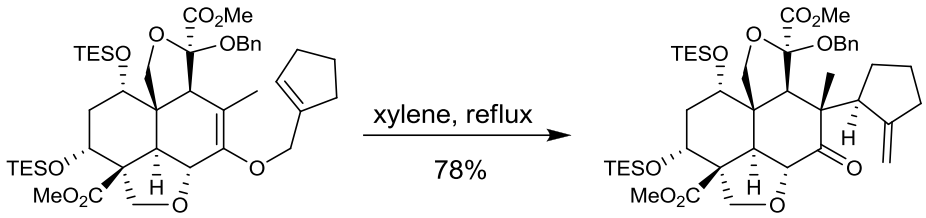
Due to the poor results obtained with the attempted epoxide incorporation, a more reactive electrophile was investigated. In this regard, it has been shown in the literature that triflate **107**, obtained from methyl lactate, is very reactive towards nucleophilic attack.[149] In addition, this derivative of a naturally occurring material can easily be obtained as a single isomer and, if successful, would install the chiral methyl group required in the asymmetric version of this synthesis. As can be seen from **Scheme 139**, the enone **7** was treated with LDA before being quenched with triflate **107**, however no conversion to the desired product was observed and the starting material was recovered.



Scheme 139

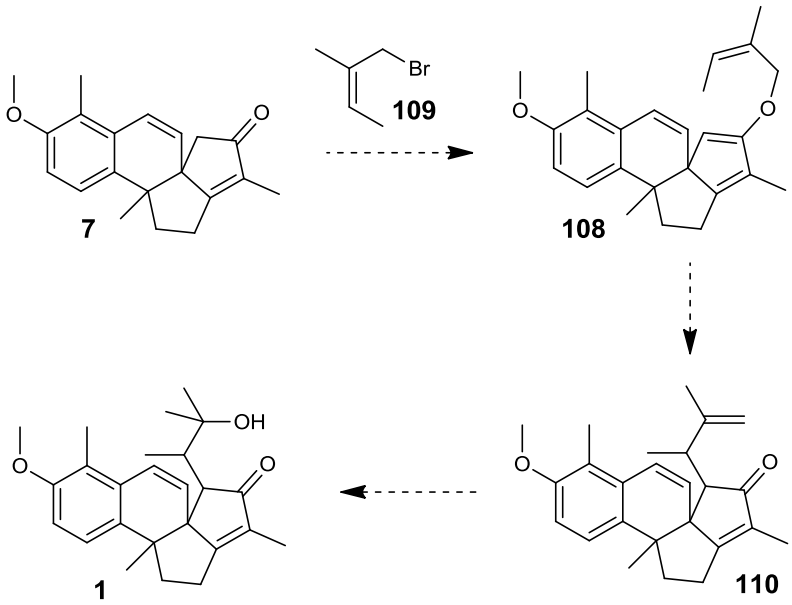
Due to the difficulties encountered in the previous set of reactions, attempting to trap the enolate at the α-position, an alternative approach was considered. In this regard, it was noted that there were similarities between the final steps of this synthesis with the

closing transformations within Ley's synthesis of Azadirachtin. In the case of Azadirachtin, a Claisen approach was used to functionalise a carbonyl group at the α-position.[150] The authors reported a range of Claisen transformations during the optimisation of the key step in the natural product synthesis. An example of such a transformation involving a tri-substituted allylic ether is shown in **Scheme 140**.



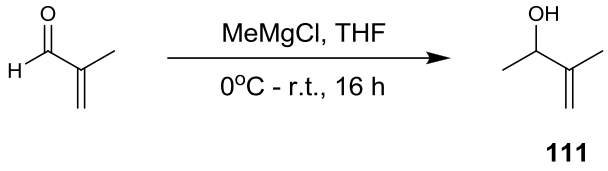
Scheme 140

With this in mind, it was proposed that a similar approach could be adopted within the current synthesis, as outlined in **Scheme 141**. The required allyl vinyl ether **108** could be accessed from enone **7** and allyl bromide **109**. Again, with an asymmetric variant in mind, it was decided that the *Z*-allyl bromide **109** would give the correct stereochemistry required for the pendent methyl group in the final product. Subsequently, a Claisen rearrangement of **108** would deliver olefin **110**, which, following acid-catalysed hydration, would lead to the desried target compound **1**.



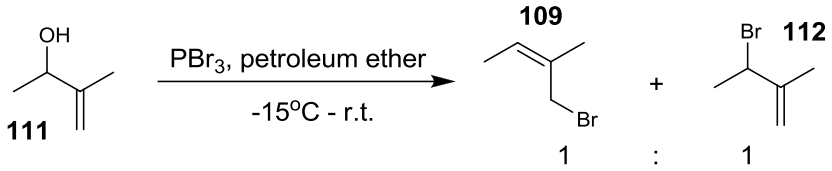
Scheme 141

In this regard, the allyl bromide material **109** required for the current synthesis was investigated. Preparation of this material has previously been reported in the literature in a *Z*-selective manner.[151] Firstly however, it was essential to prepare the starting allylic alcohol **111** in order to form compound **109**. Allylic alcohol **111** was prepared by the 1,2-addition of methylmagnesium chloride into methacrolein (**Scheme 142**). Due to the volatility of the alcohol, the crude product contained residual THF and was taken onto the next step without further purification.



Scheme 142

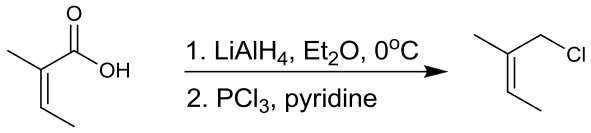
With allylic alcohol **111** in hand, preparation of the required allylic bromide **109** could be undertaken. The alcohol **111** was treated with phosphorous tribromide in petroleum ether (**Scheme 143**). Following the reaction, the product was purified by distillation.



Scheme 143

Following distillation, the product was obtained as a 1:1 mixture of the desired allylic bromide **109** and the undesired regioisomer **112**, formed *via* a direct S_N2 reaction. A literature search following this poor selectivity showed that the undesired isomer **112** can be obtained selectively under these conditions by switching the reaction solvent to diethyl ether. Consequently, it is thought that the residual THF present in the allylic alcohol **111** may have increased the polarity of the reaction media enough to allow the formation of this undesired product under these conditions.

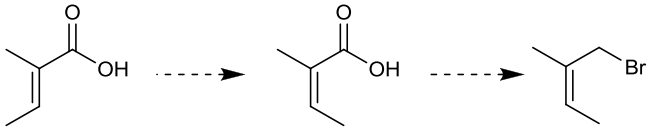
In this regard, an alternative approach towards this allylic bromide **109** was investigated. A relatively short synthesis of the chloro-analogue of this material was reported in the literature, starting from (*Z*)-2-methylbutenoic acid **113** (**Scheme 144**).[152]



113 35%

Scheme 144

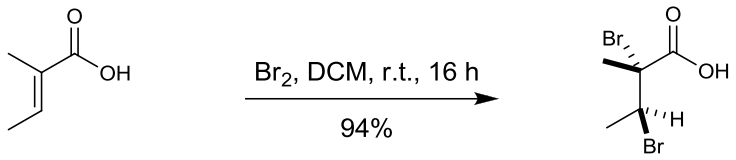
It was proposed that a similar approach could be adopted for the formation of the desired allylic bromide derivative **109** in the current synthesis. Firstly, angelic acid **113** would be prepared from the commercially available stereoisomer **114**, tiglic acid (**Scheme 145**). Following the preparation of angelic acid, reduction of the carboxylic acid, followed by a bromination step would deliver the desired bromide **109**.



114 **113** **109**

Scheme 145

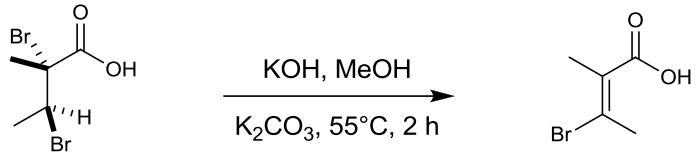
In an attempt to adopt this alternative approach, the first step towards the preparation of allylic bromide **109** was the synthesis of angelic acid **113**. However, the facile isomerisation of angelic acid ((*Z*)-2-methylbutenoic acid) to its more stable *E*-isomer (tiglic acid) **114** has been well documented.[153] Therefore, it is necessary to freshly prepare the desired acid **113** when required. The preparation of angelic acid **113** from the commercially available and thermodynamically more stable isomer, tiglic acid, **114** was carried out according to a literature procedure.[154] The first step towards this isomerisation was the bromination of the commercially available acid **114** (**Scheme 146**). The desired dibromide **115** was isolated in an excellent 94% yield.



114 **115**

Scheme 146

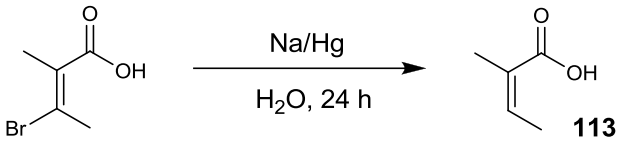
The next step in the synthesis was the potassium hydroxide mediated elimination of HBr to deliver unsaturated acid **116** (**Scheme 147**). The desired vinyl bromide **116** was recovered in 36% yield following recrystallisation.



115 **116**

Scheme 147

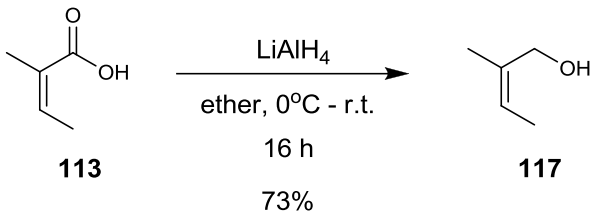
With the vinyl bromide prepared, the final step towards the preparation of (*Z*)-2-methylbutenoic acid (**113**) was removal of the bromide. This was carried out using a 6% sodium-mercury amalgam,[155] prepared *in situ*, under aqueous conditions (**Scheme 148**). The desired *Z*-isomer **113** was isolated in a 46% yield.



116 **113**

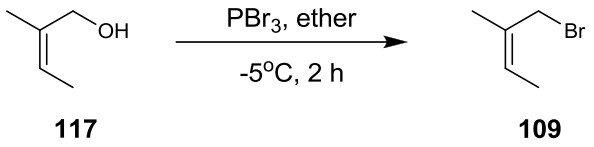
Scheme 148

With the isomerisation complete, the acid functionality was reduced with lithium aluminium hydride (**Scheme 149**).



Scheme 149

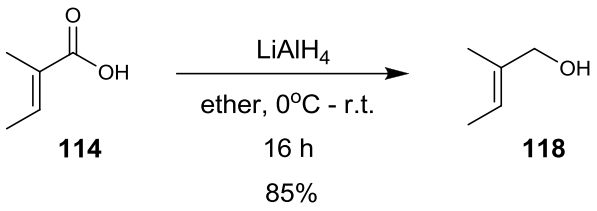
The final step towards the preparation of the required allylic bromide **109** was a bromination, mediated by phosphorous tribromide (**Scheme 170**). This reaction was performed as summarised in **Scheme 150**, with allylic alcohol **117** being treated with PBr_3 in diethyl ether at -5°C. Crude NMR following the reaction work-up showed that the desired product was present, however following the purification procedure reported in the literature,[151] only the ethereal solvent was recovered. The black residue remaining in the flask following distillation was analysed by NMR but it only showed mass degradation had occurred. In any further attempts towards this product, column chromatography would be investigated as a method of purification.



Scheme 150

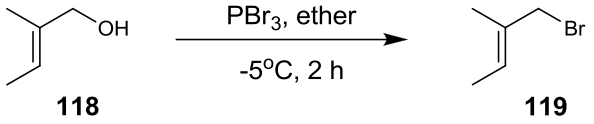
Due to the problems encountered with the previously described bromination step and the multi-step process required to prepare allylic alcohol **117**, it was decided to optimise the bromination conditions on the more accessible *E*-isomer. In this regard, the *E*-isomer

was prepared by a lithium aluminium hydride reduction of tiglic acid **114** (**Scheme 151**). This was achieved without any issue in a good 85% yield



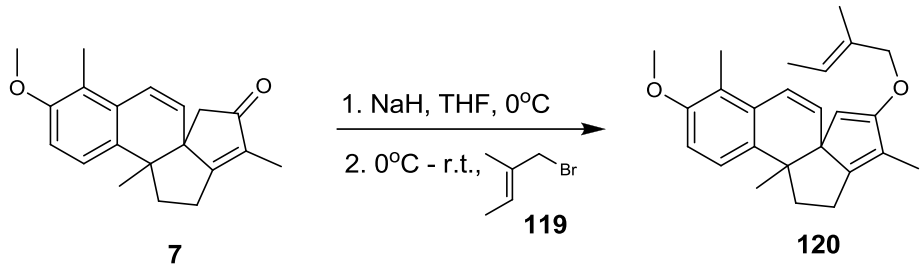
Scheme 151

Further optimisation of the bromination conditions could then be undertaken. Alcohol **118** was treated as before with phosphorus tribromide to form the allylic bromide **119** (**Scheme 152**). However, due to the difficulties associated with decomposition of the product during distillation previously, the crude product was washed 10 times with aqueous sodium bicarbonate solution in order to remove any residual phosphorous tribromide or acidic residues. The crude product was then distilled to deliver the product as a solution in diethyl ether.



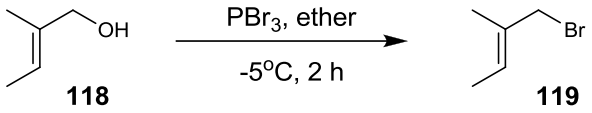
Scheme 152

With the *E*-isomer of the allylic bromide prepared, formation of the Claisen starting material was attempted. The fact that it was the *E*- and not the desired *Z*-isomer that was used was not an issue at this point as it would only become important in any asymmetric synthesis of the target natural product compound **1**. Under the conditions reported by Ley,[150] attempted formation of the allylic ether **120** was performed (**Scheme 153**).



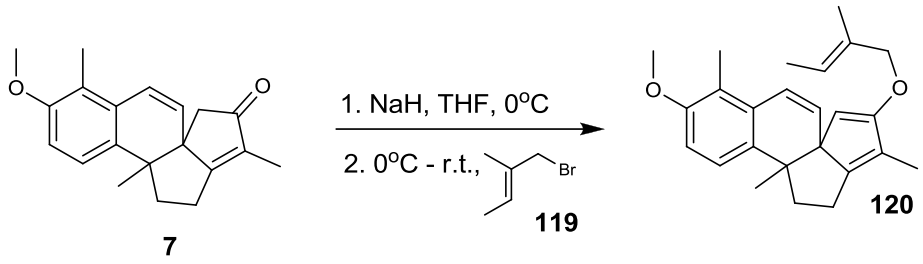
Scheme 153

Disappointingly, only starting material was obtained from this reaction. However, it was noted that a brown colour had appeared at the neck of the flask that the ethereal solution of allyl bromide **119** was stored in. It was believed that this was a result of impurites from the bromination process. Therefore, the bromination reaction was repeated and the crude product was purified by column chromatography using diethyl ether and light petroleum as the eluents (**Scheme 154**).



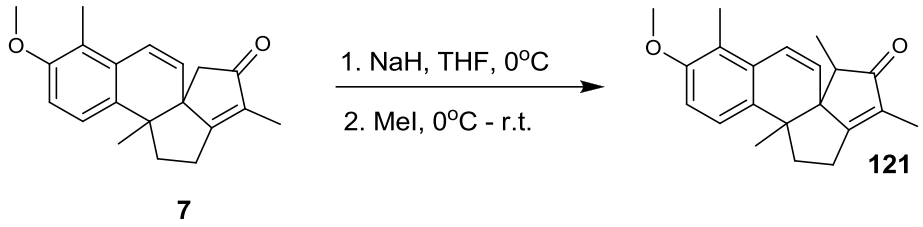
Scheme 154

The product **119** was obtained as a solution in diethyl ether and, on standing for one month, no colouration was observed within the storage flask. With the freshly prepared bromide **119** in hand, the attempted preparation of the Claisen starting material was repeated (**Scheme 155**). However, as before, none of the desired product was obtained.



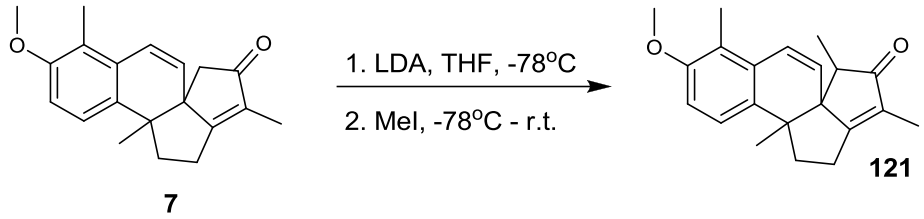
Scheme 155

With the poor results obtained so far, it was decided to attempt to alkylate the enone with a simpler electrophile. In this regard, the enone **7** was treated with sodium hydride and was quenched with methyl iodide (**Scheme 156**). However, as before, only starting material was obtained from the reaction mixture.



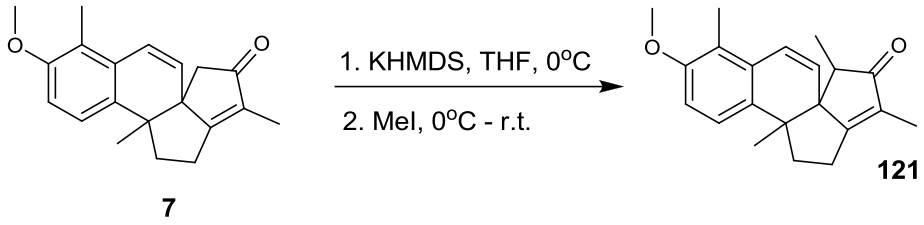
Scheme 156

In an attempt to mediate deprotonation and alkylation by alternative methods, the enone was then treated with LDA and quenched with methyl iodide (**Scheme 157**). Again, only the starting material was observed.



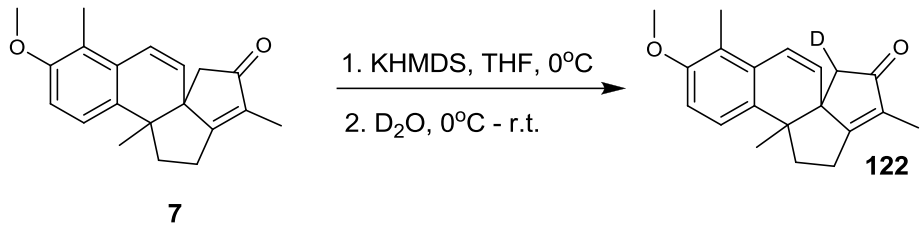
Scheme 157

Another attempt to obtain some reactivity from the enone towards electrophiles involved the use of a potassium base, KHMDS. Again, following the reaction summarised in **Scheme 158**, only starting material was obtained.



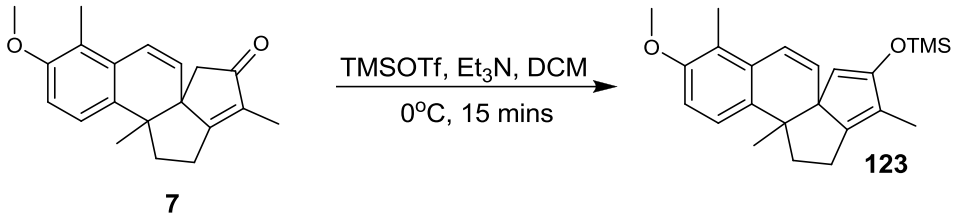
Scheme 158

As all the previous attempts to form an alkylated derivative of **7** had been unsuccessful, it was decided to quench the reaction mixture with D_2O to determine whether the enolate was actually being formed during the reaction. Following the process shown in **Scheme 178** using KHMDS as base, surprisingly, none of the deuterated material **122** was obtained (**Scheme 159**).



Scheme 159

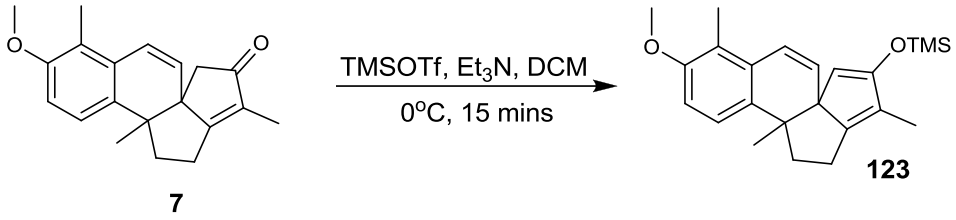
Under basic conditions it seemed apparent that the enolate was not actually being formed during the reaction or that adventitious water was present and the enolate was being quenched before the addition of the electrophile. An alternative approach towards this goal would be to prepare the enolate *in situ* from the requisite silyl enol ether. In order to successfully access the desired enol ether it was decided to adopt a different approach following to poor reactivity observed under basic conditions. Accordingly, the trimethlysilyl derivative **123** was prepared under standard Lewis acid promoted conditions (**Scheme 160**).



7 **123**

Scheme 160

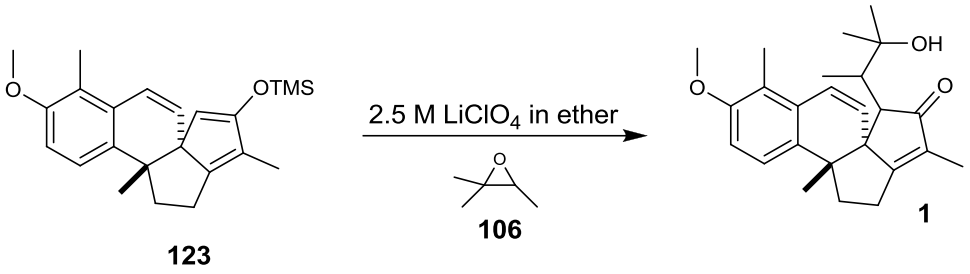
Crude NMR analysis showed that the desired product **123** had been formed and none of the starting enone **7** remained. The product was then purified by silica gel column chromatography, however, only hydrolysed material was recovered from the column. As a result, the enol ether formation was repeated and the crude product was taken on to the next synthetic step (**Scheme 161**).



7 **123**

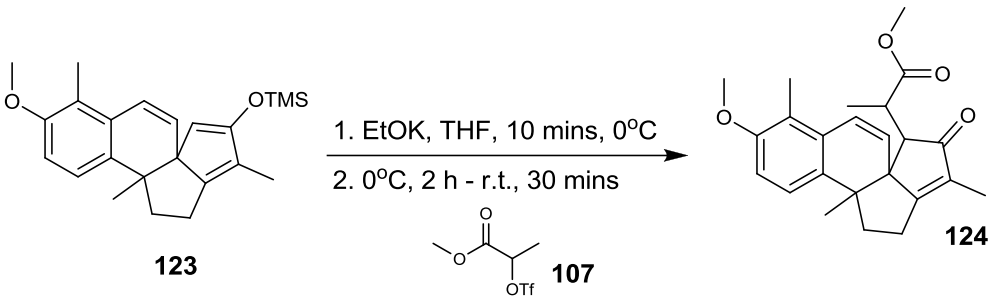
Scheme 161

The material obtained as described above was reacted with epoxide **106** under mild Lewis acidic conditions in an attempt to form the target compound **1** (**Scheme 162**). Unfortunately, under the reaction conditions, degradation of the starting material occurred and no product or starting material was recovered from the reaction mixture.



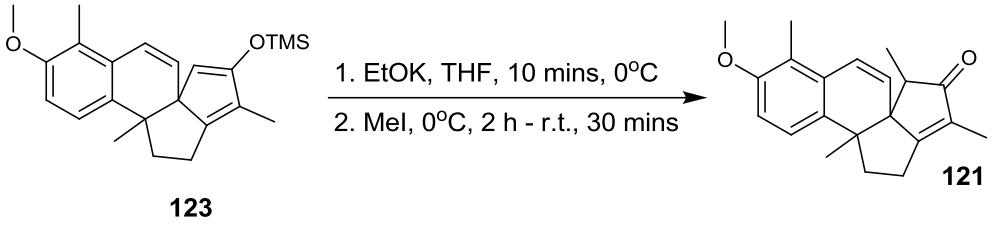
Scheme 162

Following this, using the enol ether **123** as a starting material it was decided to form the corresponding enolate before the addition of the electrophile. Following a literature procedure, the enol ether was treated with potassium ethoxide and TLC analysis showed there to be no remaining starting material after 10 minutes at 0°C. The freshly prepared triflate **107** was then introduced and after 2 hours at 0°C the reaction mixture was warmed to room temperature (**Scheme 163**). However, following an aqueous work-up, only the hydrolysed starting material was recovered.



Scheme 163

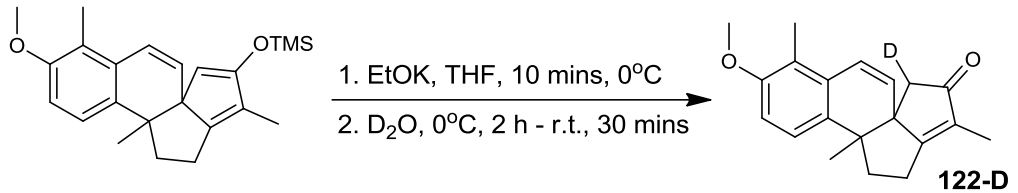
Again using silyl enol ether **123** and proceeding *via* the potassium enolate, quenching with methyl iodide was attempted. However, only enone **7** was recovered (**Scheme 164**).



123 **121**

Scheme 164

In a final attempt to further functionalise the tetracyclic system using this same approach, the reaction mixture was quenched with D_2O. Again, only hydrolysed starting material was obtained (**Scheme 165**)

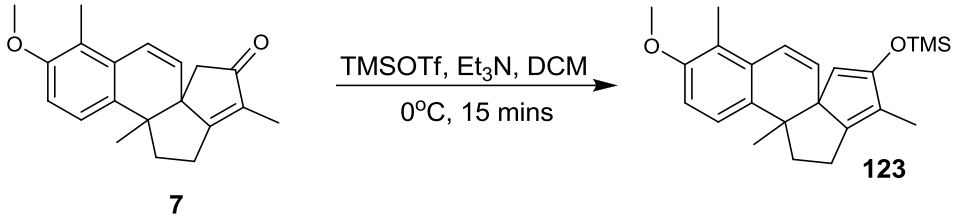


123 **122-D**

Scheme 165

Based on the reaction outcomes detailed above, it was believed that adventitious water or protic silicon by-products were present in the enol ether that was used in these attempted transformations. Consequently, such species could have quenched the enolate as soon as it was formed. In turn, there would be no enolate present when the electrophiles were added. It was deemed essential at this point that the enol ether had to be purified before it was used in any further such processes. In this regard, it was attempted to purify the enol ether using neutral alumina column chromatography,

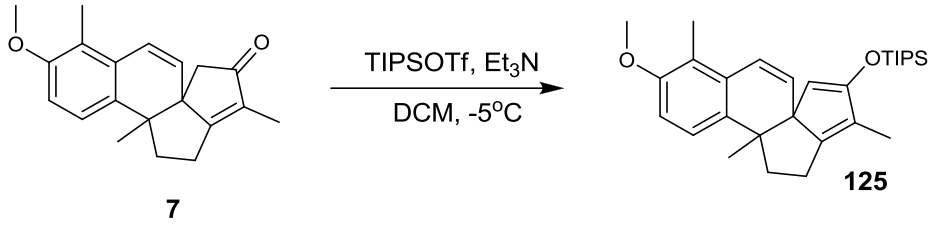
however only hydrolysed material was once again recovered following this purification attempt (**Scheme 166**).



7 **123**

Scheme 166

It was apparent that the trimethylsilyl enol ether formed here was very sensitive and hydrolysed readily during chromatography. It was therefore decided to form the more robust tri-*iso*-propylsilyl enol ether and ascertain whether this species would survive the purification process (**Scheme 167**).

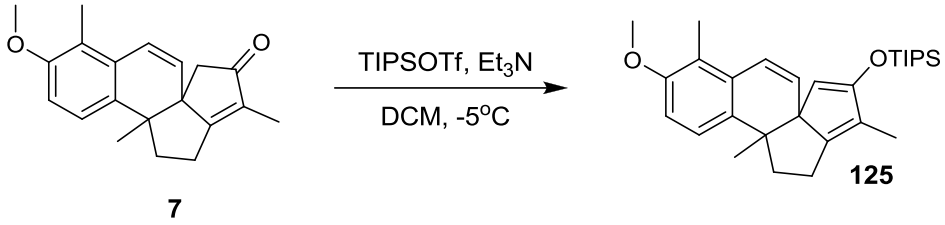


7 **125**

Scheme 167

The tri-*iso*-propylsilyl enol ether **125** was prepared in a similar fashion to the trimethylsilyl derivative **123**. NMR analysis of the crude product showed there to be no remaining starting material. A rapid pass through a plug of silica gel resulted in only hydrolysed material **7** being recovered. Interestingly, the NMR sample was re-run after 4 days and there was still only enol ether present; no hydrolysis of the starting material had occurred. Based on this, in a further attempt to isolate the desired TIPS enol ether, through less acidic silica, the enol ether was re-synthesised and 3% triethylamine was

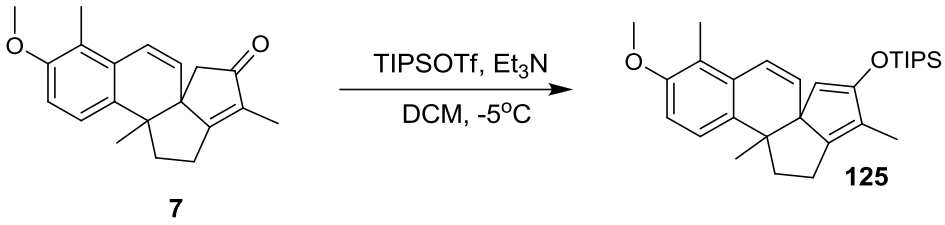
added to the eluent for the purification (**Scheme 168**). However, once again only starting material was recovered from the silica column.



7 **125**

Scheme 168

As a result of the poor outcome from the attempted purification through silica gel, the enol ether was synthesised again and purified through a pad of neutral alumina (**Scheme 169**). Unfortunately this again resulted in only hydrolysed material being recovered.



7 **125**

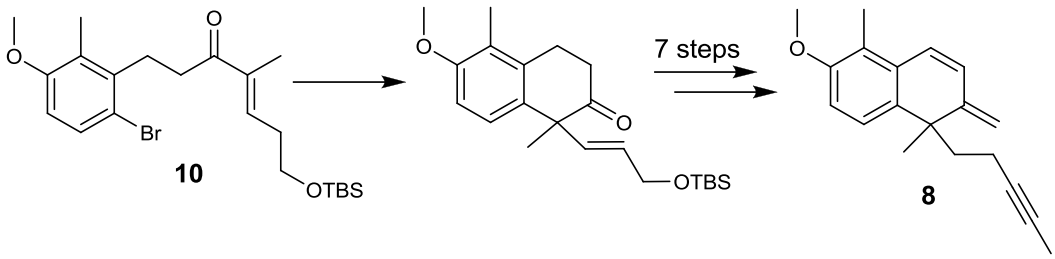
Scheme 169

Following extensive work into the further functionalisation of enone **7**, successful conditions have yet to be obtained. Various electrophiles have been employed in an attempt to alkylate the enolate of **7**, under a range of conditions, however, no alkylated product has been obtained. Consequently, an alternative approach, *via* the silyl enol ether, has also been investigated but, again, no alkylation products have been obtained. The work carried out towards the completion of this synthesis project has been hampered by the limited amounts of enone **7** available. In future, access to larger quantities of enone **7** could enable the preparation and purification of the requisite silyl

enol ether derivative, possibly *via* distillation. It is believed that with the use of purified material there would be a far greater chance of success under the previously attempted alkylation conditions.

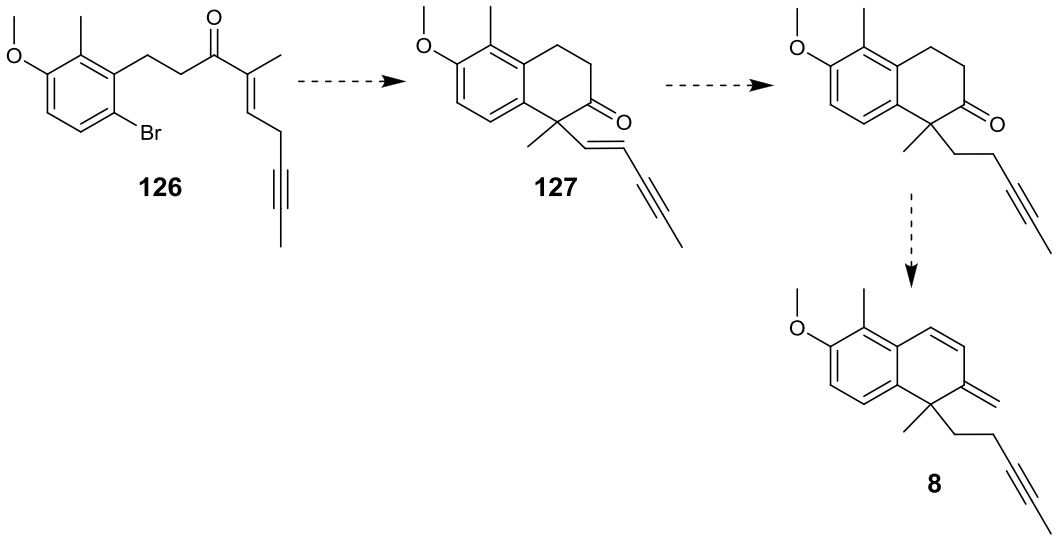
2.6 Reductive Heck Reaction Processes

Following the investigations into the preparation of the Pauson-Khand precursor **8**, it had become apparent that, although an effective synthetic route had now been established, the synthesis of this compound was rather linear in nature. A more economical approach would involve a more convergent route towards this target. In this regard, the key area of the synthesis that was targeted was between the Heck starting material **10** and the Pauson-Khand precursor **8** (**Scheme 170**).



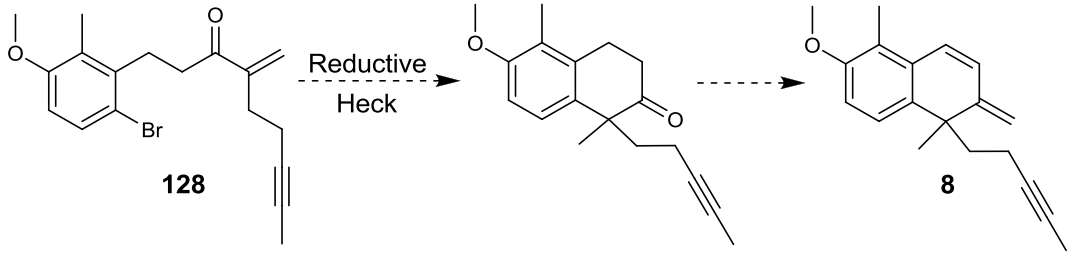
Scheme 170

The current synthesis involved an eight-step linear sequence between Heck precursor **10** and the desired product **8**. An alternative, and more convergent, approach towards target compound **8** could actually be attained by introducing the alkyne functionality into the Heck substrate side-chain. This would result in a new Heck starting material, compound **126** (**Scheme 171**). The palladium-mediated intramolecular cyclisation would then deliver compound **127**. However, reduction of the olefin in the presence of the alkyne functionality would potentially be very challenging and perhaps unproductive.



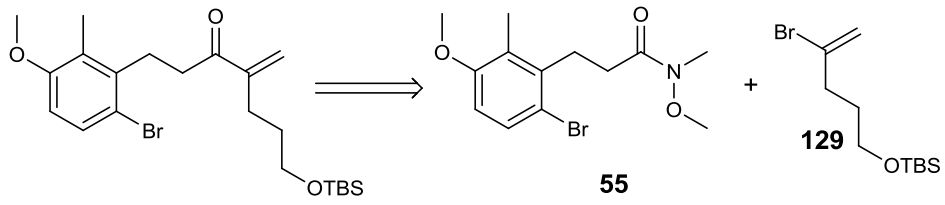
Scheme 171

To combat this problem, *reductive* Heck conditions could be employed in order to stop the olefin being introduced at all following this cyclisation. However, for this to be possible, the Heck starting material required to be engineered in a way that would prevent β-hydride elimination following the carbopalladation step in the Heck cycle. For this to be possible, the olefinic part of the enone would have to be transposed to a terminal position. This would require the synthesis of enone **128**. If the Heck reaction were successful, a further short two step sequence would deliver the Pauson-Khand precursor **8** (**Scheme 172**).



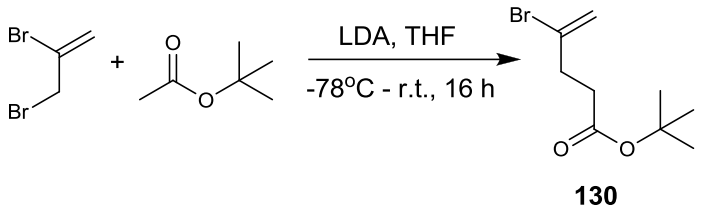
Scheme 172

In order to test this hypothesis, it was decided to simplify the Heck starting material and test the reductive Heck conditions before preparing the required vinyl bromide possessing the alkynyl unit. Therefore, the two starting materials required for this were Weinreb amide **55** (see **Scheme 54** for the preparation of this material) and vinyl bromide **129** (**Scheme 173**).



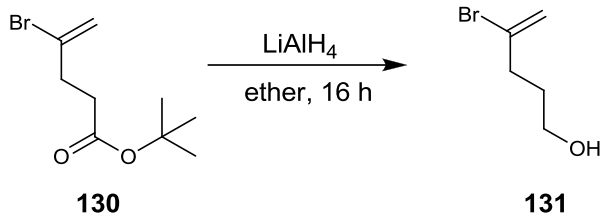
Scheme 173

With amide **55** in hand, the required vinyl bromide **129** was approached.[156] The first step towards the preparation of this material was the alkylation of *tert*-butyl acetate, as shown in **Scheme 174**. The alkylation was performed under the conditions reported in the literature and the crude product was taken through to the next step without further purification.



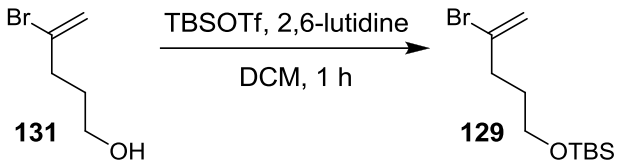
Scheme 174

The second step towards preparing vinyl bromide **129** was a lithium aluminium hydride mediated reduction of the ester functionality. The reduction of ester **130** was carried out under the reported conditions[156] and the crude product **131** was again taken on to the next step without purification (**Scheme 175**).



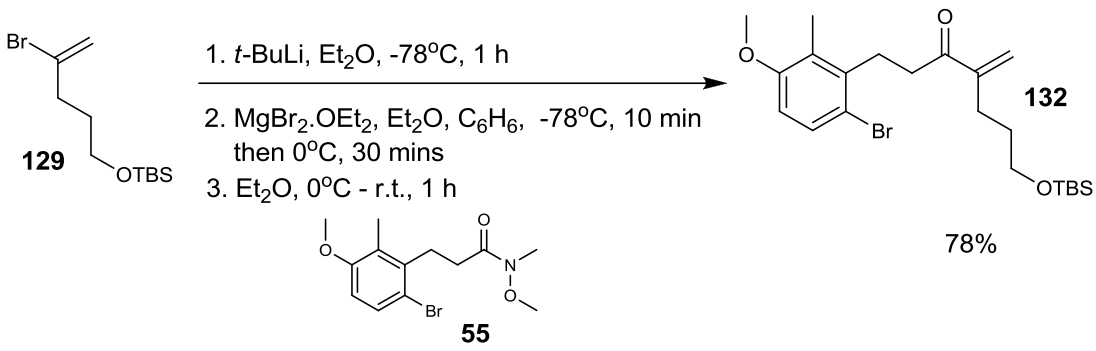
Scheme 175

The final step in the preparation of the required vinyl bromide was protection of the alcohol functionality. This was carried out under the same conditions that were used in **Scheme 76** and delivered the desired protected material **129** in a 47% yield over three steps from *tert*-butyl acetate (**Scheme 176**).



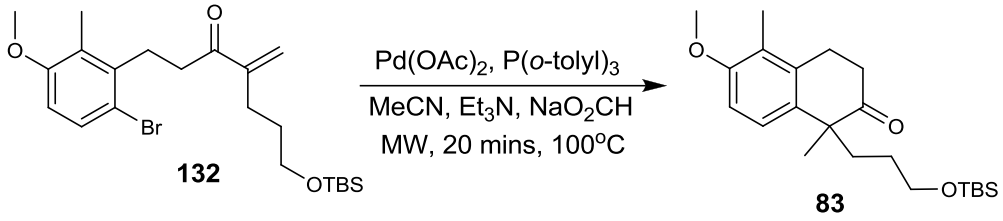
Scheme 176

Now, with both of the required compounds prepared, construction of the reductive Heck starting material **132** could be undertaken. This process was carried out under the conditions reported for the similar process shown in **Scheme 84**. Lithiation of the freshly prepared vinyl bromide **129**, followed by transmetallation to form the requisite Grignard reagent, and then delivery of this reagent into Weinreb amide **55** resulted in the desired product **132** in a respectable 78% yield (**Scheme 177**).



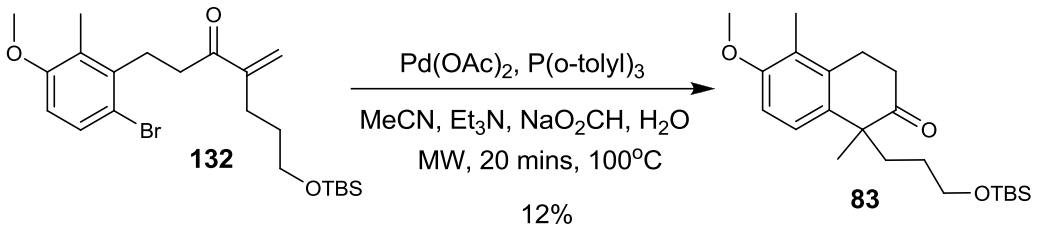
Scheme 177

Following conditions reported in the literature,[157] it was decided to integrate sodium formate into the conditions developed in **Scheme 88** for the successful intramolecular Heck reaction. As before, microwave technology was employed as the heating source but no conversion into the desired product was obtained and only the starting material was returned (**Scheme 178**).



Scheme 178

Following the poor result obtained, the literature was consulted once again. It has been shown that water is required in similar processes under sodium formate conditions in order to solubilise the salt.[157] Therefore, the reaction was repeated with the inclusion of water (**Scheme 179**).



Scheme 179

Pleasingly, conversion of the starting material into the desired product was observed. However, only a rather low 12% yield of the desired product was obtained. In addition to the 12% of the desired product **83** that was recovered, a 43% yield of the undesired product **133** was obtained. In a similar fashion to that observed in the earlier Heck reactions, this undesired material is a result of a 7-*endo*-cyclisation process. However, unlike the previous examples, the undesired product is the major product obtained from this reductive Heck reaction. It is postulated that the 7-*endo*-cyclisation pathway is more favourable here as a result of a much more accessible β-position of the enone functionality.

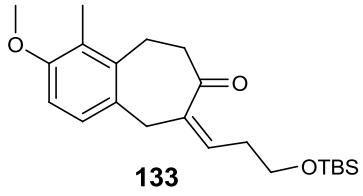


Figure 6

The preparation of enone **133** as the major product from the reductive Heck reaction was somewhat dissapointing, however, further research in this area could be focused towards optimisation of this palladium-catalysed process. In this regard, the accessability of the starting material in larger quantities is good and the potential advantages of this alternative route towards ketone **83** have been outlined. Therefore, further research into

this approach should be considered. Initially, modification of the enone moiety could be performed in an attempt to alter the electronics of the olefin and deliver the desried product as the major product. Either reduction or acetalisation of the carbonyl group would be expected to reduce the tendancy of the carbopalladation to favour the terminal carbon of the olefin and drive the cyclisation towards a 6-*exo*-pathway, leading to the desired six-membered ring product **83**.

3 **Conclusions**

Extensive efforts towards the total synthesis of agariblazeispirol C have been made. In relation to this, a variety of routes for the preparation of advanced intermediates within the synthesis have been formulated and optimised. The initial goal within this project was to establish the synthetic pathway towards the Pauson-Khand product. This has been achieved with very good levels of efficiency.

In more specific terms, the first major area of development was centred on the preparation of vinyl bromide **56**. The initial eight-step procedure, for the synthesis of this early intermediate, required significant effort and resource to allow preparation in large quantities. Ultimately, an extremely efficient, two-step, procedure was developed, allowing vinyl bromide **56** to be accessed readily in large quantities.

Following the development of an efficient approach towards compound **56**, significant work was carried out on the first of the key metal-mediated cyclisations. The initial conditions for the Heck reaction involved the use of 20 mol% of an expensive palladium catalyst and required at least 48 hours reaction time in order to return a suitable yield of the cyclised product. Following significant optimisation and, specifically, the incorporation of microwave technology enabled the development of extremely efficient reaction conditions, which allowed the desired cyclisation process to be performed reproducibly in only 20 minutes and with a low 5 mol% loading of the palladium catalyst.

With highly efficient conditions in hand for the Heck reaction, the next area of development was the synthetic pathway between the Heck product and the starting material for the second of the key metal-mediated cyclisations. There were four main areas within this pathway that required to be fully established. The introduction of the enone functionality to ketone **83**, the olefination of enone **84**, and the oxidation of alcohol **90** to sensitive aldehyde **94**, and, ultimately, the preparation of alkyne **91**, were

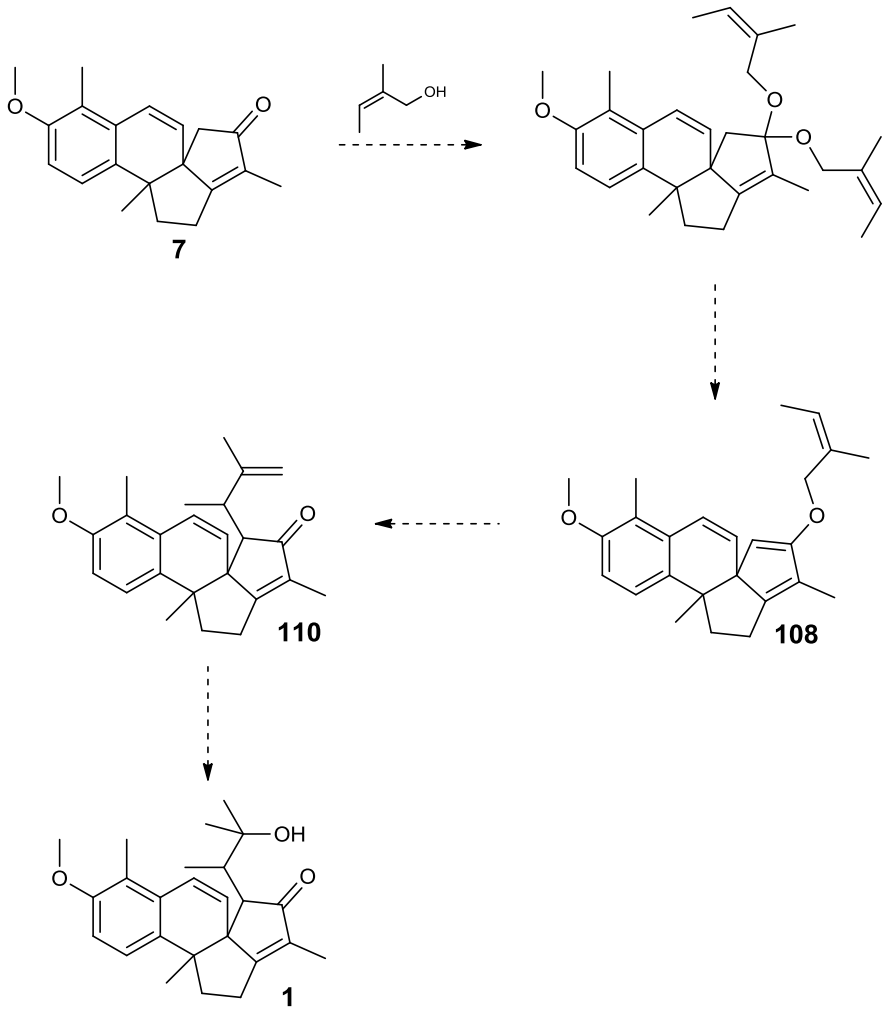
the key areas of development within this section of the project. Following the efforts recorded here, the enone functionality can now be installed effectively using Saegusa methodology. Olefination reaction conditions were attempted under a range of conditions and an efficient set of conditions have now been developed which utilise Wittig methodology. Following development work on the transformation of alcohol **90** into alkyne **91**, and despite this being achieveable, a truly effective pathway remains to be established and this is a key challenge for the preparation of larger quantities of advanced intermediates. Due to the problems associated with the required oxidation process, an alternative pathway was investigated. More specifically, installation of the sensitive diene was delayed until later in the synthesis in an attempt to alleviate the problems encountered at this point. However, following a significant body of work, difficulties were again encountered during the development of this pathway and it was not as efficient as had been initially envisaged.

After the (partially) successful realisation of the synthesis of the key enyne precursor, efforts were focused on the development of the second of the key metal-mediated cyclisations. Satisfyingly, following the development work detailed here, conditions were developed that allow the preparation of the Pauson-Khand product **7** in an excellent yield, especially considering the challenging nature of this particular transformation. The Pauson-Khand product **7** was synthesised in a 15% overall yield in 15 synthetic transformations from commercially available starting materials.

Finally, work towards the completion of the synthesis was carried out and a range of avenues were investigated. Disappointingly, in spite of the efforts made towards this goal, conditions that would enable access to the final compound remain elusive.

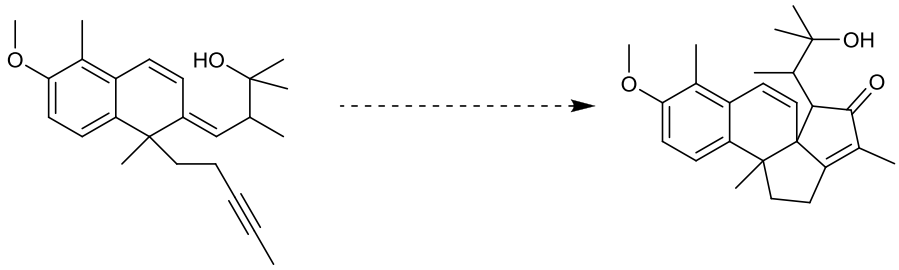
4 Future Work

The primary goal of subsequent work on this project will undoubtably be completion of the synthesis. In this regard, there are two approaches that could be adopted. Firstly, continuation along the current synthetic pathway with the aim of producing appreciable quantities of the Pauson-Khand product **7**, would enable the attempted alkylation reactions to be carried out on a larger scale than was possible during the current body of work. This may lessen the problems associated with, perhaps, adventitious water within the reaction manifolds. In addition, purification of silyl enol ether **123** may be possible *via* distillation, which would provide the opportunity to prepare the enolate *in situ*; this could be an advantage during the subsequent alkylation chemistry. An alternative approach towards the Claisen starting material **108** could also be employed in the attempt to install the oxygenated side-chain. In contrast to the enolate-type chemistry that has currently been followed, the desired enol-ether could be accessed from the requisite dially acetal of the parent enone **7**, as outlined in **Scheme 180**. It has been shown in the literature that this type of transformation can lead to an *in situ* Claisen rearrangement, which would deliver olefin **110**, the proposed precursor to the desired product **1**.[158]



Scheme 180

The second approach towards the completion of the synthesis would involve the incorporation of the requisite side-chain earlier in the synthesis, which would avoid the problematic alkylation reactions on the Pauson-Khand cyclopentenone product. This approach would mean a Pauson-Khand reaction on a trisubstiuted alkene would be required. Under the optimised reaction conditions this may well be possible. An outline of this approach is shown in **Scheme 181**.



Scheme 181

In addition the the completion of the synthesis of agariblazeispirol C in a racemic fashion, an asymmetric variant of the synthesis would be of major importance. The key step within such a synthesis would be an asymmetric intramolecular Heck reaction for which there are many literature precedents.[18]

5 Experimental

5.1 General Experimental

All reagents were obtained from commercial suppliers (Aldrich or Alfa Aesar) and used without further purification, unless otherwise stated. Purification was carried out according to standard laboratory methods.[i]

Tetrahydrofuran, diethyl ether, toluene, and benzene were dried by heating to reflux over sodium wire, using benzophenone ketyl as an indicator, then distilled under nitrogen.

Dichloromethane, 1,2-dichloroethane, acetonitrile, and DodSMe was dried by heating to reflux over calcium hydride then distilled under nitrogen.

Triphenylphosphine and tri-*o*-tolylphosphine were purified by recrystallisation from ethanol.

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV_{254}. This was analysed using a Mineralight UVGL-25 lamp or developed using vanillin solution.

Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh).

IR spectra were obtained on a Perkin Elmer Spectrum 1 machine.

^{1}H, ^{13}C, and ^{31}P spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz, 100 MHz, and 162 MHz, respectively. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions, unless otherwise specified.

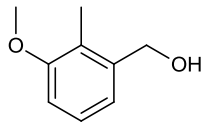
Reactions performed under microwave irradiation were carried out in a CEM Discover instrument using sealed glass tubes.

Melting points were obtained (uncorrected) on a Gallenkamp Griffin melting point apparatus.

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC Mass Spectrometry facility at the University of Wales, Swansea.

[i] D. D. Perrin, W. L. F. Amarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, **1998**.

Preparation of (3-methoxy-2-methylphenyl)methanol, 57.[159]



Scheme 47:

A stirred solution of 3-methoxy-2-methylbenzoic acid **11** (39.88 g, 240 mmol) in dry THF (500 ml) was cooled to 0°C. Lithium aluminium hydride (9.11 g, 240 mmol) was added portionwise to the THF solution to minimise the exotherm. Following the addition, the resultant slurry was allowed to warm to room temperature and stirred for 3 hours. Water (9.1 ml) was added to the reaction mixture and this was stirred for a further 10 minutes. After this time, 15% sodium hydroxide solution (9.1 ml) was added and the reaction mixture stirred for 10 minutes. A second portion of water (18.3 ml) was added followed by solid sodium bicarbonate (2 g). The resulting mixture was stirred for 20 minutes. The reaction mixture was then filtered through celite with ethyl acetate as the eluent. The filtrate was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (eluent: 50% ether in petroleum ether) to yield the desired product **57** (36.51 g, 100%) as a white solid.

Scheme 48:

A stirred solution of 3-methoxy-2-methylbenzoic acid **11** (9.97 g, 60 mmol) in dry THF (120 ml) was cooled to 0°C. Lithium aluminium hydride (2.28 g, 60 mmol) was added portionwise to the THF solution to minimise the exotherm. Following the addition, the resultant slurry was allowed to warm to room temperature and stirred for 3 hours. Water (2.28 ml) was added to the reaction mixture and this was stirred for a further 10 minutes. After this time, 15% sodium hydroxide solution (2.28 ml) was added and the reaction mixture stirred for 10 minutes. A second portion of water (6.84 ml) was added followed

by solid sodium bicarbonate (0.5 g). The resulting mixture was stirred for 20 minutes. The reaction mixture was then filtered through celite with ethyl acetate as the eluent. The filtrate was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography (eluent: 50% ether in petroleum ether) to yield the desired product **57** (4.03 g, 44%) as a white solid.

Scheme 49:

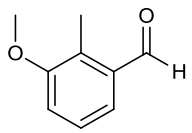
A stirred solution of 3-methoxy-2-methylbenzoic acid **11** (39.88 g, 240 mmol) in dry THF (500 ml) was cooled to 0^oC. Borane dimethylsulfide complex (25 ml, 264 mmol) was added cautiously to the stirred solution and stirring was continued for a further 30 minutes before the reaction mixture was allowed to warm to room temperature. The resulting solution was then warmed to reflux and stirred at this temperature for 16 hours. The reaction mixture was then allowed to cool to room temperature before being further cooled to 0^oC. Methanol (48 ml) was then added dropwise to quench the reaction mixture followed by dilution with diethyl ether (500 ml). The reaction mixture was washed with water followed by saturated sodium bicarbonate and finally brine. The organic phase was then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by recrystallisation (hexane) to yield the desired product **57** (36.36 g, 100%) as a white solid.

Melting point: 60-61^oC

FTIR (CH_2Cl_2): 2985, 3066, 3605 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.53 (m, 1H, OH), 2.24 (s, 3H, $ArCH_3$), 3.85 (s, 3H, OCH_3), 4.71 (d, J = 4.4 Hz, 2H, benzylic CH_2), 6.84 (d, J = 8.2 Hz, 1H, ArH), 7.00 (d, J = 7.5 Hz, 1H, ArH), 7.19 (t, J = 7.9 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 157.8, 140.0, 126.3, 124.8, 120.1, 110.0, 63.7, 55.6, 10.8 ppm.

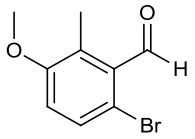
Preparation of 3-methoxy-2-methylbenzaldehyde, 58.[98]



Dimethylsulfoxide (32.9 ml, 552 mmol) was added slowly to a stirred solution of oxalyl chloride (26.4 ml, 312 mmol) in dry DCM (400 ml) at -78°C and the solution was stirred for 10 minutes. A dry DCM (200 ml) solution of (3-methoxy-2-methylphenyl)methanol **57** (36.51 g, 240 mmol) was added and the solution stirred for 15 minutes before the addition of triethylamine (167 ml, 1.2 mol). Following the addition, the solution was warmed to room temperature and was stirred at this temperature for 16 hours. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and then washed with brine. The organic phase was dried over Na_2SO_4, and concentrated *in vacuo* to yield product **58** (36 g, 100%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1698 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.54 (s, 3H, $ArCH_3$), 3.87 (s, 3H, OCH_3), 7.08 (d, J = 8.0 Hz, 1H, ArH), 7.30 (t, J = 7.9 Hz, 1H, ArH), 7.42 (dd, J = 7.7 and ^4J = 0.9 Hz, 1H, ArH), 10.32 (s, 1H, ArCHO). ^{13}C NMR δ(100 MHz, $CDCl_3$): 193.2, 158.6, 135.7, 130.2, 127.1, 123.5, 115.8, 56.4, 10.9 ppm.

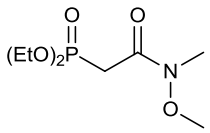
Preparation of 6-bromo-3-methoxy-2-methylbenzaldehyde, 59.[98]



Bromine (4.92 ml, 96.9 mmol) was added to a stirred solution of 3-methoxy-2-methylbenzaldehyde **58** (14.5 g, 96.9 mmol) in acetic acid (250 ml). The solution was stirred at room temperature for 18 hours prior to the addition of excess water. The resulting precipitate was filtered, washed with water, dried over Na_2SO_4, concentrated *in vacuo*, and recrystallised (hexane) to yield the desired product **59** (18.3 g, 82%) as an off-white solid.

Melting point: 69-71°C
FTIR (CH_2Cl_2): 1698, 3053 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.44 (s, 3H, $ArCH_3$), 3.86 (s, 3H, OCH_3), 6.89 (d, J = 8.8 Hz, 1H, ArH), 7.46 (d, J = 8.8 Hz, 1H, ArH), 10.47 (s, 1H, ArCHO). ^{13}C NMR δ(100 MHz, $CDCl_3$): 194.9, 157.6, 132.9, 131.3, 131.1, 117.1, 115.4, 56.0, 12.0 ppm.

Preparation of diethyl (*N*-methoxy-*N*-methylcarbamoyl)methylphosphonate, 60.[101]

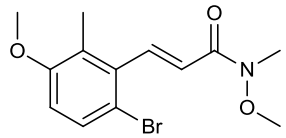


Triethylamine (55.75 ml, 395 mmol) was added to a stirred mixture of *N*-methoxymethylamine hydrochloride (19.5 g, 200 mmol) in dry DCM (500 ml) at 0°C. Chloroacetyl chloride (16 ml, 200 mmol) was added dropwise to the resulting solution, which was then warmed to room temperature and stirred for 1 hour. The reaction

mixture was quenched with saturated sodium bicarbonate solution. The organics were separated, washed with 1 M HCl solution followed by brine, dried over Na_2SO_4, and concentrated *in vacuo*. To the resulting oil was added triethyl phosphite (24 ml, 140 mmol) and the mixture was stirred at 80°C for 24 hours. The solution was allowed to cool to room temperature before being concentrated *in vacuo* to remove any unreacted triethyl phosphite. The crude product was purified by bulb-to-bulb distillation (150°C (oven temp.)/0.03 mmHg) to yield the desired product **60** (26.79 g, 80%) as a colourless liquid.

FTIR (CH_2Cl_2): 1662 cm^{-1}.
^{1}H NMR δ(400 MHz, $CDCl_3$):1.35 (t, J = 7.0 Hz, 6H, alkyl CH_3), 3.14-3.24 (m, 5H, NCH_3 and PCH_2), 3.78 (s, 3H, OCH_3), 4.06-4.24 (m, 4H, OCH_2). ^{13}C NMR δ(100 MHz, $CDCl_3$): 166.1, 62.5 (d, $^2J_{C\text{-}P}$ = 6.1 Hz), 61.7, 32.1, 31.4 (d, $^1J_{C\text{-}P}$ = 138.4 Hz), 16.3 (d, $^3J_{C\text{-}P}$ = 6.1 Hz). ^{31}P NMR δ(162 MHz, $CDCl_3$): 21.1 ppm.

Preparation of (*E*)-3-(6-bromo-3-methoxy-2-methylphenyl)-*N*-methoxy-*N*-methylacrylamide, 61.[96]

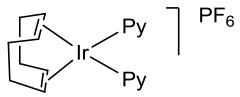


A stirred solution of phosphonate **60** (18.4 g, 77 mmol) in dry THF (300 ml) was cooled to 0°C before the cautious addition of *n*-BuLi (1.6 M, 52.5 ml, 84 mmol). The resulting solution was stirred for 10 minutes. A dry THF (200 ml) solution of aldehyde **59** (17.16 g, 70 mmol) was then added slowly to the reaction mixture which was subsequently warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The organic phase was

washed with water, and then with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 30% ether in petroleum ether) to yield the desired product **61** (21.55 g, 98%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1627, 1658 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.25 (s, 3H, $ArCH_3$), 3.34 (s, 3H, NCH_3), 3.74 (s, 3H, $NOCH_3$), 3.83 (s, 3H, $ArOCH_3$), 6.69-6.73 (m, 2H, ArH and olefinic CH), 7.41 (d, J = 8.8 Hz, 1H, ArH), 7.75 (d, J = 16.1 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 166.5, 157.3, 142.2, 137.0, 130.6, 127.5, 123.9, 114.2, 111.5, 62.3, 56.0, 32.8, 14.2 ppm.

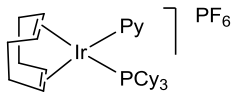
Preparation of (η^4-1,5-cyclooctadiene)*bis*(pyridine)iridium(I) hexafluorophosphate, 64.[102]



The η^4-cycloocta-1,5-dieneiridium(I) chloride dimer **63** (3.0 g, 4.47 mmol) and potassium hexafluorophosphate (2.47 g, 13.41 mmol) were added to a stirred solution of pyridine (5 ml, 62 mmol) in, a previously degassed, acetone/water (50:50, 150 ml) solution. The pale yellow solution was stirred at room temperature for 48 hours. The resulting bright yellow slurry was concentrated under high vacuum to remove the acetone. The yellow precipitate was filtered, washed with degassed water, and dried under vacuum in an oven at 40°C overnight to yield the desired product **64** (5.13 g, 95%) as a yellow solid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.81-1.87 (m, 4H, COD CH_2), 2.48-2.51 (m, 4H, COD CH_2), 3.85 (d, *J* = 2.4 Hz, 4H, olefinic H), 7.49 (t, *J* = 7.2 Hz, 4H, ArH), 7.75 (t, *J* = 7.7 Hz, 2H, ArH), 8.72 (d, *J* = 5.0 Hz, 4H, ArH).

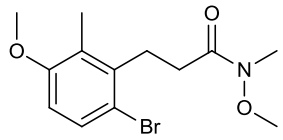
Preparation of Crabtree's Catalyst, 62.[102]



To a stirred slurry of iridium complex **64** (5.126 g, 8.49 mmol) in degassed methanol (100 ml) was added tricyclohexylphosphine (2.86 g, 10.2 mmol) resulting in an immediate colour change from yellow to orange. The orange slurry was stirred at room temperature for 1 hour. The volume of methanol was reduced to ~30 ml *in vacuo* followed by the addition of diethyl ether (50 ml). The precipitate was filtered, washed with diethyl ether, and dried under vacuum in an oven at 40°C overnight to yield the desired product **62** (6.802 g, 99.5%) as an orange powder.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.01-1.92 (m, 37H, CyCH and COD CH_2), 2.31-2.39 (m, 4H, COD CH_2), 4.02 (d, ^2J = 28.8 Hz, 4H, olefinic CH), 7.66 (t, *J* = 7.1 Hz, 2H, ArH), 7.90 (t, *J* = 7.7 Hz, 1H, ArH), 8.78 (d, *J* = 5.1 Hz, 2H, ArH).

Preparation of 3-(6-bromo-3-methoxy-2-methylphenyl)-*N*-methoxy-*N*-methylpropanamide, 55.[96]



General procedure:

Crabtree's catalyst **62** was added to a stirred solution of enamide **61** in dry DCM. The resulting solution was cooled to -78°C, the vessel evacuated and back-filled with hydrogen *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. This process was repeated three times. Upon the final refill the mixture was allowed to warm to room temperature and stirred for the allotted reaction time. The reaction mixture was concentrated *in vacuo* and the crude product purified by column chromatography (eluent: petroleum ether to 50% ether in petroleum ether) to yield the desired product **55** as a pale yellow oil.

Following the **General procedure**, data are reported as (a) amount of Crabtree's catalyst **61**, (b) amount of enamide **60**, (c) amount of DCM, (d) reaction time, and (e) product yield.

Scheme 54

(a) 1.288 g, 1.59 mmol (b) 5.0 g, 15.9 mmol, (c) 50 ml, (d) 16 h, and (e) 4.72 g, 94%.

Table 7, *entry 1*

(a) 1.2 g, 1.5 mmol, (b) 6.28 g, 20 mmol, (c) 63 ml, (d) 16 h, and (e) 6.24 g, 99%.

Table 7, *entry 2*

(a) 3.465 g, 4.3 mmol, (b) 18.0 g, 57.4 mmol, (c) 180 ml, (d) 8 h, and (e) 16.09 g, 89%.

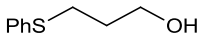
Table 7, *entry 3*

(a) 2.859 g, 3.6 mmol, (b) 27.94 g, 88.8 mmol, (c) 280 ml, (d) 24 h, and (e) 24.75 g, 88%.

FTIR (CH_2Cl_2): 1657 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 2.26 (s, 3H, $ArCH_3$), 2.63 (t, J = 8.4 Hz, 2H, alkyl CH_2), 3.12-3.16 (m, 2H, alkyl CH_2), 3.22 (s, 3H, NCH_3), 3.67 (s, 3H, $NOCH_3$), 3.82 (s, 3H, $ArOCH_3$), 6.62 (d, J = 8.8 Hz, 1H, ArH), 7.36 (d, J = 8.7 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 173.5, 157.1, 139.5, 130.1, 127.0, 115.9, 109.9, 61.3, 55.7, 32.2, 30.9, 28.5, 12.3 ppm.

Preparation of 3-(phenylthio)propan-1-ol, 66.[103]

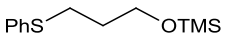


Sodium metal (4.968 g, 216 mmol) was added portionwise to ethanol (400 ml) with stirring. Once the metal had dissolved, thiophenol (22.2 ml, 216 mmol) was added to the solution and this mixture was stirred for 30 minutes. 3-Chloropropanol (20.4 g, 216 mmol) was added to the solution, the reaction vessel was fitted with a condenser, and heated to 80°C for 16 hours. On cooling, the reaction mixture was quenched with saturated ammonium chloride and extracted with DCM. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to yield the product **66** (35.73 g, 98%) as a colourless oil.

FTIR (CH_2Cl_2): 1618 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.91 (quintet, J = 6.5 Hz, 2H, alkyl CH_2), 3.06 (t, J = 7.1 Hz, 2H, SCH_2), 3.78 (t, J = 6.1 Hz, OCH_2), 7.20 (t, J = 7.3 Hz, 1H, ArH), 7.31 (t, J = 6.9 Hz, 2H, ArH), 7.37 (d, J = 7.3 Hz, 2H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 136.2, 129.2, 128.9, 126.0, 61.5, 31.7, 30.3 ppm.

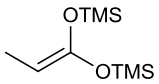
Preparation of (3-(trimethylsiloxy)propyl)(phenyl)sulfide 67.[103]



Triethylamine (65 ml, 466 mmol) was added to a stirred solution of alcohol **66** (35.73 g, 212 mmol) in dry THF (500 ml) at 0°C. The solution was stirred at this temperature for 30 minutes followed by the cautious addition of TMSCl (35.1 ml, 233 mmol). The resulting slurry was warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated ammonium chloride and extracted with ether. The organic extracts were washed with water, and then with brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield the desired product **67** (49.66 g, 97%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1093 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 0.12 (s, 9H, OTMS), 1.86 (quintet, J = 7.4 Hz, 2H, alkyl CH_2), 3.01 (t, J = 7.2 Hz, 2H, SCH_2), 3.70 (t, J = 6.1 Hz, 2H, OCH_2), 7.17 (t, J = 7.2 Hz, 1H, ArH), 7.28 (t, J = 6.3 Hz, 2H, ArH), 7.35 (d, J = 8.3 Hz, 2H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 137.2, 129.5, 129.4, 126.3, 61.3, 32.5, 30.5, 0.0 ppm.

Preparation of 1,1-di(trimethylsiloxy)prop-1-ene, 68.[104]



General procedure:
n-BuLi was added slowly to a stirred solution of di-*iso*-propylamine in dry THF at 0°C. Upon complete addition, the solution was cooled to -78°C. Propionic acid was added to the freshly prepared LDA and the solution was stirred for 30 minutes. TMSCl was added slowly to the reaction mixture, such that the internal temperature did not exceed -70°C.

The resulting solution was allowed to warm to room temperature and stirred for 15 hours. The reaction mixture was concentrated *in vacuo*, diethyl ether was added and the resulting precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and the crude product purified by bulb-to-bulb distillation (50°C - 70°C/0.03 mmHg) to yield the desired product **68** as a colourless oil.

Following the **General procedure**, data are reported as (a) amount of *n*-BuLi, (b) amount of di-*iso*-propylamine, (c) amount of dry THF, (d) amount of propionic acid, (e) amount of TMSCl, and (f) product yield.

Scheme 58, run 1

(a) 2.5 M, 88 ml, 220 mmol, (b) 30.8 ml, 220 mmol, (c) 200 ml, (d) 7.41 ml, 100 mmol, (e) 28.1 ml, 220 mmol, and (f) 9.615 g, 44%.

Scheme 58, run 2

(a) 2.5 M, 88 ml, 220 mmol, (b) 30.8 ml, 220 mmol, (c) 200 ml, (d) 7.41 ml, 100 mmol, (e) 28.1 ml, 220 mmol, and (f) 13.916 g, 64%.

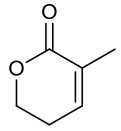
Scheme 59:

n-BuLi (2.2 M, 50 ml, 110 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (15.4 ml, 110 mmol) in dry THF (100 ml) at 0°C. Upon complete addition, the solution was cooled to -78°C. Propionic acid (3.73 ml, 50 mmol) was added to the freshly prepared LDA and the solution was stirred for 30 minutes. The resulting solution was then cooled to -196°C. TMSCl (14.06 ml, 110 mmol) was added slowly down the inside edge of the reaction vessel. The frozen reaction mixture was then warmed to -98°C and stirred at this temperature for 3 hours. Following this, the cooling bath was opened to the atmosphere (i.e., the insulation (cotton wool) was removed) and the reaction mixture was allowed to warm to room temperature over 16 hours. The reaction mixture was concentrated *in vacuo*, diethyl ether was added and the resulting precipitate was removed by filtration. The filtrate was concentrated *in vacuo* and the crude product

purified by bulb-to-bulb distillation (50°C to 70°C at 0.03 mmHg) to yield the desired product **68** (7.27 g, 67%) as a colourless oil.

FTIR (CH_2Cl_2): 1067 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 0.21 (s, 18H, OTMS), 1.47 (d, *J* = 6.5 Hz, 3H, allylic CH_3), 3.57 (q, *J* = 6.5 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 150.5, 76.5, 9.9, 0.2, -0.3, ppm.

Preparation of 5,6-dihydro-3-methylpyran-2-one, 65.[103]



Scheme 60

N-Chlorosuccinimide (6.41 g, 48 mmol) was added to a stirred solution of sulfide **67** (9.62 g, 40 mmol) in carbon tetrachloride (30 ml). The slurry was refluxed for 3 hours, cooled to room temperature, filtered, and concentrated *in vacuo*. The resulting oil was dissolved in dry DCM (50 ml). To this stirred solution was added ketene acetal **68** (10.5 g, 48 mmol) and (flame dried) anhydrous zinc bromide (200 mg), and the resulting mixture was stirred for 2 hours. The reaction mixture was transferred to a separating funnel and diethyl ether (200 ml) and 2 M HCl (100 ml) were added. The solution was shaken and the aqueous layer removed. Fresh HCl (100 ml) was added and the solution shaken for approximately 5 minutes. The organic layer was separated, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was then added, as a dry DCM (50 ml) solution, to a stirred mixture of *m*-CPBA (13.81 g, 80 mmol) in dry DCM (150 ml) at 0°C. The solution was stirred at room temperature for 2.5 hours. The reaction mixture was quenched with saturated sodium sulfite solution, the organic phase was separated, washed with saturated sodium bicarbonate, and then with brine, and dried

over Na_2SO_4. The solution was filtered and DBU (12 ml, 80 mmol) was added to the filtrate. The solution was stirred at room temperature for 16 hours, concentrated *in vacuo*, and the crude product purified by column chromatography (eluent: petroleum ether to 50% ether in petroleum ether) to yield the desired product **65** (2.8 g, 62%) as a pale yellow liquid.

General procedure:

n-BuLi was added slowly to a stirred solution of di-*iso*-propylamine in THF at 0°C. The freshly prepared LDA solution was cooled to -78°C before the addition of lactone **71** as a THF solution. The solution was stirred at this temperature for 1 hour before the addition of the sulfur reagent **72**. The solution was then warmed to room temperature and stirred for 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Purification method A: The crude product was purified by column chromatography (eluent: petroleum ether to 50% ether in petroleum ether). Purification method B: The crude product was first purified by distillation (66°C/0.03 mbar) then further purified by column chromatography (eluent: petroleum ether to 50% ether in petroleum ether). The desired product **65** was obtained as a colourless oil.

Following the **General procedure**, data are reported as (a) amount of *n*-BuLi, (b) amount of di-*iso*-propylamine, (c) amount of THF, (d) amount of lactone **71**, in THF, (e) amount of sulfur reagent **72**, (f) purification method, and (g) product yield.

Scheme 69, *run 1*

(a) 2.5 M, 56.6 ml, 142 mmol, (b) 21.4 ml, 153 mmol, (c) 400 ml, (d) 13.47 g, 118 mmol, in 40 ml of THF, (e) 28 g, 130 mmol, (f) method A, and (g) 8.11 g, 60%.

Scheme 69, *run 2*

(a) 2.2 M, 60 ml, 132 mmol, (b) 18.5 ml, 132 mmol, (c) 400 ml, (d) 12.6 g, 110 mmol, in 40 ml of THF, (e) 28.48 g, 132 mmol, (f) method B, and (g) 4.64 g, 38%.

Scheme 70

2-Iodoxybenzoic acid (1.594 g, 5.69 mmol) was added to a stirred solution of lactone **71** (500 mg, 4.38 mmol) in a mixture of DMSO (14.6 ml) and toluene (29.2 ml). The mixture was heated to 75°C and stirred for 16 hours. TLC analysis showed no conversion of the starting material. The temperature was increased and the reaction mixture was refluxed for a further 16 hours. TLC analysis showed no conversion to product. The reaction was abandoned and the starting material was recovered.

Scheme 71

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.849 g, 8.1 mmol) was added to a stirred solution of lactone **71** (310 mg, 2.7 mmol) in 1,4-dioxane (25 ml). The reaction mixture was then heated to reflux and stirred for 16 hours. TLC analysis did show that some starting material still remained. The solid material was removed by filtration of the reaction mixture through a pad of celite (eluent: ether) and the filtrated was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: petroleum ether to 50% ether in petroleum ether) to yield the desired product **65** (36 mg, 12%) as a colourless oil. The mass balance was made up by recovered starting material.

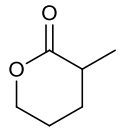
Scheme 73

Dibromo lactone **77** (100 mg, 0.37 mmol) was stirred in DCM (2 ml) at room temperature. Saturated sodium sulfite solution (2 ml) was added and the biphasic mixture was stirred vigorously for 1 hour. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis of this material showed a 58% conversion of starting material into the unsaturated product. Indicative peaks used to determine the ratio were the olefinic proton peak of compound **65** at 6.63 ppm versus the peak for the proton at the 4-position of compound **77** at 4.76 ppm.

FTIR (CH_2Cl_2): 1718 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.92 (s, 3H, CH_3), 2.38-2.44 (m, 2H, allylic CH_2), 4.37 (t, J = 6.3 Hz, 2H, OCH_2), 6.63 (s, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 165.5, 139.5, 128.8, 66.7, 24.3, 17.2 ppm.

Preparation of tetrahydro-3-methylpyran-2-one, 71.[107]



Scheme 61:

n-BuLi (2.5 M, 4.8 ml, 12 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (1.68 ml, 12 mmol) in THF (10 ml) at 0°C. The solution was cooled to -16°C and HMPA (2.09 ml, 12 mmol) was added. Following this, δ-valerolactone (0.93 ml, 10 mmol) was added and the solution was stirred for 30 minutes before being cooled to -78°C. Methyl iodide (0.81 ml, 13 mmol) was then added dropwise to the reaction mixture. The solution was stirred at this temperature for 30 minutes before being warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in* vacuo. The crude product was purified by column chromatography (eluent: petroleum ether to 40% ether in petroleum ether) to yield the desired product **71** (311 mg, 27%) as a colourless liquid.

Scheme 62:

Di-*iso*-propylamine (3.08 ml, 22 mmol) was stirred in THF (20 ml) at 0°C. *n*-BuLi (2.5 M, 8.8 ml, 22 mmol) was added slowly to the solution followed by the addition of DMPU (2.65 ml, 22 mmol). The reaction mixture was stirred at this temperature for 10

minutes before being cooled to –78°C. δ-Valerolactone (1.86 ml, 20 mmol) was added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. Methyl iodide (1.62 ml, 26 mmol) was then added dropwise to the reaction mixture, which was stirred at this temperature for 30 minutes before being warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate and transferred to a separating funnel. Diethyl ether was added and the mixture was shaken vigorously. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 40% ether in petroleum ether) to yield the desired product **71** (465 mg, 20%) as a colourless liquid.

Scheme 63:

Di-*iso*-propylamine (59.7 ml, 426 mmol) was added to a stirred mixture of lithium chloride (30.1 g, 710 mmol) in THF (400 ml) at 0°C. *n*-BuLi (2.2 M, 178 ml, 391 mmol) was added slowly to the mixture followed by the addition of DMPU (21.4 ml, 177.5 mmol). The reaction mixture was stirred at this temperature for 10 minutes before being cooled to –78°C. δ-Valerolactone (35.5 ml, 355 mmol) was added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. Methyl iodide (28.7 ml, 462 mmol) was then added dropwise to the reaction mixture, which was stirred at this temperature for 30 minutes before being warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate and transferred to a separating funnel. Diethyl ether was added and the mixture was shaken vigorously. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 40% ether in petroleum ether) to yield the desired product **71** (12.62g, 31%) as a colourless liquid.

Scheme 64:

Di-*iso*-propylamine (42 ml, 300 mmol) was added to a stirred mixture of flame-dried lithium chloride (21.2 g, 500 mmol) in THF (400 ml) at 0°C. *n*-BuLi (2.5 M, 100 ml, 275 mmol) was added slowly to the mixture followed by the addition of DMPU (15.1 ml, 125 mmol). The reaction mixture was stirred at this temperature for 10 minutes before being cooled to –78°C. δ-Valerolactone (23.2 ml, 250 mmol) was added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. Methyl iodide (20.2 ml, 325 mmol) was then added dropwise to the reaction mixture, which was stirred at this temperature for 30 minutes before being warmed to room temperature and stirred for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate and diluted with diethyl ether. The mixture was stirred vigorously before being allowed to separate. This was then transferred to a separating funnel and the organic layer was collected. The aqueous layer was returned to the round-bottomed flask and diluted with diethyl ether. The above procedure was repeated and the organic layer was separated. The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 40% ether in petroleum ether) to yield the desired product **71** (19.64 g, 69%) as a colourless liquid.

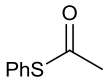
Scheme 65:

Di-*iso*-propylamine (42 ml, 300 mmol) was added to a stirred mixture of flame-dried lithium chloride (21.2 g, 500 mmol) in THF (400 ml) at 0°C. *n*-BuLi (2.5 M, 100 ml, 275 mmol) was added slowly to the mixture followed by the addition of DMPU (15.1 ml, 125 mmol). The reaction mixture was stirred at this temperature for 10 minutes before being cooled to –78°C. δ-Valerolactone (23.2 ml, 250 mmol) was added dropwise over 30 minutes and the mixture stirred for a further 30 minutes. Methyl iodide (20.2 ml, 325 mmol) was then added dropwise to the reaction mixture, which was stirred at this temperature for 30 minutes before being warmed to room temperature and stirred for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by

distillation (112°C/19 mbar) to yield the desired product **71** (20 g, 70%) as a colourless liquid.

FTIR (CH_2Cl_2): 1727 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.26 (d, J = 6.9 Hz, 3H, CH_3), 1.50-1.60 (m, 1H, ring CH), 1.87-1.94 (m, 2H, ring CH_2), 2.06-2.14 (m, 1H, ring CH), 2.53-2.63 (m, 1H, CH_3CH), 4.27-4.37 (m, 2H, OCH_2). ^{13}C NMR δ(100 MHz, $CDCl_3$): 174.5, 68.6, 34.7, 27.1, 22.0, 16.7 ppm.

Preparation of *S*-phenylthioacetate, 73.[160]



Acetyl chloride (75 ml, 1.05 mol) was added dropwise to a stirred solution of thiophenol (103 ml, 1 mol) and triethylamine (146 ml, 1.05 mol) in DCM (1.5 l) at 0°C. The resulting yellow slurry was stirred at this temperature for 2 hours before being warmed to room temperature and stirred for a further hour. The precipitate was filtered and washed with DCM (2 x 500 ml). The organics were combined, washed with saturated sodium bicarbonate, dried over Na_2SO_4, and concentrated *in vacuo* to deliver the desired product **73**. The product was further purified by high vacuum distillation (106°C/10 mbar) to yield the desired product **73** (91.304 g, 60%) as a colourless liquid.

FTIR (CH_2Cl_2): 1705, 3045 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.43 (s, 3H, CH_3), 7.43 (s, 5H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 194.1, 134.5, 129.5, 129.2, 128.0, 30.2 ppm.

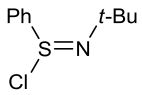
Preparation of *N*,*N*-dichloro-*tert*-butylamine, 74.[114]

t-$BuNCl_2$

t-Butylamine (25.6 g, 350 mmol) was added to a stirred, heterogeneous, mixture of calcium hypochlorite (175.2 g, 1.225 mol, tech. grade, 65% available Cl) in DCM (500 ml) at 0°C. 3 N HCl (900 ml) was added dropwise to the solution over a period of 1 hour. Following the addition, the solution was stirred at 0°C for 3 hours. The organic layer was then separated and the aqueous layer extracted with DCM. The organic extracts were combined, dried over Na_2SO_4, and carefully concentrated *in vacuo* (150 mbar, bath at r.t.) into a previously weighed flask to yield the desired product **74** (49.26 g, 99%) as a yellow liquid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.40 (s, 9H, CH_3). ^{13}C NMR δ(100 MHz, $CDCl_3$): 72.6, 25.9 ppm.

Preparation of *N*-*tert*-butylbenzenesulfinimidoyl chloride, 72.[114]

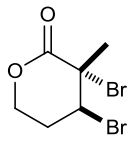


N-*N*-Dichloro-*t*-butylamine **74** (23.86 g, 168 mmol) was dissolved in benzene (100 ml) in a pre-weighed 250 ml single-neck flask. A reflux condenser was fitted to the reaction vessel followed by the addition of *S*-phenylthioacetate **73** (24.36 g, 160 mmol). The resulting solution was refluxed for 90 minutes. Once cool, an oven dried one-piece distillation kit was fitted to the reaction vessel and the volatiles were removed by distillation (100°C), first at atmospheric pressure and then under reduced pressure (15 mmHg) followed by high vacuum (0.05 mmHg). An orange semi-solid was obtained which, upon standing, solidified to give the desired product **72** (32.43 g, 94%) as a

yellow solid. This product was stored under nitrogen at -18°C and used without further purification.

FTIR (CH_2Cl_2): 1390, 1480, 2990 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.57 (s, 9H, CH_3), 7.58-7.66 (m, 3H, ArH), 8.13-8.15 (m, 2H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 142.9, 133.4, 129.3, 126.2, 64.4, 29.8 ppm.

Preparation of *trans*-3,4-dibromotetrahydro-3-methylpyran-2-one, 77.[161]



General procedure:
Bromine was added to a stirred solution of lactone **65** in dry DCM and the solution was stirred for 3 hours at room temperature. The reaction mixture was then poured slowly into a vigorously stirred mixture of saturated sodium sulfite solution and ice contained within a beaker. The mixture was diluted with ether and the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 10% ether in petroleum ether) to yield the desired product **77** as a colourless liquid.

Following the **General procedure**, data are reported as (a) amount of bromine, (b) amount of lactone **65**, (c) amount of DCM, and (d) product yield.

Scheme 72, run 1
(a) 1.54 ml, 30 mmol, (b) 3.36 g, 30 mmol, (c) 80 ml, and (d) 1.935 g, 24%.

Scheme 72, run 2

(a) 0.97 ml, 18.9 mmol, (b) 2.124 g, 18.9 mmol, (c) 50 ml, and (d) 1.212 g, 28%.

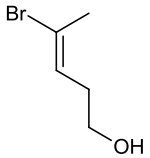
Scheme 74

Bromine (1.99 ml, 38.8 mmol) was added to a stirred solution of lactone **65** (4.35 g, 38.8 mmol) in dry DCM (100 ml) and the solution was stirred for 3 hours. The reaction mixture was concentrated *in vacuo* and the crude product was purified by column chromatography (eluent: petroleum ether to 10% ether in petroleum ether) to yield the desired product **77** (8.181 g, 78%) as a colourless liquid.

FTIR (CH_2Cl_2): 1742 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 2.14 (m, 4H, CH_3 and ring CH_2), 3.26-3.35 (m, 1H, ring CH_2), 4.61-4.66 (m, 1H, ring OCH_2), 4.76 (t, J = 2.5 Hz, 1H, BrCH), 4.91 (td, ^2J = 11.8 and J = 4.4 Hz, 1H, ring OCH_2). ^{13}C NMR δ(100 MHz, $CDCl_3$): 166.8, 67.1, 55.2, 54.4, 29.7, 29.3 ppm.

Preparation of (*E*)-4-bromopent-3-en-1-ol, 78.[161]

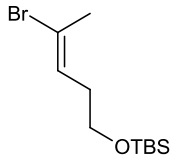


Lithium hydroxide monohydrate (2.014 g, 48 mmol) was added to a stirred DMF/water (60 ml, 4:1) solution of lactone **77** (4.352 g, 16 mmol). The mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with brine and extracted with DCM (x 5). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to

30% ether in petroleum ether) to yield the desired product **78** (1.923 g, 73%) as a colourless liquid.

FTIR (CH_2Cl_2): 1629, 3426 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.96 (s, 1H, OH), 2.29-2.35 (m, 5H, allylic CH_2 and CH_3), 3.69 (t, J = 6.4 Hz, 2H, OCH_2), 5.91 (t, J = 7.7 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 128.2, 121.8, 61.5, 33.0, 23.4 ppm.

Preparation of (*E*)-2-bromo-5-(^{t}butyldimethylsiloxyl)pent-2-ene, 56.[96]



Scheme 76
2,6-Lutidine (5.1 ml, 43.6 mmol) was added to a stirred solution of alcohol **78** (3.27 g, 19.8 mmol) in dry DCM (60 ml). TBSOTf (5 ml, 21.8 mmol) was added to the solution and stirring was continued for a further hour. The reaction mixture was quenched with saturated sodium bicarbonate, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether) to yield the desired product **56** (5.263 g, 95%) as a colourless liquid.

Scheme 79
Copper cyanide (2.24 g, 25 mmol) was stirred in a mixture of THF (30 ml) and ether (50 ml) at –40°C. *n*-BuLi (2.5 M, 20 ml, 50 mmol) was added to the slurry and the resulting brown mixture was stirred for 5 minutes. The mixture was then warmed to room temperature and stirred for 15 minutes before being cooled to –40°C. Tributyltin hydride

(13.5 ml, 50 mmol) was then added and the resulting orange solution was stirred at –40°C for 70 minutes.

Simultaneously, a solution of 2,3-dihydrofuran (1.89 ml, 25 mmol) in THF (25 ml) was cooled to –60°C. *t*-BuLi (1.7 M, 17.5 ml, 30 mmol) was added and the bright yellow solution was stirred at –60°C for a further 10 minutes. The solution was then warmed to 0°C and stirred for 55 minutes. The solution was transferred to the above-generated mixture *via* cannula and the resulting dark orange solution was stirred at 0°C for 1.5 h. Methyl iodide (11 ml, 175 mmol) was added and the mixture was allowed to warm to room temperature over 1 hour. The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then poured into a mixture of saturated ammonium chloride (500 ml) and ammonium hydroxide solution (125 ml) at 0°C. The mixture was stirred vigorously for 30 minutes, the aqueous layer was separated, extracted with ether, and the organic extracts were combined. The combined organic portions were then dried over Na_2SO_4 and concentrated *in vacuo*. The colourless oil was dissolved in DCM (25 ml) and cooled to 0°C. A solution of bromine (1.38 ml, 27 mmol) in DCM (225 ml) was added until the brown colour persisted. Imidazole (5 g, 74 mmol) was then added followed by TBSCl (11.15 g, 74 mmol) and the slurry was stirred at 0°C for 30 minutes. The reaction mixture was quenched with sodium thiosulfate solution (125 ml) and stirred for 5 minutes. The aqueous layer was separated and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether) followed by distillation (60°C/0.005 mbar) to yield the desired product **56** (11.77 g, 86%) as a colourless oil.

Scheme 80

Copper cyanide (7.613 g, 85 mmol) was stirred in a mixture of THF (100 ml) and ether (170 ml) at –40°C. *n*-BuLi (2.5 M, 68 ml, 170 mmol) was added to the slurry and the resulting brown mixture was stirred for 5 minutes. The mixture was then warmed to room temperature and stirred for 15 minutes before being cooled to –40°C. Tributyltin

hydride (45.7 ml, 170 mmol) was then added and the resulting orange solution was stirred at –40^{o}C for 70 minutes.

Simultaneously, a solution of 2,3-dihydrofuran (6.43 ml, 85 mmol) in THF (80 ml) was cooled to –60^{o}C. *t*-BuLi (1.7 M, 60 ml, 102 mmol) was added and the bright yellow solution was stirred at –60^{o}C for a further 10 minutes. The solution was then warmed to 0^{o}C and stirred for 55 minutes. The solution was transferred to the above-generated mixture *via* cannula and the resulting dark orange solution was stirred at 0^{o}C for 1.5 h. Methyl iodide (37 ml, 595 mmol) was added and the mixture was allowed to warm to room temperature over 1 hour. The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then poured into a mixture of saturated ammonium chloride (1 l) and ammonium hydroxide solution (250 ml) at 0^{o}C. The mixture was stirred vigorously for 30 minutes, the aqueous layer was separated, extracted with diethyl ether, and the organic extracts were combined. The combined organic portions were then dried over Na_2SO_4 and concentrated *in vacuo*. The colourless oil was dissolved in DCM (85 ml) and cooled to 0^{o}C. A solution of bromine (4.7 ml, 91.8 mmol) in DCM (415 ml) was added until the brown colour persisted and the reaction mixture was stirred for 5 minutes. The reaction mixture was quenched with sodium thiosulfate solution (500 ml) and stirred for 5 minutes. The aqueous layer was separated and extracted with diethyl ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography to remove the non-polar tin residues. The column was flushed with petroleum ether to remove these impurities and then the eluent was increased to 75% ether in petroleum ether to elute the desired alcohol **78** as a yellow oil. The crude alcohol **78** was then dissolved in dry DCM (320 ml) and stirred at room temperature. 2,6-Lutidine (21.78 ml, 187 mmol) was added to the solution followed by TBSOTf (23.4 ml, 102 mmol) and stirring was continued for 1 hour. The reaction mixture was quenched with saturated sodium bicarbonate, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography

(eluent: petroleum ether) to yield the desired product **56** (20.18 g, 85%) as a colourless liquid.

Scheme 81

Copper cyanide (4.48 g, 50 mmol) was stirred in a mixture of THF (60 ml) and ether (100 ml) at –40°C. *n*-BuLi (2.5 M, 40 ml, 100 mmol) was added to the slurry and the resulting brown mixture was stirred for 5 minutes. The mixture was then warmed to room temperature and stirred for 15 minutes before being cooled to –40°C. Tributyltin hydride (26.9 ml, 100 mmol) was then added and the resulting orange solution was stirred at –40°C for 70 minutes.

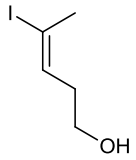
Simultaneously, a solution of 2,3-dihydrofuran (3.78 ml, 50 mmol) in THF (50 ml) was cooled to –60°C. *t*-BuLi (1.7 M, 35.3 ml, 60 mmol) was added and the bright yellow solution was stirred at –60°C for a further 10 minutes. The solution was then warmed to 0°C and stirred for 55 minutes. The solution was transferred to the above-generated mixture *via* cannula and the resulting dark orange solution was stirred at 0°C for 1.5 h. Methyl iodide (22 ml, 350 mmol) was added and the mixture was allowed to warm to room temperature over 1 hour. The mixture was then stirred at room temperature for 16 hours. The reaction mixture was then poured into a mixture of saturated ammonium chloride (1 l) and ammonium hydroxide solution (250 ml) at 0°C. The mixture was stirred vigorously for 30 minutes, the aqueous layer was separated, extracted with diethyl ether, and the organic extracts were combined. The combined organic portions were then dried over Na_2SO_4 and concentrated *in vacuo*. The colourless oil was dissolved in DCM (50 ml) and cooled to 0°C. A solution of bromine (2.77 ml, 54 mmol) in DCM (450 ml) was added until the brown colour persisted and the reaction mixture was stirred for 5 minutes. The reaction mixture was quenched with sodium thiosulfate solution (500 ml) and stirred for 5 minutes. The aqueous layer was separated and extracted with diethyl ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography to remove the non-polar tin residues. The column was flushed with petroleum ether to

remove these impurities and then the eluent was increased to 75% ether in petroleum ether to elute the desired alcohol **78** as a yellow oil. The crude alcohol **78** was then dissolved in dry DCM (190 ml) and stirred at room temperature. 2,6-Lutidine (12.81 ml, 110 mmol) was added to the solution followed by TBSOTf (13.76 ml, 60 mmol) and stirring was continued for 1 hour. The reaction mixture was quenched with saturated sodium bicarbonate, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether) to yield the desired product **56** (14%) as a colourless liquid. As a result of the poor recovery, the non-polar material eluted from the column during the purification of the alcohol was purified by column chromatography (eluent: petroleum ether to 10% ether in petroleum ether) to investigate what by-products were formed. This resulted in the recovery of ether **81** which was heavily contaminated with byproducts from the reaction.

FTIR (CH_2Cl_2): 1097 cm^{-1}.
^{1}H NMR δ(400 MHz, $CDCl_3$): 0.06 (s, 6H, $SiCH_3$), 0.86 (s, 9H, $^tBuCH_3$), 2.21-2.27 (m, 5H, vinyl CH_2 and CH_3), 3.64 (t, J = 6.6 Hz, 2H, OCH_2), 5.86 (t, J = 6.6 Hz, 1H, olefinic H). ^{13}C NMR δ(100 MHz, $CDCl_3$): 129.0, 121.1, 62.2, 33.1, 26.1, 23.4, 18.5, -5.1 ppm.

Spectral details for **81**:
^{1}H NMR δ(500 MHz, $CDCl_3$): 2.24 (s, 3H, vinyl CH_3), 2.24-2.32 (m, 2H, vinyl CH_2), 3.35 (s, 3H, OMe), 3.40 (t, J = 6.7 Hz, 2H, OCH_2), 5.88 (t, J = 7.5 Hz, 1H, olefinic H)

Preparation of (*E*)-4-iodopent-3-en-1-ol, 80.[121]



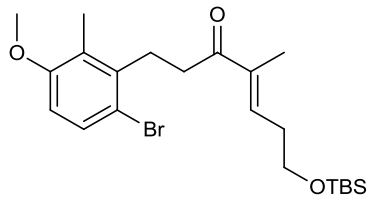
Copper cyanide (448 mg, 5 mmol) was stirred in a mixture of THF (6 ml) and ether (10 ml) at –40°C. *n*-BuLi (2.5 M, 4 ml, 10 mmol) was added to the slurry and the resulting brown mixture was stirred for 5 minutes. The mixture was then warmed to room temperature and stirred for 15 minutes before being cooled to –40°C. Tributyltin hydride (2.7 ml, 10 mmol) was then added and resulting orange solution was stirred at –40°C for 70 minutes.

Simultaneously, a solution of 2,3-dihydrofuran (378 µl, 5 mmol) in THF (5 ml) was cooled to –60°C. *t*-BuLi (1.7 M, 3.5 ml, 6 mmol) was added and the bright yellow solution was stirred at –60°C for a further 10 minutes. The solution was then warmed to 0°C and stirred for 55 minutes. The solution was transferred to the above-generated mixture *via* cannula and the resulting dark orange solution was stirred at 0°C for 1.5 h. Methyl iodide (2.2 ml, 35 mmol) was added and the mixture was allowed to warm to room temperature over 1 hour. The mixture was then stirred at room temperature for 3 hours. The reaction mixture was then poured into a mixture of saturated ammonium chloride (100 ml) and ammonium hydroxide solution (25 ml) at 0°C. The mixture was stirred vigorously for 30 minutes, the aqueous layer was separated, extracted with diethyl ether, and the organic extracts were combined. The combined organic portions were then dried over Na_2SO_4 and concentrated *in vacuo*. The colourless oil was dissolved in DCM (5 ml) and cooled to 0°C. A solution of iodine (1.4 g, 5.4 mmol) in DCM (45 ml) was added until the brown colour persisted and the solution was stirred for a further 5 minutes. The reaction mixture was quenched with sodium thiosulfate solution (25 ml) and stirred for 5 minutes. The aqueous layer was separated and extracted with diethyl ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in*

vacuo. The crude product was purified by column chromatography (eluent: petroleum ether to 40% ether in petroleum ether) to yield the desired product **80** (935 mg, 88%) as a colourless oil.

FTIR (CH_2Cl_2): 1629, 3426 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.51 (s, 1H, OH), 2.29-2.34 (m, 2H, allylic CH_2), 2.42 (m, 3H, allylic CH_3), 3.37 (t, J = 6.4 Hz, 2H, OCH_2), 5.91 (tq, J = 7.6 and ^4J = 1.5 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 137.1, 96.2, 61.4, 33.9, 27.7 ppm.

Preparation of (*E*)-1-(6-bromo-3-methoxy-2-methylphenyl)-7-(ᵗbutyldimethylsiloxy)-4-methylhept-4-en-3-one, 10.[96]



t-BuLi (1.7 M, 58.3 ml, 82.6 mmol) was added slowly to a stirred solution of vinyl bromide **56** (13.85 g, 49.6 mmol) in dry diethyl ether (175 ml) at -78°C. The resulting solution was stirred for 1 hour.

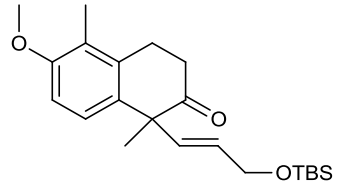
Simultaneously, a 3-necked flask, fitted with a condenser, was charged with magnesium turnings (1.78 g, 73.6 mmol), flame dried under vacuum, and cooled under nitrogen. Once cool, benzene (18 ml) and diethyl ether (54 ml) were added and the slurry was stirred at room temperature. Dibromoethane (6.2 ml, 70 mmol) was added to the slurry at such a rate that it refluxed gently without external heating. After the addition was complete, the reaction mixture was heated so as to maintain a gentle reflux (50°C) for 1 hour. Heating and stirring were discontinued and the mixture (1 M anhydrous $MgBr_2.OEt_2$) was allowed to settle.

The 1 M anhydrous $MgBr_2.OEt_2$ solution (53.7 ml, 53.7 mmol) was added to the previously prepared vinyllithium reagent at -78°C. The solution was stirred at this temperature for 10 minutes prior to warming to 0°C. The solution was stirred for 30 minutes at 0°C before the addition of Weinreb amide **55** (13 g, 41.3 mmol) as a dry diethyl ether (45 ml) solution. The solution was stirred for 30 minutes at 0°C prior to warming to room temperature for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, the organic phase was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 3% ether in petroleum ether) to yield the desired product **10** (18.248 g, 97%) as a colourless oil.

FTIR (CH_2Cl_2): 1573, 1666 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 0.06 (s, 6H, $SiCH_3$), 0.89 (s, 9H, $^tBuCH_3$), 1.83 (s, 3H, allylic CH_3), 2.22 (s, 3H, $ArCH_3$), 2.46 (q, *J* = 6.5 Hz, 2H, allylic CH_2), 2.83-2.88 (m, 2H, alkyl CH_2), 3.08-3.12 (m, 2H, alkyl CH_2), 3.72 (t, *J* = 6.6 Hz, 2H, OCH_2), 3.81 (s, 3H, $ArOCH_3$), 6.62 (d, *J* = 8.8 Hz, 1H, ArH), 6.68-6.72 (m, 1H, olefinic H), 7.36 (d, *J* = 8.7 Hz, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 200.6, 157.1, 139.8, 139.3, 138.3, 130.1, 127.0, 115.9, 109.8, 61.7, 55.7, 36.1, 32.8, 28.7, 25.9, 18.3, 12.3, 11.6, -5.3 ppm.

Preparation of (*E*)-3,4-dihydro-1-(3-(*tert*-butyldimethylsiloxy)prop-1-enyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one, 9.[96]



General procedure A:

A mixture of palladium acetate in dry toluene was stirred until the mixture became homogeneous. Triphenylphosphine was added to the resulting solution and an immediate colour change from brown to yellow was observed. Aryl halide **10** was then added as a dry toluene solution followed by triethylamine. The solution was heated gently to reflux over an hour and held at this temperature for 48 hours. The reaction mixture was cooled, concentrated *in vacuo*, and filtered through celite (eluent: ethyl acetate). The ethyl acetate was removed *in vacuo* and the crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **9** as a pale yellow oil.

Following **General procedure A**, data are reported as (a) amount of palladium acetate, (b) amount of toluene, (c) amount of triphenylphosphine, (d) amount of aryl halide **10**, (e) amount of dry toluene, (f) amount of triethylamine, and (g) product yield.

Scheme 85, *run 1*

(a) 94 mg, 0.42 mmol, (b) 50 ml, (c) 439 mg, 1.67 mmol, (d) 950 mg, 2.09 mmol, (e) 5 ml, (f) 2.91 ml, 20.9 mmol, and (g) 651 mg, 83%.

Scheme 85, *run 2*

(a) 314 mg, 1.4 mmol, (b) 150 ml, (c) 1.469 g, 5.6 mmol, (d) 3.2 g, 7 mmol, (e) 30 ml, (f) 9.76 ml, 70 mmol, and (g) 1.078 g, 41%.

Scheme 85, *run 3*

(a) 320 mg, 1.43 mmol, (b) 170 ml, (c) 1.496 g, 5.7 mmol, (d) 3.25 g, 7.13 mmol, (e) 10 ml, (f) 9.94 ml, 71.3 mmol, and (g) 1.557 g, 58%.

General procedure B:

A microwave vessel was charged with palladium acetate and the reaction solvent. The mixture was stirred for 5 minutes before the addition of the phosphine. A light coloured precipitate formed immediately and the mixture was stirred for a further 5 minutes. Aryl halide **10** was then added to the stirred mixture followed by triethylamine. The microwave tube was sealed and heated under microwave irradiation for the given time at the given temperature. The reaction mixture was then allowed to cool, concentrated *in vacuo*, and filtered through celite (eluent: ethyl acetate). The ethyl acetate was removed *in vacuo* and the crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **9** as a pale yellow oil.

Following **General procedure B**, data are reported as (a) amount of palladium acetate, (b) solvent and amount, (c) phosphine and amount, (d) amount of aryl halide **10**, (e) amount of triethylamine, (f) time of reaction, (g) temperature of reaction, and (h) product yield.

Scheme 86

(a) 2.2 mg, 0.01 mmol, (b) toluene, 1 ml, (c) triphenylphosphine, 10.4 mg, 0.04 mmol, (d) 23 mg, 0.05 mmol, (e) 0.07 ml, 0.5 mmol, (f) 30 minutes, with the cooling function on (g) 110^{o}C, and (h) 0%.

Scheme 87

(a) 49 mg, 0.22 mmol, (b) DMF, 4.4 ml, (c) tri-*o*-tolylphosphine, 267 mg, 0.88 mmol, (d) 2.0 g, 4.39 mmol, (e) 6.1 ml, 43.9 mmol, (f) 5 minutes, with the cooling function on, (g) 150^{o}C, and (h) 410 mg, 25%.

Scheme 88

(a) 17 mg, 0.0745 mmol, (b) acetonitrile, 1.5 ml, (c) tri-*o*-tolylphosphine, 91 mg, 0.298 mmol, (d) 680 mg, 1.49 mmol, (e) 0.21 ml, 1.49 mmol, (f) 20 minutes, with the cooling function on (g) 100^{o}C, and (h) 502 mg, 90%.

Table 9, entry 1

(a) 79 mg, 0.35 mmol, (b) acetonitrile, 7 ml, (c) tri-*o*-tolylphosphine, 428 mg, 1.41 mmol, (d) 3.2 g, 7.03 mmol, (e) 1.96 ml, 14.06 mmol, (f) 20 minutes, with the cooling function on (g) 100^{o}C, and (h) 4.208 g, 91%.

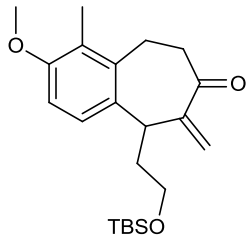
Table 9, entry 2

(a) 150 mg, 0.67 mmol, (b) acetonitrile, 13.37 ml, (c) tri-*o*-tolylphosphine, 814 mg, 2.67 mmol, (d) 7.0 g, 13.37 mmol, (e) 3.73 ml, 26.74 mmol, (f) 20 minutes + 20 minutes + 10 minutes, with the cooling function on (g) 100^{o}C, and (h) 4.382 g, 87%.

FTIR (CH_2Cl_2): 1598, 1714 cm^{-1}.

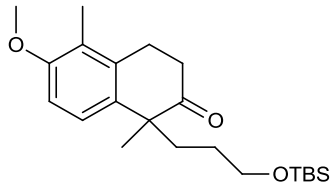
^{1}H NMR δ(400 MHz, $CDCl_3$): 0.09 (s, 6H, $SiCH_3$), 0.88 (s, 9H, $^{t}BuCH_3$), 1.54 (s, 3H, alkyl CH_3), 2.21 (s, 3H, $ArCH_3$), 2.46-2.54 (m, 1H, ring CH_2), 2.75-2.81 (m, 1H, ring CH_2), 3.03 (q, J = 6.8 Hz, 2H, ring CH_2), 3.83 (s, 3H, $ArOCH_3$), 4.13 (d, J = 4.7 Hz, 2H, OCH_2), 5.35 (dt, J = 15.5 and 4.9 Hz, 1H, olefinic H), 5.69 (dt, J = 15.6 and ^{4}J = 1.7 Hz, 1H, olefinic CH), 6.81 (d, J = 8.7 Hz, 1H, ArH), 7.09 (d, J = 8.6 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 200.8, 157.3, 140.1, 139.5, 138.5, 130.3, 127.1, 116.1, 110.0, 61.9, 55.9, 36.3, 33.0, 28.9, 26.1, 18.5, 12.2, 11.5, -5.1 ppm.

Data for by-product **82**:



^{1}H NMR δ(400 MHz, $CDCl_3$): 0.01 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$) 0.89 (s, 9H, $^{t}BuCH_3$), 2.14-2.19 (m, 2H, CH_2), 2.22 (s, 3H, $ArCH_3$), 2.67-2.74 (m, 1H, CH_2), 2.77-2.83 (m, 1H, CH_2), 3.12-3.15 (m, 2H, CH_2), 3.60-3.68 (m, 2H, CH_2), 3.82 (s, 3H, $ArOCH_3$), 4.04 (t, *J* = 7.4 Hz, 2H, CH), 5.23 (t, ^{2}J and ^{4}J = 1.0 Hz, 1H, olefinic CH), 5.75-5.76 (m, 1H, olefinic CH), 6.74 (d, *J* = 8.5 Hz, 1H, ArH), 7.01 (d, *J* = 8.5 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 203.9, 156.3, 151.3, 138.7, 133.1, 125.0, 124.3, 119.4, 108.8, 60.5, 55.6, 42.2, 41.9, 35.7, 25.9, 24.2, 18.2, 11.7, -5.4 ppm.

Preparation of 3,4-dihydro-1-(3-(*tert*-butyldimethylsiloxy)propyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one, 83.[96]



Scheme 89

Crabtree's catalyst **62** (1.491 g, 1.85 mmol) was added to a stirred solution of olefin **9** (9.25 g, 24.69 mmol) in dry DCM (85 ml). The resulting solution was cooled to -78°C, the vessel evacuated and back filled with hydrogen *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. This process was repeated three times and, upon the final refill, the mixture was allowed to warm to room temperature and stirred

for 16 hours. The reaction mixture was concentrated *in vacuo* and the crude product purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **83** (8.787 g, 95%) as a colourless oil.

Scheme 178

A microwave vessel was charged with palladium acetate (11.2 mg, 0.05 mmol) and acetonitrile (0.5 ml). The mixture was stirred for 5 minutes before the addition of the tri-*o*-tolylphosphine (61 mg, 0.2 mmol). A light coloured precipitate formed immediately and the mixture was stirred for a further 5 minutes. The vessel was then charged with sodium formate (51 mg, 0.75 mmol). Aryl halide **132** (228 mg, 0.5 mmol) was then added to the stirred mixture followed by triethylamine. The microwave tube was sealed and heated under microwave irradiation for 20 minutes at 100°C. The reaction mixture was then allowed to cool, concentrated *in vacuo*, and filtered through celite (eluent: ethyl acetate). The ethyl acetate was removed *in vacuo* and the crude product was analysed by ^{1}H NMR, which showed there to be no desired product present and the reaction was abandoned. The starting material (228 mg, 100%) was recovered from the reaction mixture following purification *via* column chromatography (eluent: petroleum ether to 3% ether in petroleum ether).

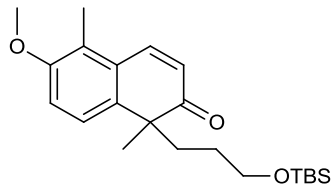
Scheme 179

A microwave vessel was charged with palladium acetate (11.2 mg, 0.05 mmol), distilled water (0.125 ml) and acetonitrile (0.375 ml). The mixture was stirred for 5 minutes before the addition of the tri-*o*-tolylphosphine (61 mg, 0.2 mmol). A light coloured precipitate formed immediately and the mixture was stirred for a further 5 minutes. The vessel was then charged with sodium formate (51 mg, 0.75 mmol). Aryl halide **132** (228 mg, 0.5 mmol) was then added to the stirred mixture followed by triethylamine. The microwave tube was sealed and heated under microwave irradiation for 20 minutes at 100°C. The reaction mixture was then allowed to cool, concentrated *in vacuo*, and filtered through celite (eluent: ethyl acetate). The ethyl acetate was removed *in vacuo* and the crude product was purified by column chromatography (eluent: petroleum ether

to 5% diethyl ether in petroleum ether) to yield the desired product **83** (23 mg, 12%) as a colourless oil.

FTIR (CH_2Cl_2): 1100, 1709 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): -0.02 (s, 6H, $SiCH_3$), 0.89 (s, 9H, $^tBuCH_3$), 1.12-1.23 (m, 2H, $CH_2CH_2CH_2O$), 1.40 (s, 3H, alkyl CH_3), 1.73 (td, ^2J = 12.7 and 4.4 Hz, 1H, $CH_2CH_2CH_2O$), 2.06 (td, ^2J = 12.6 and 4.9 Hz, 1H, $CH_2CH_2CH_2O$), 2.19 (s, 3H, $ArCH_3$), 2.59-2.69 (m, 2H, ring CH_2), 2.97-3.05 (m, 2H, ring CH_2), 3.42-3.50 (m, 2H, OCH_2), 3.83 (s, 3H, $ArOCH_3$), 6.82 (d, J = 8.7 Hz, 1H, ArH), 7.12 (d, J = 8.7 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 215.0, 155.6, 135.5, 134.3, 124.5, 123.3, 109.1, 63.0, 55.5, 50.9, 37.7, 36.7, 28.4, 27.4, 25.9, 25.2, 18.2, 11.4, -5.4 ppm.
Proton NMR was assigned using 2D NMR methods.

Preparation of 1-(3-(*tert*-butyldimethylsiloxy)propyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one, 84.[96]



Scheme 90

n-BuLi (2 M, 2.6 ml, 5.12 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (0.71 ml, 5.12 mmol) in THF (45 ml) at 0°C. The freshly prepared LDA solution was cooled to -78°C before the addition of ketone **83** (1.6 g, 4.27 mmol) as a THF (5 ml) solution. The solution was stirred at this temperature for 1 hour before the addition of sulfur reagent **72** (1.198 g, 5.55 mmol). The solution was then warmed to room temperature and stirred for 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated,

washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **84** (1.04 g, ~65%) as a yellow oil. The material obtained following purification was analysed by ^{1}H NMR, which showed it not to be clean and to contain many by-products.

General procedure A:

N-Bromosuccinimide was added to a stirred solution of ketone **83** in CCl_4. AIBN was added and the reaction mixture was heated to reflux and stirred for 3 hours. The mixture was then cooled to 0°C and filtered through celite (eluent: cold CCl_4). The filtrate was concentrated *in vacuo* and purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the product as a colourless oil.

Following **General procedure A**, data are reported as (a) amount of NBS, (b) amount of ketone **83**, (c) amount of CCl_4, (d) amount of AIBN, and (e) product yield.

Table 10, *entry 1*

(a) 303 mg, 1.7 mmol, (b) 638 mg, 1.7 mmol, (c) 17 ml, (d) 28 mg, 0.17 mmol, and (e) 350 mg, 55%, product was a mixture of **84**:**85** in a 3:1 ratio.

Table 10, *entry 2*

(a) 309 mg, 1.736 mmol, (b) 500 mg, 1.335 mmol, (c) 13 ml, (d) 22 mg, 0.134 mmol, and (e) 0%, inseparable mixture of compounds.

General procedure B:

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone was added to a stirred solution of ketone **83** in solvent. The reaction mixture was then heated to the required temperature and stirred for the required time. The reaction mixture was allowed to cool and the solid material was removed by filtration through a pad of celite (eluent: ether) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent:

petroleum ether to 5% ether in petroleum ether) to yield the desired product **84** as a colourless oil.

Following **General procedure B**, data are reported as (a) amount of DDQ, (b) amount of ketone **83**, (c) solvent and amount, (d) reaction temperature, (e) reaction time, and (f) product yield.

Table 11, *entry 1*
(a) 282 mg, 1.242 mmol, (b) 310 mg, 0.828 mmol, (c) 1,4-dioxane, 10 ml, (d) reflux, (e) 24 h, and (f) 112 mg, 36% (70% BRSM, 105 mg).

Table 11, *entry 2*
(a) 183 mg, 0.81 mmol, (b) 100 mg, 0.27 mmol, (c) 1,4-dioxane, 2.7 ml, (d) reflux, (e) 24 h, and (f) 12 mg, 12%.

Table 11, *entry 3*
(a) 183 mg, 0.81 mmol, (b) 100 mg, 0.27 mmol, (c) 1,4-dioxane, 2.7 ml, (d) 70°C, (e) 48 h, and (f) 12 mg, 12%.

Table 11, *entry 4*
(a) 183 mg, 0.81 mmol, (b) 100 mg, 0.27 mmol, (c) benzene, 2.7 ml, (d) 70°C, (e) 48 h, and (f) 20 mg, 20% (65% BRSM, 45 mg).

Table 12, *entry 1*
Palladium acetate (18 mg, 0.08 mmol) was added to a mixture of DPPE (28 mg, 0.07 mmol) in acetonitrile (15 ml) and the mixture was heated to reflux. Enol ether **86** (358 mg, 0.8 mmol) was added as an acetonitrile (1.5 ml) solution followed by diallylcarbonate (0.16 ml, 1.12 mmol) and the reaction mixture was stirred at reflux for 42 hours. NMR analysis showed a 25% conversion to product. Diallycarbonate was added (0.16 ml, 1.12 mmol) and the mixture was stirred for a further 24 hours. NMR

analysis still showed a 25% conversion to product. The reaction was abandoned at this stage.

Table 12, *entry 2*

Palladium acetate (24 mg, 0.106 mmol) was added to a mixture of DPPE (37 mg, 0.095 mmol) in acetonitrile (10 ml) and the mixture was heated to reflux. Enol ether **86** (236 mg, 0.53 mmol) and diallylcarbonate (0.16 ml, 1.12 mmol) were added as a solution in acetonitrile (1 ml) down the inside of the condenser and the reaction mixture was stirred at reflux for 114 hours. The reaction mixture was allowed to cool to room temperature then concentrated *in vacuo*, and purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **84** (80 mg, 40%) as a colourless oil.

General procedure C:

A microwave vessel was charged with enol ether **86** and acetonitrile. To the vessel was added palladium acetate and the chosen phosphine. Finally, diallylcarbonate was added and the reaction mixture was heated to the required temperature under microwave irradiation for the required time. The reaction mixture was analysed by ^{1}H NMR.

Following **General procedure C**, data are reported as (a) amount of enol ether **86**, (b) amount of acetonitrile, (c) amount of palladium acetate, (d) phosphine and amount, (e) amount of diallylcarbonate, (f) reaction temperature, (g) reaction time, and (h) product yield.

Table 13, *entry 1*

(a) 15 mg, 0.033 mmol, (b) 0.5 ml, (c) 0.7 mg, 0.0033 mmol, (d) DPPE, 1.2 mg, 0.003 mmol, (e) 6.6 mg, 0.0462 mmol, (f) 120°C, with the cooling function off, (g) 10 mins, and (h) 21% conv.

Table 13, *entry 2*

(a) 33 mg, 0.074 mmol, (b) 0.5 ml, (c) 1.7 mg, 0.0074 mmol, (d) DPPE, 2.7 mg, 0.0067 mmol, (e) 14.7 mg, 0.104 mmol, (f) 120°C, with the cooling function off, (g) 120 mins, and (h) hydrolysis and extensive degradation.

General procedure D:

Ketone **83** was stirred in DCM at –5°C. Triethylamine was added followed by a solution of TMSOTf in DCM and the reaction mixture was stirred for 15 minutes at this temperature. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 2% ether in petroleum ether) to yield the desired enol ether **86** as a colourless oil. Enol ether **86** was then stirred in acetonitrile at room temperature. $Pd(OAc)_2$ was added and the reaction mixture was stirred at the allotted temperature for the allotted time. The reaction mixture was concentrated *in vacuo* and the residue was filtered through a pad of celite (eluent: DCM). The filtrate was washed with sodium bicarbonate, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **84** as a colourless oil.

Following **General procedure D**, data are reported as (a) amount of ketone **83**, (b) amount of DCM, (c) amount of triethylamine, (d) amount of TMSOTf, (e) amount of DCM, (f) amount of acetonitrile (g) amount of palladium acetate, (h) allotted temperature, (i) allotted time, and (j) product yield.

Table 14, *entry 1*

(a) 1.68 g, 4.48 mmol, (b) 100 ml, (c) 1.87 ml, 13.44 mmol, (d) 0.97 ml, 5.38 mmol, (e) 30 ml, (f) 100 ml, (g) 1.056 g, 4.7 mmol, (h) r.t., (i) 72 h, and (j) 1.146 g, 70%.

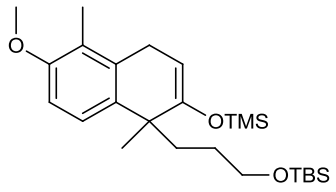
Table 14, *entry 2*

(a) 3.35 g, 7.47 mmol, (b) 165 ml, (c) 3.12 ml, 22.41 mmol, (d) 1.62 ml, 8.96 mmol, (e) 50 ml, (f) 165 ml, (g) 1.76 g, 7.84 mmol, (h) 50°C, (i) 48 h, and (j) 2.405 g, 86%.

FTIR (CH_2Cl_2): 1095, 1572, 1655 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): -0.04 (s, 3H, $SiCH_3$), -0.03 (s, 3H, $SiCH_3$), 0.86 (s, 9H, $^tBuCH_3$), 0.95-1.17 (m, 2H, $CH_2CH_2CH_2O$), 1.41 (s, 3H, alkyl CH_3), 1.88 (td, ^2J = 12.6 and J = 4.2 Hz, 1H, $CH_2CH_2CH_2O$), 2.14 (td, ^2J = 12.5 and J = 4.9 Hz, 1H, $CH_2CH_2CH_2O$), 2.36 (s, 3H, $ArCH_3$), 3.37-3.45 (m, 2H, OCH_2), 3.86 (s, 3H, $ArOCH_3$), 6.19 (d, J = 10.2 Hz, 1H, olefinic H), 6.93 (d, J = 8.6 Hz, 1H, ArH), 7.22 (d, J = 8.7 Hz, 1H, ArH), 7.81 (d, J = 10.1 Hz, 1H, olefinic H). ^{13}C NMR δ(100 MHz, $CDCl_3$): 204.7, 155.9, 141.0, 138.4, 128.8, 125.2, 124.9, 124.4, 112.1, 63.0, 55.7, 50.8, 38.8, 28.8, 28.2, 26.0, 18.2, 10.7, -5.39, -5.41 ppm.

Preparation of 1-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-6-methoxy-1,5-dimethyl-2-trimethylsilanyloxy-1,4-dihydronaphthalene 86.



Ketone **83** (3.6 mg, 9.56 mmol) was stirred in DCM (96 ml) at –5°C. Triethylamine (4.0 ml, 28.68 mmol) was added followed by TMSOTf (2.08 ml, 11.47 mmol) and the reaction mixture was stirred for 15 minutes at this temperature. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 2% ether in petroleum ether) to yield the desired product **86** (4.25 mg, 99%) as a colourless oil.

FTIR (CH_2Cl_2): 1686 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): -0.02 (s, 3H, $SiCH_3$), -0.01 (s, 3H, $SiCH_3$), 0.26 (s, 9H, $SiCH_3$) 0.87 (s, 9H, $^tBuCH_3$), 0.94-1.02 (m, 1H, alkyl CH), 1.26-1.36 (m, 1H, alkyl CH) 1.38 (s, 3H, alkyl CH_3), 1.55 (m, 1H, alkyl CH), 1.97 (ddd, *J* = 13.0, 11.9 and 4.6 Hz, 1H, alkyl CH), 2.12 (s, 3H, $ArCH_3$), 3.29 (d, *J* = 3.7 Hz, 2H, ring CH_2) 3.39-3.48 (m, 2H, OCH_2), 3.82 (s, 3H, $ArOCH_3$), 5.00 (t, *J* = 3.7 Hz, 1H, olefinic CH), 6.78 (d, *J* = 8.7 Hz, 1H, ArH), 7.13 (d, *J* = 8.7 Hz, 1H, ArH) ^{13}C NMR δ(100 MHz, $CDCl_3$): 154.5, 151.7, 134.0, 133.0, 123.8, 122.3, 108.6, 98.5, 63.3, 55.2, 41.6, 36.9, 28.8, 28.2, 27.6, 25.6, 17.9, 10.7, 0.0, -5.7 ppm.

Accurate mass data could not be obtained for this sensitive compound; accordingly, the material was used immediately in subsequent transformations.

Preparation of 1-(3-hydroxypropyl)-6-methoxy-1,5-dimethyl-1H-naphthalen-2-one, 87.

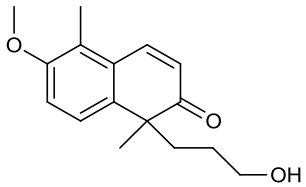


Table 14, *entry 3*

Ketone **83** (94.2 mg, 0.25 mmol) was stirred in DCM (2.5 ml) at –5°C. Triethylamine (77 µl, 0.55 mmol) was added followed by TMSOTf (50 µl, 0.275 mmol) and the reaction mixture was stirred for 15 minutes at this temperature. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 2% ether in petroleum ether) to yield the desired enol ether **86** as a colourless oil. Enol ether **86** was then stirred in DMSO (5 ml) at room temperature. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) was added and the vessel was evacuated and back filled with oxygen

via a three way tap attached to a vacuum manifold and an oxygen balloon. This process was repeated three times and, upon the final refill, the mixture was warmed to 80°C and stirred for 16 hours. The reaction mixture was allowed to cool to room temperature before being diluted with diethyl ether (45 ml). The organic phase was washed with water (x 3) and the aqueous washes were combined and extracted with diethyl ether (x 3). The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 100% ether) to yield the desired product **87** (43 mg, 66%) as a colourless oil.

Scheme 108

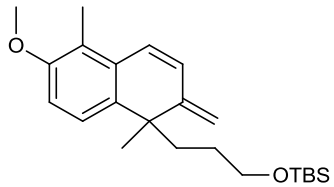
Enone **84** (4.68 g, 12.49 mmol) was stirred in dry THF (63 ml) at room temperature. Tetrabutylammonium fluoride (1 M in THF, 18.7 ml, 18.7 mmol) was added dropwise to the reaction mixture and this was stirred for 16 hours. Sodium bicarbonate was added followed by diethyl ether and the organic layer was separated. The organic layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 10% petroleum ether in diethyl ether to 100% diethyl ether) to yield the desired product **87** (2.922 mg, 90%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1096, 1572, 1654, 3617 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.12-1.20 (m, 2H, alkyl CH_2), 1.38 (s, 3H, alkyl CH_3), 1.81-1.91 (m, 2H, alkyl CH_2 and OH), 2.26 (ddd, J = 13.4, 10.7 Hz, and 5.9 Hz, 1H, alkyl CH_2), 2.34 (s, 3H, $ArCH_3$), 3.33-3.43 (m, 2H, alkyl OCH_2), 3.83 (s, 3H, $ArOCH_3$), 6.17 (d, J = 10.2 Hz, 1H, olefinic CH), 6.93 (d, J = 8.6 Hz, 1H, ArH), 7.21 ppm (d, J = 8.6 Hz, 1H, ArH), 7.81 (d, J = 10.3 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 205.0, 156.0, 141.3, 138.2, 128.8, 125.13, 125.05, 124.4, 112.2, 62.5, 55.8, 50.8, 38.1, 29.2, 28.3, 10.7 ppm.

HRMS *m/z* (ESI) Calc. for $C_{16}H_{21}O_3$ (M^++H): 261.1489. Found 261.1485.

Preparation of 1-(3-(*tert*-Butyldimethylsiloxy)propyl)-1,2-dihydro-6-methoxy-1,5-dimethyl-2-methylennaphthalene, 88.[96]



Scheme 92

n-BuLi (2.26 M, 0.17 ml, 0.38 mmol) was added slowly to a stirred solution of methyltriphenylphosphonium bromide (149 mg, 0.42 mmol) in THF (10 ml) at -78°C. The solution was stirred at this temperature for 30 minutes before the addition of enone **84** (118 mg, 0.32 mmol) as a THF (5 ml) solution. The resulting solution was stirred at this temperature for a further 30 minutes before being warmed to room temperature and stirred for 1 hour. The reaction mixture was quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer was then separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **88** (66 mg, 55%) as a colourless oil.

General procedure A:

Trimethylsilylmethyllithium (1 M in pentane) was added dropwise to a solution of ketone **84** in dry diethyl ether at 0°C. The reaction mixture was stirred at 0°C for the allotted time before being added to a 2% aqueous hydrochloric acid solution. The resulting mixture was extracted with diethyl ether and the extracts were dried over Na_2SO_4 and concentrated *in vacuo*.

Following **General procedure A**, data are reported as (a) amount of trimethylsilyl methyllithium (1 M in pentane), (b) amount of ketone **84**, (c) amount of diethyl ether,

(d) reaction time, (e) amount of 2% hydrochloric acid solution, and (f) reaction conversion (calculated from diagnostic peaks in the ^{1}H NMR: enone **84** peak at 7.81 ppm, intermediate **89** peak at 5.94 ppm, and product **88** peak at 5.15 ppm.

Table 15, entry 1

(a) 1 M in pentane, 84 µl, 0.084 mmol, (b) 28 mg, 0.07 mmol, (c) 5 ml, (d) 6 h, (e) 25 ml, and (f) 59% conversion.

Table 15, entry 2

(a) 1 M in pentane, 120 µl, 0.12 mmol, (b) 23 mg, 0.06 mmol, (c) 5 ml, (d) 6 h, (e) 25 ml, and (f) 88% conversion.

Table 15, entry 3

Trimethylsilylmethyllithium (1 M in pentane, 1.59 ml, 1.59 mmol) was added dropwise to a solution of ketone **84** (200 mg, 0.53 mmol) in dry diethyl ether (25 ml) at 0^{o}C. The reaction mixture was stirred at 0^{o}C for 1 hour before being added to a 2% aqueous hydrochloric acid solution (125 ml). The resulting mixture was extracted with diethyl ether and the extracts were dried over Na_2SO_4. Flash chromatography silica gel was added and the solvent was removed *in vacuo*. The dry powder was rotated on the rotary evaporator at 50^{o}C for 2 hours. TLC analysis showed incomplete conversion of intermediate β-hydroxysilane to product (60:40, product:intermediate). The silica gel was washed with ether and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **88** (56 mg, 28%) as a colourless oil. Intermediate **89** was also recovered from the reaction mixture (102 mg, 45%).

Scheme 93

β-Hydroxytrimethylsilylalkane **89** (30 mg, 0.065 mmol) was stirred in dry DCM (5 ml) at 0°C. Boron trifluoride diethyl etherate (0.1 ml, 0.81 mmol) was added dropwise to the reaction mixture. On addition of the $BF_3.Et_2O$ the reaction mixture turned black. TLC

analysis showed multiple products. This was confirmed by ^{1}H NMR analysis and the reaction was abandoned.

Scheme 94

Methyltriphenylphosphonium bromide (5.684 g, 15.9 mmol) was stirred in dry THF (10 ml) at 0°C. Potassium *t*-butoxide (1 M in THF, 15.3 ml, 15.3 mmol) was added slowly to the slurry and the resulting yellow solution was stirred at this temperature for a further 30 minutes. Ketone **84** (1.145 g, 3.04 mmol) was added as a THF (5 ml) solution and the reaction mixture was stirred for 30 minutes before being warmed to room temperature and stirred for a further 1 hour. The reaction mixture was quenched with ammonium chloride and diluted with diethyl ether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **88** (1.003 g, 88%) as a colourless oil.

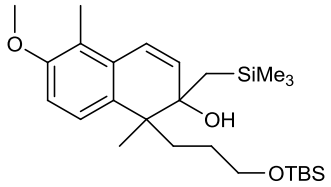
Scheme 95

A THF (50 ml) solution of ketone **84** (3.3 g, 8.8 mmol) was added to a stirred slurry of methyltriphenylphosphonium bromide (9.43 g, 26.4 mmol) in THF (100 ml). The resulting mixture was cooled to 0°C and stirred for a further 5 minutes. Solid potassium *t*-butoxide (2.864 g, 25.5 mmol) was added to the slurry portion wise resulting in the immediate appearance of a bright yellow colour. Following complete addition, the reaction mixture was stirred for 30 minutes before being warmed to room temperature and stirred for a further 1 hour. The reaction mixture was quenched with ammonium chloride and diluted with diethyl ether. The organic layer was separated and the aqueous layer was extracted with diethyl ether. The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **88** (3.087 g, 94%) as a colourless oil.

FTIR (CH_2Cl_2): 1572, 1597, 2931, 2956 cm^{-1}.

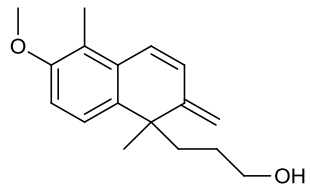
^1H NMR δ(400 MHz, $CDCl_3$): -0.01 (s, 6H, $SiCH_3$), 0.87 (s, 9H, $^tBuCH_3$), 1.07-1.17 (m, 1H, alkyl CH), 1.27-1.38 (m, 1H, alkyl CH), 1.42 (s, 3H, alkyl CH_3), 1.71 (td, *J* = 4.5 and 12.0 Hz, 1H, alkyl CH), 1.91 (td, *J* = 12.7 and 4.4 Hz, 1H, alkyl CH), 2.25 (s, 3H, $ArCH_3$), 3.45 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.82 (s, 3H, $ArOCH_3$), 5.15 (s, 1H, terminal olefinic CH), 5.17 (s, 1H, terminal olefinic CH), 6.37 (d, *J* = 10.0 Hz, 1H, olefinic CH), 6.64 (d, *J* = 9.4 Hz, 1H, olefinic CH), 6.73 (d, *J* = 8.6 Hz, 1H, ArH), 7.17 (d, *J* = 8.6 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 155.6, 150.4, 135.7, 131.7, 129.9, 123.4, 122.3, 121.9, 113.2, 109.3, 63.4, 55.6, 42.1, 42.0, 32.5, 28.4, 25.9, 18.3, 10.6, -5.3 ppm.

Data for intermediate **89**:



^1H NMR δ(400 MHz, $CDCl_3$): -0.05 (s, 3H, $SiCH_3$), -0.04 (s, 3H, $SiCH_3$), 0.02 (s, 9H $SiCH_3$), 0.08 (s, 2H, $SiCH_2$), 0.82 (s, 9H, $^tBuCH_3$), 1.29 (s, 3H, alkyl CH_3), 1.30-1.48 (m, 3H, alkyl CH and alkyl CH_2), 1.93-2.02 (m, 1H, alkyl CH), 2.18 (s, 3H, $ArCH_3$), 3.38-3.41 (m, 2H, OCH_2), 3.81 (s, 3H, $ArOCH_3$), 5.94 (d, *J* = 10.1 Hz, 1H, olefinic CH), 6.52 (d, *J* = 10.1 Hz, 1H, olefinic CH), 6.63 (d, *J* = 8.6 Hz, 1H, ArH), 6.96 (d, *J* = 8.4 Hz, 1H, ArH).

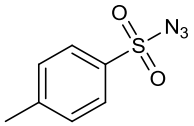
Preparation of 3-(1,2-Dihydro-6-methoxy-1,5-dimethyl-2-methylennaphthalen-1-yl)propan-1-ol, 90.[96]



Diene **88** (2.39 g, 6.42 mmol) was stirred in dry THF (30 ml) at room temperature. Tetrabutylammonium fluoride (1 M in THF, 9.63 ml, 9.63 mmol) was added dropwise to the reaction mixture and this was stirred for 4 hours. Sodium bicarbonate was added followed by diethyl ether and the organic layer was separated. The organic layer was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 50% diethyl ether in petroleum ether) to yield the desired product **90** (1.654 g, 100%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1572, 1597, 3618 cm^{-1}.
^{1}H NMR δ(400 MHz, $CDCl_3$): 1.11-1.21 (m, 1H, alkyl CH), 1.33-1.45 (m, 4H, alkyl CH and alkyl CH_3), 1.72 (td, J = 4.5 Hz, ^2J = 12.6 Hz, 1H, alkyl CH), 1.93 (td, J = 4.5 Hz, ^2J = 12.6 Hz, 1H, alkyl CH), 2.25 (s, 3H, $ArCH_3$), 3.48 (t, J = 6.5 Hz, 2H, OCH_2), 3.82 (s, 3H, $ArOCH_3$), 5.15 (s, 1H, terminal olefinic CH), 5.17 (s, 1H, terminal olefinic CH), 6.38 (d, J = 10.0 Hz, 1H, olefinic CH), 6.65 (d, J = 10.0 Hz, 1H, olefinic CH), 6.74 (d, J = 8.6 Hz, 1H, ArH), 7.18 ppm (d, J = 8.7 Hz, 1H, ArH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 155.7, 150.4, 135.5, 131.8, 130.0, 123.4, 122.4, 122.0, 113.3, 109.3, 63.3, 55.6, 42.5, 42.1, 32.2, 28.5, 10.7 ppm.

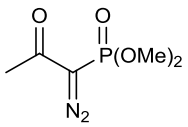
Preparation of *para*-toluenesulfonyl azide, 93.[162]



Sodium azide (6.436 g, 99 mmol) was added to a stirred solution of tosyl chloride (14.299 g, 75 mmol) in acetone (87 ml) and water (60 ml). The reaction mixture was heated to reflux and stirred for 5 hours. The reaction mixture was then allowed to cool to ambient temperature before the addition of water (125 ml). The mixture was extracted with DCM and the organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo* to yield the desired product **93** (15.89 g, 100%) as a colourless oil which solidified on storage at -18°C.

FTIR (CH_2Cl_2): 1170, 1372, 1596, 2130 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.49 (s, 3H, $ArCH_3$), 7.41 (d, J = 8.0 Hz, 2H, ArH), 7.85 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 146.2, 135.5, 130.3, 127.6, 21.8 ppm.

Preparation of Dimethyl 1-diazo-2-oxopropylphosphonate, 92.[135]

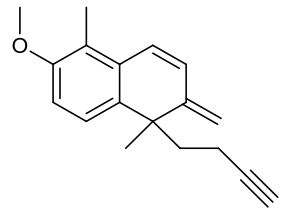


Sodium hydride (95% in mineral oil, 531 mg, 21 mmol) was added portionwise to a stirred solution of dimethyl 2-oxopropylphosphonate (3.33 g, 20 mmol) in toluene (60 ml) and THF (10 ml) at 0°C. The reaction mixture was stirred for 1 hour before the addition of azide **93** (4.2 g, 20 mmol) in toluene (20 ml). The reaction mixture was then allowed to warm to room temperature and was stirred for 16 hours. The solvent was

removed *in vacuo* and the crude product was purified by column chromatography (eluent: 10% diethyl ether in ethyl acetate) to yield the desired product **92** (2.801 g, 73%) as a yellow liquid.

FTIR (CH_2Cl_2): 1031, 1275, 1656, 2129 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 2.23 (s, 3H, C(O)CH_3), 3.81 (d, J = 11.9 Hz, 6H, OCH_3).
^{13}C NMR δ(100 MHz, $CDCl_3$): 189.8 (d, ^2J = 13.0 Hz), 63.5 (d, ^1J = 218.5 Hz), 53.5 (d, ^2J = 5.6 Hz), 27.1 ppm.

Preparation of 1-(But-3-ynyl)-1,2-dihydro-6-methoxy-1,5-dimethyl-2-methylennaphthalene, 91.[96]



General procedure A:
Alcohol **90** was stirred in dry DCM. 4-Methylmorpholine *N*-oxide monohydrate and powdered 4Å molecular sieves were added to the solution and this mixture was stirred at room temperature for 1 hour before being cooled to 0°C. Tetrapropylammonium perruthenate was added and stirring was continued for 3 hours. Ammonium chloride was added, the organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was dissolved in dry methanol and potassium carbonate was added. Phosphonate **92** was added as a solution in methanol and the reaction mixture was stirred for 3 hours. The solution was diluted with diethyl ether, washed with sodium bicarbonate, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 3% ether in petroleum ether) to yield the desired product **91** as a colourless oil.

Following **General procedure A**, data are reported as (a) amount of alcohol **90**, (b) amount of DCM, (c) amount of 4-methylmorpholine *N*-oxide monohydrate, (d) amount of powdered 4Å molecular sieves, (e) amount of tetrapropylammonium perruthenate, (f) amount of methanol, (g) amount of potassium carbonate, (h) amount of phosphonate **92**, (i) amount of methanol, and (j) product yield.

Scheme 98

(a) 165 mg, 0.64 mmol, (b) 15 ml, (c) 138 mg, 1.02 mmol, (d) 300 mg, (e) 11 mg, 0.032 mmol, (f) 15 ml, (g) 133 mg, 0.96 mmol, (h) 184 mg, 0.96 mmol, (i) 1.5 ml, and (j) 32 mg, 20%.

Scheme 99

(a) 1.246 g, 4.8295 mmol, (b) 110 ml, (c) 1.041 g, 7.70 mmol, (d) 2.264 g, (e) 83 mg, 0.24 mmol, (f) 110 ml, (g) 1.004 g, 7.24 mmol, (h) 1.388 g, 7.24 mmol, (i) 11 ml, and (j) 556 mg, 46%.

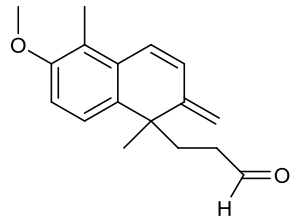
Scheme 100

Dess-Martin reagent (159 mg, 0.375 mmol) was added to a stirred solution of alcohol **90** (65 mg, 0.25 mmol) in DCM (5 ml) at room temperature. After 30 minutes a white precipitate was observed within the stirred reaction mixture. The reaction mixture was stirred for a total of 4 hours before being quenched with a 1:1 mixture (5 ml) of sodium thiosulfate and sodium bicarbonate solutions. The reaction mixture was diluted with diethyl ether (15 ml) and the organic phase was separated. The organic phase was then washed with a 1:1 mixture of sodium bicarbonate and sodium thiosulfate solution (x 5) and then washed with water and finally with brine. The organic mixture was then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in methanol (4 ml) and potassium carbonate was added (52 mg, 0.375 mmol). Phosphonate **92** (72 mg, 0.375 mmol) was added to the stirred mixture as a solution in methanol (5 ml) and the resulting reaction mixture was stirred at room temperature. The reaction mixture was observed to have turned green after 30 minutes and TLC analysis showed no starting

material to be remaining after 2.5 hours. The reaction mixture was diluted with diethyl ether, washed with sodium bicarbonate solution, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 3% ether in petroleum ether), however none of the desired product was recovered.

FTIR (CH_2Cl_2): 1572, 1598, 2117, 3304 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.44 (s, 3H, alkyl CH_3), 1.67-1.76 (m, 1H, alkyl CH_2), 1.86 (t, ^4J = 2.6 Hz, 1H, alkyne CH), 1.92-2.02 (m, 2H, alkyl CH_2), 2.13-2.22 (m, 1H, alkyl CH_2), 2.25 (s, 3H, $ArCH_3$), 3.83 (s, 3H, $ArOCH_3$), 5.18 (s, 1H, terminal olefinic CH), 5.20 (s, 1H, terminal olefinic CH), 6.36 (d, *J* = 10.0 Hz, 1H, olefinic CH), 6.64 (d, *J* = 10.0 Hz, 1H, olefinic CH), 6.75 (d, *J* = 8.8 Hz, 1H, ArH), 7.18 (d, *J* = 8.4 Hz, 1H, ArH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 155.9, 149.5, 134.4, 131.7, 129.8, 123.4, 122.5, 122.2, 113.7, 109.5, 85.1, 67.6, 55.6, 45.3, 42.1, 32.3, 14.4, 10.7 ppm.

Preparation of 3-(1,2-Dihydro-6-methoxy-1,5-dimethyl-2-methylennaphthalen-1-yl)propanal, 94.



Scheme 101

Pyridinium dichromate (61 mg, 0.162 mmol) was added to a stirred solution of alcohol **90** (38 mg, 0.147 mmol) in DCM (5 ml) at room temperature and the resulting solution was stirred for 1 hour. TLC analysis showed multiple spots including a spot which indicated remaining starting material. The reaction mixture was filtered through celite (eluent: DCM) and washed with saturated sodium bicarbonate solution. The organic

layer was separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was analysed by ^1H NMR which indicated mass degradation and by-product formation had occurred. The reaction was abandoned at this point.

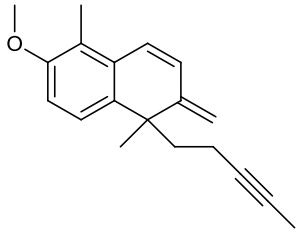
Scheme 103

Diacetoxyiodo benzene (294 mg, 0.91 mmol) was added to a stirred solution of alcohol **90** (118 mg, 0.46 mmol) in DCM (38 ml). A solution of TEMPO (7.1 mg, 0.046 mmol) in DCM (7 ml) was added to the solution and this mixture was stirred at room temperature for 16 hours. TLC analysis showed there to be remaining starting material and a second portion of TEMPO (21.3 mg, 0.138 mmol) was added and the reaction mixture was stirred for a further 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography, however, none of the desired product was isolated.

Scheme 104

Diacetoxyiodo benzene (1.496 g, 4.65 mmol) was added to a stirred solution of alcohol **90** (600 mg, 2.32 mmol) in DCM (195 ml). A solution of TEMPO (181 mg, 1.16 mmol) in DCM (35 ml) was added to the solution and the mixture was stirred at room temperature for 8 hours. A second portion of TEMPO (181 mg, 1.16 mmol) was then added and the reaction mixture was stirred for a further 30 minutes. TLC analysis showed there to be no starting alcohol or desired product remaining and the reaction was abandoned.

Preparation of 1,2-Dihydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)naphthalene, 8.[96]



Scheme 105

n-BuLi (2.5 M, 1.19 ml, 2.98 mmol) was added dropwise to a stirred solution of alkyne **91** (556 mg, 2.206 mmol) in dry THF (90 ml) at -78°C. The solution was stirred for 30 minutes before the dropwise addition of methyl iodide (185 μl, 2.98 mmol) and stirring was continued for a further 30 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for a further 30 minutes. The reaction mixture was quenched with ammonium chloride, diluted with water, and extracted with diethyl ether. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% diethyl ether in petroleum ether) to yield the desired product **8** (534 mg, 91%) as a colourless oil.

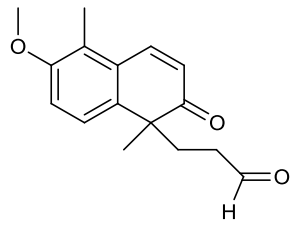
Scheme 122

n-BuLi (2.5 M, 0.93 ml, 2.33 mmol) was added dropwise to a stirred solution of **102**, **103**, and **91**, (1.1:1:3) as obtained from the procedure shown in **Scheme 134** and recorded on page 207 (468 mg, 1.55 mmol), in dry THF (78 ml) at -78°C. The solution was stirred for 30 minutes before the dropwise addition of methyl iodide (0.29 ml, 4.66 mmol) and stirring was continued for a further 30 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for a further 30 minutes. The reaction mixture was quenched with ammonium chloride, diluted with water, and extracted with diethyl ether. The organic extracts were combined, washed with brine,

dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% diethyl ether in petroleum ether) to yield the desired product **8** (405 mg, 98%) as a colourless oil.

FTIR (CH_2Cl_2): 1572, 1597 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.43 (s, 3H, alkyl CH_3), 1.65-1.74 (m, 4H, alkynyl CH_3 and alkyl CH_2), 1.86-1.96 (m, 2H, alkyl CH_2), 2.08-2.14 (m, 1H, alkyl CH_2), 2.25 (s, 3H, $ArCH_3$), 3.82 (s, 3H, $ArOCH_3$), 5.16 (s, 1H, terminal olefinic CH), 5.18 (s, 1H, terminal olefinic CH), 6.36 (d, *J* = 10.0 Hz, 1H, olefinic CH), 6.63 (d, *J* = 9.4 Hz, 1H, olefinic CH), 6.74 (d, *J* = 8.6 Hz, 1H, ArH), 7.18 (d, *J* = 8.6 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 154.7, 148.6, 133.6, 130.7, 128.8, 122.3, 121.4, 121.0, 112.5, 108.4, 78.6, 73.9, 54.6, 44.7, 41.1, 31.4, 13.5, 9.7, 2.4 ppm.

Preparation of 3-(1,2-Dihydro-6-methoxy-1,5-dimethyl-2-oxo-naphthalen-1-yl)propionaldehyde, 95.

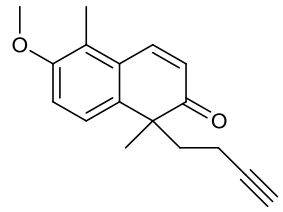


Dimethylsulfoxide (0.2 ml, 2.83 mmol) was added slowly to a stirred solution of oxalyl chloride (0.14 ml, 1.6 mmol) in dry DCM (3.5 ml) at -78°C and the solution was stirred for 10 minutes. A dry DCM (2 ml) solution of alcohol **87** (300 mg, 1.23 mmol) was added and the solution stirred for 15 minutes before the addition of triethylamine (0.86 ml, 6.15 mmol). Following the addition, the solution was warmed to room temperature and was stirred at this temperature for 16 hours. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine. The organic phase

was dried over Na_2SO_4, and concentrated *in vacuo* to yield the desired product **95** (314 mg, 100%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1572, 1655, 1722 cm^{-1}.
^1H NMR δ(400 MHz, $CDCl_3$): 1.44 (s, 3H, alkyl CH_3), 1.91-2.00 (m, 1H, alkyl CH_2), 2.15-2.21 (m, 2H, alkyl CH_2), 2.37 (s, 3H, $ArCH_3$), 2.41-2.50 (m, 1H, alkyl CH_2), 3.86 (s, 3H, $ArOCH_3$), 6.21 (d, *J* = 10.4 Hz, 1H, olefinic CH), 6.94 (d, *J* = 8.4 Hz, 1H, ArH), 7.21 (d, *J* = 8.8 Hz, 1H, ArH), 7.84 (d, *J* = 10.0 Hz, 1H, olefinic CH), 9.55 (s, 1H, ArCHO). ^{13}C NMR δ(125 MHz, $CDCl_3$): 203.9, 201.4, 156.3, 141.3, 137.2, 128.8, 125.5, 125.1, 124.3, 112.2, 55.8, 50.2, 39.8, 33.5, 28.9, 10.8 ppm.
HRMS *m/z* (ESI) Calc. for $C_{16}H_{19}O_3$ (M^++H): 259.1333. Found 259.1329.

Attempted Preparation of 1-(But-3-ynyl)-6-methoxy-1,5-dimethyl-1H-naphthalen-2-one, 96.

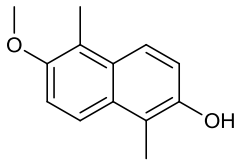


Scheme 110
Aldehyde **95** (1.07 g, 4.42 mmol) was dissolved in dry methanol (130 ml) and potassium carbonate (827 mg, 6 mmol) was added. Phosphonate **92** (1.15 g, 6 mmol) was then added as a solution in methanol (13 ml) and the reaction mixture was stirred for 3 hours. The solution was diluted with diethyl ether, washed with sodium bicarbonate, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 20% ether in petroleum ether). None of the desired product **96** was isolated. Naphthol by-product **97** (626 mg, 70% yield) was isolated following column chromatography as a yellow solid.

Scheme 121

Dibromide **98** (228 mg, 0.55 mmol) was stirred in THF (5.5 ml) at 0°C. Potassium *t*-butoxide (130 mg, 1.16 mmol) was added to the reaction mixture in two portions and the resulting deep purple mixture was stirred at this temperature for 30 minutes. The reaction mixture was quenched by the addition of saturated brine solution and was extracted with diethyl ether. The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed mass degradation and the reaction was abandoned.

Data for Naphthol **97**:



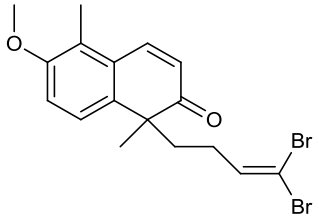
Melting point: 155-157°C.

FTIR (CH_2Cl_2): 1400, 1464, 1515, 1604, 3592 cm^{-1}.

^{1}H NMR δ(400 MHz, $CDCl_3$): 2.54 (s, 3H, $ArCH_3$), 2.55 (s, 3H, $ArCH_3$), 3.94 (s, 3H, $ArOCH_3$), 7.10 (d, J = 9.1 Hz, 1H, ArH), 7.30 (d, J = 9.2 Hz, 1H, ArH), 7.76 (d, J = 9.1 Hz, 1H, ArH), 7.81 (d, J = 9.3 Hz, 1H, ArH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 152.7, 148.7, 129.44, 129.40, 122.8, 122.2, 120.2, 118.0, 115.6, 114.4, 57.1, 10.82, 10.76 ppm.

HRMS *m/z* (ESI) Calc. for $C_{13}H_{14}O_2$ (M^+): 202.0982. Found 202.0988.

Preparation of 1-(4,4-Dibromobut-3-enyl)-6-methoxy-1,5-dimethyl-1H-naphthalen-2-one, 98.



Scheme 112

A solution of carbon tetrabromide (1.738 g, 5.24 mmol) in dry DCM was added to a stirred slurry of zinc dust (343 mg, 5.24 mmol) and triphenylphosphine (1.374 g, 5.24 mmol) in dry DCM (15 ml) and the suspension was stirred at room temperature for 16 hours. The reaction mixture was cooled to 0^{o}C and aldehyde **95** (298 mg, 1.23 mmol) was added as a dry DCM solution. The mixture was stirred for 2 hours at 0°C before the addition of pentane (50 ml). The mixture was filtered through celite, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 15% diethyl ether in petroleum ether) to yield the desired product **98** (268 mg, 55%) as a pale yellow oil.

Scheme 114

Triphenylphosphine (551 mg, 2.1 mmol) was added to a stirred solution of aldehyde **95** (258 mg, 1 mmol) in DCM (7 ml) at 0°C. Carbon tetrabromide (349 mg, 1.05 mmol) was added to the reaction mixture and it was stirred for 1 hour. TLC analysis showed only starting material to be present. The reaction mixture was allowed to warm to room temperature and was stirred for a further 16 hours. Again, TLC analysis showed only starting material to be present. Hexane (7 ml) was added and the reaction mixture was filtered through celite (eluent: 15% ether in hexane). The solution was then concentrated *in vacuo* to return the starting material **95** (255 mg, 99%).

Scheme 115

Carbon tetrabromide (346 mg, 1.04 mmol) was added to a slurry of triphenylphosphine (545 mg, 2.08 mmol) in DCM (5 ml) at 0°C. A bright yellow solution formed immediately and this was stirred for a further 5 minutes at this temperature. A DCM (2 ml) solution of aldehyde **95** (255 mg, 0.99 mmol) was added to the yellow solution and it was stirred for a further 1 hour. Hexane (7 ml) was added and the reaction mixture was filtered through celite (eluent: 15% ether in hexane) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: petroleum ether to 15% ether in petroleum ether) to yield the desired product **98** (274 mg, 67%) as a pale yellow oil.

General procedure:

Dimethylsulfoxide was added slowly to a stirred solution of oxalyl chloride in dry DCM at -78°C and the solution was stirred for 10 minutes. A dry DCM solution of alcohol **87** was added and the solution stirred for 15 minutes before the addition of triethylamine. Following the addition, the solution was warmed to room temperature and was stirred at this temperature for 16 hours. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine. The organic phase was then dried over Na_2SO_4 and filtered to deliver the desired aldehyde **95** as a solution in DCM. In a separate flask, carbon tetrabromide was added to a slurry of triphenylphosphine in DCM at 0°C. A bright yellow solution formed immediately and it was stirred for a further 5 minutes at this temperature. The above generated DCM solution of aldehyde **95** was added to the yellow solution and this was stirred for a further 1 hour. Hexane was added and the reaction mixture was filtered through celite (eluent: 15% ether in hexane) and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (eluent: petroleum ether to 15% ether in petroleum ether) to yield the desired product **98** as a pale yellow oil.

Following the **General procedure**, data are reported as (a) amount of dimethylsulfoxide, (b) amount of oxalyl chloride, (c) amount of DCM, (d) amount of

DCM, (e) amount of alcohol **87**, (f) amount of triethylamine, (g) amount of carbon tetrabromide, (h) amount of triphenylphosphine, (i) amount of DCM (j) amount of hexane, and (k) product yield.

Scheme 116

(a) 0.34 ml, 4.78 mmol, (b) 0.236 ml, 2.7 mmol, (c) 5 ml, (d) 2 ml, (e) 542 mg, 2.08 mmol, (f) 1.45 ml, 10.4 mmol, (g) 726 mg, 2.18 mmol, (h) 1.146 g, 4.34 mmol, (i) 10 ml, (j) 17 ml, and (k) 685 mg, 80%.

Scheme 117

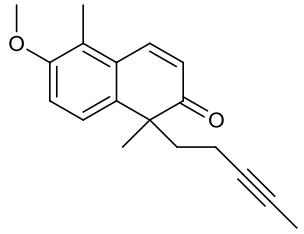
(a) 1.76 ml, 24.7 mmol, (b) 1.22 ml, 14.0 mmol, (c) 25 ml, (d) 10 ml, (e) 2.8 g, 10.8 mmol, (f) 7.5 ml, 53.78 mmol, (g) 3.757 mg, 11.29 mmol, (h) 5.925 g, 22.588 mmol, (i) 50 ml, (j) 85 ml, and (k) 1.8 g, 40%.

FTIR (CH_2Cl_2): 1572, 1655 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.40 (s, 3H, alkyl CH_3), 1.62-1.76 (m, 2H, alkyl CH_2), 1.93 (ddd, J = 13.3 and J = 9.7 and J = 6.0 Hz, 1H, alkyl CH_2), 2.32-2.39 (m, 4H, $ArCH_3$ and alkyl CH_2), 3.87 (s, 3H, $ArOCH_3$), 6.14 (t, J = 7.4 Hz, 1H, olefinic CH), 6.22 (d, J = 10.2 Hz, 1H, olefinic CH), 6.96 (d, J = 8.7 Hz, 1H, ArH), 7.22 (d, J = 8.6 Hz, 1H, ArH), 7.85 (d, J = 10.2 Hz, 1H, olefinic CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 203.9, 156.2, 141.2, 138.0, 137.4, 128.9, 125.4, 125.0, 124.4, 112.2, 89.1, 55.8, 50.6, 39.8, 29.3, 29.1, 10.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{17}H_{19}Br_2O_2$ (M^++H): 412.9749. Found 412.9746.

Attempted preparation of 6-methoxy-1,5-dimethyl-1-pent-3-ynyl-1H-naphthalen-2-one, 99.



Scheme 118

Dibromide **98** (250 mg, 0.63 mmol) was stirred in THF (10 ml) at -78°C. *n*-BuLi (2.5 M, 0.55 ml, 1.38 mmol) was added slowly and the reaction mixture was stirred for 45 minutes. Methyl iodide (0.12 ml, 1.89 mmol) was added and the solution was warmed to room temperature and was stirred for 1 hour. The reaction mixture was quenched with sodium bicarbonate solution and diluted with diethyl ether. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed mass degradation and multiple product formation. Accordingly, the reaction was abandoned.

Scheme 119

Dibromide **98** (150 mg, 0.36 mmol) was stirred in THF (3.6 ml) at -78°C. *t*-BuLi (1.35 M, 0.94 ml, 1.27 mmol) was added slowly and the reaction mixture was stirred for 30 minutes. Methyl iodide (68 μl, 1.09 mmol) was added and the solution was warmed to room temperature and was stirred for a further 30 minutes. The reaction mixture was quenched with sodium bicarbonate solution and diluted with diethyl ether. The organic layer was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed mass degradation and the reaction was abandoned.

Preparation 1-(4,4-Dibromobut-3-enyl)-6-methoxy-1,5-dimethyl-2-methylen-1,2-dihydronaphthalene, 102.

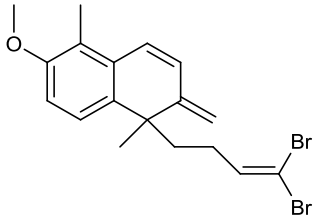


Table 16, *entry 1*

Enone **98** (50 mg, 0.12 mmol) and methyltriphenylphosphonium bromide (128 mg, 0.36 mmol) were stirred in THF (5 ml) at 0°C. Potassium *t*-butoxide (34 mg, 0.3 mmol) was added to the reaction mixture and the resulting solution was stirred for 30 minutes before being allowed to warm to room temperature. The reaction mixture was stirred for 16 hours before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer was then separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield the desired product **102** and by-product **103** (25 mg, 56%) as an inseparable mixture.

Table 16, *entry 2*

Enone **98** (50 mg, 0.12 mmol) and methyltriphenylphosphonium bromide (85 mg, 0.24 mmol) were stirred in THF (5 ml) at 0°C. Potassium *t*-butoxide (20.4 mg, 0.18 mmol) was added to the reaction mixture and the resulting solution was stirred for 30 minutes before being allowed to warm to room temperature. The reaction mixture was stirred for 16 hours before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer was then separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 5% ether in petroleum ether) to yield bromoalkyne **104** (24 mg, 60%) as a colourless oil.

Table 16, *entry 3*

Potassium *t*-butoxide (169 mg, 0.98 mmol) was added to a stirred mixture of methyltriphenylphosphonium bromide (466 mg, 1.30 mmol) in THF (20 ml) at 0°C. The resulting bright yellow mixture was stirred for a further 30 minutes before the addition of enone **98** (270 mg, 0.65 mmol) as a solution in THF (7 ml). The reaction mixture was stirred for 1 hour before being warmed to room temperature. The reaction mixture was stirred for 16 hours before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer was then separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 20% ether in petroleum ether) to yield a mixture of **103**, **104**, **109**, and **98** in a combined yield of 51% (8%, 22%, 9% and 12%, respectively).

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.44 (s, 3H, alkyl CH_3), 1.67-1.78 (m, 2H, alkyl CH_2), 1.85-1.99 (m, 2H, alkyl CH_2), 2.26 (s, 3H, $ArCH_3$), 3.83 (s, 3H, $ArOCH_3$), 5.16 (s, 1H, terminal olefinic CH), 5.20 (s, 1H, terminal olefinic CH), 6.22 (t, J = 7.2 Hz, 1H, olefinic CH), 6.38 (d, J = 10.1 Hz, 1H, olefinic CH), 6.66 (d, J = 10.1 Hz, 1H, olefinic CH), 6.74 (d, J = 8.6 Hz, 1H, ArH), 7.17 (d, J = 8.6 Hz, 1H, ArH).

Preparation 1-(4-Bromobut-3-ynyl)-6-methoxy-1,5-dimethyl-2-methylene-1,2-dihydronaphthalene, 103.

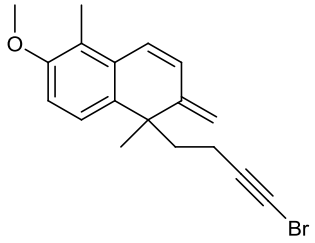


Table 17, *entry 1*

Potassium *t*-butoxide (81 mg, 0.72 mmol) was added to a stirred mixture of methyltriphenylphosphonium bromide (268 mg, 0.75 mmol) in THF (8 ml) at 0°C. The resulting bright yellow mixture was stirred for a further 30 minutes before the addition of enone **98** (100 mg, 0.24 mmol) as a solution in THF (2 ml). The reaction mixture was stirred for 1 hour and TLC analysis indicated that none of the starting enone remained. Potassium *t*-butoxide (81 mg, 0.72 mmol) was added and the reaction mixture was stirred for 30 minutes before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 2% ether in petroleum ether) to yield a mixture of **103** and **91** (34 mg, 55%) in a 1:3.65 ratio.

Table 17, *entry 2*

Potassium *t*-butoxide (309 mg, 2.75 mmol) was added to a stirred mixture of methyltriphenylphosphonium bromide (1.146 g, 3.21 mmol) in THF (30 ml) at 0°C. The resulting bright yellow mixture was stirred for a further 30 minutes before being cooled to -78°C. Enone **98** (380 mg, 0.92 mmol) was added as a solution in THF (8 ml) and the reaction mixture was stirred for 1 hour. TLC analysis indicated that none of the starting enone remained. Potassium *t*-butoxide (309 mg, 2.75 mmol) was added and the reaction

mixture was stirred for 30 minutes before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 2% ether in petroleum ether) to yield a mixture of **103** and **91** (119 mg, 46%) in a 1:1 ratio.

Table 17, *entry 3*

Potassium hexamethyldisilazane (0.5 M, 2.53 ml, 1.27 mmol) was added dropwise to a stirred mixture of methyltriphenylphosphonium bromide (517 mg, 1.45 mmol) in THF (9 ml) at 0°C. The resulting bright yellow mixture was stirred for a further 30 minutes before being cooled to -78°C. Enone **98** (150 mg, 0.36 mmol) was added as a solution in THF (3 ml) and the reaction mixture was stirred for 1 hour before being warmed to room temperature. The reaction mixture was stirred for 30 minutes before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 2% ether in petroleum ether) to yield a mixture of **102** and **103** (101 mg, 72%) in a 1:0.38 ratio.

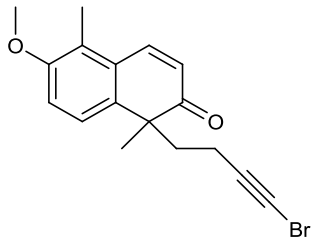
Table 17, *entry 4*

Potassium hexamethyldisilazane (0.5 M, 17.7 ml, 8.85 mmol) was added dropwise to a stirred mixture of methyltriphenylphosphonium bromide (3.620 g, 10.13 mmol) in THF (40 ml) at 0°C. The resulting bright yellow mixture was stirred for a further 30 minutes before being cooled to -78°C. Enone **98** (1.050 g, 2.53 mmol) was added as a solution in THF (10 ml) and the reaction mixture was stirred for 1 hour before the addition of potassium hexamethyldisilazane (0.5 M, 10.1 ml, 5.05 mmol). The resulting mixture was stirred for 30 minutes before being warmed to room temperature. The reaction mixture was stirred for 16 hours before being quenched with saturated ammonium chloride, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column

chromatography (eluent: petroleum ether to 2% ether in petroleum ether) to yield a mixture of **102**, **103**, and **91** (468 mg, 61%) in a 1.1:1:3 ratio.

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.43 (s, 3H, alkyl CH_3), 1.71-1.79 (m, 2H, alkyl CH_2), 1.85-1.99 (m, 2H, alkyl CH_2), 2.24 (s, 3H, $ArCH_3$), 3.83 (s, 3H, $ArOCH_3$), 5.17 (s, 1H, terminal olefinic CH), 5.19 (s, 1H, terminal olefinic CH), 6.35 (d, *J* = 10.0 Hz, 1H, olefinic CH), 6.64 (d, *J* = 10.1 Hz, 1H, olefinic CH), 6.74 (d, *J* = 8.6 Hz, 1H, ArH), 7.17 (d, *J* = 8.6 Hz, 1H, ArH).

Preparation of 1-(4-Bromobut-3-ynyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one, 104.



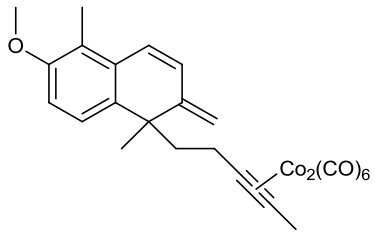
A yellow solution of dibromide **98** (160 mg, 0.39 mmol) in THF (3.9 ml) was stirred at -78°C. Potassium hexamethyldisilazane (0.5 M, 1.93 ml, 0.97 mmol) was added dropwise and the resulting dark blue solution was stirred for 30 minutes. Methyl iodide (72 µl, 1.16 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 30 minutes before being quenched with saturated sodium bicarbonate, diluted with diethyl ether, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 10% ether in petroleum ether) to yield the desired product **104** (106 mg, 82%) as a pale yellow oil.

FTIR (CH_2Cl_2): 1572, 1656 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.40 (s, 3H, alkyl CH_3), 1.72-1.91 (m, 2H, alkyl CH_2), 2.02-2.09 (m, 1H, alkyl CH), 2.36 (s, 3H, $ArCH_3$), 2.46-2.54 (m, 1H, alkyl CH), 3.87 (s, 3H, $ArOCH_3$), 6.20 (d, *J* = 10.2 Hz, 1H, olefinic CH), 6.95 (d, *J* = 8.6 Hz, 1H, ArH), 7.21 (d, *J* = 8.6 Hz, 1H, ArH), 7.81 (d, *J* = 10.3 Hz, 1H, olefinic CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 203.5, 156.2, 141.0, 137.1, 128.9, 125.4, 125.1, 124.4, 112.1, 79.6, 55.8, 50.5, 40.3, 38.3, 29.1, 15.8, 10.8 ppm.

HRMS *m/z* (ESI) Calc. for $C_{17}H_{18}BrO_2$ (M^++H): 333.0489. Found 333.0485.

Preparation of 1,2-dihydro-6-methoxy-1,5-dimethyl-2-methylen-1-(pent-3-ynyl)naphthalene dicobalt hexacarbonyl, 105.



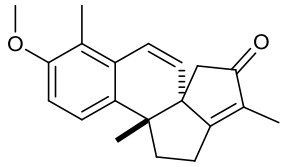
Alkyne **8** (267 mg, 1.00 mmol) was stirred in distilled light petroleum ether (15 ml) at room temperature. Dicobalt octacarbonyl (412 mg, 1.20 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. The deep red solution was concentrated and the crude product was purified by column chromatography (eluent: petrol) to yield the desired product **105** (513 mg, 96%) as a dark red oil.

FTIR (CH_2Cl_2): 1572, 1597, 2018, 2046, 2086 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.46 (s, 3H, alkyl CH_3), 2.01-2.09 (m, 1H, alkyl CH_2), 2.19-2.38 (m, 5H, $ArCH_3$ and alkyl CH_2), 2.50-2.15 (m, 4H, alkynyl CH_3 and alkyl CH_2), 3.82 (s, 3H, $ArOCH_3$), 5.19 (s, 1H, terminal olefinic CH), 5.22 (s, 1H, terminal

olefinic CH) 6.41 (d, *J* = 7.4 Hz, 1H, olefinic CH), 6.69 (d, *J* = 7.4 Hz, 1H, olefinic CH), 6.76 (d, *J* = 6.0 Hz, 1H, ArH), 7.20 (d, *J* = 6.0 Hz, 1H, ArH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 200.2, 155.9, 150.1, 134.7, 131.6, 129.8, 123.2, 122.5, 122.2, 113.3, 109.6, 100.8, 93.8, 55.6, 46.6, 42.2, 34.2, 28.5, 20.3, 10.7 ppm.
HRMS *m/z* (ESI) Calc. for $C_{25}H_{23}Co_2O_7$ (M^++H): 553.0093. Found 553.0102.

Preparation of (5a*S,11b*R**)-5,11b-Dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-*a*]naphthalen-4(2*H*)-one, 7**.[96]



General procedure A:
Sulfide additive was added to a stirred solution of cobalt complex **105** in 1,2-DCE at room temperature. The reaction mixture was heated to reflux and stirred at this temperature for the allotted time. The reaction mixture was then allowed to cool to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petrol ether to 20% ether in petroleum ether) to yield the desired product **7** as a pale yellow oil.

Following **General procedure A**, data are reported as (a) sulfide and amount, (b) amount of cobalt complex **105**, (c) amount of 1,2-DCE (d) reaction time, and (e) product yield.

Table 18, *entry 1*
(a) DodSMe, 0.17 ml, 0.63 mmol, (b) 100 mg, 0.18 mmol, (c) 5 ml, (d) 48 h, (e) 19 mg, 36%.

Table 18, *entry 2*

(a) DodSMe, 0.085 ml, 0.32 mmol, (b) 50 mg, 0.09 mmol, (c) 2.5 ml, (d) 120 h, (e) 12 mg, 45%.

Table 18, *entry 3*

(a) *n*-BuSMe, 0.064 ml, 0.51 mmol, (b) 80 mg, 0.145 mmol, (c) 4 ml, (d) 120 h, (e) 12 mg, 28%.

Table 18, *entry 4*

(a) DodSMe, 0.926 ml, 3.5 mmol, (b) 536 mg, 1 mmol, (c) 10 ml, (d) 48 h, (e) 80 mg, 28%.

Table 18, *entry 5*

(a) DodSMe, 0.345 ml, 1.31 mmol, (b) 200 mg, 0.37 mmol, (c) 3.7 ml, (d) 60 h, (e) 67 mg, 61%.

General procedure B:

DodSMe was added to a stirred solution of cobalt complex **105** in 1,2-DCE in a microwave vessel. The vessel was sealed and the reaction mixture was heated under the conditions specified for 10 minutes. The reaction mixture was then concentrated *in vacuo*. The crude product was purified by column chromatography to yield the material specified.

Following **General procedure B**, data are reported as (a) amount of DodSMe, (b) amount of cobalt complex **105**, (c) amount of 1,2-DCE, (d) heating conditions, (e) eluent, and (f) material recovered.

Table 18, *entry 6*

(a) DodSMe, 85 μl, 0.32 mmol, (b) 50 mg, 0.09 mmol, (c) 2.5 ml, (d) 90°C with cooling function on, (e) petroleum ether, and (f) cobalt complex **105**, 42 mg.

Table 18, *entry 7*

(a) DodSMe, 85 µl, 0.32 mmol, (b) 50 mg, 0.09 mmol, (c) 2.5 ml, (d) 150°C with cooling function off, (e) petroleum ether to 20% diethyl ether in petroleum ether, and (f) decomplexed alkyne **8**, 19 mg.

Scheme 127

Alkyne **8** (50 mg, 0.19 mmol) was stirred in toluene (1.6 ml) in a microwave vessel. DodSMe (60 µl, 0.23 mmol) was added followed by dicobalt octacarbonyl (13 mg, 0.038) and the vessel was sealed immediately. The reaction mixture was heated to 120°C for 50 minutes, with the cooling function off. The reaction mixture was then concentrated *in vacuo* and the crude product was purified by column chromatography to recover the unreacted alkyne **8** (41 mg).

Scheme 128

Alkyne **8** (40 mg, 0.15 mmol) was stirred in 1,2-DCE (0.3 ml). The reaction vessel was evacuated and back filled with carbon monoxide *via* a three way tap attached to a vacuum manifold and a carbon monoxide balloon. This process was repeated three times before the addition of dichlorotetracarbonyldirhodium(I) (2.9 mg, 0.0075 mmol). The vessel was once again evacuated and back filled with carbon monoxide. The mixture was then warmed to 60°C and stirred for 16 hours. TLC analysis showed only starting material to be present, therefore the reaction mixture was warmed to 70°C and was stirred for a further 16 hours. TLC analysis showed multiple spots and the reaction was abandoned.

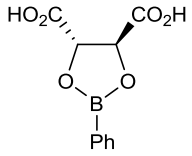
Scheme 129

Dichlorotetracarbonyldirhodium(I) (29.2 mg, 0.075 mmol) was added to a stirred solution of alkyne **8** (40 mg, 0.15 mmol) in 1,2-DCE (0.3 ml). The deep purple solution was warmed to 60°C and was stirred for 16 hours. TLC analysis showed multiple spots and the reaction was abandoned.

FTIR (CH_2Cl_2): 1577, 1665, 1702 cm^{-1}.

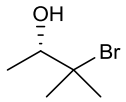
^1H NMR δ(400 MHz, $CDCl_3$): 1.23 (s, 3H, alkyl CH_3), 1.73-1.79 (m, 4H, alkyl CH_2 and vinyl CH_3), 2.11 (d, ^2J = 18.2 Hz, 1H, $C(O)CH_2$), 2.23-2.28 (m, 4H, $ArCH_3$ and alkyl CH_2), 2.50 (d, ^2J = 18.4 Hz, 1H, $C(O)CH_2$), 2.50-2.61 (m, 2H, alkyl CH_2), 3.83 (s, 3H, $ArOCH_3$), 5.58 (d, J = 9.9 Hz, 1H, olefinic CH), 6.77 (d, J = 8.5 Hz, 1H, ArH), 6.80 (d, J = 9.9 Hz, 1H, olefinic CH), 7.21 (d, J = 8.5 Hz, 1H, ArH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 210.4, 186.3, 156.4, 133.6, 133.0, 132.6, 130.3, 123.6, 123.1, 122.7, 109.1, 57.0, 55.6, 44.2, 43.1, 42.7, 24.7, 19.8, 10.8, 8.6 ppm.

Preparation of (4*S*,5*S*)-2-phenyl-1,3,2-dioxaborolan-4,5-dicarboxylic acid.



THF (50 ml) was added to a flask containing D-(-)-tartaric acid (1.501 g, 10 mmol), phenyl boronic acid (1.219 g, 10 mmol), and calcium hydride (842 mg, 20 mmol). The reaction mixture was refluxed for 1 hour and then allowed to cool to room temperature. The white precipitate was removed by filtration to deliver a 0.2 M solution of the desired product in THF.

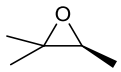
Preparation of (*S*)-3-bromo-3-methylbutan-2-ol, **107**.



Boronic ester (0.2 M in THF, 45 ml, 9 mmol) was added to a flask containing ketone **108** (558 µl, 4.5 mmol). The reaction mixture was cooled to 0°C and was stirred for 15 minutes. Sodium borohydride (340.5 mg, 9 mmol) was added in one portion and the reaction mixture was stirred for 2 hours. The reaction mixture was quenched with ammonium chloride (45 ml) resulting in the formation of a white precipitate. Water (50 ml) was added to dissolve the precipitate and the reaction mixture was extracted with diethyl ether. The organic extracts were combined, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* (100 mbar/19°C). The crude product was purified by column chromatography (eluent: petroleum ether to 20% ether in petroleum ether) to yield the desired product **107** (549 mg, 73%, 94% e.e.) as a colourless liquid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.25 (d, J = 6.3 Hz, 3H, $CH(OH)CH_3$), 1.73 (s, 3H, $CBrCH_3$), 1.81 (s, 3H, $CBrCH_3$), 3.65 (q, J = 6.3 Hz, 1H, CHOH).
Enantiomeric excess was determined using gas chromatography. Gas chromatography was carried out using a Carlo Erba HRGC 5300 gas chromatograph fitted with a CP Chirasil-DEX CB column. Detection was by flame ionisation and the chromatograph was interpreted using JLC 6000 computer software. Conditions: temperature 70-120^{o}C, flow rate 5^{o}C/min.

Preparation of (*S*)-2,2,3-trimethyloxirane, **106**.



Scheme 133

A 25 ml flask was fitted with a one piece distillation kit, a pig receiver adaptor, and three 5 ml flasks to collect the distillate. The apparatus was then flame dried and allowed to cool under an atmosphere of nitrogen. The flask was charged with potassium metal (936 mg, 23.9 mmol) and was cooled in an ice/water bath. Hexanol (12 ml) was added and the mixture was stirred for 15 minutes. The cooling bath was removed and the mixture was stirred for a further 30 minutes. The mixture became very viscous and solid potassium metal remained. The mixture was gently warmed with a heat gun until the solid dissolved and the mixture was allowed to cool to room temperature. Alcohol **107** (800 mg, 4.79 mmol) was added as a solution in hexanol (3 ml) and the immediate formation of a white precipitate was observed. The flask used to collect the distillate was then cooled in an acetone/dry ice bath. The reaction mixture was stirred at room temperature for 30 minutes before being warmed to 90°C. The mixture was heated for 3 hours, however no distillate was collected.

Scheme 134

A 25 ml flask was fitted with a one piece distillation kit, a pig receiver adaptor, and three 5 ml flasks to collect the distillate. The apparatus was then flame dried and allowed to cool under an atmosphere of nitrogen. The flask was charged with sodium metal (138 mg, 6 mmol) and was cooled in an ice/water bath. Hexanol (8 ml) was added and the mixture was stirred for 15 minutes. The cooling bath was removed and the mixture was stirred for a further 30 minutes. Alcohol **107** (500 mg, 2.99 mmol) was added as a solution in hexanol (2 ml) and the immediate formation of a white precipitate was observed. The flask used to collect the distillate was then cooled in an acetone/dry ice bath. The reaction mixture was stirred at room temperature for 30 minutes before being

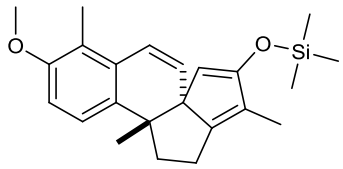
warmed to 70°C. The mixture was heated for 15 minutes before being warmed to 90°C and was stirred for 1 hour. As no distillate was collected at this temperature, the temperature was raised to 100°C for 30 minutes and then 120°C for 1 hour, however no distillate was collected.

Scheme 135

A 25 ml flask was fitted with a one piece distillation kit, a pig receiver adaptor, and three 5 ml flasks to collect the distillate. The apparatus was then flame dried and allowed to cool under an atmosphere of nitrogen. The flask was charged with potassium *t*-butoxide (1.5 g, 13.4 mmol), hexanol (5 ml), and alcohol **107** (450 mg, 2.7 mmol) as a solution in THF (2 ml). The flask used to collect the distillate was then cooled in an acetone/dry ice bath. The reaction mixture was stirred at room temperature for 30 minutes before being warmed to 120°C. The distillate (fraction 1) was collected and a further portion of THF (2 ml) was added. Again, the distillate (fraction 2) was collected and a further portion of THF (2 ml) was added. The distillate (fraction 3) was collected as before. ^{1}H NMR of the three individual fractions showed only fractions 1 and 2 to contain the desired epoxide. Fractions 1 and 2 were combined and fraction 3 was discarded. Sodium hydride (230 mg, 9.6 mmol) was added to the combined fractions and the mixture was stirred at room temperature for 1 hour. A distillation kit was fitted to the flask, the reaction mixture was then warmed to 90°C, and the epoxide **106** (76 mg, 33%) recovered *via* distillation as a solution in THF. The yield was calculated from the ratio of desired product to solvent as determined by ^{1}H NMR analysis.

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.24 (s, 3H, alkyl CH_3), 1.25 (d, J = 5.5 Hz, 3H, alkyl CH_3), 1.28 (s, 3H, alkyl CH_3), 2.82 (q, J = 5.5 Hz, 1H, OCH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 59.9, 58.1, 24.7, 18.4, 14.2 ppm.

Preparation of ((5a*R, 11a*R**)-2,11b-Dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-*a*]naphthalene-4-yloxy)trimethylsilane, 123**.



Scheme 160

Triethylamine (26 µl, 0.18 mmol) was added to a stirred solution of enone **7** (23 mg, 0.09 mmol) in DCM (5 ml) at 0°C. TMSOTf (25 µl, 0.14 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 20% ether in petroleum ether) but only starting material was recovered from the purification process.

Scheme 161

Triethylamine (20 µl, 0.14 mmol) was added to a stirred solution of enone **7** (18 mg, 0.07 mmol) in DCM (5 ml) at 0°C. TMSOTf (20 µl, 0.11 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was taken onto the next step without further purification.

Scheme 166

Triethylamine (26 µl, 0.18 mmol) was added to a stirred solution of enone **7** (23 mg, 0.09 mmol) in DCM (5 ml) at 0°C. TMSOTf (25 µl, 0.14 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by filtration through a plug of neutral alumina

(eluent: petroleum ether to 10% diethyl ether in petroleum ether) but only starting material was recovered.

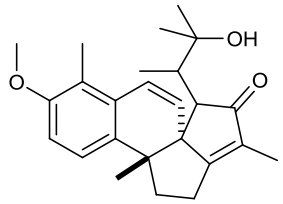
FTIR (CH_2Cl_2): 1577, 1628 cm^{-1}.

^1H NMR δ(500 MHz, $CDCl_3$): 0.22 (s, 9H, OTMS), 1.44 (s, 3H, alkyl CH_3), 1.70-1.73 (m, 4H, alkyl CH_2 and vinyl CH_3), 2.19 (dd, J = 15.4 Hz and J = 3.5 Hz, 1H, alkyl CH_2) 2.27 (s, 3H, $ArCH_3$), 2.74 (dd, ^2J = 22.3 Hz and J = 16.1 Hz, 2H, alkyl CH_2), 3.83 (s, 3H, $ArOCH_3$), 5.35 (s, 1H, vinyl CH), 5.79 (d, J = 10.0 Hz, 1H, vinyl CH), 6.72 (d, J = 10.0 Hz, 1H, vinyl CH), 6.75 (d, J = 8.5 Hz, 1H, ArH), 7.24 (d, J = 8.5 Hz, 1H, ArH).

^{13}C NMR δ(125 MHz, $CDCl_3$): 157.7, 157.3, 156.1, 134.5, 132.8, 131.2, 122.8, 122.0, 120.1, 112.6, 112.4, 108.6, 56.4, 55.6, 53.8, 47.0, 38.8, 22.1, 10.8, 8.8, 0.6 ppm.

Accurate mass data could not be obtained for this sensitive compound.

Attempted Preparation of (5a*R*,11b*R*)-5,11b-Dihydro-5-(3-hydroxy-3-methylbutan-2-yl)-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-*a*]naphthalen-4(2*H*)-one, 1.**



Scheme 136

n-BuLi (2.5 M, 27 µl, 0.068 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (14 µl, 0.102 mmol) in THF (2.5 ml) at 0°C. The reaction mixture was stirred for 30 minutes before being cooled to -78°C. Enone **7** (10 mg, 0.034 mmol) was added as a solution in THF (0.5 ml) and the mixture was stirred for a further 30 minutes. Epoxide **106** (36 µl, 0.34 mmol) was added, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 16 hours. The reaction mixture was

quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed there to be none of the desired product **1** present in the crude reaction mixture.

Scheme 137

n-BuLi (2.5 M, 27 µl, 0.068 mmol) was added slowly to a stirred mixture of di-*iso*-propylamine (14 µl, 0.102 mmol) and lithium chloride (2.9 mg, 0.068 mmol) in THF (2.5 ml) at 0°C. DMPU (2 µl, 0.017 mmol) was then added and the reaction mixture was stirred for 30 minutes before being cooled to -78°C. Enone **7** (10 mg, 0.034 mmol) was added as a solution in THF (0.5 ml) and the mixture was stirred for a further 30 minutes. Epoxide **106** (36 µl, 0.34 mmol) was added, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed there to be none of the desired product **1** present in the crude reaction mixture.

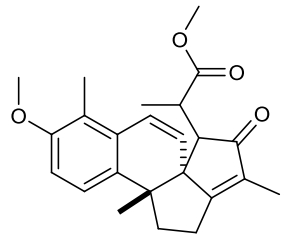
Scheme 138

n-BuLi (2.5 M, 27 µl, 0.068 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (14 µl, 0.102 mmol) in THF (2.5 ml) at 0°C. The reaction mixture was stirred for 30 minutes before being cooled to -78°C. Enone **7** (10 mg, 0.034 mmol) was added as a solution in THF (0.5 ml) and the mixture was stirred for a further 30 minutes. Epoxide **106** (36 µl, 0.34 mmol) was added in a solution of THF (1 ml) containing anhydrous lithium perchlorate (18.1 mg, 0.17 mmol), the reaction mixture was allowed to warm to room temperature, and stirring was continued for 16 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed there to be none of the desired product **1** present in the crude reaction mixture.

Scheme 162

Epoxide **106** (76 µl, 0.72 mmol) was added to a stirred mixture of lithium perchlorate (38 mg, 0.36 mmol) in DCM (1 ml). The solution was stirred for 5 minutes before the addition of enol ether **123** (crude product from the reaction described in **Scheme 181**) as a solution in DCM (1 ml). The reaction mixture was stirred for 3 hours but TLC analysis showed only starting material (enol ether **121**) to be present. Excess lithium perchlorate (114 mg, 1.08 mmol) was added and the reaction mixture was stirred for 16 hours. After this time, TLC analysis showed there to be remaining enol ether and a faint spot corresponding to enone **7**. The reaction mixture was made up to 2.5 M with lithium perchlorate (378 mg) and the reaction mixture was stirred overnight. TLC analysis showed mass degradation and the reaction was abandoned.

Attempted Preparation of Methyl 2-((5a*R,11b*R**)-2,4,5,11b-tetrahydro-9-methoxy-3,8,11b-trimethyl-4-oxo-1H-pentaleno[1,6a-*a*]naphthalen-5-yl)propanoate, 124.**



Scheme 139

A 12mM solution of LDA was prepared by the addition of *n*-BuLi (2.5 M, 0.48 ml, 1.2 mmol) to a solution of di-*iso*-propylamine (0.198 ml, 1.4 mmol) in THF (100 ml) at 0°C. In a separate flask, a portion (2 ml) of the LDA solution was cooled to -78°C and enone **7** (5 mg, 0.02 mmol) was added as a solution in THF (1 ml). The mixture was stirred for 30 minutes. Meanwhile, trifluoromethanesulfonic anhydride (48 µl, 0.285 mmol) was added to a solution of methyl lactate (29.5 µl, 0.26 mmol) in DCM (6 ml) at 0°C. The

solution was stirred for 5 minutes before the addition of pyridine (23.5 µl, 0.292 mmol), after which a white precipitate formed immediately. The mixture was stirred for a further 5 minutes before 2/3 of the solvent was removed *in vacuo*. Hexane (5 ml) was added and the suspension was washed with water. The water washings were extracted with hexane and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The freshly prepared triflate **107** was dissolved in THF (0.5 ml) and was added to the previously prepared enolate solution. Stirring was continued for 30 minutes before being warmed to room temperature overnight. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over Na_2SO_4, and concentrated *in* vacuo. ^{1}H NMR analysis showed there to be none of the desired product **124** present in the crude reaction mixture.

Scheme 163

A solution of enol ether **123** (0.08 mmol) in THF (0.11 ml) was added to a stirred mixture of potassium ethoxide (6.7 mg, 0.08 mmol) in THF (0.22 ml) at 0°C. The bright yellow solution was stirred for 10 minutes and TLC analysis confirmed that there was no remaining enol ether after this time. Meanwhile, trifluoromethanesulfonic anhydride (74 µl, 0.44 mmol) was added to a solution of methyl lactate (38 µl, 0.4 mmol) in DCM (0.93 ml) at 0°C. The solution was stirred for 5 minutes before the addition of pyridine (37 µl, 0.0.45 mmol), after which a white precipitate formed immediately. Hexane (2 ml) was added and the suspension was washed with water. The water washings were extracted with hexane and the organic layers were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The freshly prepared triflate **107** was dissolved in THF (0.1 ml) and was added to the previously prepared enolate solution. The resulting reaction mixture was stirred for 2 hours at 0°C before being warmed to room temperature and being stirred for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed only enone **7** to be present and the reaction was abandoned.

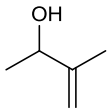
Scheme 164

A solution of enol ether **123** (0.08 mmol) in THF (0.11 ml) was added to a stirred mixture of potassium ethoxide (6.7 mg, 0.08 mmol) in THF (0.22 ml) at 0°C. The bright yellow solution was stirred for 10 minutes and TLC analysis confirmed that there was no remaining enol ether after this time. Methyl iodide (25 μl, 0.4 mmol) was added and the resulting reaction mixture was stirred for 2 hours at 0°C before being warmed to room temperature and being stirred for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed only enone **7** to be present and the reaction was abandoned.

Scheme 165

A solution of enol ether **123** (0.08 mmol) in THF (0.11 ml) was added to a stirred mixture of potassium ethoxide (6.7 mg, 0.08 mmol) in THF (0.22 ml) at 0°C. The bright yellow solution was stirred for 10 minutes and TLC analysis confirmed that there was no remaining enol ether after this time. Deuterium oxide (0.1 ml) was added and the resulting reaction mixture was stirred for 2 hours at 0°C before being warmed to room temperature and being stirred for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed only enone **7** to be present and the reaction was abandoned.

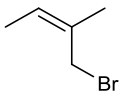
Preparation of 3-methylbut-3-en-2-ol, 111.[163]



Methylmagnesium chloride (3 M, 7.67 ml, 23 mmol) was stirred in THF (30 ml) at 0°C. Methacrolein (1.65 ml, 20 mmol) was added dropwise over 15 minutes and the reaction mixture was stirred for 1 hour before being allowed to warm to room temperature overnight. The reaction mixture was then poured into aqueous hydrochloric acid (25 ml) at 0°C. The mixture was then extracted with diethyl ether and the organic extracts were combined. The organic extracts were then washed with saturated sodium bicarbonate solution, dried over Na_2SO_4, and carefully concentrated *in vacuo*. The product, which contained residual THF, was taken through to the next step without further purification. ^{1}H NMR analysis of this material was in agreement with previously reported data for this compound.[163]

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.28-1.30 (m, 3H, alkyl CH_3), 1.76 (s, 3H, vinyl CH_3), 4.24-4.25 (m, 1H, OCH), 4.80 (s, 1H, olefinic CH), 4.97 (s, 1H, olefinic CH).

Preparation of (*Z*)-1-bromo-2-methylbut-2-ene, 109.[151]



Scheme 143

A solution of phosphorous tribromide (0.81 ml, 8.6 mmol) in light petroleum ether (23 ml) was slowly added to a stirred mixture of allyl alcohol **111** (1.72 g, 20 mmol) and pyridine (0.32 ml, 4 mmol) at -15°C. The mixture was stirred for 1 hour before the

stirring was stopped. The reaction mixture was left to stand overnight before the solvent was decanted. The remaining precipitate was washed with light petroleum ether and the solvent extracts were combined. The desired product **109** and by-product **112** was isolated as a 1:1 mixture *via* distillation (b.p. 90-95°C).

Data for **109**:

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.64 (d, *J* = 6.8 Hz, 3H, vinyl CH_3), 1.77 (s, 3H, vinyl CH_3), 3.99 (s, 2H, vinyl CH_2), 5.70 (q, *J* = 6.7 Hz, 1H, olefinic CH).

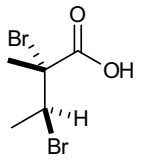
Data for **112**:

^{1}H NMR δ(500 MHz, $CDCl_3$): 1.80 (d, *J* = 6.8 Hz, 3H, alkyl CH_3), 1.90 (s, 3H, vinyl CH_3), 4.74 (q, *J* = 6.8 Hz, 1H, CHBr), 4.88 (s, 1H, olefinic CH), 5.10 (s, 1H, olefinic CH).

Scheme 150

Allylic alcohol **117** (333 mg, 3.78 mmol) was stirred in diethyl ether (7.5 ml) at -5°C. Phosphorous tribromide (178 µl, 1.89 mmol) was added dropwise and the mixture was stirred at this temperature for a further 2 hours. The reaction mixture was then washed with aqueous potassium carbonate, then with brine, and dried over Na_2SO_4. The solvent was removed by distillation, however none of the desired product was recovered from the residue, as outlined in the literature procedure. Instead, only a black tar was obtained.

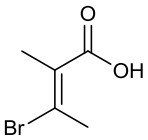
Preparation of (2*R,3*S**)-2,3-Dibromo-2-methylbutanoic acid, 115**.[154]



Bromine (2.15 ml, 41.9 mmol) was added to a stirred solution of tiglic acid **114** (4 g, 40.0 mmol) in DCM (100 ml) and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the solid residue was recrystallised from petroleum ether. The desired product **115** (9.76 g, 94%) was obtained as a white crystalline solid.

M.P. = 75-77°C (Lit. M. P. = 82-88°C)[154]
FTIR (CH_2Cl_2): 1715, 2993 cm^{-1}.
^1H NMR δ(500 MHz, $CDCl_3$): 1.93 (d, J = 6.9 Hz, 3H, CH_3), 2.01 (s, 3H, CH_3), 4.85 (q, J = 6.8 Hz, 1H, CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 175.4, 61.5, 51.0, 21.1, 20.9 ppm.

Preparation of (*E*)-3-Bromo-2-methylbut-2-enoic acid, 116.[154]

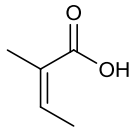


A 25% solution of potassium hydroxide in methanol (56 g) was added to a stirred solution of dibromide **115** (9.76 g, 37.5 mmol) in methanol (6 ml). Anhydrous potassium carbonate (1 g) was added and the reaction mixture was warmed to 55°C and was held at this temperature for 2 hours. Excess potassium hydroxide was removed by bubbling carbon dioxide through the reaction mixture for 15 minutes. The warm reaction mixture

was filtered and the salt was washed with warm methanol (50 ml). The methanolic solution was concentrated *in vacuo* and the residue was dissolved in distilled water (10 ml). The aqueous solution was acidified to Congo Red with 6 M hydrochloric acid. The precipitate was then filter, dried, and recrystallised from petroleum ether to deliver the desired product **116** (2.73 g, 36%) as a white solid.

M.P. = 90-91°C (Lit. M. P. = 92-94.5°C)[154]
FTIR (CH_2Cl_2): 1605, 1710, 2989 cm^{-1}.
^1H NMR δ(500 MHz, $CDCl_3$): 2.11 (s, 3H, CH_3), 2.75 (s, 3H, CH_3). ^{13}C NMR δ(125 MHz, $CDCl_3$): 170.9, 140.2, 126.9, 28.1, 14.5 ppm.

Preparation of (*Z*)-2-methylbut-2-enoic acid, 113.[154]

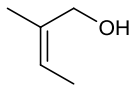


Firstly, a 6% sodium mercury amalgam was prepared according to the modification of a procedure reported by Sibert for the preparation of a 2% amalgam.[155] Mercury (11.33 g) was added in one portion to a flask containing sodium metal (690 mg) which was gently, but efficiently, stirred with a stir bar. The flask was heated with a flame to initiate the reaction. The amalgam was then allowed to stir for 5 minutes before being heated intermittently with a flame for 5 minutes. The solid 6% amalgam was then allowed to cool to room temperature. The amalgam was then cooled to 5°C and 5 ml of distilled water was added. Bromo acid **116** (300 mg, 1.69 mmol) was added and the mixture was stirred for 3 hours at this temperature. The cooling bath was then removed and the mixture was allowed to warm to room temperature. Stirring was continued for a further 21 hours. The aqueous layer was decanted and the mercury was washed with water (10 ml). The aqueous mixtures were combined and were acidified to Congo Red with

concentrated HCl. The resulting white precipitate was filtered, air-dried, and finally recrystallised from light petroleum ether to yield the desired product **113** (77 mg, 46%) as a white solid.

M.P. = 50-52°C (Lit. M. P. = 44-46°C)[154]
FTIR (CH_2Cl_2): 1644, 1683, 2928 cm^{-1}.
^1H NMR δ(500 MHz, $CDCl_3$): 1.92 (m, 3H, CH_3), 2.05 (dq, *J* = 7.4 and 1.5 Hz, 3H, CH_3), 6.24 (qq, *J* = 7.3 and 1.5 Hz, 1H, olefinic CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 173.9, 141.1, 127.2, 20.3, 16.0 ppm.

Preparation of (*Z*)-2-methylbut-2-en-1-ol, 117.[164]

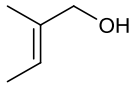


Lithium aluminium hydride (37 mg, 0.98 mmol) was added to a stirred solution of angelic acid **113** (77 mg, 0.78 mmol) in diethyl ether (7.8 ml) at 0°C. The mixture was then allowed to warm to room temperature and was stirred for 16 hours. Water (37 μl) was then added and the mixture was stirred for a further 10 minutes. After this time, 15% sodium hydroxide solution (37 μl) was added and stirring was continued for 10 minutes. A second portion of water (111 μl) was added followed by solid sodium bicarbonate (20 mg) and the mixture was stirred for 20 minutes. The reaction mixture was filtered through celite with diethyl ether as the eluent. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. The desired product **117** (49 mg, 73%) was used in the next step without further purification.

FTIR (CH_2Cl_2): 3361 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.66 (d, J = 6.9 Hz, 3H, CH_3), 1.81 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 5.40 (q, J = 6.9 Hz, 1H, olefinic CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 134.4, 122.1, 60.8, 12.8, 12.6 ppm.

Preparation of (*E*)-2-methylbut-2-en-1-ol, 118.[165]

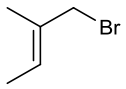


Lithium aluminium hydride (1.90 g, 75 mmol) was added to a stirred solution of tiglic acid **112** (5 g, 50 mmol) in diethyl ether (250 ml) at 0°C. The mixture was then allowed to warm to room temperature and was stirred for 16 hours. Water (1.9 ml) was then added and the mixture was stirred for a further 10 minutes. After this time, 15% sodium hydroxide solution (1.9 ml) was added and stirring was continued for 10 minutes. A second portion of water (5.7 ml) was added followed by solid sodium bicarbonate (400 mg) and the mixture was stirred for 20 minutes. The reaction mixture was filtered through celite with diethyl ether as the eluent. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. The desired product **118** (3.65 g, 85%) was used in the next step without further purification.

FTIR (CH_2Cl_2): 3343 cm^{-1}.

^1H NMR δ(500 MHz, $CDCl_3$): 1.61 (m, 3H, CH_3), 1.65 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 5.45-5.50 (m, 1H, olefinic CH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 135.5, 120.6, 68.9, 13.3, 13.1 ppm.

Preparation of (*E*)-2-methylbut-2-en-1-ol, 119.[151]



Scheme 152

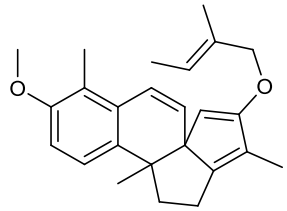
Allylic alcohol **118** (1.5 g, 17.05 mmol) was stirred in diethyl ether (34 ml) at -5°C. Phosphorous tribromide (0.8 ml, 8.53 mmol) was added dropwise and the mixture was stirred at this temperature for a further 2 hours. The reaction mixture was then washed with aqueous potassium carbonate, washed with brine, and dried over Na_2SO_4. The solvent was removed by distillation, and the desired product was obtained *via* distillation as a solution in diethyl ether.

Scheme 154

Allylic alcohol **118** (1.5 g, 17.05 mmol) was stirred in diethyl ether (34 ml) at -5°C. Phosphorous tribromide (0.8 ml, 8.53 mmol) was added dropwise and the mixture was stirred at this temperature for a further 2 hours. The reaction mixture was then washed with aqueous potassium carbonate, washed with brine, and dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: light petroleum ether to 10% diethyl ether in light petroleum ether) to yield the desired product **119** as a solution in diethyl ether.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.63-1.65 (m, 3H, CH_3), 1.77 (s, 3H, CH_3), 3.99 (s, 2H, CH_2), 5.68-5.73 (m, 1H, olefinic CH).

Preparation of (5a*R, 11b*R**)-2,11b-Dihydro-9-methoxy-3,8,11b-trimethyl-4((*E*)-2-methylbut-2-enyloxy)-1H-pentaleno[1,6a-*a*]naphthalene, 120**.



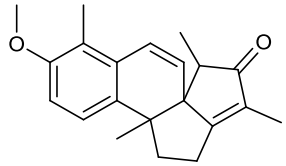
Scheme 153

A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred mixture of sodium hydride (2.4 mg, 0.1 mmol) in THF (1.5 ml) at 0°C. The mixture was stirred for 30 minutes before the addition of allylic bromide **119** (45 mg, 0.3 mmol) as a solution in THF. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product showed that there was only starting material present.

Scheme 155

A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred mixture of sodium hydride (2.4 mg, 0.1 mmol) in THF (1.5 ml) at 0°C. The mixture was stirred for 30 minutes before the addition of allylic bromide **119** (45 mg, 0.3 mmol) as a solution in THF. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product showed that there was only starting material present.

Preparation of (5a*R, 11a*R**)-5,11b-Dihydro-9-methoxy-3,5,8,11b-tetramethyl-1H-pentaleno[1,6a-*a*]naphthalene-4(2H)-one, 121**.



Scheme 156

A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred mixture of sodium hydride (2.4 mg, 0.1 mmol) in THF (1.5 ml) at 0°C. The mixture was stirred for 30 minutes before the addition of methyl iodide (13 µl, 0.2 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product showed that only starting material was present and the reaction was abandoned.

Scheme 157

A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred solution of LDA (0.04 mmol, from a stock solution) in THF (1.5 ml) at -78°C. The mixture was stirred for 30 minutes before the addition of methyl iodide (13 µl, 0.2 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis of the crude product showed that there was only starting material present and the reaction was abandoned.

Scheme 158

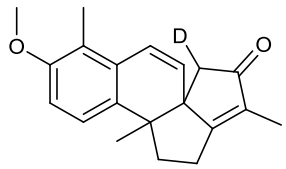
A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred solution of KHMDS (0.5 M, 80 µl, 0.04 mmol) in THF (1.5 ml) at 0°C. The mixture was stirred for 30 minutes before the addition of methyl iodide (13 µl, 0.2 mmol). The reaction mixture

was allowed to warm to room temperature and was stirred for 16 hours. The reaction was quenched with saturated sodium bicarbonate solution, washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis of the crude product showed that there was only starting material present and the reaction was abandoned.

Scheme 154

A solution of enol ether **123** (0.08 mmol) in THF (0.11 ml) was added to a stirred mixture of potassium ethoxide (6.7 mg, 0.08 mmol) in THF (0.22 ml) at 0°C. The bright yellow solution was stirred for 10 minutes and TLC analysis confirmed that there was no remaining enol ether after this time. Methyl iodide (25 µl, 0.4 mmol) was added and the resulting reaction mixture was stirred for 2 hours at 0°C before being warmed to room temperature and being stirred for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis showed only enone **7** to be present and the reaction was abandoned.

Preparation of (5a*R*, 11b*R***)-5-Deutero-5,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-*a*]naphthalene-4(2H)-one, 120**.



Scheme 159

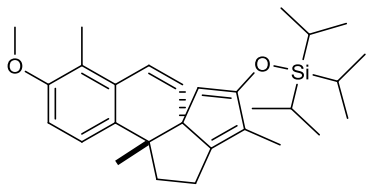
A THF (0.5 ml) solution of enone **7** (5 mg, 0.02 mmol) was added to a stirred solution of KHMDS (0.5 M, 80 µl, 0.04 mmol) in THF (1.5 ml) at 0°C. The mixture was stirred for 30 minutes before the addition of deuterium oxide (0.5 ml). The reaction mixture was allowed to warm to room temperature and was stirred for 16 hours. The reaction was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^1H NMR analysis of

the crude product showed that there was only starting material present and the reaction was abandoned.

Scheme 165

A solution of enol ether **123** (0.08 mmol) in THF (0.11 ml) was added to a stirred mixture of potassium ethoxide (6.7 mg, 0.08 mmol) in THF (0.22 ml) at 0°C. The bright yellow solution was stirred for 10 minutes and TLC analysis confirmed that there was no remaining enol ether after this time. Deuterium oxide (0.1 ml) was added and the resulting reaction mixture was stirred for 2 hours at 0°C before being warmed to room temperature and being stirred for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, washed with water, and brine, dried over Na_2SO_4, and concentrated *in vacuo*. ^{1}H NMR analysis showed only enone **7** to be present and the reaction was abandoned.

Preparation of Triisopropyl-(5a*R,11a*R**)-2,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-*a*]naphthalene-4-yloxy)silane, 125**.



Scheme 167

Triethylamine (22 μl, 0.16 mmol) was added to a stirred solution of enone **7** (20 mg, 0.08 mmol) in DCM (5 ml) at 0°C. TIPSOTf (32 μl, 0.12 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with

sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: petroleum ether to 20% ether in petroleum ether) but only starting material was recovered from the purification process.

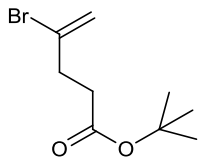
Scheme 168

Triethylamine (22 μl, 0.16 mmol) was added to a stirred solution of enone **7** (20 mg, 0.08 mmol) in DCM (5 ml) at 0°C. TIPSOTf (32 μl, 0.12 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent: petroleum ether to 20% ether in petroleum ether (all solvent used during this chromatography was doped with 3% triethylamine)) but only starting material was recovered from the purification process.

Scheme 169

Triethylamine (22 µl, 0.16 mmol) was added to a stirred solution of enone **7** (20 mg, 0.08 mmol) in DCM (5 ml) at 0°C. TIPSOTf (32 µl, 0.12 mmol) was added and the reaction mixture was stirred for 15 minutes. The reaction mixture was quenched with sodium bicarbonate, extracted with DCM, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography through a plug of neutral alumina (eluent: petroleum ether to 20% ether in petroleum ether) but only starting material was recovered from the purification process.

Preparation of *tert*-Butyl 4-bromopent-4-enoate, 130.[156]

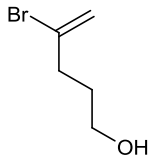


n-BuLi (2.5 M, 4.2 ml, 10.5 mmol) was added slowly to a stirred solution of di-*iso*-propylamine (1.68, 12 mmol) in THF (10 ml) at 0°C and the reaction mixture was stirred for 30 minutes. The LDA was then transferred dropwise *via* cannula into a stirred solution of *tert*-butyl acetate (1.35 ml, 10 mmol) in THF (10 ml) at -78°C. The solution was stirred for 1 hour before the dropwise addition of 2,3-dibromopropene (1.29 ml, 10 mmol). The reaction mixture was then stirred at -78°C for 1 hour before being warmed to room temperature and allowed to stir for a further 16 hours. The reaction mixture was concentrated *in vacuo* and water (50 ml) was added. The aqueous mixture was extracted with ethyl acetate and the organic extracts were combined. The organic extracts were then washed with brine, dried over Na_2SO_4, and concentrated *in* vacuo. The crude product was taked onto the next step without further purification.

FTIR (CH_2Cl_2): 1153, 1631, 1732, 2980 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.48 (s, 9H, *t*-Bu), 2.51 (t, *J* = 7.6 Hz, 2H, CH_2), 2.73 (t, *J* = 7.5 Hz, 2H, CH_2), 5.44 (d, *J* = 1.8 Hz, 1H, olefinic CH), 5.64 (t, *J* = 1.7 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 170.8, 132.1, 116.8, 59.9, 36.2, 33.7, 27.6 ppm.

Preparation of 4-bromopent-4-en-1-ol, 131.[156]

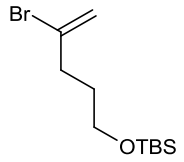


A solution of ester **130** (crude product from **Scheme 194**, 10 mmol) in diethyl ether (5 ml) was added to a stirred mixture of lithium aluminium hydride (418 mg, 11 mmol) in diethyl ether (10 ml) at a rate as to maintain a gentle reflux. Following the addition of the ester, the reaction mixture was stirred for 16 hours. The reaction mixture was quenched by the addition of water (0.46 ml) followed by 15% sodium hydroxide (0.46 ml) and finally a second protion of water (1.38 ml). The resulting precipitate was filtered and washed with diethyl ether. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to deliver alcohol **131**. The alcohol was taken onto the next step without further purification.

FTIR (CH_2Cl_2): 1629, 3426 cm^{-1}.

^1H NMR δ(400 MHz, $CDCl_3$): 1.96 (s, 1H, OH), 2.29-2.35 (m, 5H, allylic CH_2 and CH_3), 3.69 (t, *J* = 6.4 Hz, 2H, OCH_2), 5.91 (t, *J* = 7.7 Hz, 1H, olefinic CH). ^{13}C NMR δ(100 MHz, $CDCl_3$): 128.2, 121.8, 61.5, 33.0, 23.4 ppm.

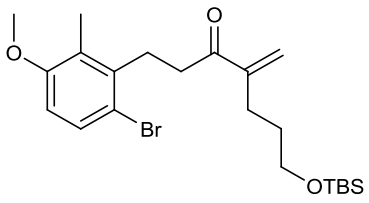
Preparation of (4-bromopent-4-enyloxy)(tert-butyl)dimethylsilane, 129.[156]



2,6-Lutidine (1.75 ml, 15 mmol) was added to a stirred solution of alcohol **131** (crude product from **Scheme 195**, 10 mmol) in dry DCM (30 ml). TBSOTf (2.53 ml, 11 mmol) was added to the solution and stirring was continued for a further hour. The reaction mixture was quenched with saturated sodium bicarbonate, the organic layer separated, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether) to yield the desired product **127** (1.308 g, 47%) as a colourless liquid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 0.06 (s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, *t*-BuCH_3), 1.78 (quintet, *J* = Hz, 2H, alkyl CH_2), 2.52 (t, *J* = Hz, 2H, vinyl CH_2), 3.65 (t, *J* = Hz, 2H, OCH_2), 5.41 (s, 1H, olefinic CH), 5.59 (s, 1H, olefinic CH).

Preparation of 1-(6-bromo-3-methoxy-2-methylphenyl)-7-(tert-butyldimethylsilyloxy)-4-methyleneheptan-3-one, 132.



t-BuLi (1.7 M, 5.5 ml, 9.36 mmol) was added slowly to a stirred solution of vinyl bromide **129** (1.3 g, 4.68 mmol) in dry diethyl ether (20 ml) at -78°C. The resulting solution was stirred for 1 hour.

Simultaneously, a 3-neck flask fitted with a condenser was charged with magnesium turnings (1.78 g, 73.6 mmol), flame dried under vacuum, and cooled under nitrogen. Once cool, benzene (18 ml) and diethyl ether (54 ml) were added and the slurry was stirred at room temperature. Dibromoethane (6.2 ml, 70 mmol) was added to the slurry at such a rate that it refluxed gently without external heating. After the addition was complete, the reaction mixture was heated so as to maintain a gentle reflux (50°C) for 1 hour. Heating and stirring were discontinued and the mixture (1 M anhydrous $MgBr_2.OEt_2$) was allowed to settle.

The 1 M anhydrous $MgBr_2.OEt_2$ solution (5.1 ml, 5.1 mmol) was added to the previously prepared vinyl lithium reagent at -78°C. The solution was stirred at this temperature for 10 minutes prior to warming to 0°C. The solution was stirred for 30 minutes at 0°C before the addition of Weinreb amide **55** (1.23 g, 3.9 mmol) as a dry diethyl ether (5 ml) solution. The solution was stirred for 30 minutes at 0°C prior to warming to room temperature for a further 30 minutes. The reaction mixture was quenched with saturated ammonium chloride, the organic phase was separated, washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether to 3% ether in petroleum ether) to yield the desired product **132** (1.379 g, 78%) as a colourless oil.

FTIR (CH_2Cl_2): 1573, 1677 cm^{-1}.

^1H NMR δ(500 MHz, $CDCl_3$): 0.06 (s, 6H, $Si(CH_3)_2$), 0.91 (s, 9H, *t*-$BuCH_3$), 1.64-1.69 (m, 2H, alkyl CH_2), 2.23 (s, 3H, $ArCH_3$), 2.35-2.38 (m, 2H, alkyl CH_2), 2.86-2.89 (m, 2H, alkyl CH_2), 3.08-3.11 (m, 2H, alkyl CH_2), 3.64 (t, J = 6.4 Hz, OCH_2), 3.81 (s, 3H, $ArCH_3$), 5.76 (s, 1H, olefinic CH), 6.04 (s, 1H, olefinic CH), 6.62 (d, J = 8.8 Hz, ArH), 7.36 (d, J = 8.8 Hz, ArH). ^{13}C NMR δ(125 MHz, $CDCl_3$): 200.8, 157.1, 148.3, 139.6, 130.2, 126.9, 124.3, 115.9, 109.9, 62.6, 55.7, 36.6, 31.51, 28.36, 27.26, 25.9, 18.3, 12.4, -5.3 ppm.

HRMS *m/z* (ESI) Calc. for $C_{22}H_{26}BrO_3Si$ (M^++H^+): 455.1608. Found 455.1612.

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