Towards the Total Synthesis of Agariblazeispirol C

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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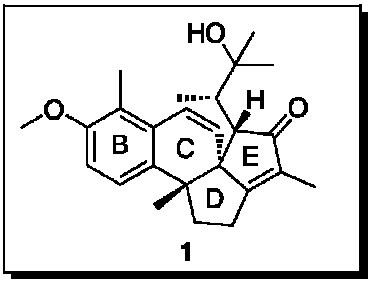
Abstract

The research described herein concerns the efforts towards the synthesis of the natural target Agariblazeispirol C, **1**. Within the Kerr laboratory, a synthetic route towards this novel steroid had been proposed. At the outset, work focused on this initially envisaged preparative pathway, however, in due course, an additional and more convergent route was devised. Both proposed pathways for gaining access to Agariblazeispirol C centre on the strategic employment of metal-mediated cyclisation chemistry, specifically, a novel intramolecular Heck reaction and an intramolecular Pauson-Khand cyclisation.

With regards to the construction of the main core of the molecule, the synthesis of a late stage intermediate has been accomplished. Various new strategies towards the completion of the synthesis have been devised and work has been initiated to execute these tactics. In addition to this, a series of optimisation studies on many of the individual steps have led to enhancements with respect to the overall efficiency of the route towards the natural product target.

In addition to the above, X-ray crystallography was used to unambiguously determine the relative stereochemistry of a key tetracyclic synthetic intermediate.



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Abbreviations

)))	Ultrasound
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aromatic
atm.	Atmospheres
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
CAN	Ceric ammonium nitrate
CNC	Colloidal cobalt nanoparticles on charcoal support
COD	Cyclooctadiene
Conv.	Conversion
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCHCC	Dicobalthexacarbonyl complex
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIOP	4,5-bis(diphenylphosphinomethyl)-2,2-dimethyldioxolane)
DMA	Dimethylacetamide
DME	Dimethoxyethane
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
e.e	Enantiomeric excess
Eq.	Equivalents

e.r.	Enantiomeric ratio
Et	Ethyl
IR	Infrared
g	Grammes
h	Hours
HPLC	High-performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IR	Infrared
LDA	Lithuim di-*iso*-propylamine
LUMO	Lowest Unoccupied Molecular Orbital
M	Molar
Me	Methyl
MeCN	Acetonitrile
mg	Milligrammes
MHz	Megahertz
Min	Minutes
ml	Millilitres
mmol	Millimoles
mol	Moles
MOM	Methoxymethyl ether
Ms	Methylsulfonyl
MS	Molecular sieves
MWI	Microwave irradiation
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance spectra; s – singlet d – doublet dd – double doublet t – triplet tq – triplet of quartets

	q – quartet
	m – multiplet
o	Ortho
p	Para
Ph	Phenyl
P-K	Pauson-Khand
PKR	Pauson-Khand Reaction
PMB	*para*-Methoxybenzyl ether
PMP	Pentamethyl piperidine
ppm	Parts per million
Pr	Propyl
Py	Pyridine
r.t.	Room temperature
s	seconds
SM	Starting material
Spec.	Spectroscopy
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Temp.	Temperature
Tf	trifluoromethanesuflonyl
THF	Tetrahydrofuran
TIPS	Tri-*iso*-propylsilyl
TLC	Thin layer chromatography
TMANO	Trimethylamine *N*-oxide
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol.	Toluene
Ts	*p*-Toluenesulfonyl

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Chapter 1

Thesis Overview

Thesis Overview

The following thesis contains an account of novel research in the area of synthetic organic chemistry, carried out in part fulfilment of the requirements of a Ph.D. degree at the University of Strathclyde. Specifically, the work carried out centres on the strategic application of metal-mediated cyclisation methods within the arena of natural product synthesis. The novel target in question is Agariblazeispirol C, a natural steroidal-type target, which was recently isolated from the cultured mycelia of *Agaricus blazei*.[1]

The text begins with a chapter containing general introductory aspects. More specifically, this section includes a short segment on the essence of natural product synthesis, followed by a brief introduction of Agariblazeispirol C and our proposed synthetic pathway to the preparation of this molecule. Following this, comprehensive reviews on the specific metal-mediated cyclisation methods used within this research programme are detailed. In particular, these reviews include a description of the discovery and development of the specific key reactions, together with a discussion of the mechanistic features and the use of this reaction in the total synthesis of complex molecules.

The next chapter comprises the actual research carried out during this Ph.D. programme, along with strategy plans and discussions of the results obtained. Following this, a brief summary of the work carried out, as well as an outline of some proposed extensions to the described research programme, is detailed.

The final chapters consist of details of experimental methods utilised throughout this research and the resultant analytical data recorded. In addition to this, the various publications referenced throughout the whole thesis are described, along with an appendix section, which contains specific structural data information.

Chapter 2

Introductory Aspects

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2.1 The Essence of Total Synthesis

The art and science of natural product synthesis has captured the attention of many scientists for over a century.[2] The ability to construct molecules that Nature produces has, naturally, invoked sheer intellectual stimulation. Becoming the flagship of organic synthesis, natural product synthesis symbolises the strength of preparative chemistry, in addition to defining its scope and limitations. Indeed, any attempt to catalogue the accomplishments within the broad history of natural product synthesis would be a colossal task; therefore, these introductory paragraphs simply exist to exemplify the physical act of creation that is synthesis.

The birth of natural product synthesis involved the preparation of urea from ammonium cyanate by Freidrich Wöhler in 1828.[3] At this time, this synthesis served to expose the concept that Nature exclusively created certain molecules. These days, the field of natural product synthesis continually attracts new researchers and one should consider the varied reasons for this interest. For example, the synthesis of a natural product can often provide the only real proof of the assigned chemical structure. The extraction of organic compounds from nature's sources can prove costly and, in the majority of cases, provides molecules only in minute quantities. Therefore, the preparation of natural products within a laboratory can, potentially, allow larger quantities of the target molecules to be accessed, which, allows more thorough examination of chemical structure. Indeed, the chemical literature is filled with adjustments of the originally proposed structures of natural products. In terms of biologically important molecules, countless natural products, and their derivatives, demonstrate intriguing properties. As such, many total synthesis research projects are striving to synthesise molecules, which display enhanced physiological properties, or completely novel modes of action within biology. In addition to this, for some chemists, natural product synthesis is used to depict the real capacity of their own developing methodology. Undoubtedly, the synthetic pathways towards natural products represent an incredibly challenging domain in which to sustain efficiency, robustness, and selectivity of a particular chemical transformation. Finally, there are chemists who will proudly declare that they embark upon the synthesis of

nature's creations for the sheer intellectual challenge and indisputable excitement that it will bestow.

In terms of recognition, the awarding of the Nobel Prize in Chemistry has commended the field of natural product synthesis.[4] As early as 1902, E. Fischer was awarded this prestigious recognition for his research into the synthesis of sugars and purine. Following this, research into the constitution and synthesis of haemin delivered the prize to H. Fischer in 1930; to R. Robinson in 1947 for the examination of the biological importance of alkaloids and, in 1965, to R. B. Woodward for his exceptional advances in organic synthesis. The most recent recognition was granted to E. J. Corey in 1990 for his growth of the methodology and theory within the arena of organic synthesis.

Today, the interest in natural product synthesis is exceptionally high, enticing many of this century's talented chemists. This field continues to deliver outstanding science, and acts as a channel for new discoveries within both synthetic organic chemistry and the biological sphere. With its history having been so rewarding, the future of natural product synthesis appears just as promising. Undoubtedly, there is a vast amount of Nature's intriguing compounds still to be revealed, and, when they are, they will inevitably incite new pieces of chemical research. This will continue to deliver new tools for the growth of molecular complexity, and diversity, within chemical synthesis and will develop our knowledge and understanding of organic chemistry overall.

2.2 Agariblazeispirol C

2.2.1 Introduction

Agariblazeispirol C, **1**, was recently isolated from the cultured mycelia of *Agaricus blazei*,[1] a precious fungus that produces many bioactive compounds in its fruiting bodies (**Figure 1**). As described in Hirotani's publication, the cultured mycelia of *Agaricus blazei* Murill were extracted with methanol at room temperature. This extract was reduced *in vacuo*, diluted with water and partitioned with chloroform and ethyl acetate. Purification of the chloroform extract by silica gel column chromatography and reversed-phase HPLC afforded Agariblazeispirol C.

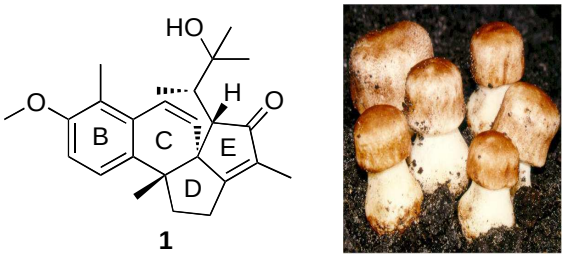

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Figure 1

As it turns out, *Agaricus blazei* is an important fungus for producing bioactive compounds. Indeed, molecules isolated from this fungus are known for their immuno-stimulating, cytotoxic, antimutagenic, and bactericidal effects.[5] Having stated this, the biological activity of Agariblazeispirol C is presently unreported.

Motifs of note within the relatively unfunctionalised Agariblazeispirol C structure include two synthetically challenging quaternary carbon centres, forming the juncture between rings C and D, as well as an (*S*) designated stereocentre α to the enone carbonyl group. The culmination of the four contiguous and inherently different stereocentres within the structure make **1** an extremely interesting and challenging target for total synthesis.

Furthermore, of particular interest to our research group is the presence of the cyclopentenone moiety that is ring E. Over the last two decades, a selection of the research within our laboratories has centred on the preparation of such ring structures *via* the cobalt-mediated Pauson-Khand reaction (PKR). Specifically, the work conducted has involved the extension of the scope of this process, the development of novel methods of promoting this reaction, and also examined its applicability in the field of total synthesis.[6]

From a biological perspective, the core ring structure of Agariblaziespirol C is an interesting and unusual type of steroid. Indeed, conventional steroids display a core ring structure in the form of three six-membered rings and one five-membered ring with the connectivity as shown in **2** (**Figure 2**).

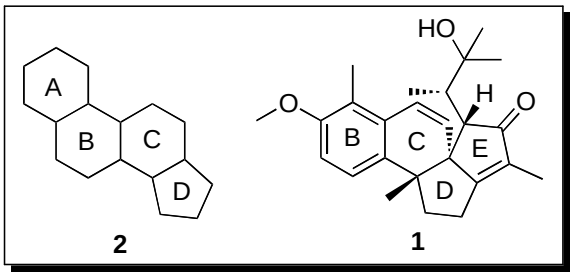


Figure 2

As can be seen from **Figure 2**, the structural core of Agairblazeispirol C differs in two ways to a customary steroid. Firstly, the A ring, present within a typical steroidal structure, is missing, and secondly, our natural target contains an extra cyclopentenone unit (ring E). In fact, compounds with the A ring of the conventional steroid absent have previously been reported within the chemical literature and are referred to as des-A-ergostanes. Shown in **Figure 3** are compounds of the type **3**, which were the first sedimentary des-A-ergostanes to be discovered; isolated from a Cretaceous black shale in Italy.[7]

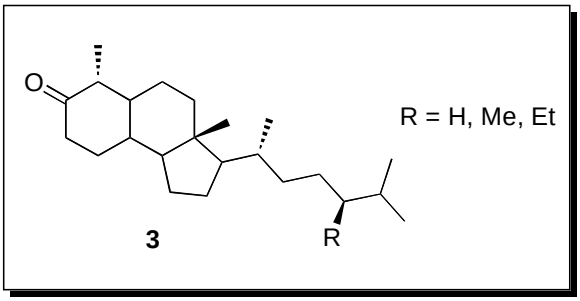
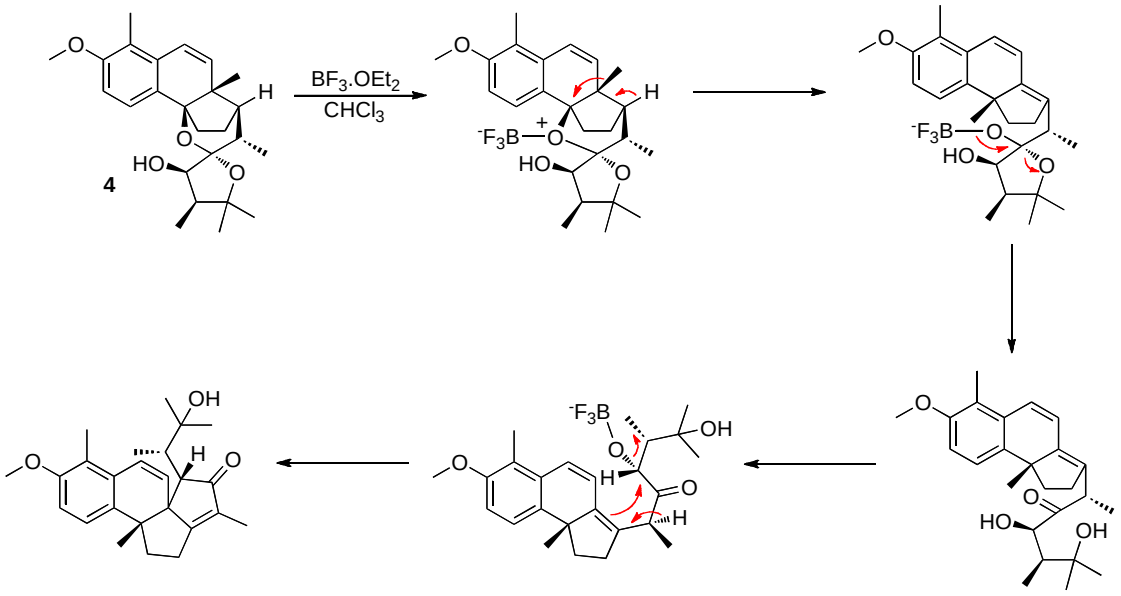


Figure 3

2.2.2 Biosynthesis

Within Hirotani's publication,[1] detailing the isolation and structure elucidation of Agariblazeispirol C, the authors suggest the formation of our target natural product is related to the further reactions of Blazeispirol A, **4**. Indeed, upon reaction of **4** with boron trifluoride diethyl etherate, Agariblazeispirol C was furnished. The authors explain this interesting transformation *via* the mechanism shown in **Scheme 1**.



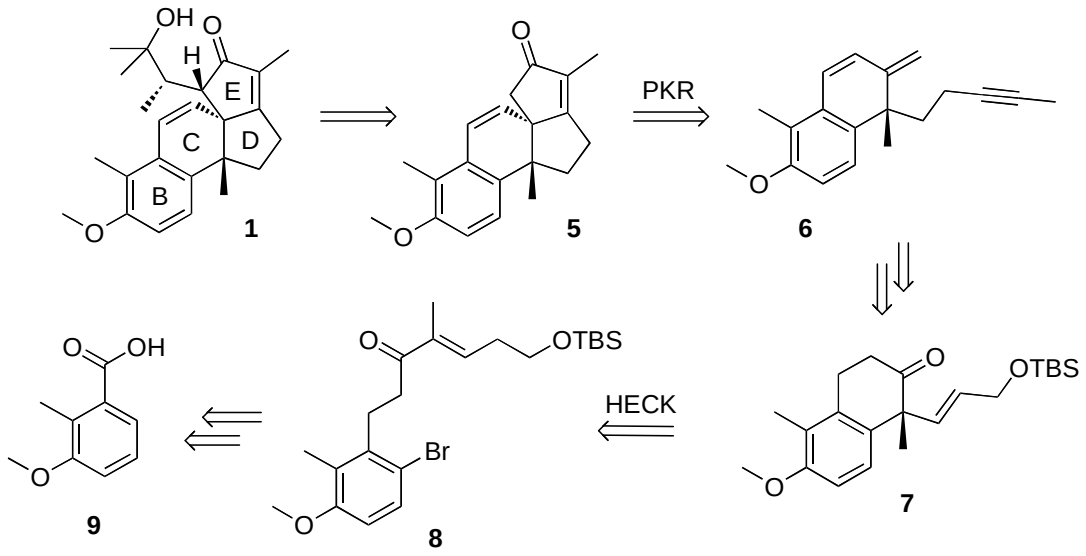
Scheme 1

The biosynthetic origin of Agariblazeispirol C can be traced back further as the origin of the precursor, Blazeispirol A, has been studied in far greater detail *via* extensive ^{13}C-labeling studies. For reasons of brevity, discussion of this biosynthetic pathway will not be covered in this thesis. For a more details the reader is directed to the publications of Hirotani[8] and references cited therein.

Having discussed the above, the combination of the potential biological activity of Agariblazeispirol C, and the opportunity to apply developing methodology from our laboratories, have led us towards a programme of work targeting the first total synthesis of this natural product. In addition to this, the synthesis of Agariblazeispirol C will also serve to confirm the structure of this novel target.

2.2.3 Retrosynthetic Analysis

Our proposed pathway for gaining access to Agariblazeispirol C centres on the strategic employment of metal-mediated cyclisation chemistry. Specifically, the key steps are (i) an intramolecular Pauson-Khand reaction (PKR), which is used to construct the D/E ring section, and (ii) a novel intramolecular Heck reaction, which establishes the key all carbon quaternary centre between the C and D rings (**Scheme 2**).



Scheme 2

Initial removal of the oxygenated side chain present in Agariblazeispirol C yields polycyclic intermediate **5**. As mentioned, we envisaged that the 5,5-fused portion of the molecule could be constructed *via* the employment of an intramolecular Pauson-Khand reaction. This would allow the intricate tetracyclic carbon skeleton to be constructed, in a single step, from the relatively simple, bicyclic precursor **6**, which, in turn, could be further simplified to bicycle **7**. The synthesis of intermediate **7** could be achieved *via* a novel intramolecular Heck reaction from compound **8**, whose ultimate precursor is the commercially available and relatively inexpensive carboxylic acid **9**.

It is important to note at this stage, that in any enantioselective synthesis of Agariblazeispirol C the stereocentre present in **7** is crucial, and must be controlled. We envisage that application of an asymmetric Heck reaction will establish this key all carbon quaternary stereocentre. In addition to this, we believe that this stereocentre also will serve to control the diastereoselectivity of the downstream Pauson-Khand reaction.

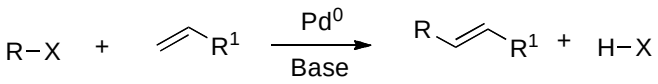
The following section will detail comprehensive reviews on the research development to date of our two key metal-mediated cyclisation methods.

2.3 The Mizoroki-Heck Reaction[9]

2.3.1 Introduction

The basic purpose of synthetic organic chemistry is the construction of organic molecules, and, as a result, the formation of carbon-carbon bonds is of paramount importance. In particular, catalysis by transition metal complexes to affect the synthesis of organic molecules from simple building blocks has attracted interest over the past four decades.[10] In relation to this, the Mizoroki-Heck reaction is a prime example of a transition metal-mediated process of considerable importance and utility within organic chemistry. In this respect, the 2010 Nobel Prize in Chemistry was awarded to Richard F. Heck**,** Ei-ichi Negishi, and Akira Suzuki for the development of palladium-catalyzed cross coupling reactions.[11] This incredible, and entirely deserved, recognition exemplifies the fact that this chemical tool has vastly improved the possibilities for chemists to create sophisticated molecules.

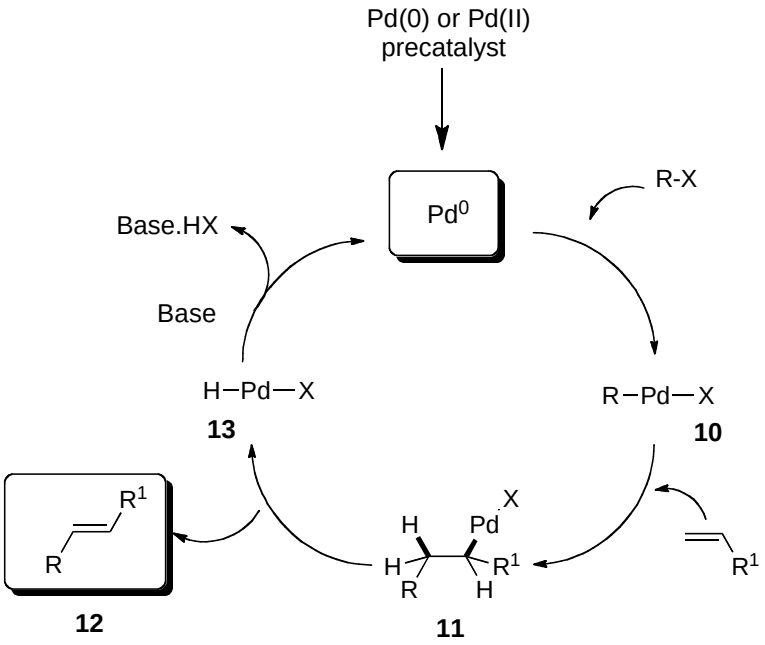
The Mizoroki-Heck reaction was first discovered in independent studies over 30 years ago.[12] This transformation, which has come to be more widely known as the Heck reaction, describes the Pd(0)-catalysed cross coupling between an aryl or vinyl halide or triflate and an alkene (**Scheme 3**). Since its discovery, this reaction has evolved to become an invaluable tool for synthetic chemists. In addition to this, the now well-established asymmetric variant of this reaction has emerged as a reliable method for the enantioselective formation of carbon-carbon bonds.[13]



Scheme 3

2.3.2 General Reaction Mechanism

The generally accepted mechanism for the Heck reaction is illustrated in **Scheme 4**. Initial oxidative addition of the active Pd(0) catalyst generates Pd(II) complex **10**. Following this, coordination of the alkene and subsequent migratory insertion, known as carbopalladation, results in species **11**. β-Hydride elimination furnishes the product, **12**, as well as hydridopalladium species **13**, which undergoes reductive elimination, under basic conditions, to complete the catalytic cycle.



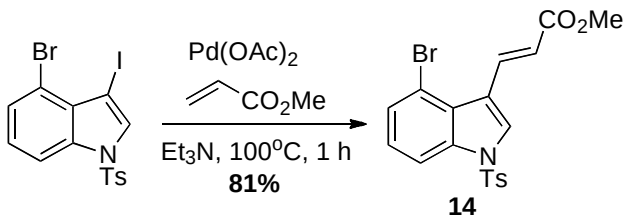
Scheme 4

2.3.3 Classical Reaction Conditions

Typical conditions for the Heck reaction involve the combination of a Pd source, a ligand, and a base. These reagents, in conjunction with the reaction substrates, are reacted in an appropriate solvent, generally at elevated temperatures.

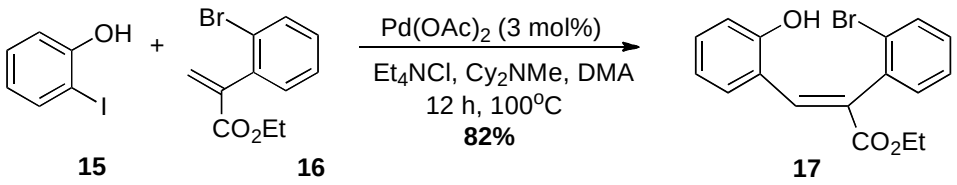
Substrates

Through the development of Heck methodology, a large variety of substrates, namely aryl iodides, bromides, chlorides, triflates, and tosylates have been coupled successfully. In terms of order of reactivity for the oxidative addition step, and typically for the overall reaction, the following decreasing order is followed: X = I > OTf > Br >> Cl. This can be attributed to the corresponding strengths of the C-X bond. One example of such chemoselectivity was revealed by Hegedus in 1984 where, under phosphine-free conditions, Heck product **14** was formed exclusively *via* the iodide moiety (**Scheme 5**).[14]



Scheme 5

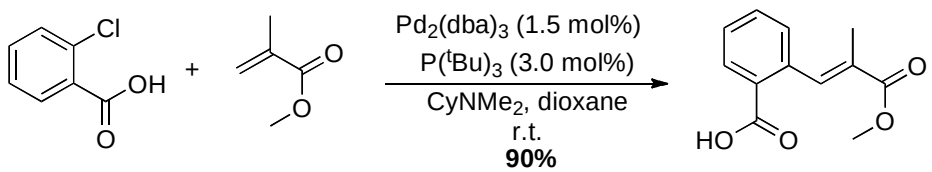
More recently, Guy and co-workers have demonstrated the efficient coupling of components **15** and **16**. Again, under phosphine free conditions, product **17** is prepared exclusively in a deliberate and controlled manner (**Scheme 6**).[15]



15 **16** **17**

Scheme 6

As described above, the general trend of reactivity between the various organohalide, and *pseuo*halide, coupling partners shows iodide, triflate, and bromide reagents to exhibit much greater reactivity than the corresponding chloride substrates. Of course, in the light of cost, and practical accessibility, chloride substrates present as much more convenient reaction precursors. In this regard, many research groups have sought to develop efficient reaction conditions for the use of chloride substrates within the Heck reaction.[16] Having said this, many of the early reported conditions were limited in scope, as well as requiring temperatures of greater than 120°C to achieve efficiency. A major breakthrough within this methodology was illustrated in 2001 by Fu, whereby the use of Pd/^{t}Bu$_3$P, in the presence of CyNMe$_2$, presented a mild and flexible system for the coupling of aryl chlorides.[17] More specifically, Fu's protocol allowed couplings to proceed at room temperature and, additionally, increased the substrate scope to incorporate sterically demanding aryl chlorides, as well as to include more heavily substituted olefin partners (**Scheme 7**). Furthermore, Fu illustrated that this catalyst system can be extended to incorporate electron-rich (less reactive) aryl chloride substrates; however, in these cases, elevated temperatures (70-120°C) are necessary.[17] This incredible enhancement in efficiency is attributed to the judicious choice of both the ligand and base used within this system.



Scheme 7

Having stated the above, in relation to the electrophilic partners within the Heck reaction i.e. the organohalides, there is an emerging drive to employ non-halogenated substrates within this overall process. Indeed, the ability to activate a specific 'inert' C-H bond and transform it to a more resourceful moiety is at the forefront of research within organic chemistry. In this respect, a direct and *oxidative* Heck reaction would evade the requirement for pre-activated reaction partners (organohalides) and lead to a more efficient process overall. Towards this, Fujiwara and Moritani have developed an efficient coupling of arenes and alkenes *via* an oxidative palladium(II)-catalyzed process and this transformation is now finding widespread use in synthesis.[18] Despite the value in this developing transformation, a review in this area will not be considered within this thesis. Accordingly, the reader is directed to a recent review on the oxidative Heck reaction.[19]

In terms of the olefin coupling partner, a diverse range of electron-rich, -poor, and -neutral species have been shown to undergo the Heck reaction very readily.[9] Selectivity issues as a consequence of such electronically different olefins will be discussed in the following sections.

Palladium source

Whilst there is a requirement for Pd(0) to initiate the catalytic cycle within the Heck process, in light of cost and stability, Pd(II) precatalysts, such as $Pd(OAc)_2$, are often used as alternatives. Therefore, the reduction of Pd(II) is required and this can be carried out *in situ* without the need to prepare and isolate the corresponding Pd(0) complex. Reagents such as phosphines, amines, and alkenes can be used to effect this reduction.

Ligands

The most widely used set of ligands described in the literature are tertiary-phosphines, for example, triphenylphosphine, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and 1,2-bis(diphenylphosphino)ethane (dppe). However, use of many alternatives such as nitrogen-,[20] sulfur-,[21] and carbene-derived ligands[22] have also been divulged. Indeed, the choice of ligand has a profound effect on the selectivity of the reaction. Furthermore, for

the more reactive aryl iodide substrates the Heck reaction can be performed under ligand-free conditions, as illustrated in **Schemes 5** and **6**. Nonetheless, the use of palladium stabilising ligands has brought advantages in terms of providing increased reactivity, selectivity, and stability to the catalyst.[23] In this regard, it has been postulated that electron-donating alkyl phosphines can accelerate the oxidative addition step and stabilise the active Pd centre very effectively. Additionally, it has been noted that bulky phosphines, such as tri-*o*-tolylphosphine, promote the key elimination steps within the catalytic cycle.

Bases

The requirement of a base in the Heck reaction is due to the need to neutralise the acid formed in the reduction elimination step of the overall process. Organic amine bases, such as triethylamine, are very commonly used; however, examples of inorganic bases, such as potassium or caesium carbonate, have been increasingly noted in the literature.[13]

Solvents

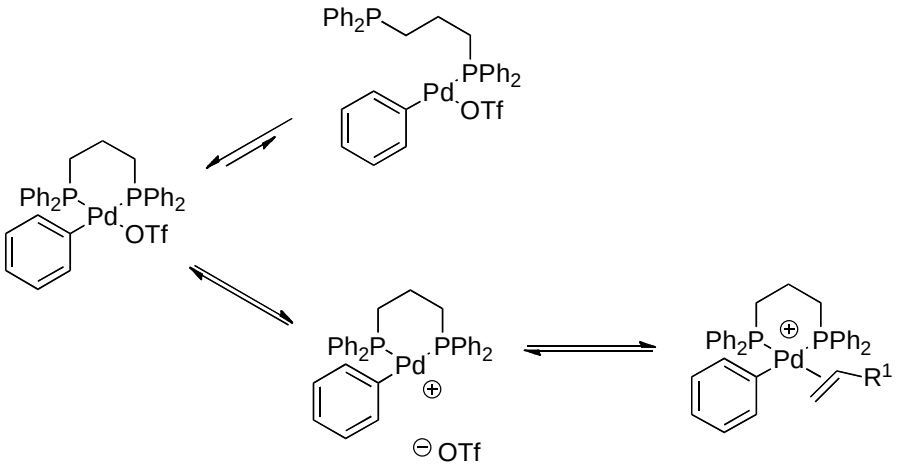
A wide variety of solvents have been successfully employed in the Heck reaction. Polar aprotic solvents, such as THF, DMF, DMA or MeCN, are often used. More recently, alcohol solvents have also been employed to address regioselectivity issues (*vide infra*).[24]

2.3.4 Mechanistic Developments

Whilst the catalytic cycle shown in **Scheme 4** provides an excellent 'textbook' analysis of the basic steps of the Heck reaction, more thorough mechanistic investigations have illustrated that this routine cycle is somewhat of an oversimplification. With differences in reactivity and selectivity being observed in Heck reactions, alternative mechanistic pathways have been postulated.

Cationic Pathway

The diphosphine-Pd(0)-mediated reaction between alkenes and aryl triflates, or halides in the presence of Ag(I) or Tl(I) salts, was first described by Cabri[25] and Hayashi[26] and was believed to proceed *via* a cationic pathway (**Scheme 8**).

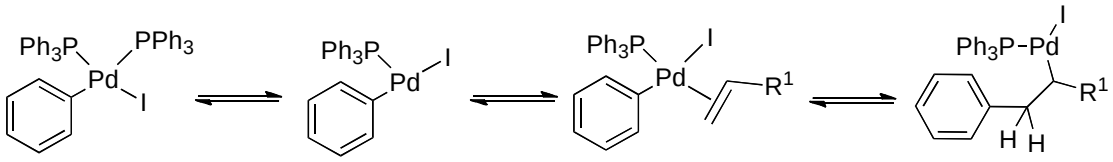


Scheme 8

With diphosphines, the chelate effect disfavours the dissociation of a phosphine, therefore, oxidative addition of the Pd(0) species is followed by halide abstraction (by the inorganic salts), or triflate dissociation, to yield a cationic Pd centre. This generates a vacant coordination site for the olefin thus permitting subsequent migratory insertion and elimination steps. The impact on the regiochemical direction of carbometallation within such cationic intermediates will be discussed below.

Neutral Pathway

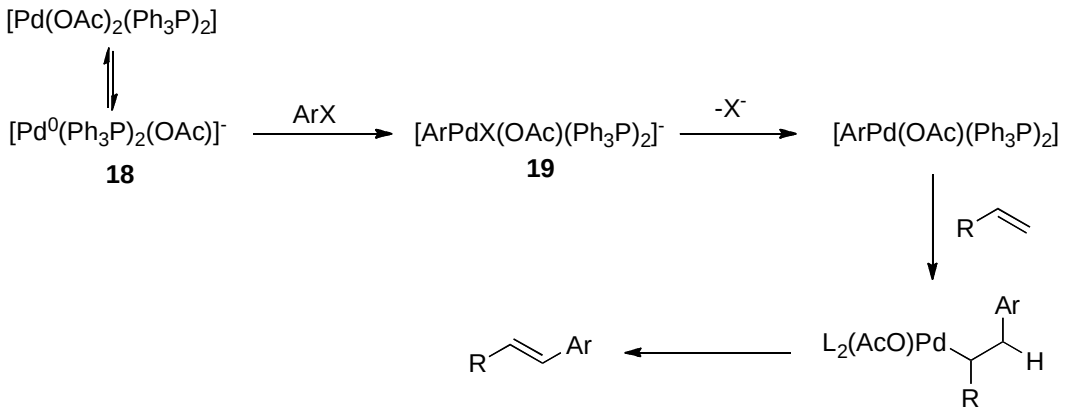
In the absence of such halide scavengers, the Heck reaction is presumed to proceed *via* a neutral pathway, as depicted in **Scheme 9**. Dissociation of a phosphine precedes coordination of the olefin to form a neutral complex; sterics dictate that the phenyl group is then attached to the least substituted end of the alkene during the carbometallation process.



Scheme 9

Anionic Pathway

Recent studies by Amatore and Jutand have brought to light a third, anionic, mechanism for the Heck reaction.[27] As shown in **Scheme 10**, the authors suggest that utilising the common mixture of palladium acetate and a phosphine ligand initiates a mechanism that involves an anionic palladium centre. It is proposed that the oxidation of the anionic catalyst **18** results in a pentacoordinate complex, **19**, in which the acetate and halide ions remain complexed to the metal centre.[28] Following the loss of the halide ion, the coordination of the olefin precedes the migratory insertion and β-hydride elimination processes.

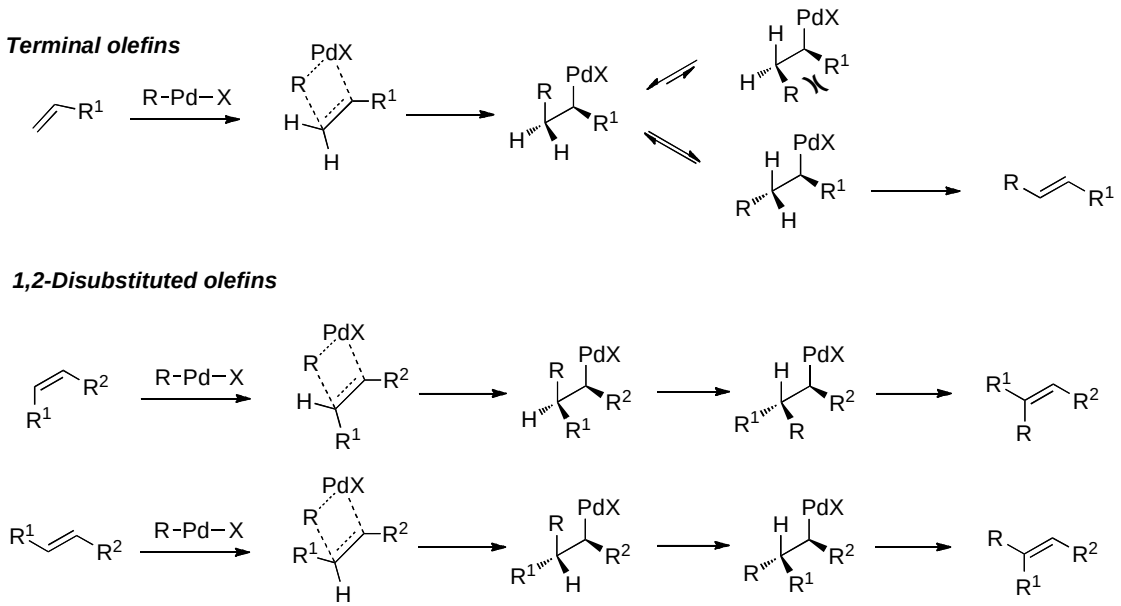


Scheme 10

2.3.5 Selectivity in the Heck Reaction

Olefin geometry

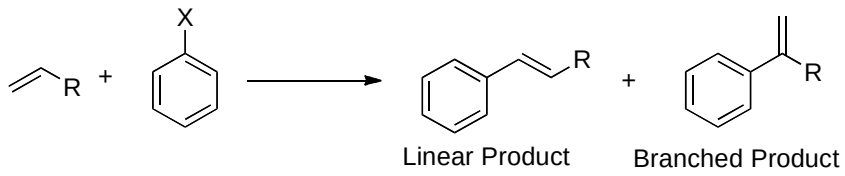
The selectivity of the Mizoroki-Heck transformation is dependent on the strict requirements for *syn*-addition of the first formed σ-arylpalladium(II) complex across the alkene, as well as *syn*-β-hydride elimination. As a result of this, terminal alkenes generally react to afford *E*-isomers, whilst 1,2-disubstitued alkenes give rise to products with inversion of stereochemistry (**Scheme 11**).



Scheme 11

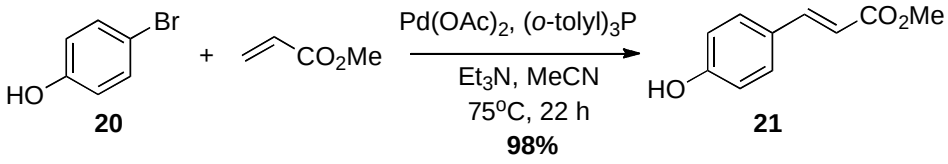
Regioselectivity

With regards to the migratory insertion step (carbopalladation), there is the possibility to form regioisomers, i.e. the formation of a linear or branched product (**Scheme 12**).



Scheme 12

It is generally accepted that this regioselectivity exists due to the competing reaction pathways in the Heck reaction (*vide supra*). It has been shown that under classical conditions electron-poor olefins promote excellent regioselectivity in favour of terminal (β-) attack, leading predominantly to the linear product. An early example from Heck illustrates this: coupling of aryl bromide **20** with methyl acrylate provides the linear product exclusively in an almost quantitative yield (**Scheme 13**).[29] Indeed, considering **Figure 4**, the regioselectivity of this reaction is not unexpected; steric, and electronic effects work in combination to direct the regioselectivity towards the formation of phenol **21**.



Scheme 13

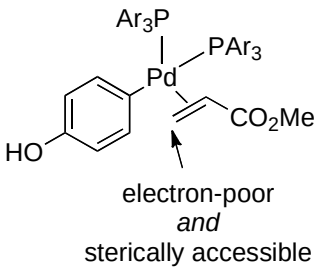
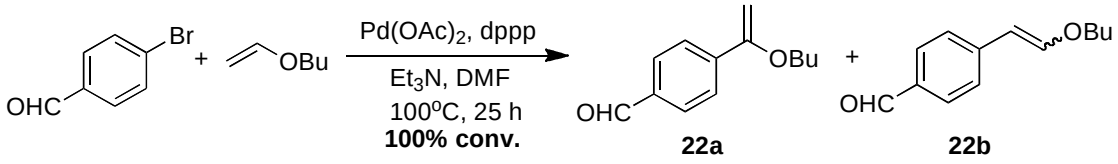


Figure 4

In contrast to that discussed above, under classical (neutral) conditions, regiocontrol tends to be poor for electron-rich olefins, where sterics and electronics are in opposition. **Scheme 14** illustrates an example from Xiao where the branched and linear products are obtained in an almost 1:1 ratio.[30]

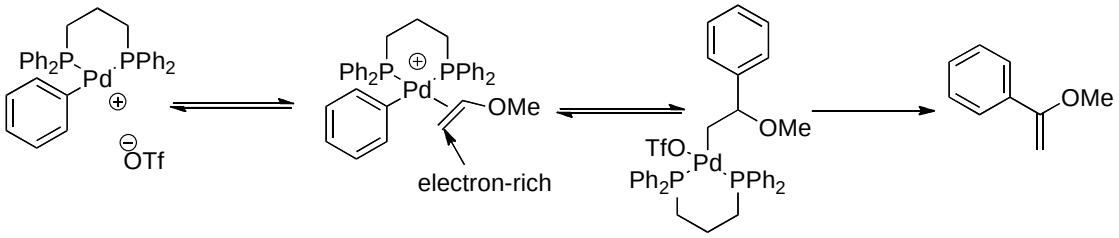


Scheme 14

22a/22b	22b E/Z
47/53	80/20

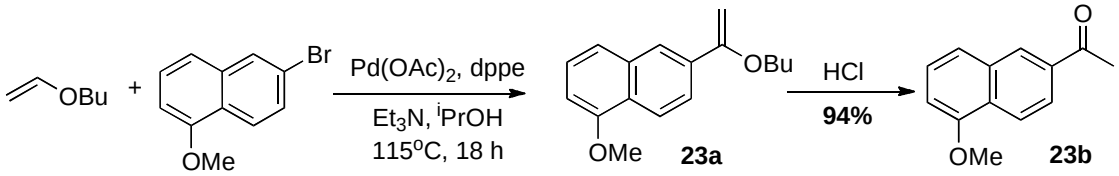
Table 1

Having stated this, research by various groups has led to the development of effective methods which address this regioselectivity issue of electron-rich olefins.[31] As mentioned previously, the addition of inorganic salts or the application of organotriflates, tosylates or mesylates, direct the Heck reaction to proceed *via* a cationic pathway. The formation of a cationic palladium centre encourages the olefin to react so as to attach the electron-rich end of the alkene to the positive Pd centre (**Scheme 15**). Such cationic conditions have been shown to deliver excellent regioselectivity with electron-rich olefins in favour of the branched reaction products.



Scheme 15

Very recently, Xiao and co-workers have reported a cleaner, more economical method for the regioselective Heck reaction of electron-rich olefins *via* the use of alcohols as the reaction solvent.[24] The authors report the reaction of various substrates with a diverse range of aryl halides, without the need for halide scavengers *or* triflates. It is proposed that the hydrogen-bond donor ability of alcohols aid the dissociation of a halide ion from the palladium centre. This would thereby enhance the concentration of an ionic centre and, hence, promote the cationic pathway. Using this system, quantitative conversion to the α-branched olefin product **23a** was observed, and, after acidification, an excellent isolated yield of ketone **23b** was obtained (**Scheme 16**).

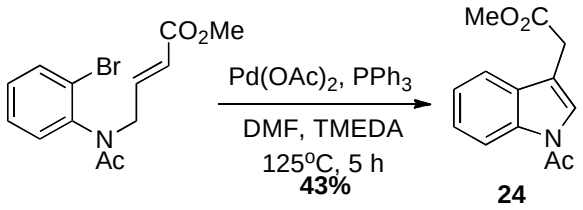


Scheme 16

2.3.6 The Intramolecular Heck Reaction

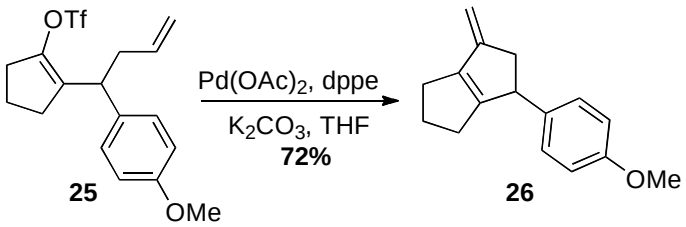
The first example of an intramolecular Heck reaction was reported by Mori and Ban in 1977,[32] and, since this first application, the intramolecular Heck process has been extensively used in modern organic synthesis. Generally, the intramolecular version of this reaction is more efficient compared to its intermolecular counterpart due to the elimination of entropic considerations. With regards to regioselectivity, regiocontrol in

the migratory insertion step is largely governed by the size of the ring being formed. Up until the late 1990's attention had been focused almost completely towards the formation of five- and six-membered rings, and, examination of this literature revealed that, in the majority of cases, products resulted from an *exo* mode of cyclisation (as opposed to an *endo* pathway). Indeed, the first example by Mori and Ban illustrated a 5-*exo* cyclisation to afford functionalised indole **24** (after double-bond isomerisation) in, albeit, a moderate yield (**Scheme 17**).[32] It is also important to bear in mind that the electron-withdrawing nature of the double bond will activate this substrate towards a 5-*exo* cyclisation as opposed to the 6-*endo* alternative.



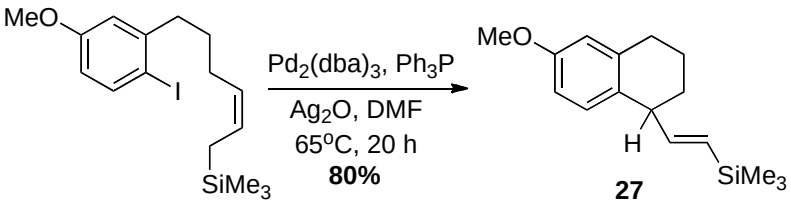
Scheme 17

A further example from Trauner demonstrates the use of an unactivated, electron-neutral olefin (**Scheme 18**).[33] The authors describe a successful annulation of vinyl triflate **25**, affording the *exo* cyclisation product **26** exclusively in a good yield.



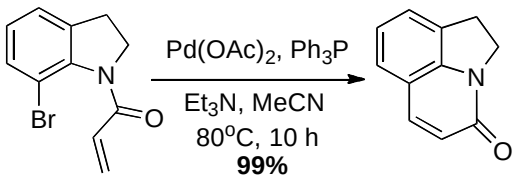
Scheme 18

Keeping with this theme, an example of the favoured 6-*exo* cyclisation over the 7-*endo* alternative is illustrated in **Scheme 19**. Tietze demonstrates the regioselective construction of a tertiary sp^3 carbon centre using an alkene component which is an allylsilane.[34] Through a 6-*exo* mode of cyclisation, compound **27** was prepared exclusively in an excellent yield.



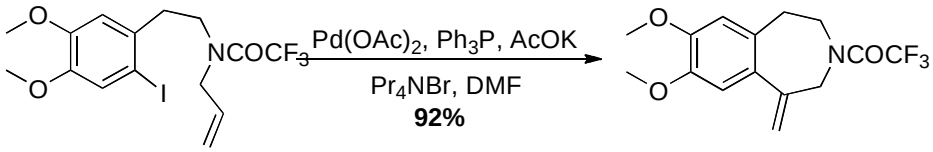
Scheme 19

Having stated all of this, there are exceptions to these typical observations. Examples have been documented where the preferred mode of cyclisation is 6-*endo* over 5-*exo*. However, this reaction selectivity is generally encountered when the β-hydride elimination step is not possible under a 5-*exo* mode.[35] On the other hand, an example from Dankwardt describes the exclusive formation of 6-*endo* products from substrates which plausibly could cyclise *via* either reaction pathway (**Scheme 20**).[36] The authors suggest that this selectivity is due to the strain involved to approach the α-position of the double bond in this instance. In addition to this, it is felt that the electronics of the α,β-unsaturated amide may also assist in the formation of the 6-*endo* cyclisation product shown.



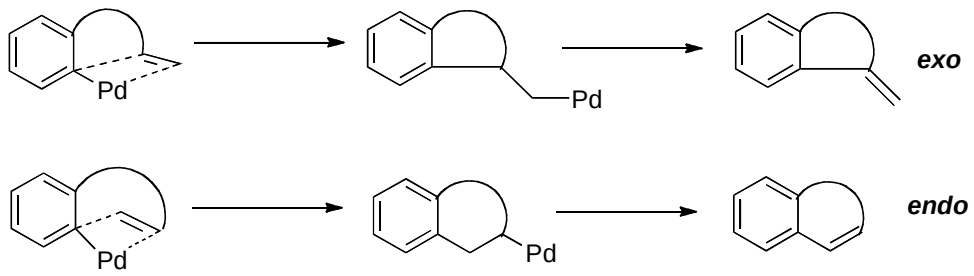
Scheme 20

Moving to the preparation of medium sized rings, one example reported by Tietze[37] showed, again, the thermodynamically favoured *exo* product being formed exclusively (over the 8-*endo* alternative) (**Scheme 21**). This facilitated the construction of the pharmacologically interesting 3-benzazepine skeleton.



Scheme 21

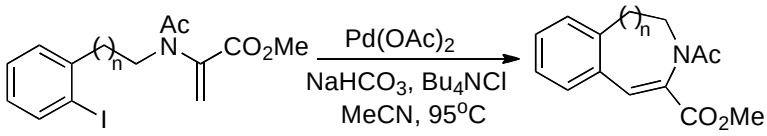
In general, an *exo* mode of cyclisation is less sterically demanding and is, therefore, favoured in the preparation of small rings, i.e. 5- and 6-membered cyclic species. In contrast, an *endo* mode of cyclisation requires the olefinic bond to move inside the loop in the intermediate complex, hence, a much more flexible tether between the alkene and the Pd-bound aromatic ring is required (**Scheme 22**). With regards to the preparation of medium and large sized rings, the increased flexibility of the substrate tether increases the possibility of competing cyclisation modes, i.e. the substrates are now able to adopt the conformation required for an *endo* cyclisation pathway. As such, there are now systems which are fine-tuned, *via* electronics or otherwise, to give selective cyclisations.



Scheme 22

In 1995 research by Gibson and co-workers revealed an efficient system which provided access to the novel seven-, eight-, and nine-membered analogues of phenylalanine

derivatives (**Scheme 23**).[38] Whilst the yields of these cyclisations are moderate, this system provided rare examples of 7- and 8-*endo* Heck cyclisations, as well as the first example of a 9-*endo* cyclisation. The selectivity of these reactions may be explained *via* electronic considerations (with the electron-poor olefin reacting as expected *via* a neutral reaction pathway).

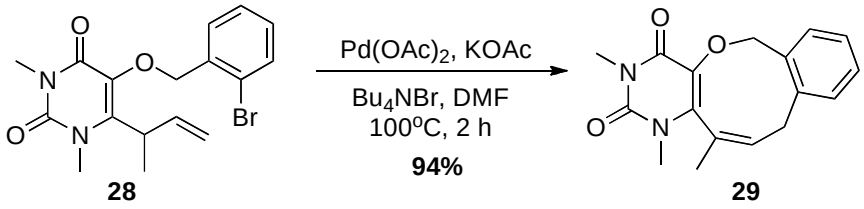


Scheme 23

n	Yield
1	54%
2	60%
3	58%

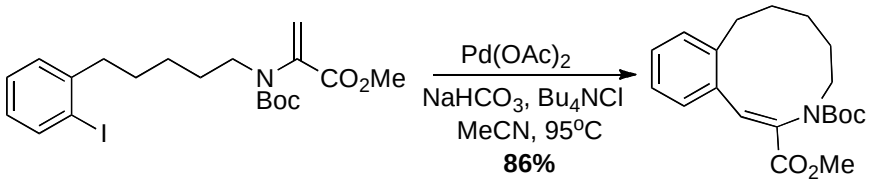
Table 2

More recently, Madjumdar and Chattopadhyay have also developed a set of reaction conditions that enable the construction of 9-membered rings *via* this unusual 9-*endo* cyclisation mode (with double-bond 'migration').[39] **Scheme 24** illustrates the elegant cyclisation of substrate **28** to afford heterocycle **29** in an excellent yield. The authors note that the use of tetrabutylammonium bromide (TBAB), known as Jeffery's conditions,[40] acts as a promoter within this reaction system.



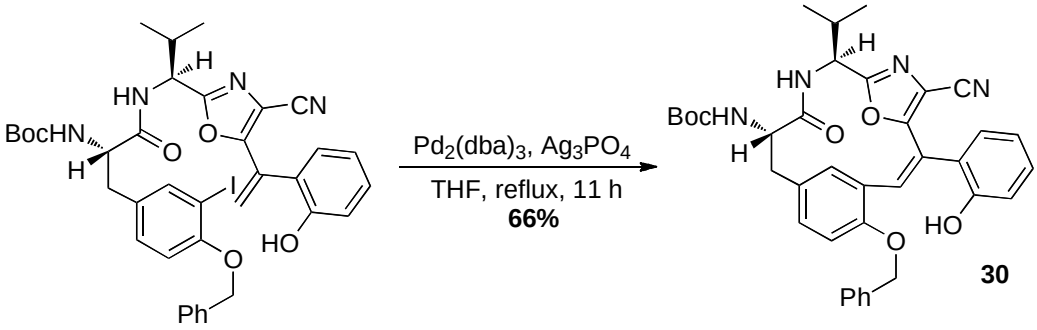
Scheme 24

In addition to that discussed above, extended studies by Gibson *et al*., described the preparation of a, previously unreported, ten-membered ring (**Scheme 25**) by this type of intramolecular Heck pathway.[41] Again, *via* an *endo* cyclisation mode, as opposed to the 9-*exo* alternative, the ten-membered ring was constructed without incident and in an excellent yield.



Scheme 25

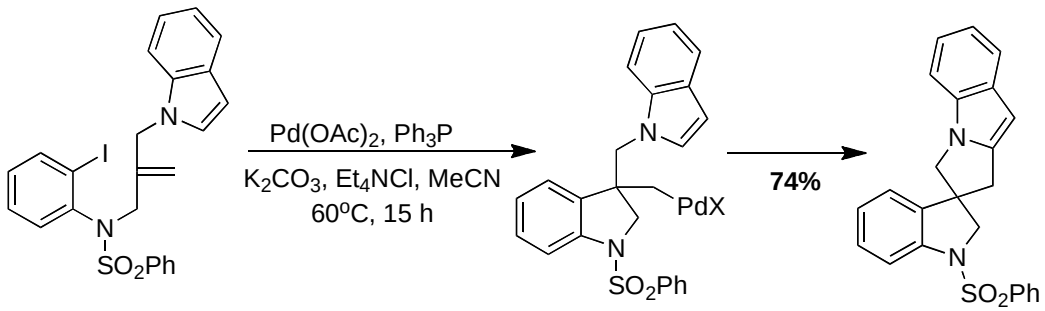
Studies directed towards the preparation of even larger rings (i.e. 13-membered and greater) reveal that the Heck cyclisation becomes *endo* selective. This provides an efficient macrocyclisation strategy, an elegant example of which was described by Harran in 1998.[42] The authors reported the formation of the 13-membered ring within diazonamide **30** (**Scheme 26**); the free phenol in this substrate may encourage the two ends of the cycle to meet *via* ligation with the palladium catalyst. As such, it is stressed that the ligand-free conditions employed are crucial in this instance.



Scheme 26

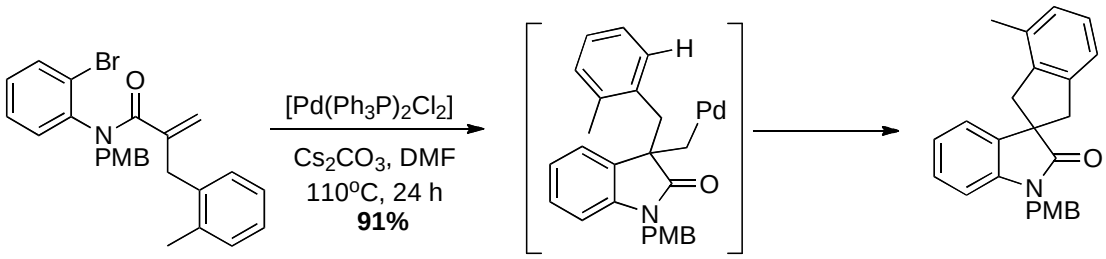
Tandem Intramolecular Heck Reactions

The application of the intramolecular Heck reaction within the realm of preparative organic chemistry continues to thrive and, in turn, offers an efficient and reliable strategy to prepare complex molecules. The true synthetic power of the Heck reaction is unlocked by its potential to participate in tandem reactions. If there are no β-protons to eliminate following an initial cyclisation, the intermediate alkyl palladium species can be involved in sequential reactions, allowing for the rapid construction of molecular complexity. An example by Grigg and co-workers demonstrates the rapid formation of various spirocycles *via* sequential Heck reactions (**Scheme 27**).[43]



Scheme 27

Continuing with this theme, a very recent example from Ruck and co-workers further showed the efficacy of the Heck transformation with the report of a novel tandem Heck reaction/C-H functionalisation process.[44] Aryl bromide **31** undergoes a 5-*exo* Heck cyclisation to afford intermediate **32**. With no β-hydrogens available, subsequent functionalisation of an unactivated C-H bond affords spiro-fused indane-oxindole **33** (**Scheme 28**). This cyclisation proceeds with excellent efficiency, generating **33** in an excellent isolated yield of 91%.



31 **32** **33**

Scheme 28

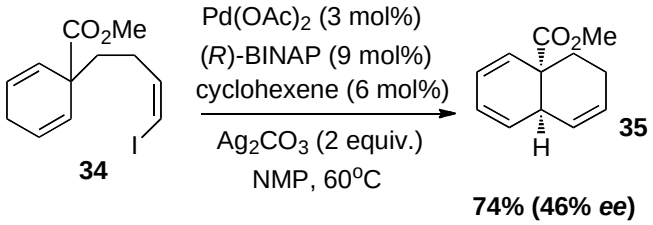
The various examples shown to this stage illustrate the generality and utility of palladium-catalysed Heck reactions to accomplish strategic carbon-carbon bond formation in complex organic molecules.

2.3.7 The Asymmetric Heck Reaction

Undoubtedly, one of the most significant breakthroughs in Heck methodology was the development of an asymmetric variant of this process *via* the use of chiral ligands.[13] Indeed, this was driven by the requirement for chemists to be able to construct tertiary and quaternary stereocentres with elevated levels of enantiocontrol by carbon-carbon bond formation.

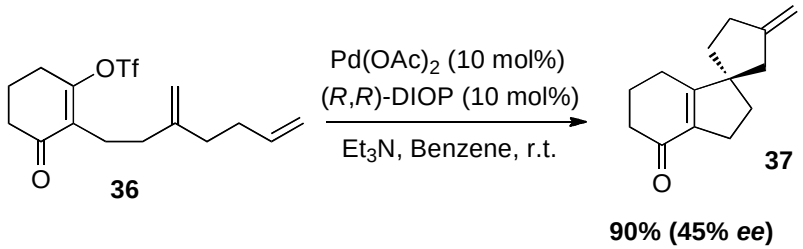
The first examples of such an asymmetric Heck system were reported, independently, by Shibasaki[45] and Overman[46] in the late 1980s. Shibasaki *et al.* reported the cyclisation of

prochiral vinyl iodide, **34**, for the formation of *cis*-decalin, **35**, in an appreciable yield and moderate enantioselectivity (**Scheme 29**).[45]



Scheme 29

In a related enantioselective Heck process, the first direct asymmetric formation of a quaternary stereocentre was revealed by Overman and co-workers (**Scheme 30**).[46] In this example, substrate **36** undergoes two sequential Heck reactions yielding spirocyclic derivative **37** in an excellent yield and, again, moderate enantiomeric excess.

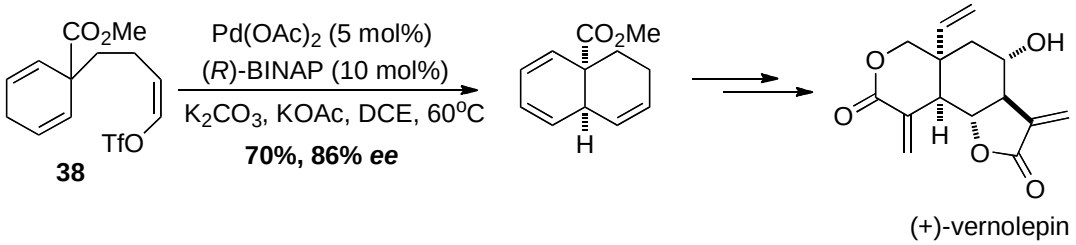


Scheme 30

Whilst the enantioselectivities for these transformations are relatively low, they demonstrated the synthetic power of the asymmetric Heck reaction for the construction of such synthetically demanding centres. As such, since the initial findings, this asymmetric version of the transformation has received intensive research attention from many synthetic chemistry groups worldwide, with some examples being given in the following section.

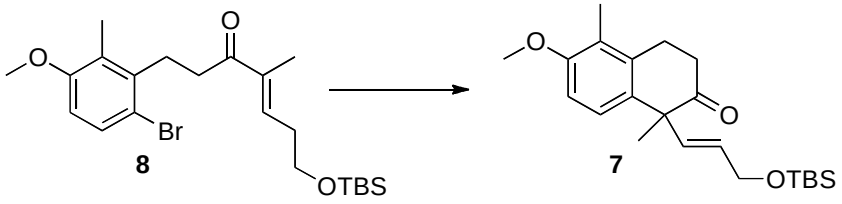
2.3.8 Applications in Natural Product Synthesis

Due to the attractive and reliable nature of this preparative method, the Heck reaction has been employed as the central strategic step in the syntheses of a vast number of natural products.[13] For example, an asymmetric Heck cyclisation was used by Shibasaki and co-workers to construct (+)-vernolepin (**Scheme 31**).[47] An efficient cyclisation of prochiral vinyl triflate **38** provided the core of the targeted molecule in an excellent yield and enantiomeric excess.



Scheme 31

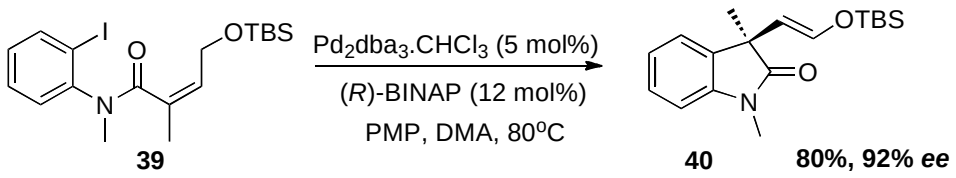
With regards to the intramolecular Heck reaction within our approach towards the synthesis of the targeted natural product (*vide infra*), we propose a 6-*exo* cyclisation onto the electronically least favourable α-position of an α,β-unsaturated ketone (**Scheme 32**).



Scheme 32

Upon examination of the literature for similar transformations, an impressive example by Overman and co-workers was revealed.[48] The authors reported a 5-*exo* cyclisation of 2-

iodoanilide **39**, under PMP-promoted conditions, providing (*R*)-**40** in excellent yield and enantiomeric excess (**Scheme 33**).



39 **40** **80%, 92% *ee***

Scheme 33

This example illustrates that our desired mode of cyclisation could be viable in order to establish the necessary quaternary carbon centre present in Agariblazeispriol C, and potentially with some degree of asymmetric control.

In summary, the Heck reaction has clearly become an invaluable tool to synthetic organic chemists. In terms of utility, there can be no disagreement that this reaction provides an array of possibilities. Evidently, this has been exemplified *via* the many applications of this reaction within total synthesis programmes, and also through the awarding of the Nobel Prize in Chemistry this year. The further power of the Heck reaction lies in its asymmetric variant; there remains no other catalytic, asymmetric, carbon-carbon bond forming reaction, which can compete with the capacity of this reaction in terms of scope, functional group tolerance, and the ability to create multiple rings through tandem processes.

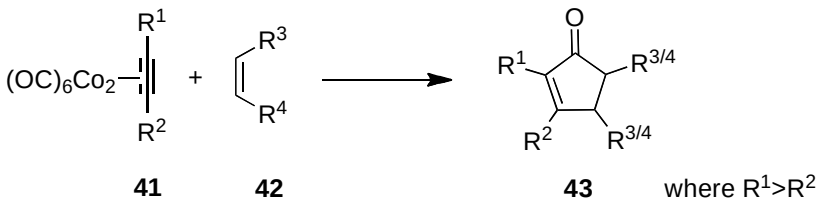
Having stating the above, in terms of future endeavours to improve the applicability of the Heck reaction even further, chemists must strive to provide a deeper understanding of the reaction mechanism(s), with the rational development of a reaction relying heavily on a thorough comprehension of reaction pathways.

2.4 The Pauson-Khand Cyclisation[49]

2.4.1 Introduction

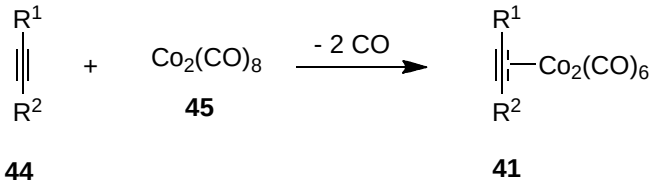
The second key metal-mediated cyclisation process we propose to make use of within our approach towards the synthesis of Agariblazeispirol C is the Pauson-Khand reaction. For the synthesis of five-membered rings, there are indeed few reactions that can compete in terms of the construction of such functionality in one step.

The Pauson-Khand reaction was first discovered at the University of Strathclyde in 1971 by Ihsan U. Khand and Peter L. Pauson.[50] The reaction involves the cycloaddition of an alkyne, present as its hexacarbonyldicobalt complex, an alkene, and carbon monoxide, in a formal [2+2+1] fashion, to furnish functionalised cyclopentenones in a one-pot process (**Scheme 34**). Examination of this diagram reveals that there are important regiochemical aspects within the realm of the intermolecular reaction manifold; discussion of these issues will be presented in a following section.



Scheme 34

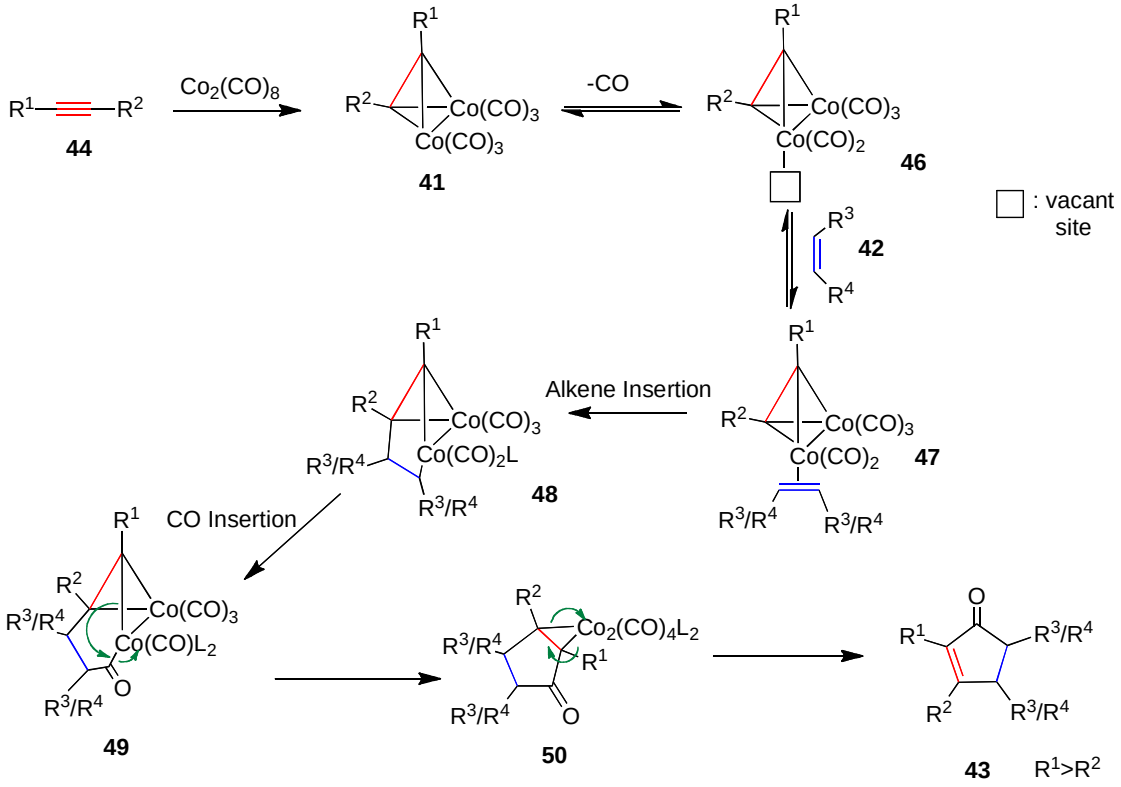
Preparation of the crucial alkynehexacarbonyldicobalt complexes, **41**, for the PKR is a simple and well established procedure.[51] A solution of the appropriate alkyne, **44**, is stirred with octacarbonyldicobalt, **45**, in an inert solvent such as petrol or DCM at room temperature to deliver the desired cobalt complexes with high yields typically being observed (**Scheme 35**).



Scheme 35

2.4.2 Reaction Mechanism

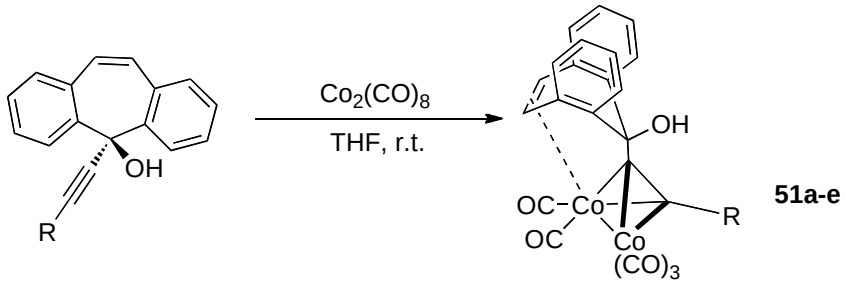
As yet, a definitive mechanism for the Pauson-Khand reaction has not been established. Having stated this, a pathway was initially proposed in 1985 by Magnus *et al*. (**Scheme 36**).[52]



Scheme 36

Following formation of the alkyne cobalt complex, **41**, the reaction proceeds with the reversible loss of a carbon monoxide ligand yielding a coordinatively unsaturated cobalt species, **46**. The alkene, **42**, can then reversibly complex to the vacant site in such a way that it is *trans* to the alkyne carbon bearing the larger R^1 substituent. Next, the irreversible insertion of the alkene occurs into the least hindered cobalt-carbon bond delivering intermediate **48**. In addition to determining the regioselectivity of the product, it is this step that is thought to be the rate-determining step of the reaction.[49] A molecule of carbon monoxide now inserts into the cobalt-carbon bond yielding intermediate **49**, which subsequently undergoes two reductive elimination steps to furnish the cyclopentenone product, **43**.

In terms of experimental evidence for the proposed intermediates, work carried out by Gordon *et al*. supported this pathway to some degree by identifying the pentacarbonyl(alkyne)dicobalt derivatives, **46**, by low temperature IR spectroscopy.[53] Additionally, independent work by Krafft,[54] and Perciàs and Riera[55] has resulted in the isolation of intermediates of type **46** whereby a sulfur atom occupies the vacant coordination side on the cobalt metal centre. With regards to compounds of type **47**, one example has been detected by electrospray ionisation spectrometry,[56] and, more recently, Evans and McGlinchey have characterised, by X-ray crystallography, compounds **51a-e** as depicted in **Scheme 37**.[57] It is interesting to note here that these latter authors go on to explain a lack of reactivity of compounds **51a-e** within the PKR. In fact, intermediates **51a-e** do not react at all to furnish the Pauson-Khand cyclopentenone adducts. The authors describe these compounds as ‘arrested Pauson-Khand intermediates’ and attribute this occurrence to molecular strain.



51a: R = Ph, **51b**: R = TMS, **51c**: R = *p*-C_6H_4CN,
51d: R = *p*-C_6H_4F, **51e**: R = *p*-$C_6H_4CF_3$

Scheme 37

To further probe Evans and McGlinchey's results, additional research has been carried out by Riera utilising phosphine-alkene ligands as mechanistic probes with in the Pauson-Khand reaction.[58]

Returning to the initially proposed pathway (**Scheme 36**), the latter steps in Magnus' proposed mechanism are based on the stereo- and regiochemical outcomes of a variety of examples of individual cyclisations. In a theoretical sense, studies performed by Nakamura,[59] Gimbert,[60] and Pericàs[61] have further supported Magnus' proposed mechanism. In 2001, Nakamura explored the reaction pathway of the Pauson-Khand annulation using Density Functional studies.[59] For the first time, valuable information on the structure and energetics of various reaction intermediates was obtained. **Figure 5** illustrates the reaction pathway in terms of energy; it is clear that the reaction pathway is, overall, thermodynamically favourable; the loss of carbon monoxide and the alkene insertion steps, as expected, have the most elevated energetic barriers to overcome.

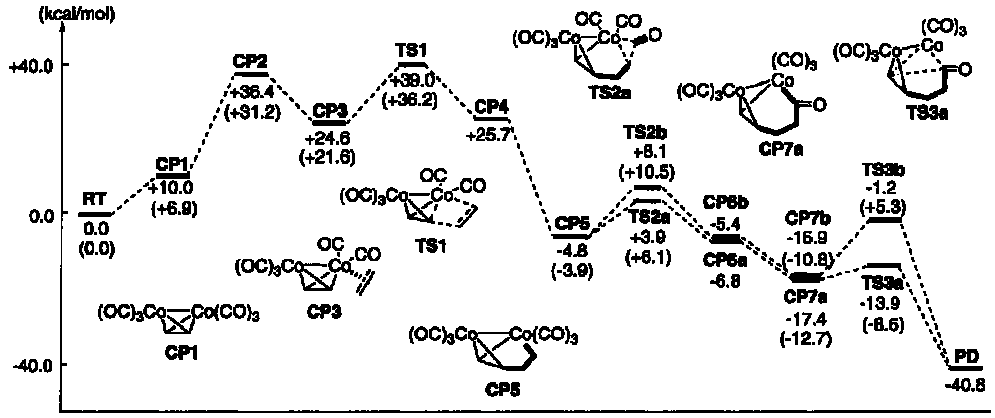
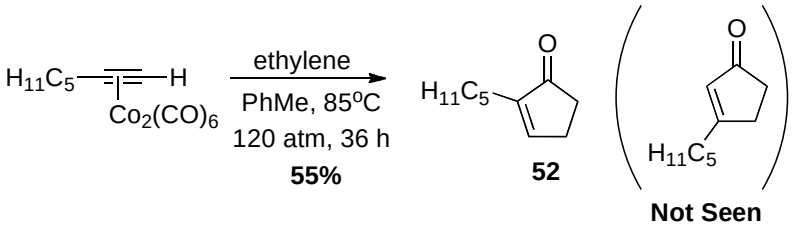


Figure 5: Courtesy of Nakamura *et al*.[59]

2.4.3 Regiochemical Aspects of the Intermolecular Pauson-Khand Reaction

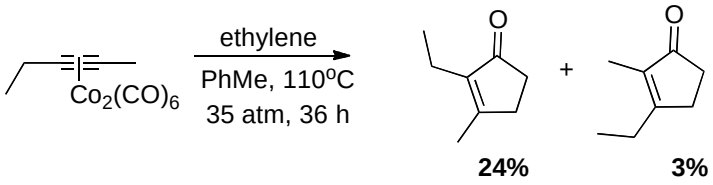
Alkyne Regioselectivity

As mentioned previously, the intermolecular Pauson-Khand reaction presents some issues over regiocontrol of both the alkyne and alkene components. With respect to the alkyne, regiochemistry is most often based on sterics, where that the alkene inserts into the least hindered cobalt-carbon bond, as described above. This will ensure that the largest substituent on the alkyne will ultimately resides α to the carbonyl group in the resulting cyclopentenone product. In contrast, insertion of the alkene into the more hindered cobalt-carbon bond would result in the less commonly seen alkyne regioisomer. Examination of the literature reveals a vast number of examples where the regioselectivity of the alkyne is complete.[62] One such example is illustrated in **Scheme 38**, where cyclopentenone product **52** is formed exclusively.[79]



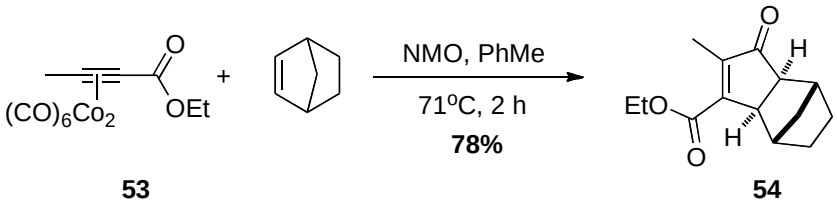
Scheme 38

Having stated the above, this rule is general, and, there are examples in which the substituents at the alkyne termini are similar in size and, consequently, cause regiochemical issues relative to the alkyne within the cyclopentenone product. **Scheme 39** illustrates one such example from Billington and Pauson where both regioisomers were observed; the unexpected regioisomer was isolated albeit in only 3% yield.[63]



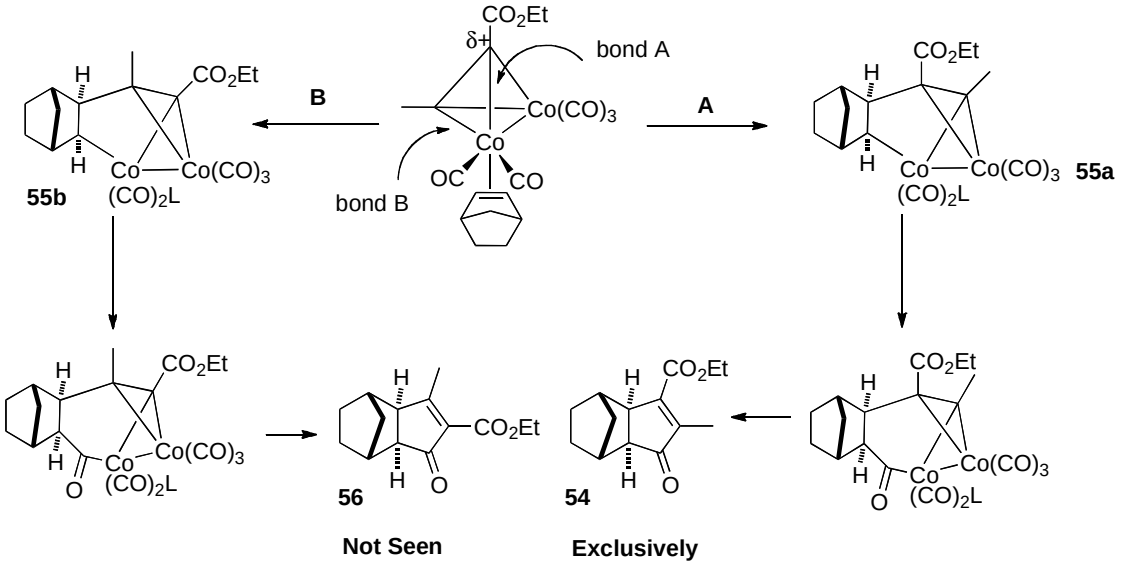
Scheme 39

Following on from this, there are some examples in the literature in which the regioselectivity of the alkyne component cannot be explained *via* the use of this steric hypothesis. In these cases, electronic considerations are required to more fully explain the alkene insertion step of the reaction mechanism and, hence, to support the regiochemical outcome of some reactions. In this regard, it has been shown by Krafft that in the case of alkynes bearing strongly electron-withdrawing groups, complete reversal of the expected regiochemistry occurs. Upon reaction of alkynoate **53** with norbornene, unexpected regioisomer **54** was formed exclusively (**Scheme 40**).[64]



Scheme 40

To rationalise the observed preference for selective formation of the 1,4-dicarbonyl compound (as opposed to the 1,3-dicarbonyl compound), Krafft postulates alkyne polarisation. **Scheme 41** illustrates that insertion into bond A would give metallocycle **55a**, which, ultimately leads to the observed product **54**. In contrast, insertion into bond B would give metallocycle **55b**, subsequently affording product **56** (which is not observed). It is anticipated that the electron-withdrawing nature of the ester functionality leads to an increase in the rate at which carbon-carbon bond formation occurs *via* polarised bond A. It is important to note that in subsequent studies by Gimbert and Green, reversal of the indicated polarisation within this alkyne is used to explain regiochemical issues within the Pauson-Khand reaction (*vide infra*).



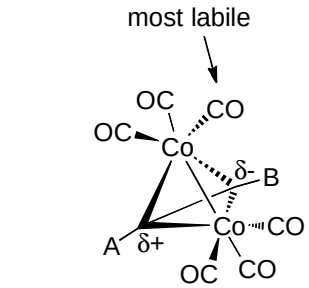
Scheme 41

One further example by Krafft, which, again, shows this polarisation effect nicely, is shown in **Scheme 42**.[65] The reaction of acetylene **57**, bearing two electronically different (but sterically similar) substituents, leads to the exclusive formation of cyclopentenone **58**; the alkene has inserted into the most electron-deficient terminus of the alkyne complex.

57 **58**

Scheme 42

With regards to the Pauson-Khand reaction mechanism, it is accepted that the loss of a carbon monoxide ligand from the pre-requisite alkyne cobalt complex precedes the co-ordination of the alkene (*vide supra*). In an attempt to probe the reaction further, Gimbert and Greene suggested that the electronic difference between the two acetylinic termini may influence the position from which the carbon monoxide is lost, and ultimately the regiochemistry of the reaction. A theoretical study was carried out to explore this theory, and it was determined that this observed regiochemistry is a result of a *trans*-effect exerted by the alkyne.[60b] As shown in **Figure 6** the weakening of a specific CO ligand results in the insertion of the olefin so as the electron-poor alkyne substituent ultimately resides β to the carbonyl group in the final cyclopentenone product.

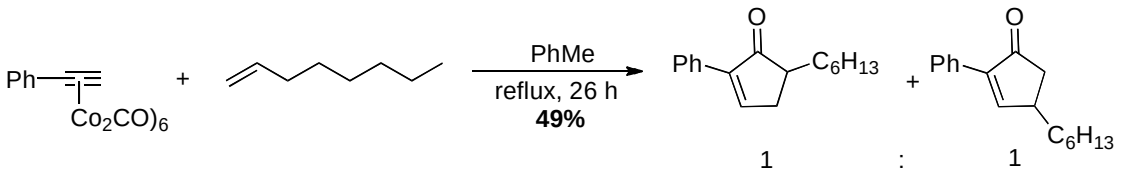


For example, A = Me; B = CO_2Me

Figure 6

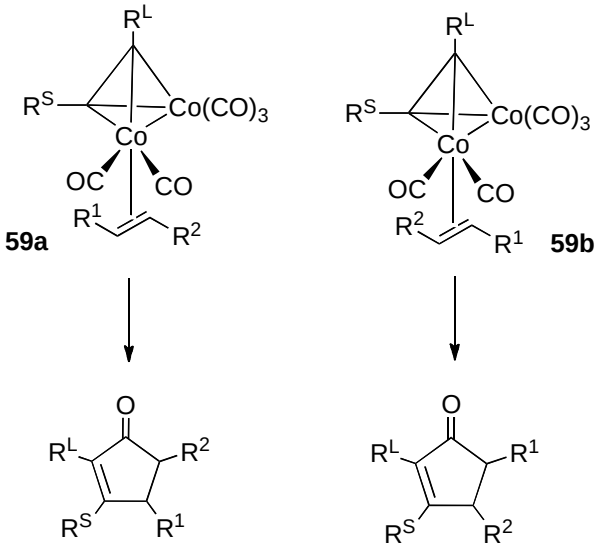
Alkene Regioselectivity

With regards to the alkene, it is evident that the regiochemistry is much less easily predictable. Indeed, with simple alkene substrates, it is common to see 1:1 mixtures of products.[49,62] One such example came from Pauson and Khand when exploring the reaction of oct-1-ene with the cobalt complex of phenylacetylene (**Scheme 43**).[66]



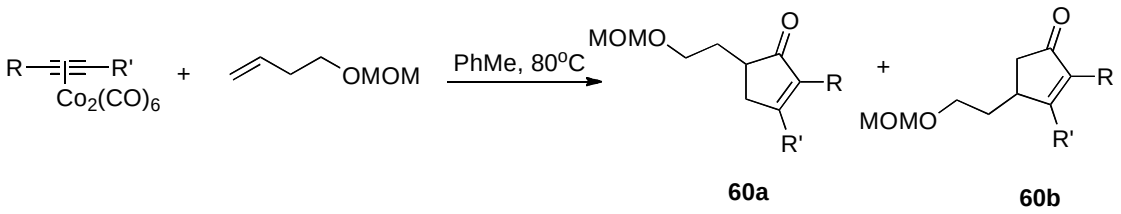
Scheme 43

Examination of **Scheme 44** can explain this commonly observed olefin regioisomeric distribution. With equal probability of forming either intermediate **59a** or **59b**, subsequent insertion and carbon-carbon bond formation, results in mixtures of cyclopentenone products.



Scheme 44

Having stated all of the above, it was shown by Krafft that the olefin regioselectivity was somewhat dependent on the alkyne present within the reaction (**Scheme 45**).[67] When using a terminal alkyne, a mixture of products was observed. However, upon moving to an internal alkyne, it was shown that the α branched regioisomer was essentially the exclusive reaction product.



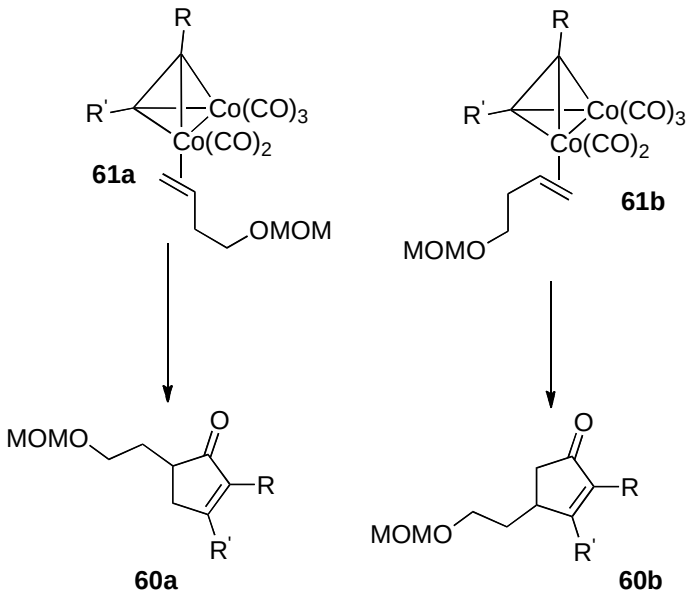
60a **60b**

Scheme 45

Entry	R	R'	60a	60b	Yield
1	Bu	H	3	2	41%
2	Ph	Me	40	1	41%

Table 3

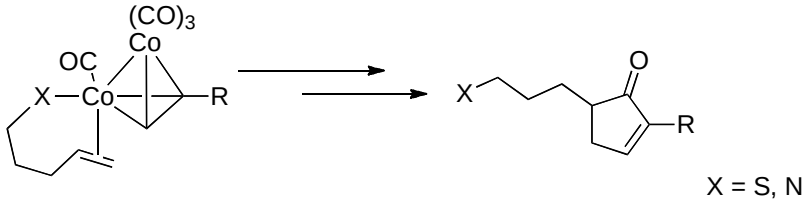
This observation can be explained by looking at the two possible rotomeric orientations that the olefin can take when co-ordinating to the cobalt centre (**Scheme 46**). In the case for the terminal alkyne (R^2 = H), there is little steric difference between rotamers **61a** and **61b**, hence this leads to a mixture of products. On the other hand, the internal alkyne (R = Ph; R' = Me), brings about increased steric hindrance, causing rotamer **61a**, and, in turn, cyclopentenone **60a**, to be favoured almost exclusively.



Scheme 46

The Directed Pauson-Khand Reaction

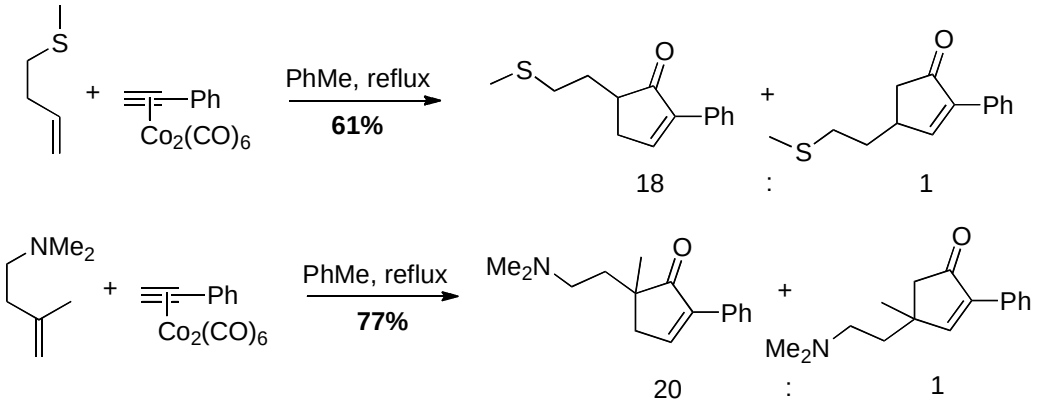
The drive to improve the regioselectivity of alkene component insertion in the Pauson-Khand reaction has led to what is now known as the directed Pauson-Khand reaction. In the late eighties, Krafft considered that the use of a heteroatom tethered to the olefin would be able to control the regiochemical outcome of the reaction *via* chelation to the cobalt atom (**Scheme 47**).[68]



Scheme 47

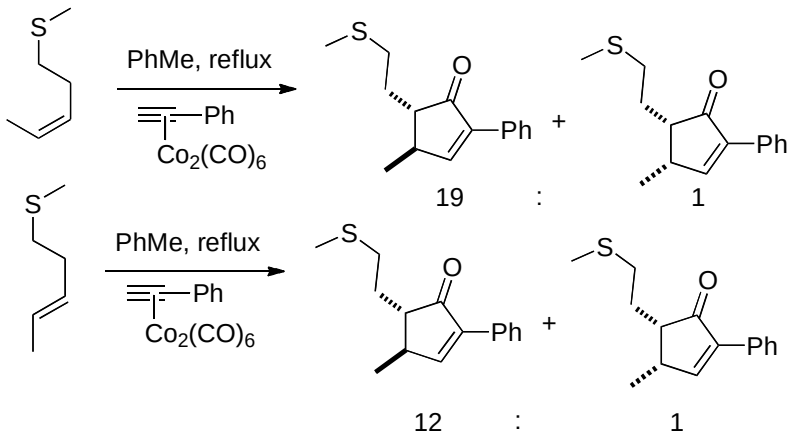
Based on the above hypothesis, the use of soft donor atoms, such as sulfur and nitrogen, were employed to great effect as directing ligands, thus improving the regioselectivity of

such intermolecular Pauson-Khand reactions. Whilst oxygen derived tethers failed to exert any regiocontrol, a variety of functionalised cyclopentenone products were accessed with ease using homoallylic or bishomoallylic sulfides or amines.[68] In addition to this, these tethered olefins also increased the rate and efficiency of previously sluggish intermolecular reactions. Examples of this protocol are shown in **Scheme 48**.



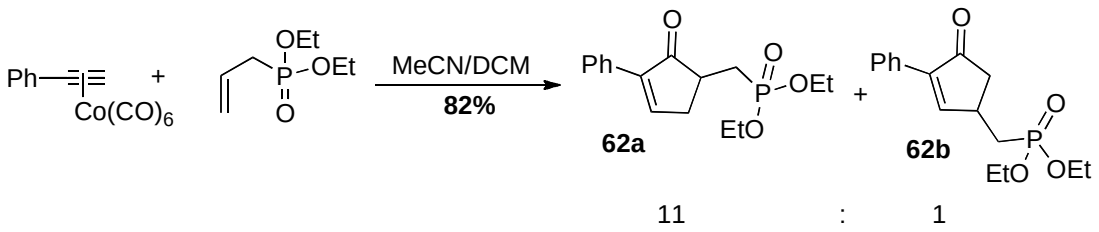
Scheme 48

Interestingly, when carrying out these experiments, Krafft made the observation that the products obtained from such directed P-K reactions with internal alkenes had almost exclusively the *trans* stereochemistry (**Scheme 48**) regardless of the geometry of the starting olefin. This demonstrates that following cyclisation, the cyclopentenone formed epimerises to the most thermodynamically stable product. Therefore, this system not only imparts an excellent level of regiocontrol but also a high degree of stereocontrol.



Scheme 49

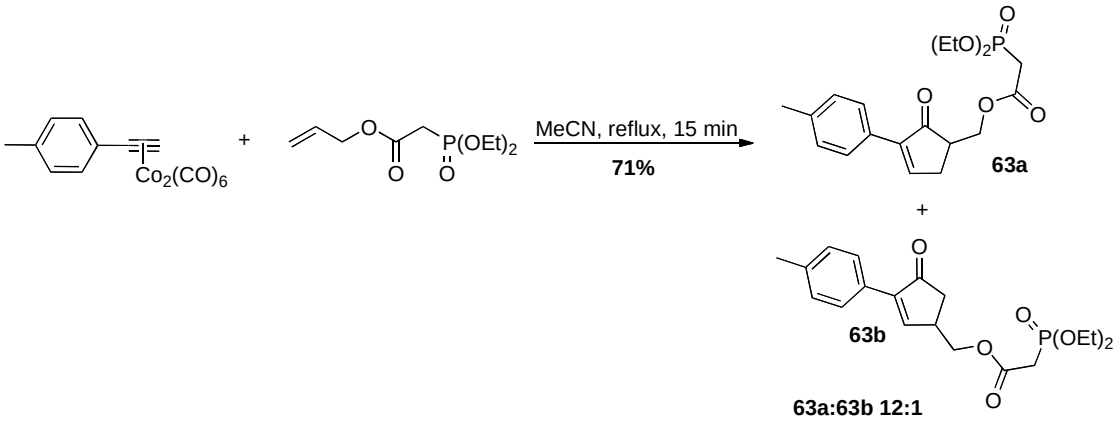
Since this pioneering early work of Krafft, Kerr and co-workers have developed an analogous system which utilises allyl phosphonates in order to control the regioselectivity of an intermolecular Pauson-Khand reaction.[69] Under optimised conditions, reaction of the cobalt complex of phenylacetylene and commercially available diethyl allylphosphonate delivered cyclopentenones **62a** and **62b** in an excellent yield and with very good levels of regioselectivity (**Scheme 50**).



Scheme 50

Following on from this success, Kerr demonstrated the use of an extended class of olefins possessing a tethered phosphonate ester unit (**Scheme 51**).[70] Under optimised reaction conditions, and without the requirement for any additional promoters or additives, these phosphorus-possessing alkenes act as effective P–K cyclisation partners and deliver

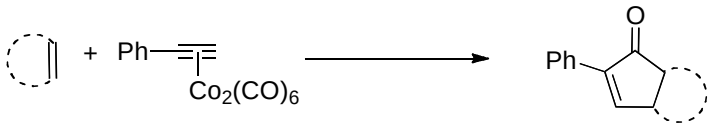
functionalised cyclopentenones, of obvious further synthetic utility, with high levels of regiochemical control.



Scheme 51

2.4.4 Alkene Reactivity

In terms of reaction scope, the Pauson-Khand annulation has always been limited by the poor reactivity and selectivity of simple alkenes. In reality, the most efficient applications of this annulation process have involved strained olefins such as norbornene or made use of the thermodynamically more favoured intramolecular variant. An interesting theoretical study by Milet, Gimbert, and co-workers explained that the reactivity of the alkene partner within the Pauson-Khand reaction is correlated to the back donation of electrons from the metal centre to the π^* orbital (lowest unoccupied molecular orbital (LUMO)) of the olefin.[60c] In addition to this, the authors note that a relationship exists between the C=C-C bond angle and the energy of the LUMO; the smaller the angle, the lower the LUMO energy. This explains nicely the experimental observations of strained olefins. The results from this study are detailed in **Scheme 52**, **Table 4**.[71]



Scheme 52

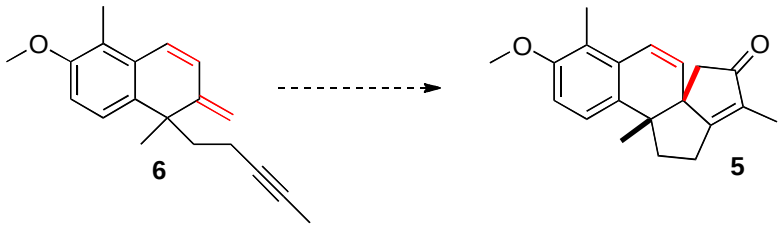
Entry	Alkene	Angle[a]	$LUMO_{coord}$	Conditions	Yield
1	Norbornene	107°	-0.087 eV	Mesitylene, 60-70°C, 4 h	59%
2	Cyclopentene	112°	+0.203 eV	Toluene, 160°C, 80 atm, 7 h	47%
3	Cyclohexene	128°	+0.336 eV	Toluene, reflux, 6 h	3%

[a] angle refers to the C=C-C angle.
[b] $LUMO_{coord}$ refers to the calcluated energy of the olefin's LUMO when coordinated to the metal centre.

Table 4

Conjugated Alkenes

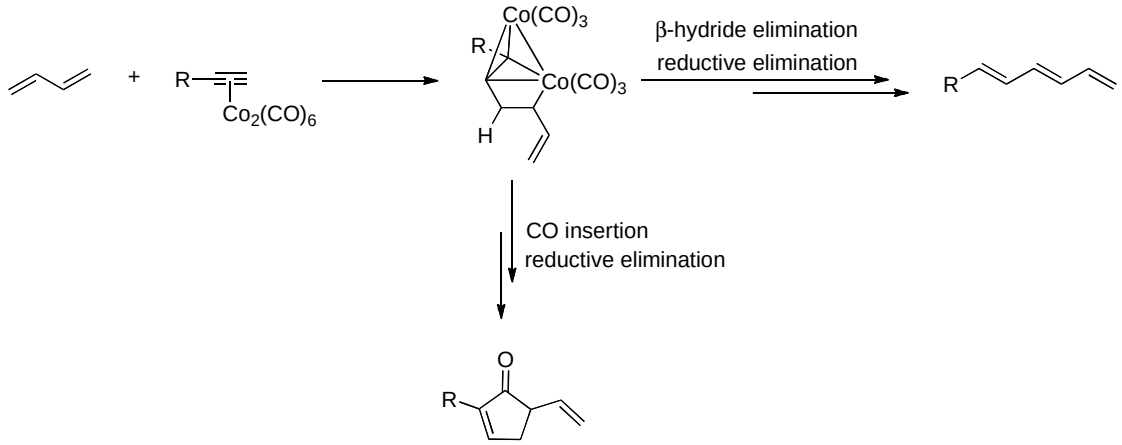
Due to the presence of a conjugated alkene system in the Pauson-Khand cyclisation substrate within our approach to build up the core skeleton of Agariblazeispirol C (**Scheme 53**), this substrate class deserves special mention.



Scheme 53

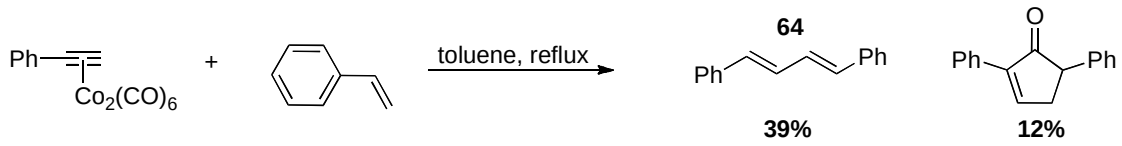
Upon reviewing the chemical literature, it is evident that conjugated alkenes prove to be more capricious coupling partners.[72] This statement is attributed to the tendency of such olefin partners to undergo alternative side reactions. More specifically, a hydrogen migration pathway competes with the insertion of carbon monoxide, which would install

the carbonyl moiety within the final cyclopentenone. This alternative process results in the formation of a conjugated alkene product as shown in **Scheme 54**.



Scheme 54

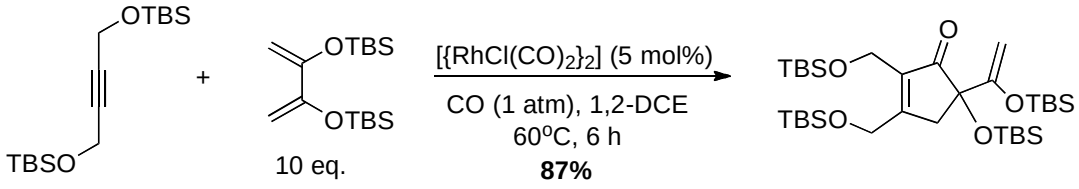
Indeed, Pauson himself provided an example of this competing pathway in the reaction of styrene with phenylacetylene cobalt complex (**Scheme 55**). Upon heating in refluxing toluene, the product from hydrogen migration dominated, leading to the formation of conjugated diene **64** in a 39% yield.[73]



Scheme 55

Having discussed the above, the full potential of conjugated alkenes has now been investigated by Wender and co-workers.[74] A remarkable increase in selectivity for the cyclopentenone product was observed when performing the Pauson-Khand reaction under rhodium-catalysed conditions. As shown in **Scheme 56**, utilising a large excess of

diene, in the presence of a carbon monoxide atmosphere and rhodium catalyst, resulted in an excellent 87% yield of the desired cyclopentenone. It is important to note at this stage that a more detailed discussion of the use of alternative metals within the Pauson-Khand annulation will be discussed in an upcoming section of this thesis.



Scheme 56

2.4.5 The Intramolecular Pauson-Khand Reaction

Undoubtedly, within the realms of Pauson-Khand methodology, the establishment of the intramolecular variant has brought a colossal amount of value to synthetic chemists. The first example of an intramolecular Pauson-Khand cyclisation was described by Schore[75] in the early 1980's, and, since this example, more and more procedures have emerged displaying increasing effectiveness. Throughout the following sections, the success of the intramolecular PKR, in terms of expansion of substrate scope, as well as applicability in catalytic and asymmetric protocols, should be evident.

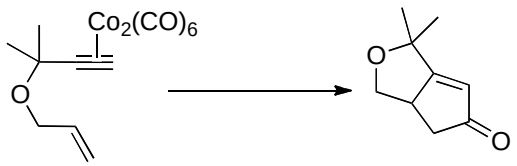
2.4.6 Promotion of the Pauson-Khand Reaction[49]

Classical Pauson-Khand cyclisations were generally carried out at undesirable, elevated temperatures for long reaction times in solvents such as benzene or toluene. Moreover, isolation and purification of the product could be difficult, based on the accompanying plethora of organometallic by-products. Thus, cyclopentenone products were generally afforded in poor yields. Based on this, there has been a considerable drive to develop milder and more dependable reaction conditions.

Mechanical Methods

Dry-State Absorption

A major advance in Pauson-Khand methodology was reported by Smit and Caple in 1986 and involved the adsorption of reagents onto solid surfaces, such as silica or alumina.[76] Utilising these techniques, the intramolecular cyclisation of dicobalthexacarbonyl complexes (DCHCC) of substituted allylpropargyl ethers were dramatically improved. An example of this technology with direct comparison to traditional thermal methods is shown in **Scheme 57**. The authors propose that donor centres on the solid surface can coordinate with the alkyne DCHCC and assist in the first step of the reaction mechanism, i.e. decarbonylation, by promoting ligand exchange. Whilst this protocol reveals efficient annulations in terms of chemical yield and reaction time, the outcome of the cyclisations is highly dependent on the reaction atmosphere applied, with an oxygen atmosphere being required for optimum efficacy. In addition to this, this technique is found to be most useful in intramolecular reactions of enynes containing heteroatoms.



Conditions: Thermal: *iso*-octane, CO, 60°C, 24 h, **29%**[77]

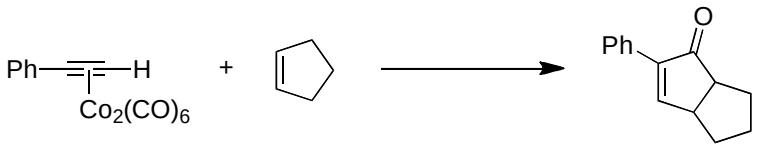
Dry State: SiO_2, O_2, 45°C, 30 min, **75%**[76a]

Scheme 57

Ultrasound

Early research showed that the use of ultrasonication can aid the removal of a carbonyl ligand from a metal centre.[78] Billington and Pauson applied this concept to the Pauson-Khand reaction in order to promote the first dissociation step of the reaction process.[79] The use of low powered ultrasound, whilst having little general effect on the product

yields, revealed a notable decrease in the required reaction time (**Scheme 58**). In addition to intramolecular cyclisations, this system illustrated the use of intermolecular examples.

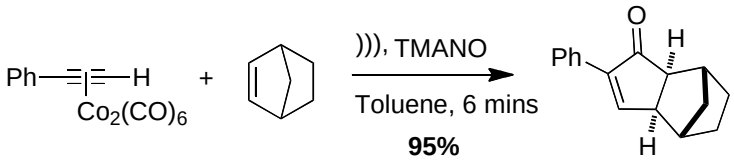


Conditions: Thermal: Toluene, 70°C, 48 h, **23%**

Low Power))): Toluene, 70°C, 3 h, **59%**

Scheme 58

In efforts to improve this system, studies conducted by Kerr *et al.* have shown that the use of high intensity ultrasound, in combination with other promoters, can dramatically improve the efficiency of Pauson-Khand cyclisations.[80] An example using an ultrasound probe in conjunction with trimethylamine *N*-oxide is shown in **Scheme 59**, with an excellent yield of 95% being delivered after only six minutes reaction time for this intermolecular process. This methodology allowed the rapid reaction of strained olefins, as well as less reactive substrates, providing considerable improvements over more traditional methods. The authors suggest that it is the enhanced pressures delivered by higher-powered sonication that triggers fast metal-carbonyl bond dissociation.

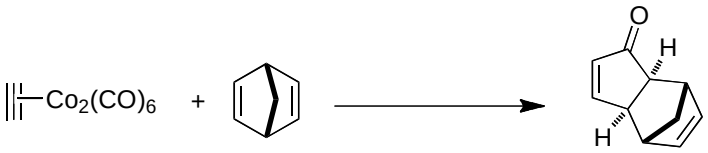


Scheme 59

Microwave Promotion

As an alternative to thermal heating, organic transformations are now being routinely carried out using the application of microwave irradiation allowing dramatic reductions

in reaction times.[81] In 2002, Evans *et al*. utilised microwave technology to improve the efficiency of a series of P-K cyclisations.[82] A variety of substrates were screened within their system, affording the corresponding cyclopentenones in excellent yields (**Scheme 60**). Evans also noted significant improvement in diastereoselectivity with microwave irradiation in comparison to the thermally-promoted process.[82]



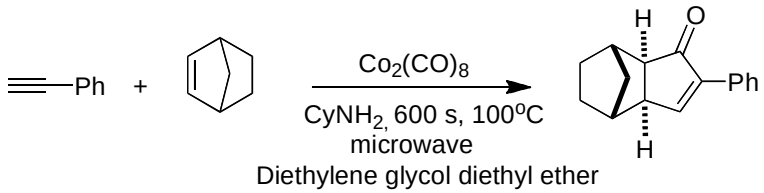
Conditions

Thermal: PhMe, 110°C, 16 h, **70%**, *exo*:*endo* 80:20

Microwave: 1,2 DCE, 90°C, 20 min, **89%**, *exo*:*endo* 95:5

Scheme 60

Also in 2002, Groth and co-workers established a microwave-promoted catalytic protocol for the Pauson-Khand annulation.[83] Their report demonstrated the use of sub-stoichiometric amounts of dicobalt octacarbonyl, in addition to cyclohexylamine, furnishing a range of cyclopentenones in moderate to good yields in as little as 10 minutes (**Scheme 61**). Notably, no additional carbon monoxide is required in this system; all of the CO consumed in the reaction is taken from the cobalt catalyst, since the process is performed in sealed vessels. A more comprehensive discussion on the development of the catalytic Pauson-Khand reaction will be presented in a following section.



Conditions: 1 – 10 mol% catalyst, **47%**

2 – 20 mol% catalyst, **53%**

3 – 50 mol% catalyst, **71%**

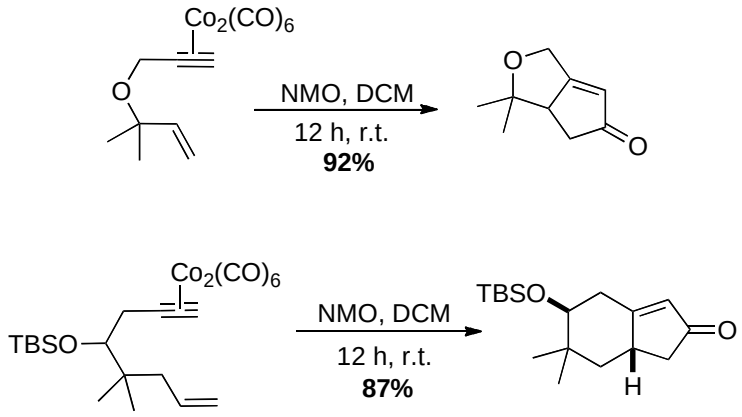
Scheme 61

Chemical Methods

Amine N-oxides

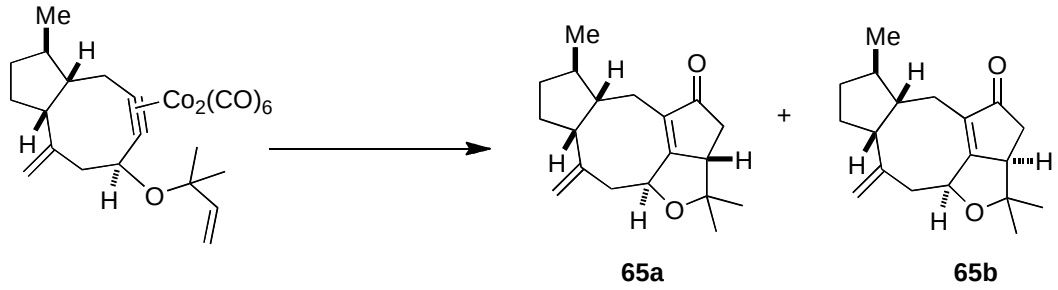
The use of amine *N*-oxides has constituted one of the biggest breakthroughs in the promotion of the PKR to date. Amine *N*-oxides are known to remove carbon monoxide ligands from transition metals by oxidation to carbon dioxide.[84] The addition of amine *N*-oxides in the PKR therefore renders the first step in the process, i.e. decarbonylation, irreversible. This prevents re-association of the carbon monoxide ligand, and hence drives the reaction forward.

The first examples utilising amine *N*-oxides as reaction promoters were reported in 1990 by Schreiber and co-workers.[85] Their work established that tertiary amine *N*-oxides, for example, *N*-methylmorpholine *N*-oxide (NMO), could be utilised to promote intramolecular P-K cyclisations at room temperature. Their studies incorporated a range of intramolecular substrates, including ethers and silyl ethers (**Scheme 62**).



Scheme 62

In their efforts towards the synthesis of (+)-epoxydictymene, the same authors have also shown that such cyclisations proceed with higher levels of selectivity compared to the use of thermal conditions (**Scheme 63, Table 5**).[85b]

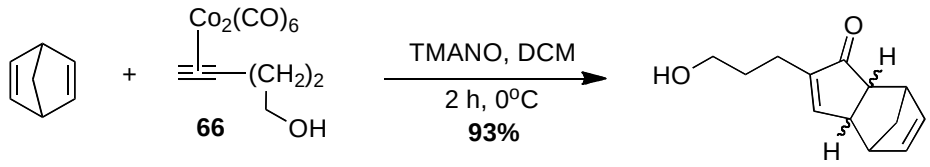


Scheme 63

Conditions	Yield	Selectivity (65a:65b)
NMO, DCM, r.t.	68%	11:1
MeCN, 82°C	75%	4:1

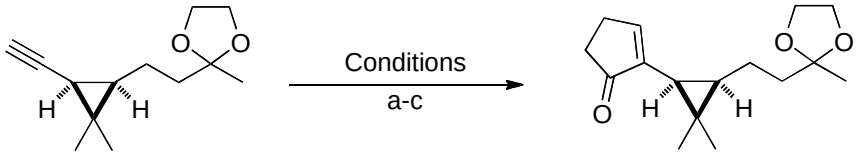
Table 5

In a similar overall sense, Jeong and Chung highlighted the use of trimethylamine *N*-oxide (TMANO) as an efficient promoter for the Pauson-Khand annulation.[86] Their study further widened the scope of the reaction, with more effective intermolecular processes being established, as well as allowing the use of substrates possessing more sensitive functional groups, such as a hydroxyl unit (**Scheme 64**). Low molecular weight alkynols such as **66**, were previously known to be very low yielding in Pauson-Khand processes.[62]



Scheme 64

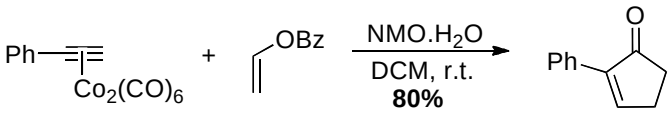
A further benefit of the use of amine *N*-oxide promoters was realised by Kerr and co-workers in 1995, when a Pauson-Khand cyclisation utilising gaseous ethylene was required to obtain a key intermediate towards the synthesis of the natural product target, Taylorione.[87] Kerr illustrated that the use of TMANO.2H_2O as an additive, under a mild autoclave pressure of ethylene (25-30 atm), resulted in an excellent yield of the desired cyclopentenone product (**Scheme 65**). Kerr went on to further widen the scope of this protocol, showing that various alkyne substrates reacted well with ethylene utilising such a mild autoclave technique. Furthermore, Kerr demonstrated that an atmospheric pressure of ethylene was proficient within this developed system over a range of alkyne substrates.[87] When compared to the optimal thermal conditions reported for the cyclisation of these particular substrates, Kerr's procedure displayed an extremely mild and convenient process, which delivered enhanced yields of the desired cyclopentenone products.



a. 25-30 atm ethylene, 40°C, TMANO.2H_2O, **81%**
b. ethylene balloon, r.t., TMANO.2H_2O, **41%**
c. 50 atm ethylene, 80-90°C, TMANO.2H_2O, **38%**

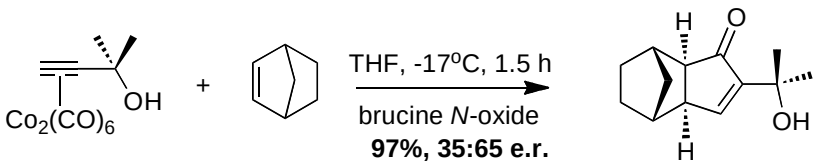
Scheme 65

As part of Kerr's ongoing endeavors to further develop the applicability and efficiency of the Pauson-Khand annulation process, an even more practically accessible set of reaction conditions were developed with regards to the cyclisation of ethylene. This new protocol employed the use of vinyl esters as ethylene equivalents, which eliminated the need for the use of capricious gaseous reagents.[88] As shown in **Scheme 66**, vinyl benzoate performed as an excellent ethylene surrogate, and, in the presence of an amine *N*-oxide promoter, provided the desired cyclopentenone products in good yields under extremely mild conditions.



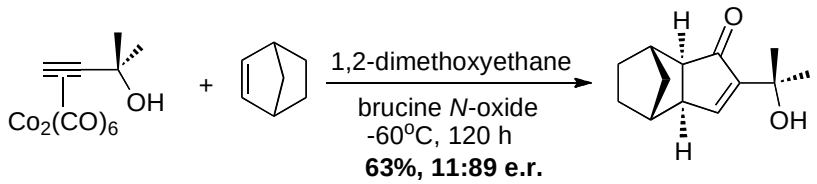
Scheme 66

Kerr *et al*. extended the use of amine *N*-oxide promoters into the asymmetric domain. In this regard, the first example of a direct enantioselective Pauson-Khand cyclisation was revealed in 1995 using a chiral *N*-oxide derived from brucine.[89] This promoter was shown to achieve appreciable enantioselectivities at unprecedented low temperatures and was applied to a variety of alkene and alkyne substrates (**Scheme 67**).



Scheme 67

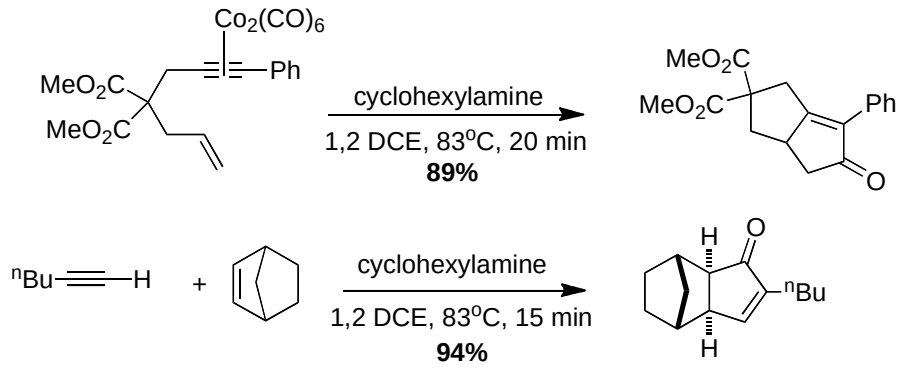
More recently, Kerr and co-workers have optimised their process, with levels of selectivity up to 11:89 e.r. being achieved (**Scheme 68**).[90]



Scheme 68

Amines

In 1997, Sugihara and Yamaguchi proposed that substitution of a carbon monoxide ligand with an alkene could be facilitated using ligands containing nitrogen or oxygen by a coordination effect.[91] Indeed, their results showed that the use of primary amines and, in particular, primary amines containing secondary alkyl functionality significantly increased the rate of various P-K annulations. These authors report cyclohexylamine to be the most efficient promoter within this class and have applied this amine to a number of intra- and intermolecular examples (**Scheme 69**). It should be noted here that, in contrast to the very mild reaction temperatures used with amine *N*-oxides, more forcing conditions are required in conjunction with amine promoters.

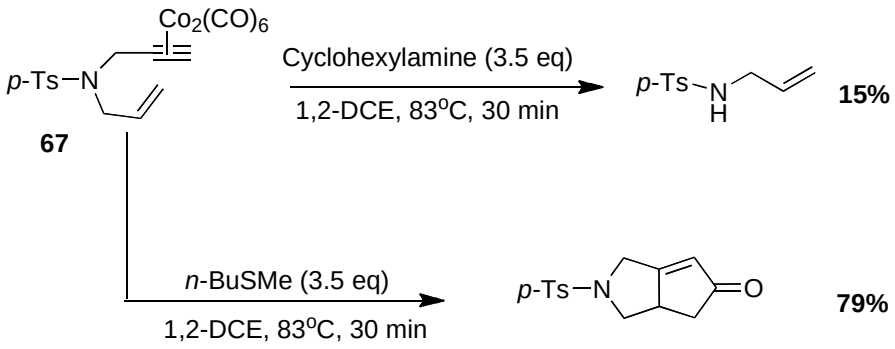


Scheme 69

Sulfides

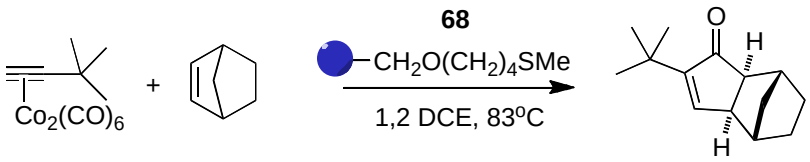
Sugihara and Yamaguchi continued their efforts to improve the efficiency of P-K cyclisations, in turn, demonstrating that sulfides could also act as reaction enhancers.[92] After exhaustive optimisation they reported that alkyl methyl sulfides were the most efficient sulfide-based promoters, affording cyclopentenones in excellent yields in a matter of minutes. The authors claimed that among methyl alkyl sulfides, those with primary or secondary alkyl groups were more effective than those with tertiary units. In particular, they recommend utilisation of *n*-butyl methyl sulfide.

Advantages of a sulfide-promoted system over the amine-promoted Pauson-Khand reaction are exemplified in **Scheme 70**. On treatment of substrate **67** with cyclohexylamine the authors observed cleavage of the alkyne cobalt complex. However, in the presence of *n*-BuSMe no such problem was encountered and the corresponding cyclopenteneone was generated in an excellent yield. An additional advantage of this system is that simple alkene substrates, such as cycloheptene, were applicable where previously these reactions were reported to be unsatisfactory.[92]



Scheme 70

Despite the enhancement in reaction times and yields for Pauson-Khand annulations, utilisation of *n*-butyl methyl sulfide does present some issues. In addition to the elevated temperatures which are, again, required, the major drawbacks of this low-molecular weight sulfide are the unpleasant smell and lachrymatory effect it exposes. Moreover, it is a fairly expensive reagent and cannot be recycled under the PKR conditions. To address these problems, Kerr *et al*. have developed an odourless, reusable polymer-supported sulfide analogue, **68**, which displays the same promoting effects as the problematic *n*-BuSMe. Moreover, this supported sulfide can be used effectively over a number of cycles (**Scheme 71, Table 6**).[93] Furthermore, the supported sulfide also provides a practical benefit, with work-up and purification of reactions merely involving filtration and minimal chromatography.

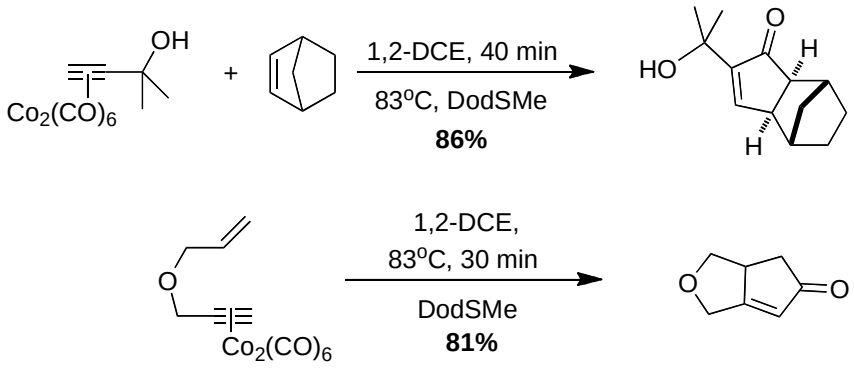


Scheme 71

Run	1	2	3	4	5
Time/min	30	30	30	30	30
Yield (%)	**89**	**92**	**87**	**86**	**88**

Table 6

Kerr and co-workers continued to seek a more economical solution-phase protocol to address the odour problem of sulfides. In this respect, the application of inexpensive and commercially available *n*-dodecyl methyl sulfide (DodSMe) has been shown to be a highly effective promoter in the Pauson-Khand annulation of both intra- and intermolecular substrates, affording good to excellent yields of cyclopentenone products (**Scheme 72**).[94]

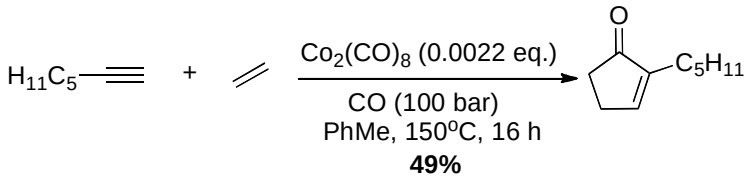


Scheme 72

2.4.7 Catalytic Pauson-Khand Processes

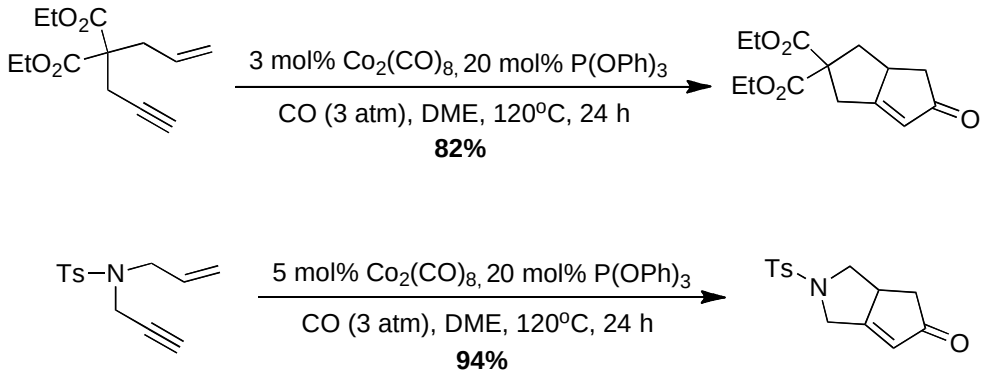
Whilst the stoichiometric Pauson-Khand reaction has displayed great synthetic significance, the drive towards a catalytic protocol, in terms of the transition metal, is one which provides a more practically efficient approach to the synthesis of cyclopentenones. As such, there have been many studies into developing an effective catalytic system.[95]

An early attempt to establish a catalytic intermolecular cyclisation was targeted by Pauson, however, this protocol resulted in only poor yields and demanded harsh reaction conditions.[50b] It was not until 20 years later that a somewhat more efficient catalytic system was reported by Rautenstrauch (**Scheme 73**).[94] The preparation of 2-pentylcyclopent-2-en-1-one was achieved in a moderate yield, with a high turnover number of 220 for dicobalt octacarbonyl being realised. The authors noted that in developing such a system the main hurdle to overcome was the formation of metal clusters or inactive cobalt carbonyl species, such as tetracobalt dodecacarbonyl, $Co_4(CO)_{12}$. Despite the high turnover number in this example, the scope of this catalytic system was limited to the use of ethylene, and, in addition to this, the extremely high pressure of CO used was far from desirable.



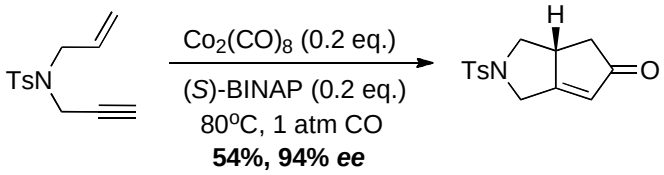
Scheme 73

In 1994 the first practically efficient catalytic Pauson-Khand system was reported by Jeong and co-workers.[97] Their findings demonstrate that the use of phosphines and phosphates allow low levels of catalyst, as well as reduced pressure of CO, to be used in the cyclisation of various enynes. **Scheme 74** illustrates the use of triphenyl phosphite, under a reduced pressure of CO (3 atm), with only 3-5 mol% of catalyst, affording cyclopentenones in excellent yields.



Scheme 74

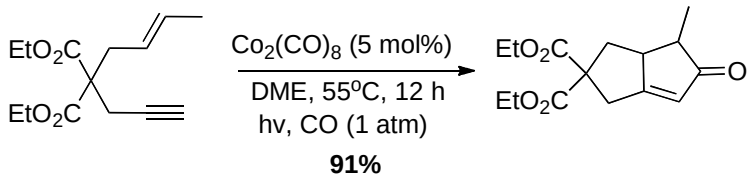
In addition to this, a variation of these protocols has recently been used in an enantioselective version of the Pauson-Khand reaction by employing chiral phosphines, such as BINAP. The established asymmetric process displays outstanding levels of enantiomeric excess in the catalytic cyclisation of enynes, albeit with moderate chemical yields (**Scheme 75**).[98] The substrate scope applicable with this set of conditions is also limited and the authors note that the best results are obtained with monosubstituted olefins and alkynes.



Scheme 75

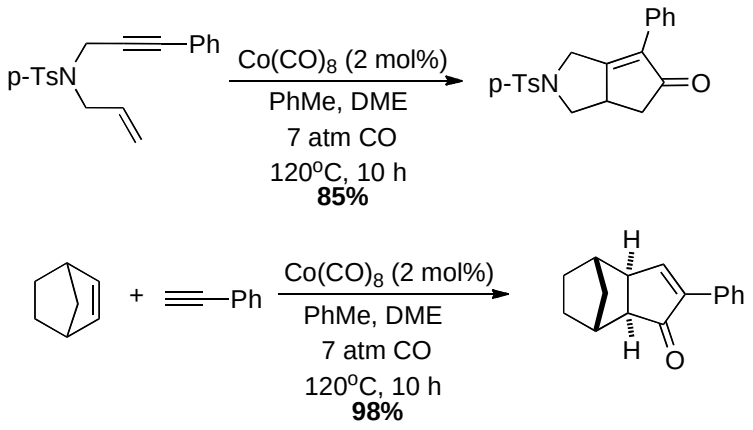
In 1996, Livinghouse described the photoinitiated cyclisation of enynes utilising catalytic quantities of cobalt (**Scheme 76**).[99] The authors stressed that a highly purified cobalt catalyst source was required in order to achieve successful cyclisations. Nevertheless, in this system a range of intramolecular cyclisations were carried out under relatively mild conditions. In relation to this system, a subsequent report from the same group explained that, with careful control of the reaction temperature, there is no need for the use of

photolytic promotion.[100] Following this work, Krafft and co-workers quashed Livinghouse's necessity for ultra high purity $Co_2(CO)_8$, noting that unpurified cobalt with base-washed glassware in DME was sufficient to produce efficient cyclisations.[101]



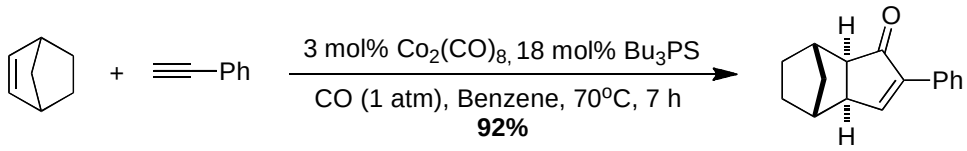
Scheme 76

Whilst the scope of the systems discussed to this point included a range of intramolecular substrates, the use of catalytic quantities of transition metal in the intermolecular counterpart proved to be more difficult to achieve in terms of delivering efficient cyclisations. Having said this, Sugihara and Yamaguchi reported the use of 'hard' Lewis bases, such as 1,2-dimethoxyethane (1,2-DME), as additives to promote the catalytic PKR, and incorporated both intra- and intermolecular cyclisations within their study (**Scheme 77**).[102] With regards to the intermolecular reactions, only particularly active alkenes performed well; norbornene, an extremely strained olefin, performed excellently within this protocol. Despite the increased pressure of CO required (7 atm), the excellent yields produced by this system made this a valuable protocol with regards to the catalytic PKR.



Scheme 77

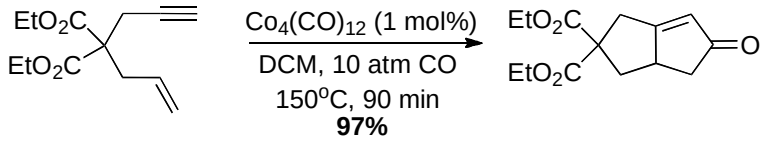
Similarly, Hashimoto described a catalytic system whereby addition of a monodentate phosphine sulfide, in particular tributylphosphine sulfide, allowed the P-K cyclisations to take place utilising just 3 mol% of catalyst, as well as using a low pressure of CO.[103] The majority of examples shown in this study were intramolecular cyclisations. However, as shown in **Scheme 78**, once again, this protocol was applicable to intermolecular annulations when particularly reactive alkenes are employed.



Scheme 78

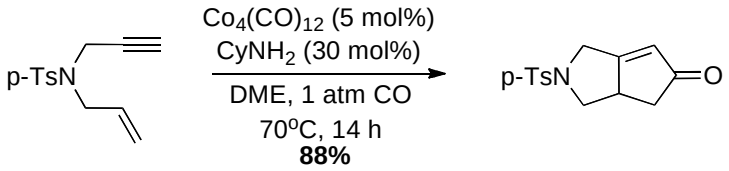
In an attempt to develop a more stable source of cobalt catalyst ($Co_2(CO)_8$ is known to be air-sensitive) Chung went on to use $Co_4(CO)_{12}$ as a pre-catalyst in a Pauson-Khand reaction (**Scheme 79**).[104] Whilst this cobalt cluster had initially been believed to be detrimental to P-K cyclisations,[96] it proved to be an excellent pre-catalyst in the reaction system developed by Chung. Both inter- and intramolecular cyclocarbonylations were carried out with high efficiency. Having said this, again, only highly strained (thus reactive) olefins were employed within the intermolecular processes. Additionally, the

main drawback with this system was the use of forcing reaction conditions (150^{o}C and 10 atm of CO).



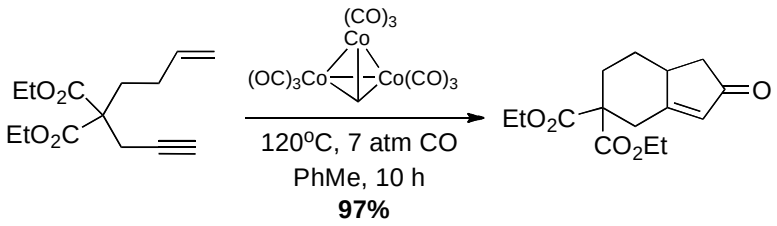
Scheme 79

In a similar fashion, Krafft demonstrated the use of a primary amine along with $Co_4(CO)_{12}$ in the PKR, allowing much milder reaction conditions to be applied.[105] Despite the higher loadings of $Co_4(CO)_{12}$ being required, reactions were now shown to proceed under an atmospheric pressure of CO (**Scheme 80**). It is thought that the cyclohexylamine helps to break down the inactive cobalt clusters and, in turn, stabilises the reactive catalytic species.



Scheme 80

The use of cobalt carbonyl clusters as a more stable source of catalytically active species has also been investigated by Sugihara and Yamaguichi.[106] Their work demonstrated that the replacement of a $Co(CO)_3$ unit within $Co_4(CO)_{12}$ with a methylidine bridge resulted in the development of an efficient catalyst (**Scheme 81**). In a further publication the authors reported that addition of a small amount of amine resulted in a further improved catalytic system.[107]

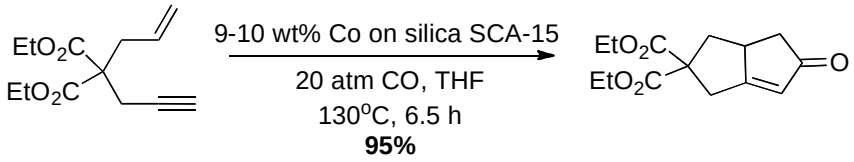


Scheme 81

Having discussed all of the above, it is evident that the catalytic Pauson-Khand reaction has come a long way since the early work of Pauson and co-workers. However, the use of highly toxic carbon monoxide presents a major drawback to these procedures. In 2000, Krafft and co-workers addressed this issue by using 35 mol% of $Co_2(CO)_8$ in DME, again with an amine additive.[108] Despite the relatively very high loading of Co, this system allowed the reactions to be carried out under an atmosphere of N_2, dispensing with the need for a CO blanket.

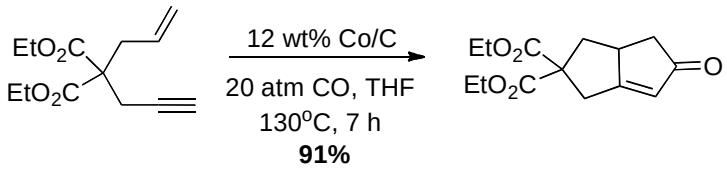
Hetereogeneous Cobalt Catalysis[109]

Up until the last decade, studies towards the development of a catalytic Pauson-Khand protocol had focused on homogenous catalysis. Of course, for industrial purposes it would be more desirable to achieve heterogeneous catalysis, which brings inherent advantages such as stability, ease of operation, and reusability of the catalyst. The first example of such a system was described by Chung, where the application of cobalt adsorbed onto a mesoporous silica support resulted in an efficient heterogeneous system (**Scheme 82**).[110] The catalyst was prepared by decomposing $Co_2(CO)_8$, in refluxing toluene, on SCA-15, which, in turn, maintained activity over four runs. Furthermore, no metal leaching was observed upon analysis of the reaction mixtures.



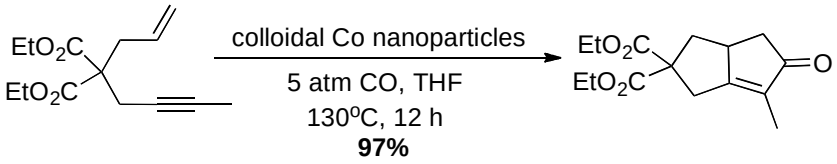
Scheme 82

In the same year, Chung developed another system whereby $Co_2(CO)_8$ decomposed in THF at reflux in the presence of charcoal was utilised (**Scheme 83**).[111] This generated a highly active species, which catalysed the cyclisation of enynes, affording cyclopentenone products in excellent yields. This, more robust, system allowed the catalyst to be recycled ten times without losing any efficiency. This study also incorporated intermolecular examples, albeit with strained alkenes only.



Scheme 83

Whilst both of Chung's initial processes displayed significance in the development of a heterogeneous system, the conditions demanded were harsh; in particular, elevated temperatures and pressures of 20 atm of CO were required. This CO pressure issue was alleviated by Chung when he used highly active cobalt nanoparticles (**Scheme 84**).[112] The authors note that, due to the high surface-to-volume ratio of the nanoparticles, a large fraction of the metal atoms are at the surface and, hence, are available for catalysis. This highly active system was demonstrated in several examples with consistently excellent isolated yields of the desired cyclopentenone products.

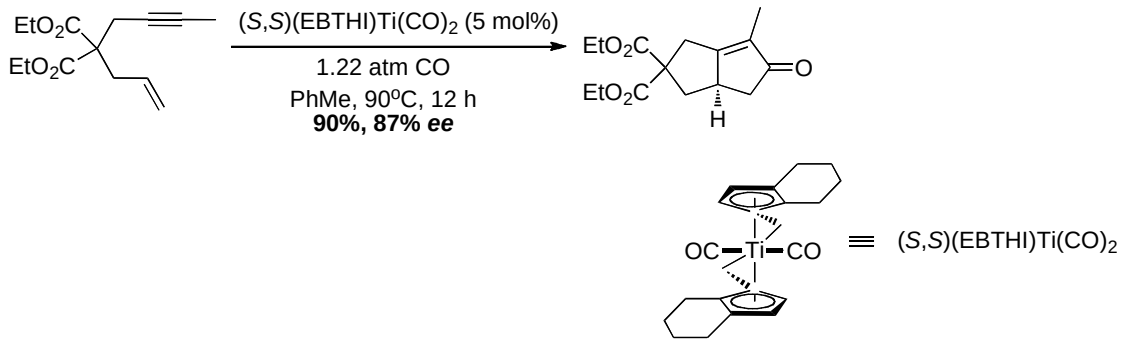


Scheme 84

Despite a positive development in the reaction conditions, there still remained inconveniences with the use and storage of colloidal cobalt nanoparticles. Once more, Chung improved the system by utilising cobalt nanoparticles on a charcoal support (CNC); this combined the virtues of highly active nanoparticles with conventional heterogeneous catalysis.[113] The CNC catalyst system is extremely robust in air and can be stored for several months without losing activity.

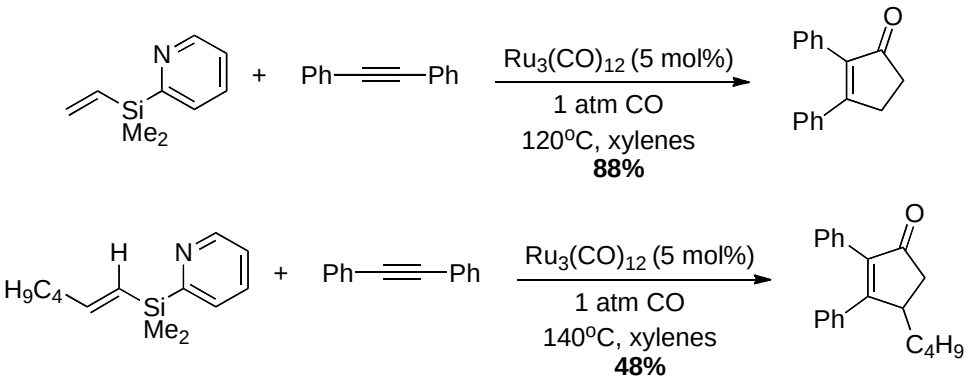
2.4.8 The Use of Other Metals

Alongside the development of this cobalt methodology, examples in the literature of Pauson-Khand reactions catalysed by other transition metals have emerged. Indeed, an early example from Buchwald demonstrated the use of titanocene complexes (**Scheme 85**).[114] Using just 5 mol% of a commercially available catalyst, a range of enynes were cyclised under low pressures of carbon monoxide. Shortly following this work, Buchwald developed an enantioselective version of this system utilising a chiral titanocene; Pauson-Khand products were prepared with excellent enantioselectivity.[115]



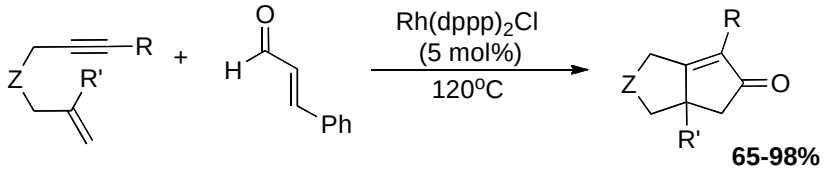
Scheme 85

Following on from the work of Buchwald, in 1997 Murai[116] and Mitsudo[117] independently reported the use of $Ru_3(CO)_{12}$ in the Pauson-Khand cyclisation of a range of enynes. Whilst terminal alkynes have been reported as excellent substrates in the cobalt-catalysed reaction, the authors noted that these substrates were not viable in this ruthenium-mediated variant. More recently, Itami and Yoshida have expanded the scope of the intermolecular Pauson-Khand reaction, using a ruthenium-catalysed protocol.[118] Their strategy involves the use of olefins bearing a pyridisilyl group, which causes complete regioselectivity *via* chelation of the pyridyl nitrogen with the metal. With the ease of removal the pyridisilyl group, this leads to a variety of substituted cyclopentenones (**Scheme 86**). Despite the rather wasteful (atom-uneconomical) nature of the process, with the dimethylpyridylsilyl unit loss, this overall process dispenses with the need for ethylene, or strained olefins, for an efficient catalytic intermolecular P-K annulation.



Scheme 86

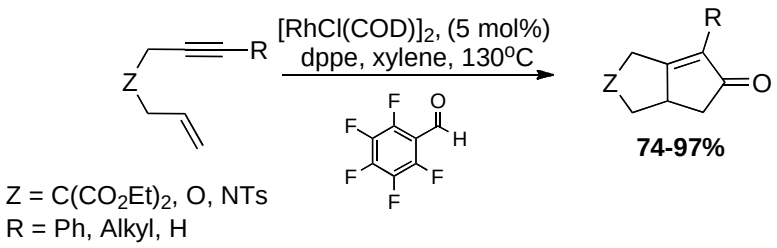
With increasing environmental awareness being demanded within preparative processes, the use of an external carbon monoxide source is extremely undesirable, and, as such, there have been attempts to eliminate the use of CO in the Pauson-Khand cyclisation (*vide supra*). One development in this area is the use of aldehydes as a source for CO. It is known that transition metals can act as decarbonylation catalysts with carbonyl compounds, and this has previously been used as a key step in transition metal-catalysed transformations.[119] In 2002, Shibata *et al*. reported the first catalytic Pauson-Khand reaction, which utilised cinnamaldehyde as an alternative carbon monoxide source. This rhodium-mediated protocol provided a clean, solvent-free, process resulting in the preparation of a range of bicyclic enones in good to excellent yields (**Scheme 87**).[120] Shibata went on to further extend this protocol within the asymmetric domain. The introduction of a chiral phosphine ligand allowed the formation of cyclopentenone products in an enantio-enriched form.[120] Despite the elimination for the requirement of toxic carbon monoxide gas, one drawback of this process is the atom inefficiency; in every reaction there is a waste of styrene by-product.



Z = O, NTs, CH_2, $C(CO_2Et)_2$
R = Me, Ar
R' = H, Me

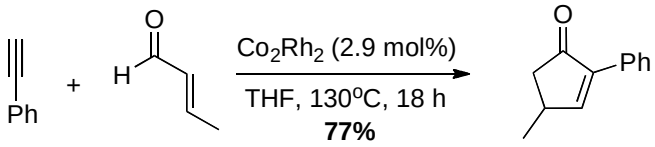
Scheme 87

In the same year, Morimoto *et al*. reported a further example of a rhodium-mediated PKR, which, this time, utilised pentafluorobenzaldehyde as an alternative source of carbon monoxide (**Scheme 88**).[121] Various enynes (now including those containing terminal alkynes) were cyclised, under an atmosphere of nitrogen, in excellent yields. A major drawback with this protocol, however, is, again, the waste of the pentafluorobenzene by-product.



Scheme 88

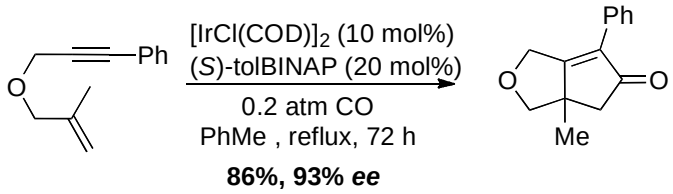
More recently, Chung has applied α,β-unsaturated aldehydes to act as both the carbon monoxide source as well as the olefin moiety within Pauson-Khand processes.[122] This atom-economical system utilises Co/Rh heterobimetallic nanoparticles, derived from $Co_2Rh_2(CO)_{12}$, to catalyse the cyclisation of various alkynes and aldehyde substrates (**Scheme 89**). Indeed, this protocol has also markedly increased the scope of the intermolecular reaction; the requirement of strained, hence reactive, olefins has been circumvented by this process. Having stated this, this protocol does demand that the requisite unsaturated aldehyde substrate is available for cyclisation, with the added complexity that such aldehydes are known to be notoriously sensitive in nature.



Scheme 89

Having established successful cyclisations utilising catalytic quantities of cobalt, titanium, ruthenium, and rhodium complexes, it was inevitable that studies would be directed towards the use of iridium. Initial studies by Shibata and Takagi demonstrated the use of catalytic quantities of $[IrCl(COD)]_2$ in the cyclisation of various enynes, however, low conversions were observed.[123] Having stated this, the authors noted that the use of phosphines as co-ligands significantly improved the efficiency of the system. With these results, Shibata and Takagi were prompted to employ chiral phosphines in an attempt to induce asymmetry in the reaction. Pleasingly, using $[IrCl(COD)]_2$, in the

presence of (*S*)-tolBINAP, several 1,6-enynes were cyclised successfully, with up to excellent enantiomeric excesses (**Scheme 90**).[124] Then again, the major limitation with this system relates to the substrate scope; reaction of enynes containing a 1,2-disubstitued olefin, a terminal alkyne, or a 1,7-enyne resulted in trace or no cyclocarbonylated product being detected.



Scheme 90

Overall, the catalytic Pauson-Khand reaction has come a long way since the initial attempts in the early 1970s. The intramolecular variant of this reaction has been shown within an array of exceptionally efficient cyclisations, allowing the preparation of a number of valuable organic structures. In contrast, the catalytic intermolecular counterpart still fails to fully satisfy the modern synthetic chemist; however, new systems are rapidly developing this technique. In terms of the transition metal, new emerging protocols continue to offer advantages with respect to environmental considerations, stability of the catalysts, scope of the substrates, and overall efficiency of the cyclisations.

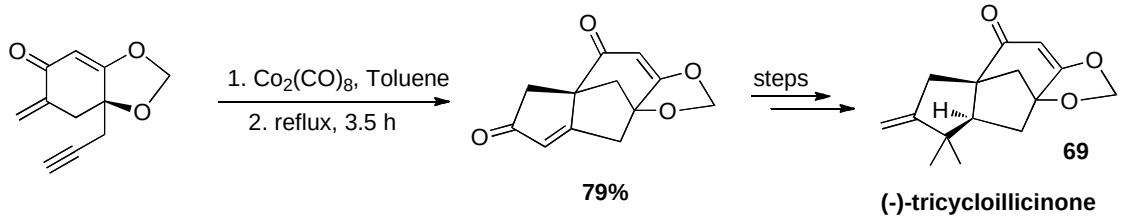
2.4.9 The Asymmetric Pauson-Khand Reaction[49]

Over the last few decades there has been a variety of methods developed to induce asymmetry in the Pauson-Khand reaction. These include the use of chiral alkyne substrates, chiral auxiliary approaches, the use of a chiral C_2Co_2 core, and the employment of chiral additives, such as chiral amine *N*-oxides. Indeed, any review in this area would be incredibly extensive, and, as such, only a few key examples have been touched upon throughout this report (*vide supra*).

2.4.10 Applications in Natural Product Synthesis

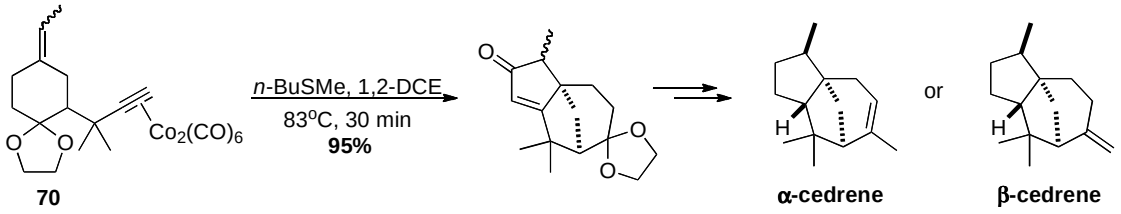
The cyclopentenone core is common to many natural products. Subsequently, the Pauson-Khand reaction has been utilised extensively to construct such compounds and there are a number of examples where this powerful reaction is used strategically as one of the central steps in the synthesis of target molecules.

In 2003, Terashima and Furuya reported the synthesis of (-)-Tricycloillicinone, **69**, a potential drug target for Alzheimer's disease.[125] This compound has a synthetically challenging tetracyclic framework bearing two quaternary carbons. The classical thermally-promoted Pauson-Khand annulation was applied, affording the key cyclopentenone intermediate in an excellent yield (**Scheme 91**).



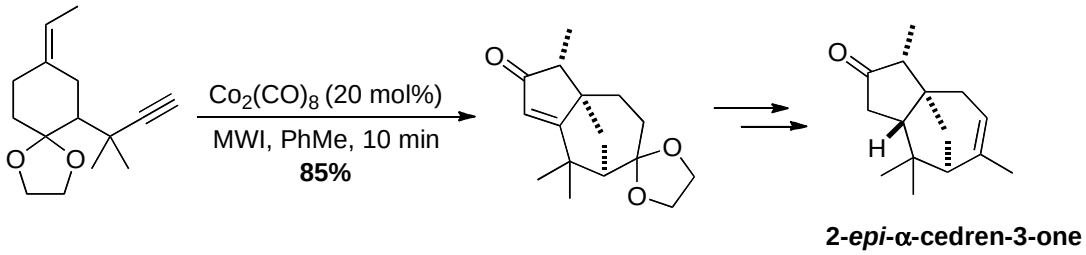
Scheme 91

Another application comes from our own research group in the 2001 syntheses of α- and β-cedrene.[126] The key step in the route to these natural products was a very efficient sulfide-promoted Pauson-Khand reaction in order to generate the tricyclic core of the molecule from the simple monocyclic 1,6-enyne **70** (**Scheme 92**).



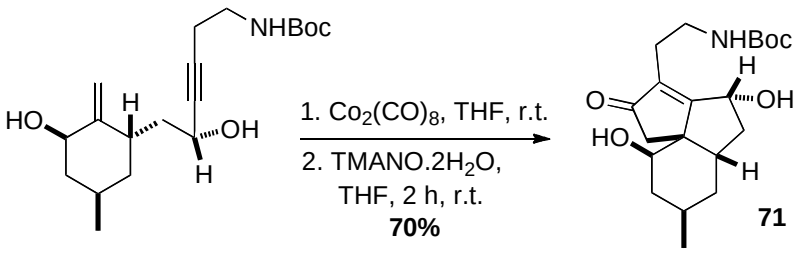
Scheme 92

In a related synthesis, the Kerr group developed a microwave-assisted, catalytic protocol, which delivered the core carbon skeleton of 2-epi-α-cedren-3-one (**Scheme 93**). Using only 20 mol% of cobalt catalyst, the desired cyclopentenone was prepared, in just ten minutes, without the need for an external source of carbon monoxide.[127]



Scheme 93

Another interesting recent example of a Pauson-Khand cyclisation is contained within Hoshino and Ishizaki's synthesis of Magelanine. As can be seen in **Scheme 94** the Pauson-Khand cyclisation was elegantly used to construct the angularly fused cyclopentenone **71**.[128] Under mild amine *N*-oxide promoted conditions tricycle **71** was prepared in just 2 h reaction time and in a good 70% yield.



Scheme 94

In summary, the Pauson-Khand reaction has provided vast synthetic value to the preparative chemistry community, and continues to be applied as a direct and highly efficient method for the construction of many challenging carbon skeletons. Since its first disclosure in the early 1970's there has been enormous progress in terms of practical efficiency, which now presents the PKR as a mild and flexible tool for the synthesis of cyclopentenones and their derivatives. The intramolecular variant of the PKR is really where the true practical potential of this disconnection is unlocked. Unaffected by the regiochemical restrictions of the intermolecular variant, the intramolecular reaction has found prominence as the key step in a number of natural product total syntheses. In addition to this, the catalytic protocols now available in the literature represent excellent alternatives to the stoichiometric reaction types. Both homogeneous and hetereogeneous systems have been developed eliminating the early problems with metallic waste, as well as product isolation. Further progress has been achieved by reactions using other transition metal complexes as catalysts; the development of such systems has brought advantages, such as the expansion of the reaction scope, as well as elimination of the need for an external source of carbon monoxide.

Having stated all of the above, there are still some concerns regarding the Pauson-Khand cyclisation. Firstly, with regards to reaction mechanism, whist the studies in the last decade have advanced considerably in the comprehension of the reaction mechanism, continuing attempts to fully interpret the reaction pathway will allow a more accurate prediction of the outcome of the reaction. As well as this, the scope of the intermolecular version of the Pauson-Khand annulation is still rather limited. In particular, unstrained

olefins still react rather sluggishly in catalytic protocols. Nevertheless, techniques such as the directed Pauson-Khand reaction have minimised this problem, allowing the use of simpler olefins and, at the same time, avoiding regioisomeric product mixtures.

Chapter 3

Efforts Towards the Synthesis of the Natural Target, Agariblazeispirol C

3.1 Previous and Proposed Work *pg. 80*

3.2 Results and Discussion *pg. 82*

*3.2.1 Towards the Preparation of Heck Precursor **8*** *pg. 82*

*3.2.2 The Intramolecular Heck Reaction: Preparation of Compound **7*** *pg. 90*

*3.2.3 Alternative Synthesis: Targeting Compound **91*** *pg. 91*

*3.2.4 Preparation of Vinyl Bromide **96*** *pg. 93*

*3.2.5 Intramolecular Heck Reaction: Preparation of Compound **94*** *pg. 96*

3.2.6 Towards the Pauson-Khand Precursor *pg. 100*

3.2.7 The Pauson-Khand Reaction *pg. 109*

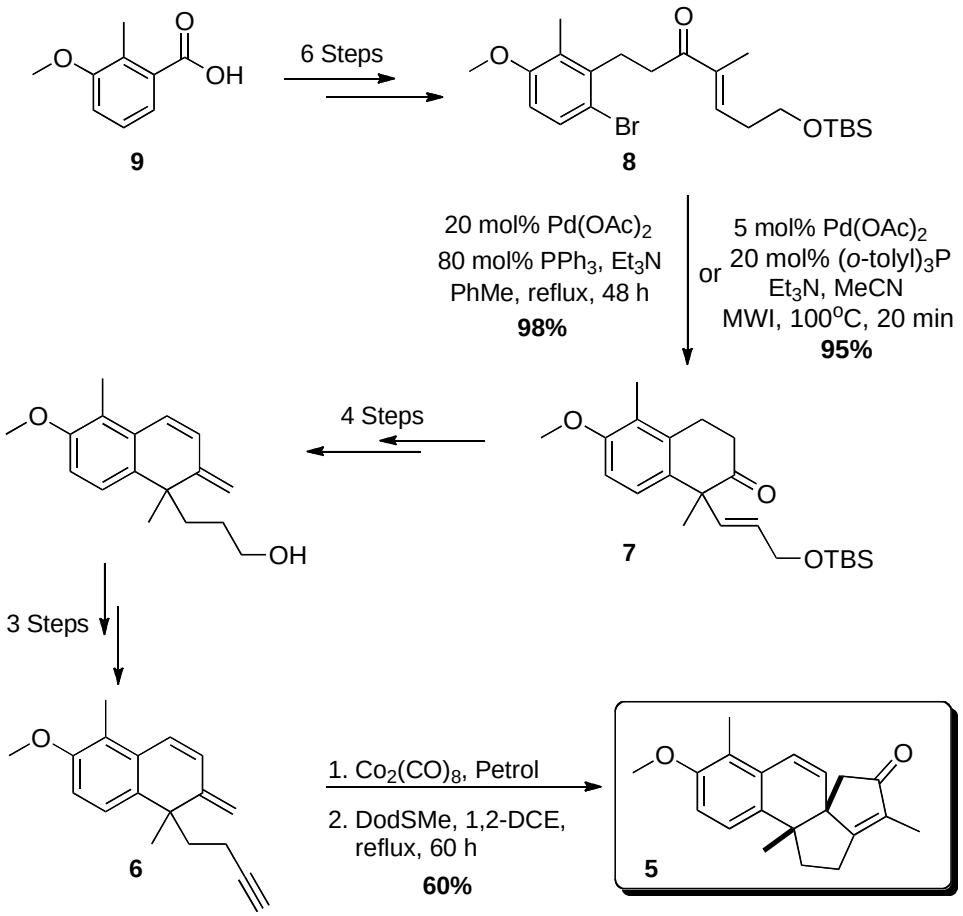
3.2.8 Towards the Completion of the Total Synthesis *pg. 112*

*3.2.9 Alternative Route Towards Compound **5**: Allylic Oxidation Approach* *pg. 127*

3.2.10 Final Strategy: Wittig Olefination Approach *pg. 135*

3.1 Previous and Proposed Work

Progress towards the total synthesis of Agariblazeispirol C was initiated during a previous short and preliminary body of work carried out within the Kerr group.[129] From this research, an initial and unoptimised pathway towards the tetracyclic core of our targeted natural product has been formulated



Scheme 95

As shown in **Scheme 95**, starting from the commercially available carboxylic acid **9**, an efficient process had been established for the preparation of Heck precursor **8**. With regards to our first metal-mediated cyclisation, initial conditions generated bicyclic intermediate **7**, using high catalyst and ligand loadings, in an excellent yield after 48 h reaction time. On further

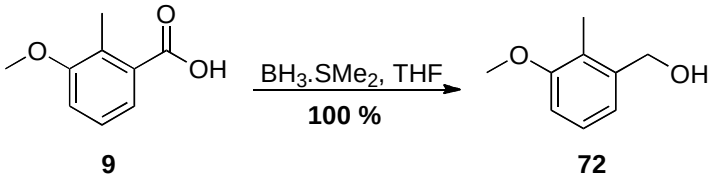
optimisation, microwave conditions were developed which produced a 95% yield of the desired compound **7**, in 20 minutes using only 5 mol% palladium catalyst.[124] Following the implementation of this Heck technology, efforts were focused on the synthesis of the Pauson-Khand precursor **6**. Following seven synthetic steps this desired enyne substrate was synthesised with moderate efficiency. Turning to the intramolecular P-K reaction, initial results proved somewhat promising. In this regard, after the preparation of the requisite cobalt complex, cyclisation of alkyne **6** delivered the tetracyclic core of Agariblazeispirol C in a single step, constructing three new C-C bonds and setting the second challenging all carbon bearing quaternary stereocentre. Having stated this, and following some appreciable optimisation,[130] the yield of this cyclisation presently stands at a moderate 60% after a rather prolonged 60 h reaction time.[130]

With no reported synthesis of Agariblazeispirol C within the chemical literature, above all else, the first total synthesis of this target was the key aim of this piece of research. In this regard, upon initiation of this new and independent programme of work, at the outset it was decided to continue our focus on the originally envisaged preparative pathway described above.

3.2 Results and Discussion

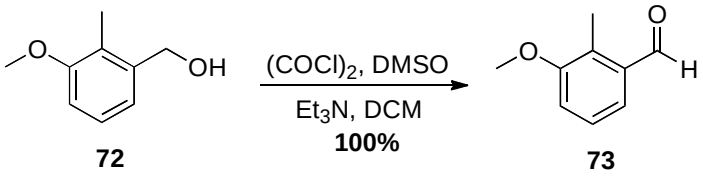
3.2.1 Towards the Preparation of Heck Precursor 8

As mentioned above, early work continued to focus on the initially devised preparative pathway described in **Scheme 95**.[129,130] Towards this goal, the synthetic sequence began with preparation of benzyl alcohol **72** *via* borane reduction of the commercially available carboxylic acid **9** (**Scheme 96**). Pleasingly, this transformation occurred without incident yielding the desired alcohol **72** in 100% yield.



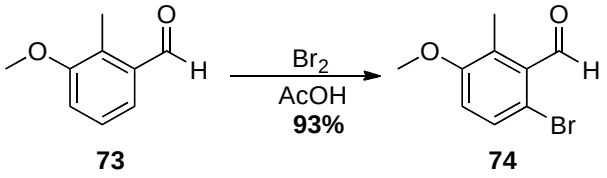
Scheme 96

The next step in our synthetic sequence involved the oxidation of primary alcohol **72** to aldehyde **73** *via* standard Swern conditions.[131] Pleasingly, the desired aldehyde was isolated in quantitative yield (**Scheme 97**).



Scheme 97

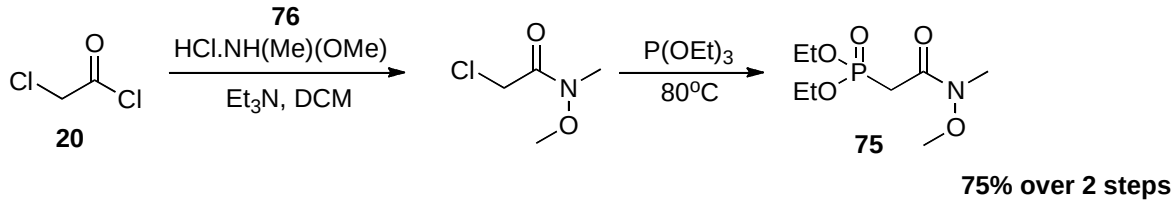
Due to the sensitivity of aldehyde **73** this species was used almost immediately in the subsequent bromination step.[132] Under relatively mild conditions, bromoaldehyde **74** was delivered in an excellent yield (**Scheme 98**). It is important to note that this reaction occurred with complete regioselectivity; no other regioisomers were observed by ^{1}H NMR spectroscopy.



73 **74**

Scheme 98

With the required halogen now in place, attention turned to extension of the carbon chain *via* the aldehyde moiety. In this regard, a standard Horner-Wadsworth-Emmons (HWE) reaction[133] was to be employed, requiring the synthesis of functionalised phosphonate ester **75**. Following a literature protocol,[134] this reagent was prepared *via* reaction of chloroacetyl chloride and Weinreb amine **76**, followed by introduction of triethylphosphite to the reaction mixture (**Scheme 99**). The overall yield for this reaction was 75%.

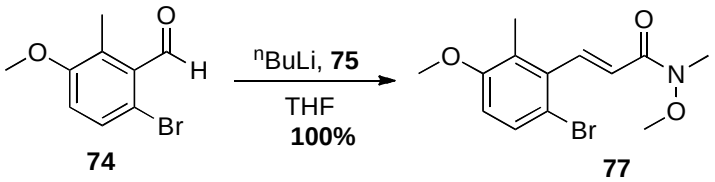


20 **75**

75% over 2 steps

Scheme 99

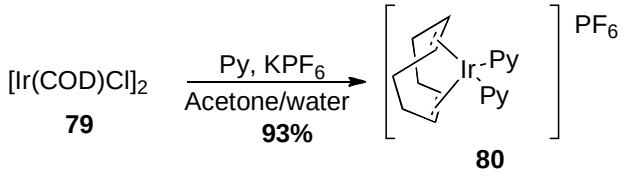
With good quantities of this functionalised phosphonate in hand, olefination was attempted under standard HWE conditions, furnishing the *E*-α,β-unsaturated amide **77** exclusively, in an excellent, quantitative, yield (**Scheme 100**).



74 **77**

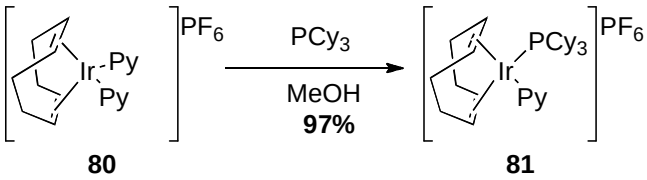
Scheme 100

It was now deemed necessary to remove the newly installed double bond to create the desired unsaturated Weinreb amide **78**. Previous work within this programme of study showed that Pd-based catalysts led to dehalogenation of the aryl ring within substrate **77**.[129] As such, iridium-based catalyst **81**, known as Crabtree's catalyst, was selected as a milder alternative to achieve the desired olefin reduction selectively. Although commercially available, Crabtree's catalyst was prepared *via* a robust and high yielding literature protocol.[135] Reaction of chloro-1,5-cyclooctadiene iridium(I) dimer **79**, with potassium hexafluorophospate, and an excess of pyridine, afforded bispyridine complex **80** in an excellent yield (**Scheme 101**).



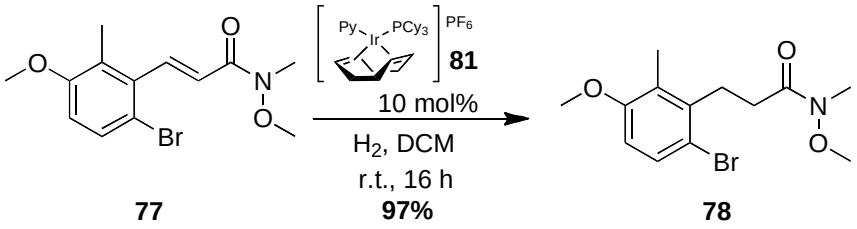
Scheme 101

Intermediate **80** was subsequently reacted with tricyclohexylphosphine to furnish Crabtree's catalyst in multi-gramme quantities (**Scheme 102**).



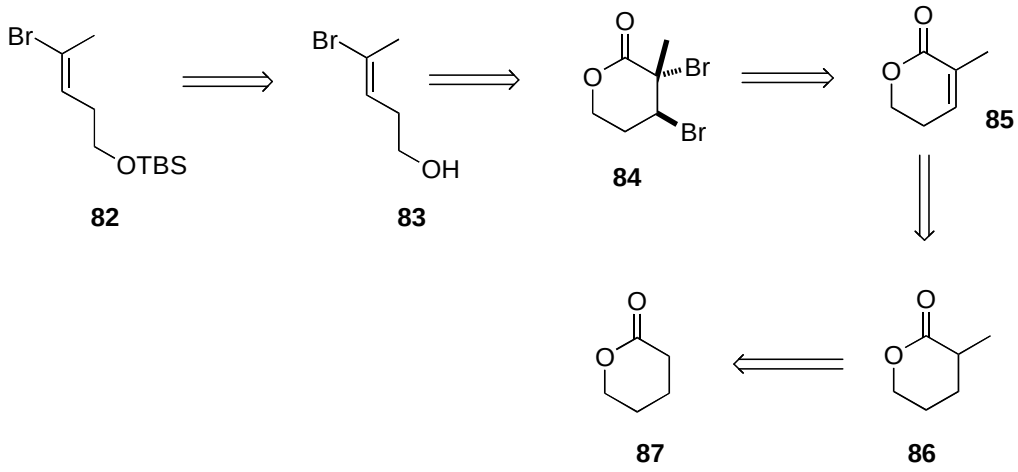
Scheme 102

With catalyst **81** in hand, hydrogenation of substrate **77** was carried out delivering an excellent yield of the required Weinreb amide (**Scheme 103**). The elevated efficiency of this process was entirely reproducible in every case as part of this programme.



Scheme 103

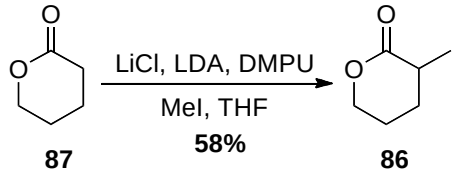
Next, attention turned to the preparation of Heck precursor **8**, an intermediate which is key to this approach to Agariblazeispirol C. Our particular pathway towards this intermediate required the preparation of vinyl bromide **82**. In this regard and in attempts to enhance the effectiveness of previously established procedures, and this total synthesis route overall, a retrosynthetic analysis for this substrate is suggested in **Scheme 104**.



Scheme 104

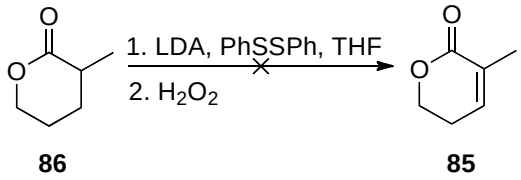
Initial removal of the TBS protecting group present in **82** furnishes free alcohol **83**, which we envisaged could be constructed *via* a saponification, decarboxylative elimination sequence. This leads us to intermediate **84**, which, in turn, could be further simplified to α,β-unsaturated lactone **85**. The synthesis of **85** could be achieved from compound **86**, whose ultimate precursor is the commercially available lactone **87**.

As such, following a literature protocol,[136] commercially available lactone **87** was alkylated at the α-position to furnish substituted lactone **86** (**Scheme 105**). Whilst the yield was modest, the relatively inexpensive starting materials allowed the reaction to be performed on a moderately large scale, providing multi-gramme quantities of desired compound **86**.



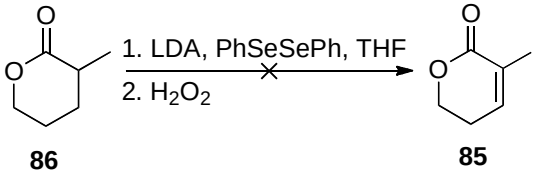
Scheme 105

Attention now focused on the oxidation of this compound to generate α,β-unsaturated lactone **85**. Unfortunately, after deprotonation of **86** and subsequent quenching with diphenyldisulfide, no product could be isolated from the reaction mixture (**Scheme 106**). Nevertheless, almost quantitative recovery of the starting material was achieved.



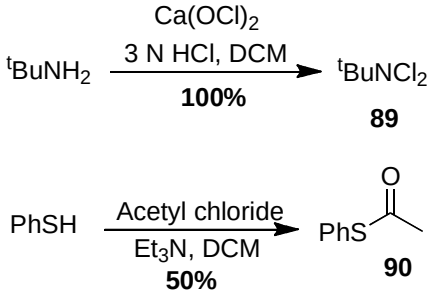
Scheme 106

At this point, the approach to the desired α,β-unsaturated lactone was modified by using diphenyldiselenide as the reagent. However, once again, only starting lactone **86** was isolated from the reaction (**Scheme 107**).



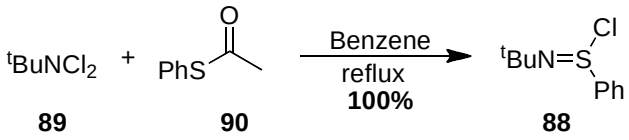
Scheme 107

Undeterred, a set of conditions previously successful within our research group[137] for such a transformation were considered. Originally developed by Mukaiyama,[138] this method utilises *N*-*t*-butylbenzenesulfinimidoyl chloride, **88**, as the oxidant. This material was readily prepared *via* a robust method, first requiring the preparation of dichloroamine **89**, and *S*-phenyl thioacetate **90** (**Scheme 108**).



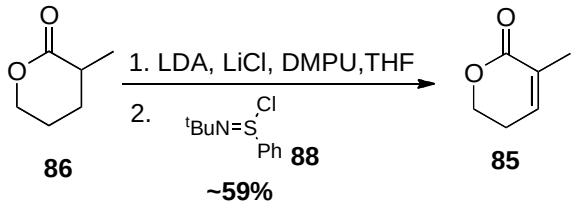
Scheme 108

Following this, reaction of components **89** and **90** under refluxing conditions afforded the desired oxidant **88** in a quantitative yield (**Scheme 109**).



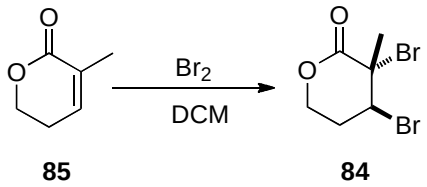
Scheme 109

With this sulfur oxidant in hand, deprotonation of lactone **86**, and quenching with **88**, pleasingly, yielded the desired α-β-unsaturated lactone **85** (**Scheme 110**). Unfortunately, purification of this unsaturated lactone proved tricky, with sulfur residues proving difficult to remove even following careful column chromatography, therefore, the yield of this reaction was estimated at ~59%.



Scheme 110

Despite this purification issue, it was decided to continue with our approach towards vinyl bromide **82**, with the anticipation that purification would perhaps prove more straightforward at a later stage in the synthetic pathway. As such, bromination of compound **85** was attempted, and, whilst the desired product was obtained, very poor yields were observed (**Scheme 111, Table 7, Entries 1 and 2**). This lack of efficiency is attributed to the sulfur residues present in the starting lactone. In an attempt to clean up the starting material, distillation was carried out, and, pleasingly, with this further purified starting material, as well the use of an increased quantity of bromine, an increased yield of the desired product was obtained (**Table 7, Entry 3**).



Scheme 111

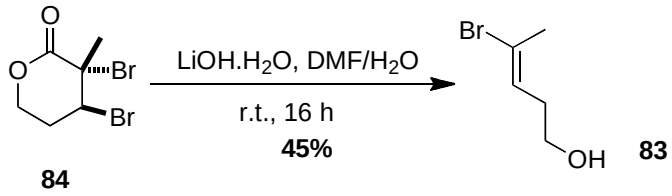
Entry	Eq. of Br_2	Yield
1	1	11%
2	1.4	22%
3[a]	2	52%

[a] with purified **85**; distilled at 140-142°C, 15 mbar

Table 7

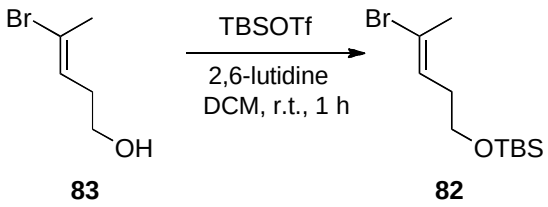
With quantities of **84** in hand, lithium hydroxide-mediated decarboxylative elimination was carried out. This provided desired alcohol **83** (**Scheme 112**). However, once again, the yield

obtained was somewhat disappointing. This could be attributed to the use of DMF, which could have rendered the extraction of the organic compound from the aqueous layer inefficient. It is also important to note that the conditions employed gave rise to the *E*-isomer exclusively by comparison with literature data.[167] This was also confirmed by further analysis later in the synthetic programme.



Scheme 112

At this stage, the final step required to gain access to the necessary vinyl bromide unit, was TBS protection of the free alcohol (**Scheme 113**). Initially, using one equivalent of base afforded only 68% of the desired protected vinyl bromide, with the mass balance made up by returned starting material (**Table 8, Entry 1**). In order to probe this reaction further, the reaction was repeated using an excess of base (2.2 eq.), and TBSOTf (1.1 eq.). Pleasingly, this resulted in an increase in yield of the desired protected alcohol **82** being obtained (**Table 8, Entry 2**).

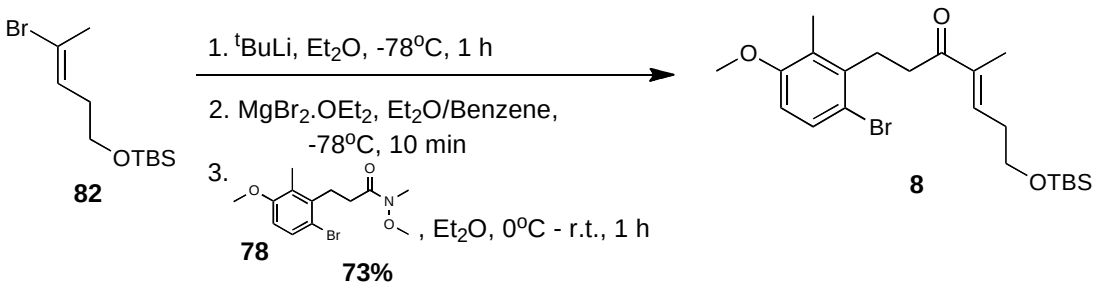


Scheme 113

Entry	2,6-lutidine (eq.)	TBSOTf (eq.)	Yield
1	1.0	1.0	68%
2	2.2	1.1	93%

Table 8

With both the Weinreb amide and vinyl bromide fragments now prepared, attention turned to the synthesis of Heck precursor **8**. Lithiation of vinyl bromide **82**, followed by transmetallation with freshly prepared $MgBr_2.OEt_2$,[139] and subsequent introduction of the previously prepared Weinreb amide **78**, resulted in a good isolated yield of the desired enone (**Scheme 114**). To note, previous conditions using solely ^{t}BuLi as the organometallic reagent resulted in competing debromination of the aryl ring followed by by-product formation (*via* intramolecular cyclisation onto the Weinreb amide unit).[129]

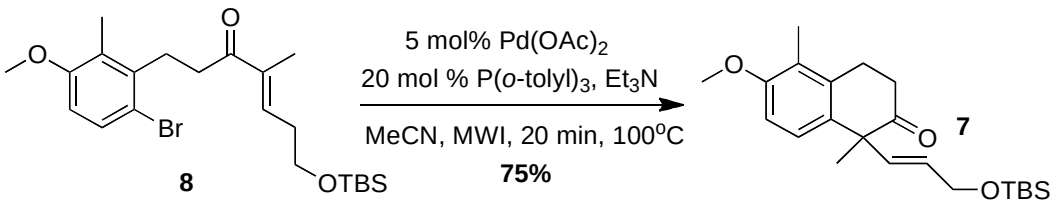


Scheme 114

With precursor **8** in hand, it was now necessary to carry out the first key metal-mediated cyclisation reaction in this approach towards the targeted natural product.

3.2.2 The Intramolecular Heck Reaction: Preparation of Compound 7

In the initial attempts at this key Heck-type cyclisation, the previously developed microwave conditions were employed.[129,130] To our delight, the desired bicycle **7** was afforded in an appreciable yield (**Scheme 115**). Clearly, this intramolecular Heck cyclisation allows the preparation of derivative, **7**, with the desired quaternary stereocentre and additional functionality in place.



Scheme 115

Despite the successful results so far, it was considered that the developed route towards Heck precursor **8** was not as robust or efficient as deemed necessary for the early stages of a total synthesis programme. In particular, the preparation of vinyl bromide **82** was considered to be undesirably lengthy, and low yielding, for such a small molecule. It was at this stage an alternative synthesis was devised and an entirely unique approach to the desired target embarked upon.

3.2.3 Alternative Synthesis: Targeting Compound 91

As described above, given the difficulties encountered in the preparation of vinyl bromide **82**, an alternative route towards the target molecule was pursued. As part of this new approach towards Agariblazeispirol C it was felt that it would be worth investigating the, perhaps, more reactive enyne substrate **91** (**Figure 7**). In comparison to the original Pauson-Khand substrate **6**, molecule **91** does not possess the additional (internal) point of unsaturation, conjugated to the exocyclic (reacting) alkene; such olefin conjugation is known to hinder the formation of the desired cyclopentenone products in P-K chemistry.[72,73]

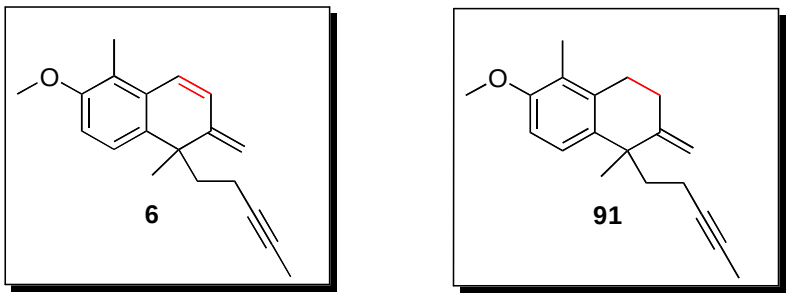
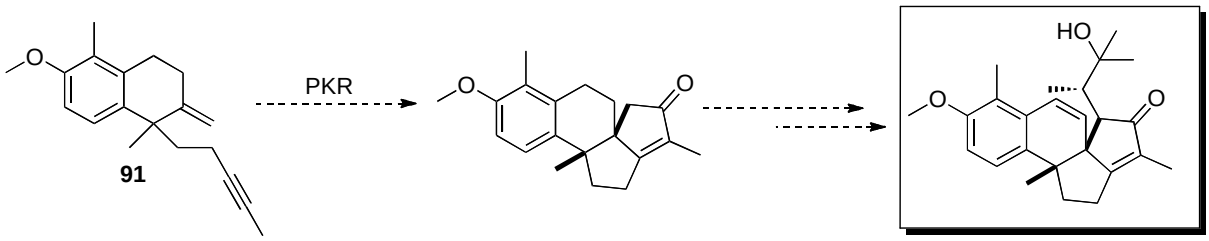


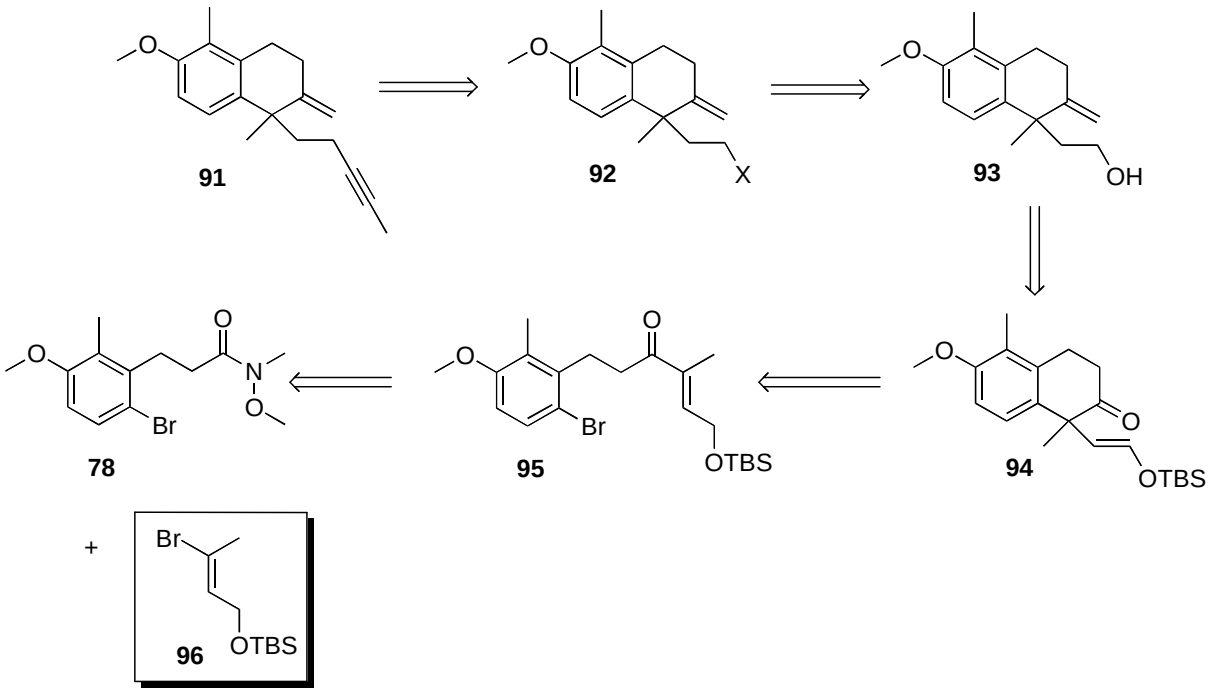
Figure 7

With this strategy, the double bond required in our final natural product would be introduced at a later stage, along with the oxygenated side chain (**Scheme 116**).



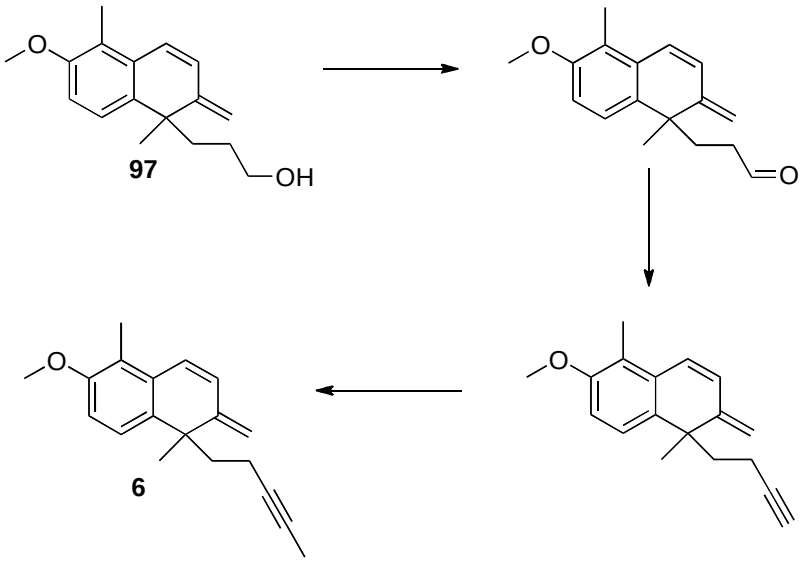
Scheme 116

With the above points in mind, returning to the retrosynthetic analysis of Agariblazeispirol C, a potentially more direct and, perhaps, elegant way of accessing the requisite Pauson-Khand precursor was also devised. This is illustrated in **Scheme 117**.



Scheme 117

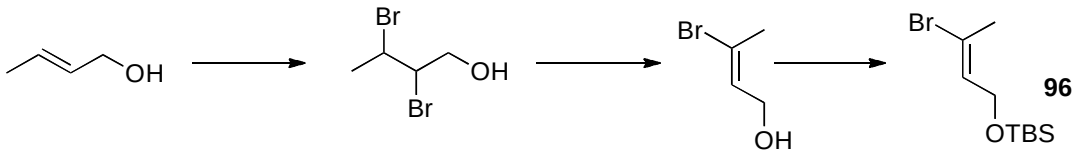
As shown, we envisaged that Pauson-Khand precursor **91** could be prepared in a more direct manner (i.e. in a single step) from intermediate **92**, possessing a suitable leaving unit (X). Potentially, this could circumvent the presently developed three-stage elaboration of **97** to enyne **6**, which is detailed in **Scheme 118**.[129,130] Further simplification leads to compound **93**, which, in turn, could be prepared from enol ether **94**. At this stage we can apply intramolecular Heck methodology to establish the first, all carbon, quaternary centre, which would lead us to compound **95**, a new, key, intermediate within this synthetic programme. The ultimate precursors within this new route are the potentially more accessible vinyl bromide **96**, as compared to the one carbon homologue compound, **82**, and the, previously utilised, Weinreb amide **78**.



Scheme 118

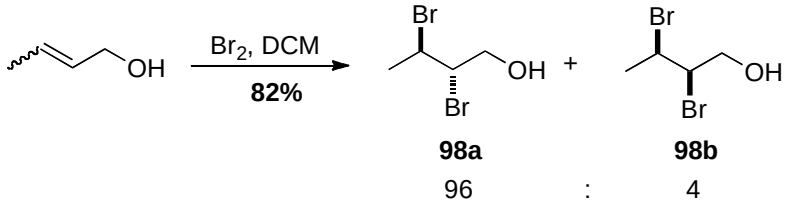
3.2.4 Preparation of Vinyl Bromide 96

In order to pursue this revised route, vinyl bromide **96** would be required as a key intermediate. Pleasingly, on searching the literature, this substrate was readily accessible, as exclusively the *E*-isomer, following a route used by Schlosser and Hammer (**Scheme 119**).[140]



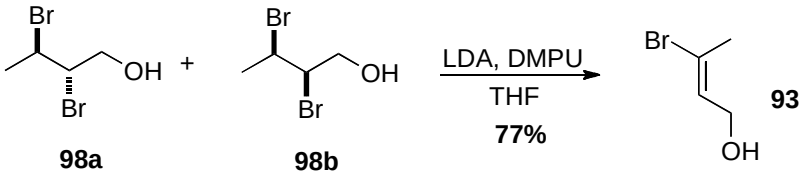
Scheme 119

Bromination of commercially available crotyl alcohol, present as a mixture of *cis* and *trans* isomers (4:96), yielded compounds **98a** and **98b**, in the corresponding ratio. A good overall yield was achieved, allowing the preparation of multi-gramme quantities of the desired product (**Scheme 120**).



Scheme 120

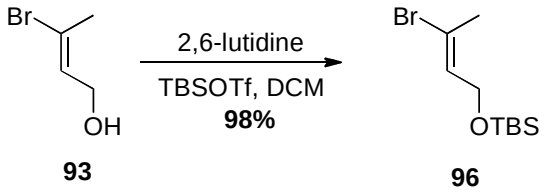
Following this, diastereomers **98a** and **98b** were treated with LDA, and, after distillation, desired alcohol **93** was obtained in a good yield (**Scheme 121**), and as the single (*E*) isomer shown.



Scheme 121

From this material, subsequent TBS protection yielded the required (*E*)-vinyl bromide **96** in an excellent yield (**Scheme 122**). Overall, this high yielding three-step pathway to prepare the

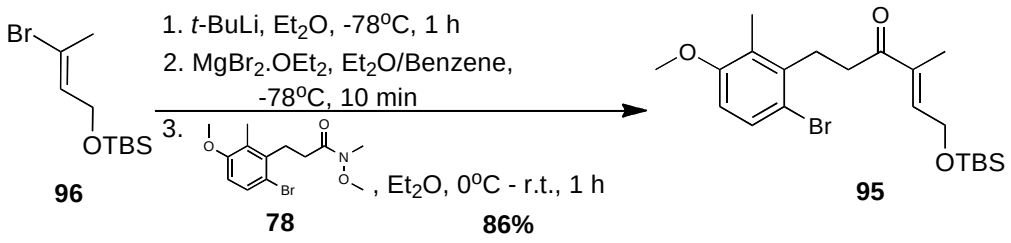
requisite vinyl bromide unit is vastly more efficient, and robust, than the previously developed five step procedure to the one carbon homologue, compound **82**.



93 **96**

Scheme 122

With compound **96** in hand, attention was turned to the addition of this species to Weinreb amide **78**. In line with the previously utilised procedure,[129,130] lithiation of the functionalised vinyl bromide followed by transmetallation with magnesium, and subsequent introduction of the Weinreb amide was attempted. Pleasingly, this furnished the desired enone **95** in an excellent isolated yield (**Scheme 123**).



96 **78** **86%** **95**

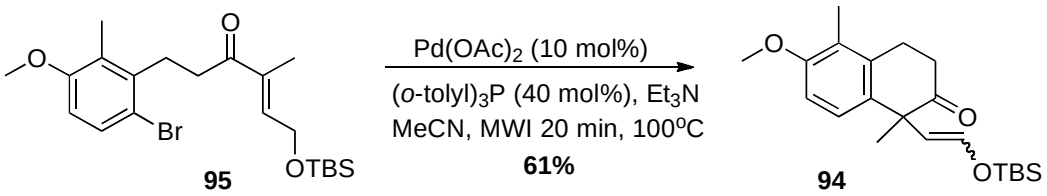
Scheme 123

As mentioned previously, the geometry of this substrate is irrelevant in our racemic synthesis of the targeted natural product. Nevertheless, the alkene geometry was confirmed to be exclusively the *E*-isomer from NOESY correlation spectra. In addition to this, it was interesting to observe what looked like second order proton NMR spectra[179] with regards to the benzylic methylene protons and adjacent methylene protons. A detailed analysis of these second order spectra revealed that this compound has a 70% preference for the *anti*-conformer, reflecting the bulk of

the methyl and bromine substituents on the aryl ring (*see appendix and the experimental section for further details*).

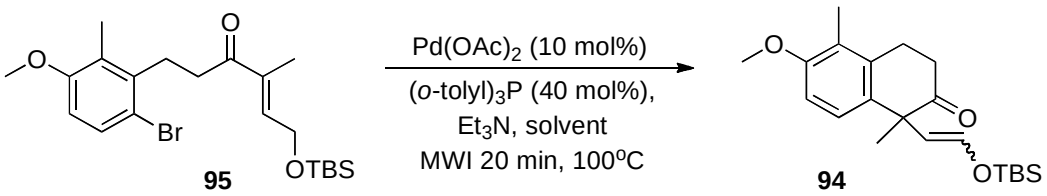
3.2.5 Intramolecular Heck Reaction: Preparation of Compound 94

Given the success in our first Pd-catalysed Heck process, the optimised microwave conditions were the first to be tried with the alternative substrate **95**, as illustrated in **Scheme 124**. Disappointingly, the yield obtained for this cyclisation was somewhat more modest with only 61% of the desired enone being furnished. Interestingly, the compound obtained was a mixture of *E* and *Z* isomers (1:0.6), an observation not met with the previous Heck substrate.



Scheme 124

At this juncture, it was decided that a number of various conditions should be screened to optimise this reaction. Initial experiments involved a solvent study. Upon studying the literature, it was evident that polar solvents were successful in many examples.[9,13] As such, a range of such solvents were screened under the conditions shown in **Scheme 125** and the results are illustrated in **Table 9**. This short study revealed that no improvement on the reaction yield was obtained. Somewhat surprisingly, DMA and THF were almost completely ineffective.

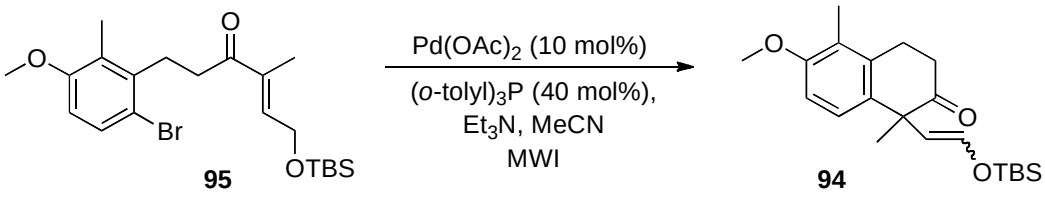


Scheme 125

Entry	Solvent	Yield
1	DMF	48%
2	DMA	trace
3	THF	trace

Table 9

Returning to the reaction in acetonitrile, it was considered that perhaps the elevated temperature used may be causing a detrimental effect on the reaction yield. In an attempt to gauge the optimum temperature, the conditions shown in **Scheme 126** were attempted. Delightfully, with a reaction time of 60 minutes at 80°C, the reaction yield was improved to an excellent 80% (**Table 10, Entry 1**). To investigate this further, the reaction temperature was lowered to 60°C, however, after 2 h under microwave irradiation, only a trace amount of product was observed by ^{1}H NMR (**Table 10, Entry 2**).

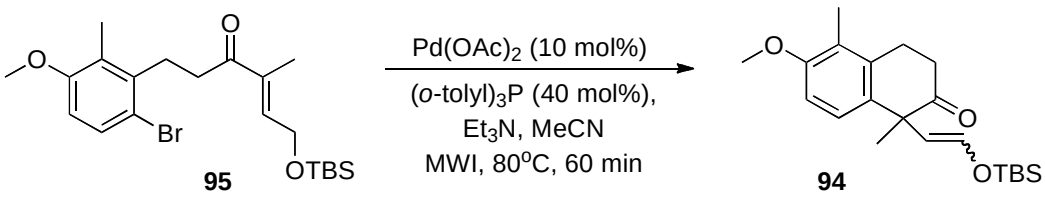


Scheme 126

Entry	Conditions	Yield
1	80°C, 60 min	80%
2	60°C, 120 min	trace

Table 10

Having described the above, it should be noted that this specific protocol sometimes proved variable with many experiments failing to reproduce this yield (**Table 11, Entries 2-4**). As such, efforts continued towards the production of a high yielding protocol, which, more importantly, would be able to repeatedly deliver multi-gramme quantities of the requisite bicyclic ketone **94**.

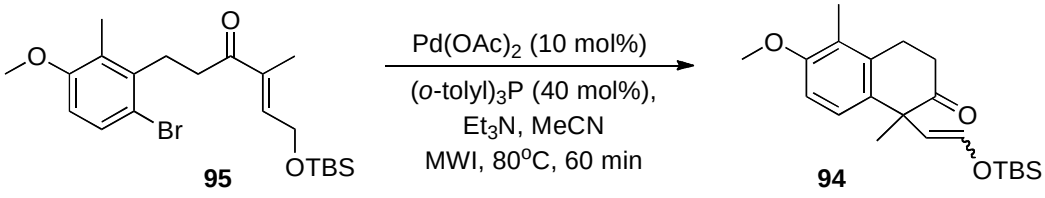


Scheme 127

Entry	Yield
1	80%
2	74%
3	54%
4	63%

Table 11

Upon reviewing the experimental procedures within the literature, it was noticed that the order of addition of the reagents was rather particular. In the majority of cases, the palladium catalyst was allowed to stir in solution, with the phosphine ligand, for a period of time before the addition of the substrate and base. In our previous experiments, however, the substrate was dissolved in solution, to which, the remainder of the reagents were added *(see experimental section for more detail)*. Indeed, when this alternative addition method was attempted, after 5 minutes a colour change was observed; this presumably is attributed to the pre-formation of the obligatory palladium(0) species. Pleasingly, the initial experiment using this alternative mode of addition produced the desired bicycle in 83% yield (**Scheme 128, Table 12 Entry 1**). Nevertheless, repetition of this reaction delivered the product in, again, varying yields (**Table 12, Entries 2 and 3**).



Scheme 128

Entry	Yield
1	83%
2	49%
3	82%

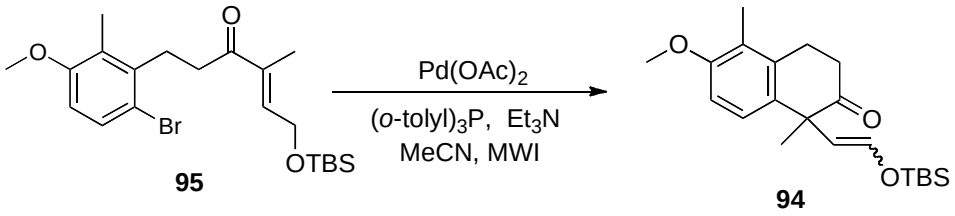
Table 12

With the varying results being obtained, our thoughts turned to the isolation procedure. Whilst substrate **95** is very similar to the previous cyclisation precursor **8**, differing in being reduced by only one carbon attached to the olefin, the Heck product obtained is different in that a sensitive silyl enol ether functionality is now present. Taking this into account, it was considered that the reduced yields could be attributed to the purification procedure; perhaps the acidity of silica column chromatography was causing hydrolysis or degradation of the sensitive silyl enol ether product. Indeed, reconsidering the purification techniques used with individual processes, experiments with the most elevated yields appeared to be those which had been columned most quickly. To investigate this, the purification procedure was carried out at different rates (**Table 13**). As anticipated, the faster the purification the higher the yield. Upon repetition of this protocol, consistent yields are now achieved producing the product from our first metal-mediated cyclisation process in multi-gramme quantities.

Entry	Purification	Yield
1	fast	83%
2	slow	59%

Table 13

With a sound grasp of what was required within the experimental procedure, attention turned to the catalyst loading. As shown in **Table 14**, using 5 mol% palladium catalyst resulted in 90% conversion after 30 minutes. This was extremely pleasing given the previous conditions used double the amount of catalyst in double the reaction time. In order to push this reaction to completion 7.5 mol% catalyst was used, which, pleasingly, delivered the desired bicycle in an excellent 86% yield in only 20 minutes.



95 **94**

Scheme 129

Entry	$Pd(OAc)_2$	$(o\text{-tolyl})_3P$	Conditions	Yield
1	5 mol%	20 mol%	100°C, 30 min	(90)[a] 82%
2	7.5% mol%	30 mol%	100°C, 20 min	86%

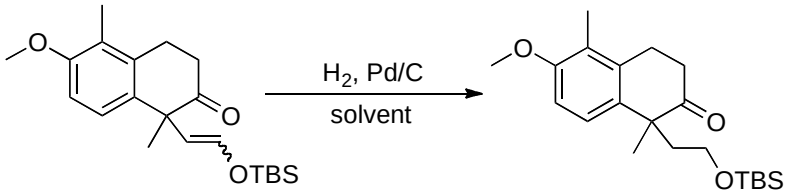
[a] Conversion

Table 14

It is important to remember the restricted rotation within compound **95**, which may have rendered this Heck cyclisation extremely sluggish. Pleasingly, our developed system delivers the desired bicyclic ketone in an excellent yield and in such a short reaction time.

3.2.6 Towards the Pauson-Khand Precursor

With our first all carbon quaternary centre in place, attention turned to the preparation of the next key Pauson-Khand precursor, compound **91**. Towards this goal, hydrogenation of the newly formed silyl enol ether was required. Initial attempts employed the use of traditional palladium on carbon as the catalyst (**Scheme 130**). Disappointingly, upon carrying out the reaction in a methanol medium, only a 53% isolated yield was obtained of the desired hydrogenated product (**Table 15, Entry 1**). Nevertheless, upon moving to ethyl acetate as the reaction solvent (**Table 15, Entry 2)**, gratifyingly, a near quantitative yield of **99** was furnished.



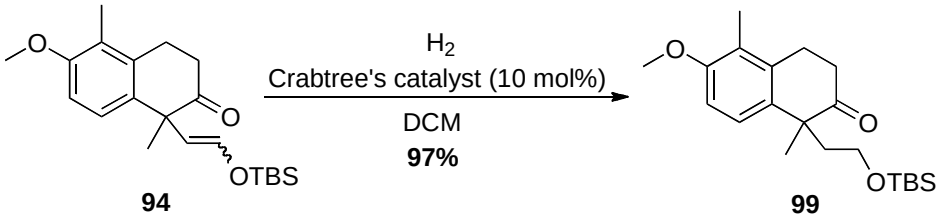
94 **99**

Scheme 130

Entry	Solvent	Yield
1	MeOH	53%
2	EtOAc	99%

Table 15

Whilst initially pleased with this outcome, upon scale up of this reaction it was not possible to obtain reproducible results. In fact, in many cases, the reaction failed to exceed 70% conversion to the desired saturated product. At this juncture, it was decided to return to the use of Crabtree's catalyst, which had proved consistently successful earlier in the synthetic program. As hoped, this catalyst system reproducibly reduced the hindered olefin in an excellent yield on a variety of scales (**Scheme 131**).

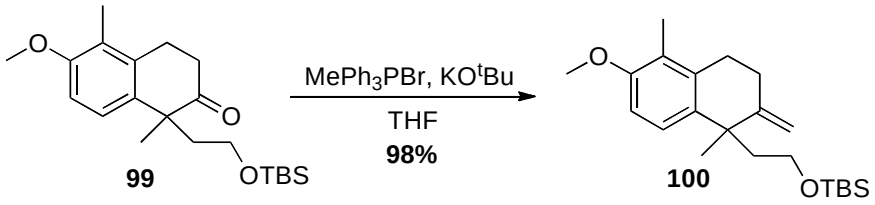


94 **99**

Scheme 131

The next step in the reaction sequence was the introduction of the required alkene moiety. As such, olefination of ketone **99**, under standard Wittig conditions,[141] afforded desired compound **100** in an excellent 98% yield (**Scheme 132**). It is important to note the choice of base within this system. An interesting publication from Schlosser and Christmann[141c] described the

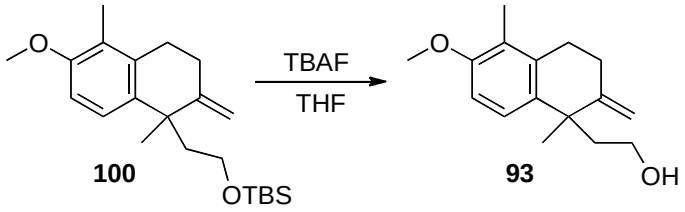
beneficial effect of potassium as a counter-ion for the base species within such Wittig olefination processes. In fact, a previous piece of research carried out within our laboratory[130] illustrated the beneficial effect of potassium *tert*-butoxide as a base, in a simlar olefination reaction, *via* a direct comparison with ^{n}BuLi. As such, our choice of base was based on all of these observations.



99 **100**

Scheme 132

Subsequently, the silyl protecting group was cleaved using the fluoride source, TBAF. This transformation yielded the desired free alcohol **93** in variable yields (**Scheme 133, Table 16**). Upon carrying out this reaction at room temperature, a moderate 65% yield was attained. Pleasingly, an improvement in yield, and reproducibility, of this transformation was achieved when the reaction mixture was cooled to 0^{o}C (**Table 16, Entry 2**).



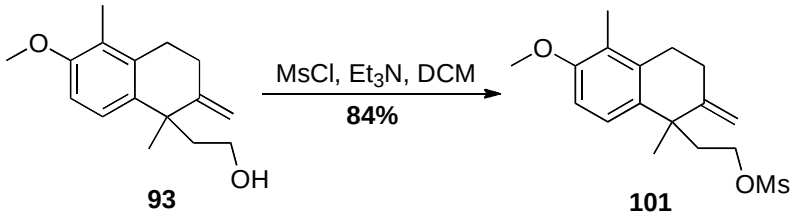
100 **93**

Scheme 133

Entry	Temperature	Yield
1	RT	65%
2	0^{o}C	98%

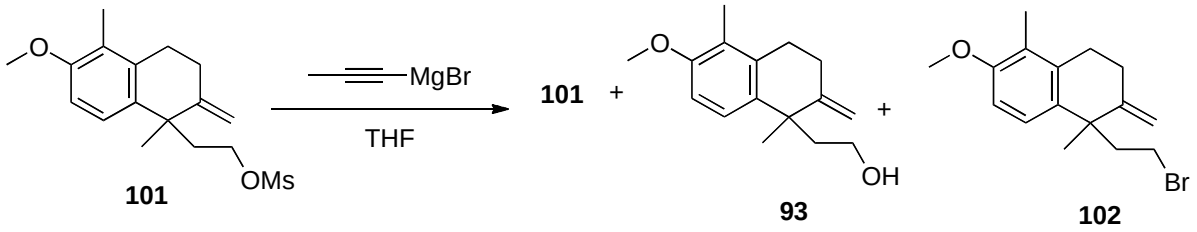
Table 16

With the required alkene functionality in place, attention now focused on the introduction of the requisite alkyne moiety. Towards this goal, it was necessary to activate the alcohol present in **93** to allow subsequent displacement with a propargyl unit. As such, it was decided to prepare mesylate **101**. Pleasingly, this intermediate was synthesised without incident in an 84% yield (**Scheme 134**).



Scheme 134

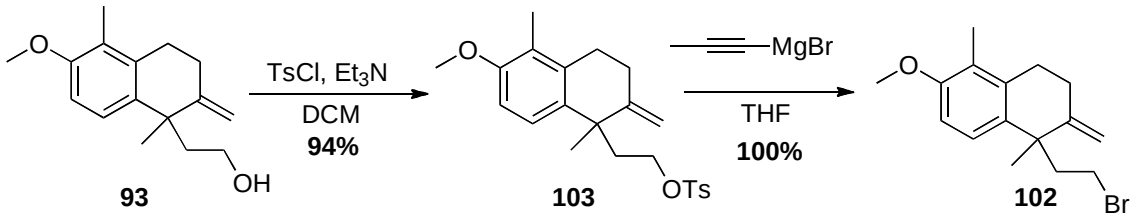
With this material in hand, introduction of the propargyl unit was attempted *via* the delivery of propynylmagnesium bromide to the mesylate substrate. Disappointingly, after a 24 h reaction time only starting material was observed by tlc analysis. The reaction mixture was then warmed to refluxing temperature and stirred for a further 24 h. Unfortunately, after this time, none of the desired product was observed by tlc or ^{1}H NMR analysis. Instead, a mixture of starting material **101**, alcohol **93**, and bromide **102** was isolated (**Scheme 135**).



Scheme 135

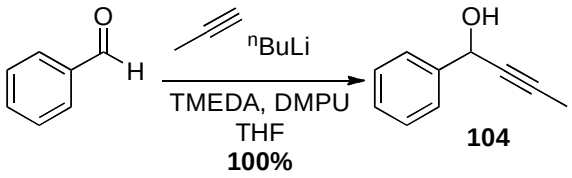
Despite these outcomes, it was decided that the tosylate functional group could be utilised as a more potentially effective unit. To this end, compound **103** was prepared in a good yield and subsequently reacted with propynylmagnesium bromide. Frustratingly, although the tosylate **103**

was completely consumed, none of the desired product was isolated from the reaction mixture. Instead, the sole product was bromide **102**, which was isolated in a quantitative yield (**Scheme 136**).



Scheme 136

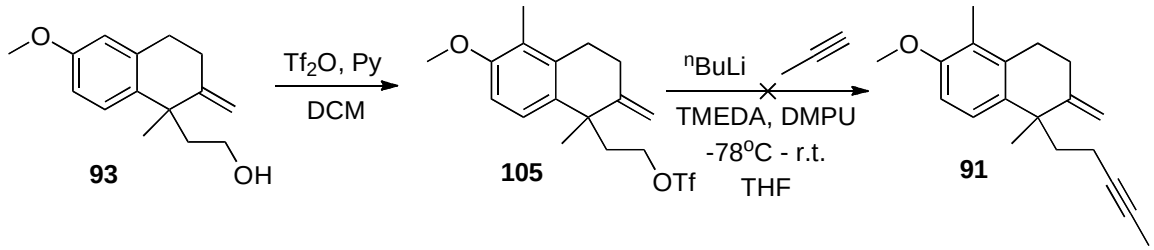
Despite the lack of success with this approach thus far, it was decided that an even more reactive system was required to deliver our desired alkyne product. As such, the use of a more reactive organometallic reagent, propynyllithium, was considered. Towards this goal, propyne and *n*-butyllithium were sought as the required starting materials. To be confident of the formation of the requiste alkynyl anion the preparation was attempted *via* bubbling propyne gas through a solution of ^{n}BuLi, TMEDA, and DMPU before quenching with a dispensable electrophile (benzaldehyde). Pleasingly, alcohol **104** was isolated in quantitative yield (**Scheme 137**).



Scheme 137

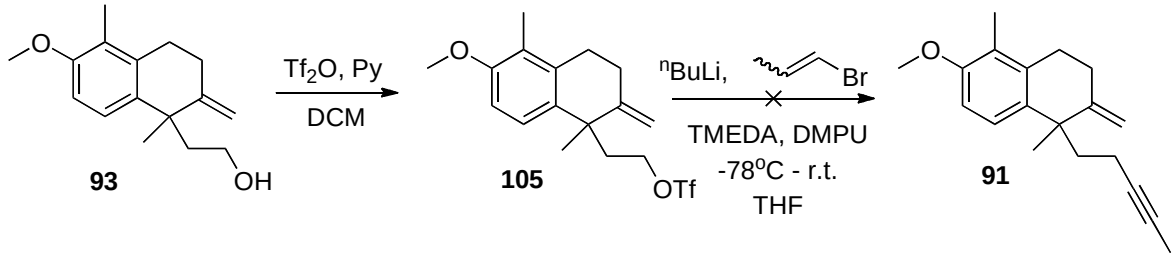
Turning to the specific target, it was decided the trifluromethane sulfonate leaving group should be employed to activate the system even further (**Scheme 138**). It was decided that this intermediate would be prepared and used immediately due to its probable sensitive nature. As such, propynyllithium was prepared as before and reacted with substrate **105**, resulting in an

instantaneous colour change from pale yellow to deep red. Frustratingly, none of the desired product, or triflate intermediate, was observed. In fact, it was not possible to isolate any product from the reaction mixture.



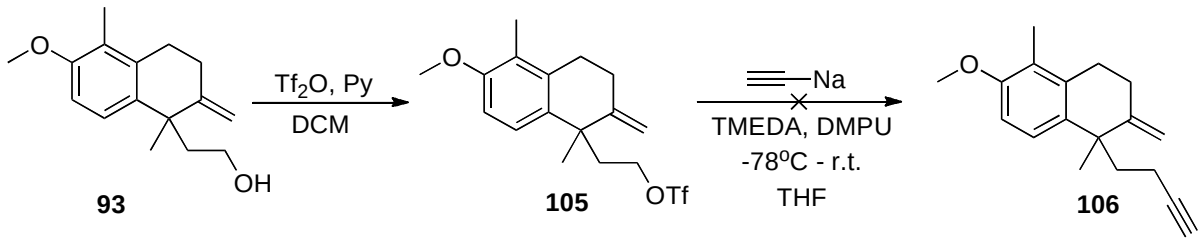
Scheme 138

At the same time, alternative conditions were attempted in order to prepare the requisite propynyl anion. A report by Suffert and Toussaint[142] illustrated the use of commercially available (*Z*/*E*)-1-bromopropene as a source of propynyllithium *via* reaction with ^{n}BuLi at -78^{o}C. However, upon following this procedure, no success was achieved in preparing the desired precursor for this second metal-mediated cyclisation step (**Scheme 139**).



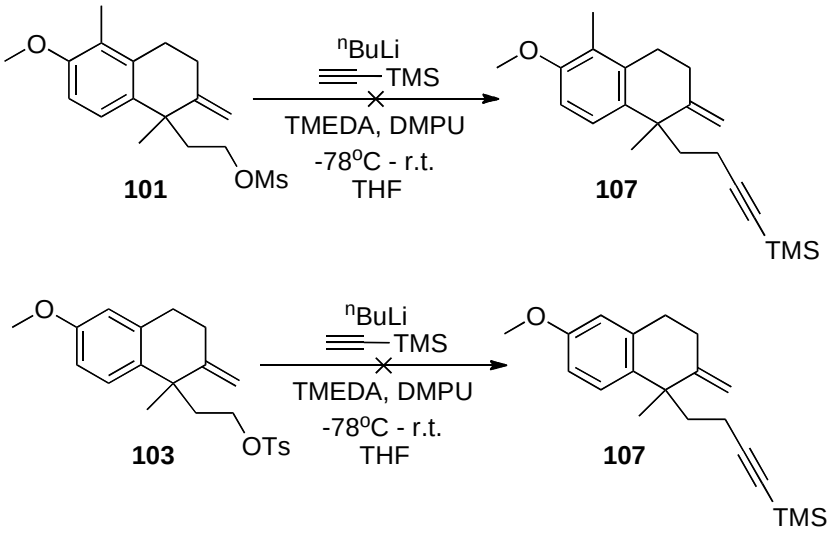
Scheme 139

In a further attempt to increase the reactivity of the nucleophilic reagent, commercially available sodium acetylide was utilised (**Scheme 140**). However, once, again, no product was observed.



Scheme 140

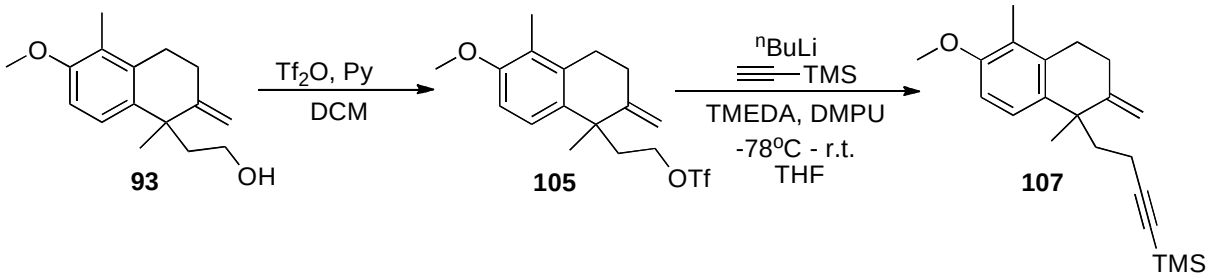
With the use of gaseous propyne proving capricious, as well as the failure of sodium acetylide to produce the desired product, it was thought that trimethylsilylacetylene as the propargylic unit could serve as a more accessible reagent to deliver a propargyl unit. In relation to this, removal of the trimethylsilyl protecting group, and subsequent methylation would be required to provide the requisite alkyne substrate for the Pauson-Khand reaction. Firstly, mesylate and tosylate substrates were utilised in combination with *in-situ* formation of TMS-acetylide, however, no product was identified in either case (**Scheme 141**). Having said this, high recovery of both mesylate and tosylate intermediates were achieved.



Scheme 141

Undeterred, the triflate intermediate was prepared and reacted immediately under the above conditions. Gratifyingly, this time, the desired enyne product was observed, albeit in a poor 31%

yield (**Scheme 142, Table 17, Entry 1**). However, upon repetition of this reaction the desired product was isolated in a, much improved, 72% yield over the two steps. It is important to note the varied yields within **Table 17**. In relation to this, it is imperative that the triflic anhydride is fresh, and the triflate intermediate is kept cool and used immediately.



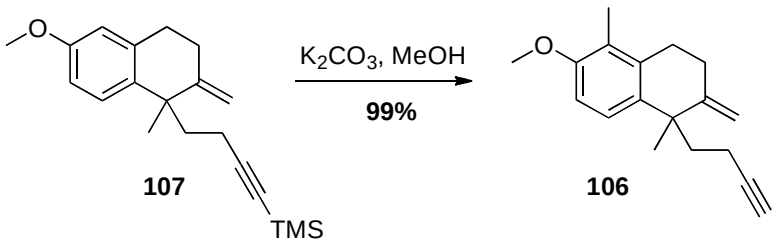
Scheme 142

Entry	Yield
1	31%
2	45%
3	72%[a]

[a]Used fresh bottle of Tf_2O, and kept triflate cool where possible.

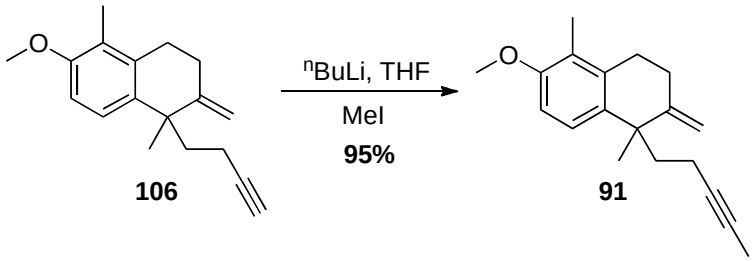
Table 17

Despite further manipulation being required towards the preparation of the desired P-K precursor, an effective system has been developed to gain efficient access to intermediate **107**; this was a truly pleasing outcome at this stage in the project. The next step required was the removal of the trimethylsilyl protecting group. This was achieved *via* extremely mild conditions to provide terminal alkyne **106** in almost quantitative yield (**Scheme 143**)



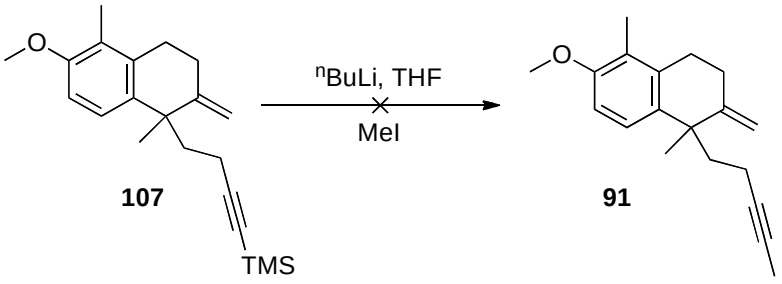
Scheme 143

Following this, treatment with ^{n}BuLi and methyl iodide provided the requisite alkyne in an excellent yield (**Scheme 144**).



Scheme 144

In an attempt to prepare alkyne **91** *via* a one-pot process, alkyne **107** was treated with ^{n}BuLi followed by methyl iodide, however, only starting material was recovered from this reaction (**Scheme 145**).

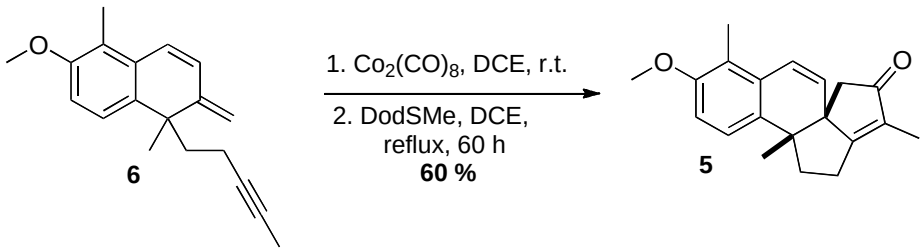


Scheme 145

During the previous body of work towards the synthesis of Agariblazeispirol C, diene **6** was utilised as the key cyclisation precursor. However, it was felt that substrate **91** may serve as a more reactive enyne precursor. Based on the preparative endeavours described to this stage and the synthetic protocols that have been established within this programme of work, this new substrate had been accessed, and the Pauson-Khand reaction beckoned.

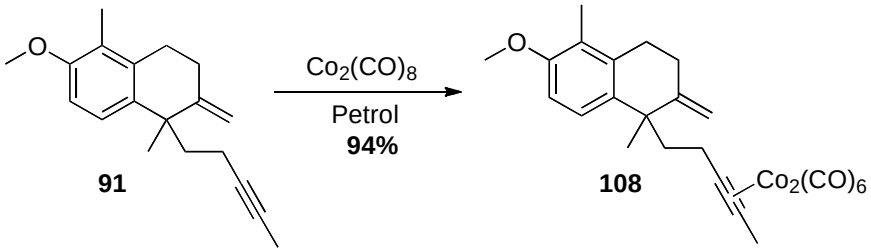
3.2.7 The Pauson-Khand Reaction

As mentioned previously, diene **6** was the initial substrate for the key intramolecular Pauson-Khand reaction. The cobalt-mediated cyclisation of alkyne **6** delivered the tetracyclic core of Agariblazeispirol C in a single step, constructing three new C-C bonds and setting the second challenging all carbon bearing quaternary stereocentre. However, the yield of this cyclisation presently stands a modest 60% after a prolonged 60 h reaction time (**Scheme 146**).[130]



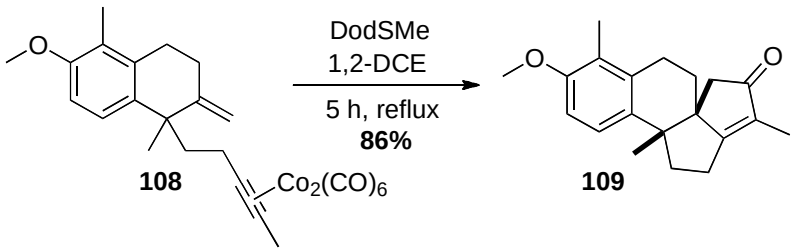
Scheme 146

Towards the determination of the efficacy of enyne substrate **91** in the Pauson-Khand reaction, cobalt complex **108** was prepared and isolated prior to cyclisation (**Scheme 147**).



Scheme 147

With cobalt complex **108** in hand, cyclisation under sulfide-promoted conditions[94] revealed the tetracyclic core of Agarablazeispirol C, not only in a much improved 86% yield but after only 5 h reaction time (**Scheme 148**). Clearly, and, as predicted, the removal of the conjugated diene system has a dramatic effect on the reactivity and efficiency of this cyclisation. It is important to note that, despite the removal of the conjugated diene system, this transformation still posed as a challenging annulation process. Notably, the cyclisation required the formation of two contiguous quaternary carbon centres from a substrate bearing an internal alkyne. Based on the observed efficiency of this P-K annulation, this constituted an outstanding outcome at this stage in the project.



Scheme 148

In order to confirm the structure of the product full analysis was obtained i.e. ^{1}H, ^{13}C, IR, and High Resolution Mass Spec). From these data it was evident that **109** had been successfully prepared as a single diastereomer. However, the required *syn* arrangement at the two adjacent stereogenic centres could not be established with certainty. In an attempt to confirm the desired relative configuration, colourless crystals were grown by slow diffusion of light petroleum ether

into a near saturated solution of **109** in diethyl ether at room temperature. The resulting crystal structure obtained is shown in **Figure 8**.

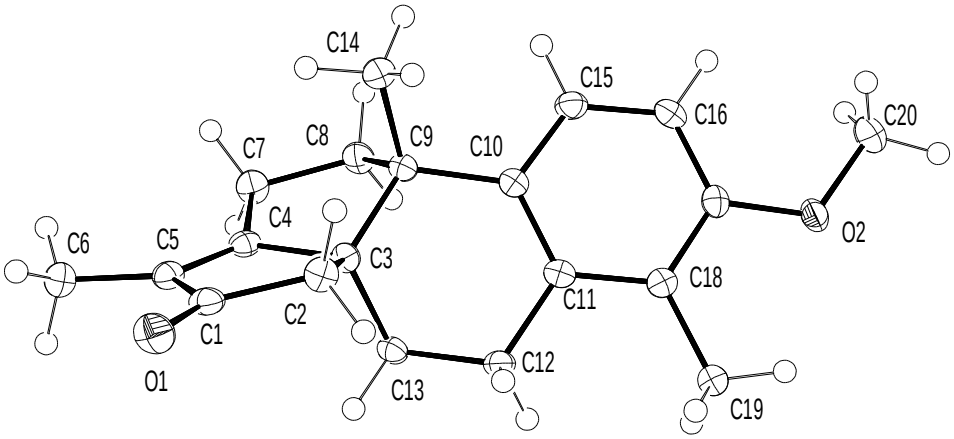
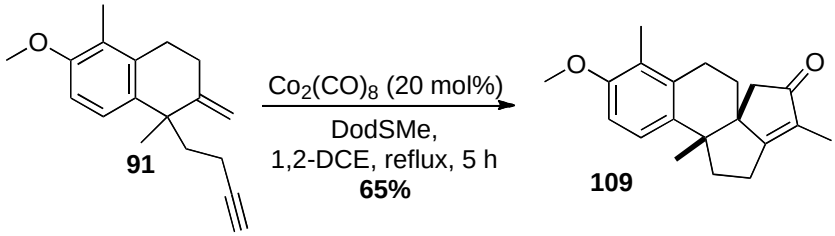


Figure 8

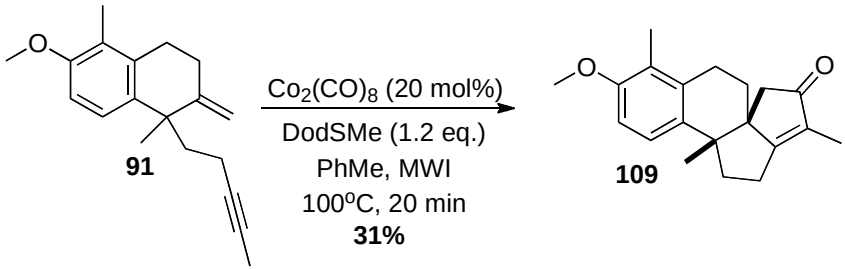
Given the proposed structure of **109**, a number of features should be evident. Importantly, the methylene carbon (C2), α to the newly installed carbonyl group, should sit *cis* to the methyl group (C14) borne by quaternary carbon centre (C9). Indeed, this is the relative arrangement depicted in **Figure 8**, confirming that the key Pauson-Khand annulation process provides the stereochemistry required in the final natural product.[143]

With the stochiometric Pauson-Khand protocol working extremely efficiently, an experiment using catalytic quantities of cobalt dioctacarbonyl was attempted. To our delight, under the sulfide promoted protocol described above, the desired carbon skeleton of the target molecule was delivered in a good 65% yield in, again, only 5 h (**Scheme 149**).



Scheme 149

In addition to this, the use of microwave-promoted conditions, with sub-stoichiometric quantities of $Co_2(CO)_8$, established within our research group[127,144] was attempted. Whilst we were pleased to isolate the desired tetracycle in only 20 minutes, the yield of this reaction stood at a less efficient 31% (**Scheme 150**).

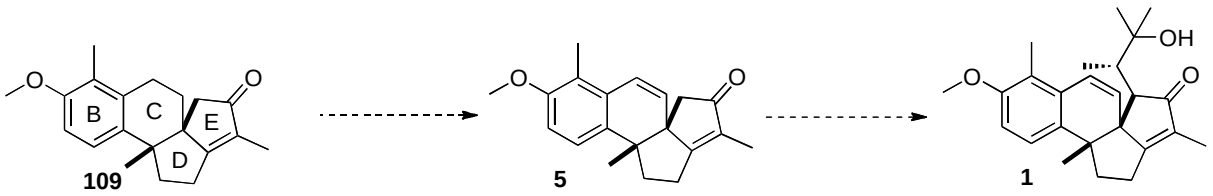


Scheme 150

Overall, the above results are extremely exciting and demonstrate a positive step towards the development of a high yielding catalytic annulation protocol, from which there are many avenues which could be pursued (*vide supra*).

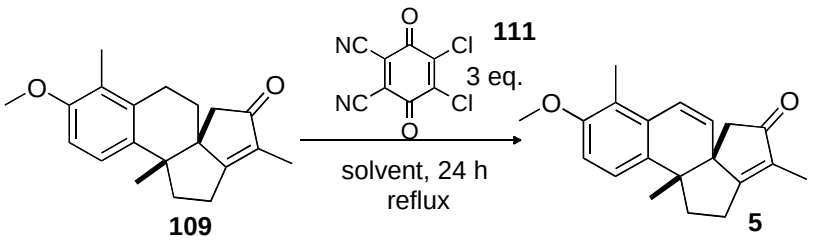
3.2.8 Towards the Completion of the Total Synthesis

With the main tetracyclic core of the natural product set in place, efforts were driven towards the completion of the synthesis. Towards this goal it was necessary to introduce unsaturation at the benzylic position within ring C (**Scheme 151**). Following this, the final step in our synthesis would be the introduction of the oxygenated side arm.



Scheme 151

With the requisite double bond being situated in a benzylic position, it was thought that simple oxidation of the molecule would deliver the desired product. As such, the first port of call was to make use of 2,3-dichloro-5,6-dicyanobenzoquinone **111**, a powerful oxidising agent used widely throughout the literature for such transformations (**Scheme 152**).[145] Due to the variety of solvents used within the literature for similar transformations, it was decided that a short solvent study would be carried out (**Table 18**). This short study revealed that after 24 h conversions were rather poor using benzene or 1,4-dioxane as the reaction solvent, and that the use of methanol was completely ineffective. In addition to this, it was frustrating to obtain substrate **109** and product **5** as an inseparable mixture.



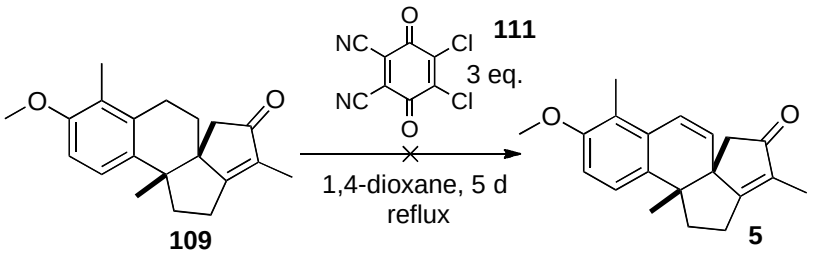
Scheme 152

Entry	Solvent	Comments[a]
1	Benzene	80:20
2	1,4-Dioxane	81:19
3	MeOH	SM only

[a] ratios are starting material:product.

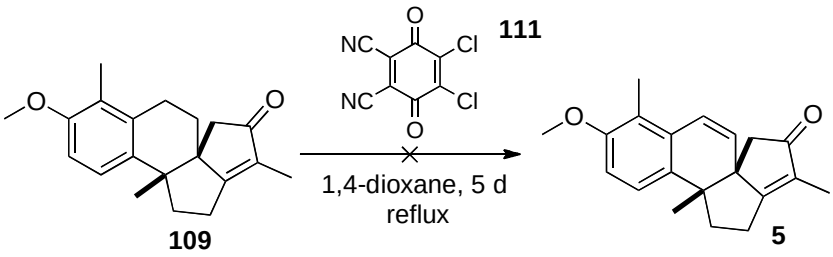
Table 18

Returning to the reaction in 1,4-dioxane, it was considered that a longer reaction time may increase the conversion of this reaction. However, after 5 days at reflux no diagnostic peaks for the desired product were observed by ^{1}H NMR analysis (**Scheme 153**). Despite repetition of this reaction, the 20% conversion achieved previously was, gallingly, unattainable.



Scheme 153

Regardless of these results, attention turned to using a greater excess of oxidant (**Scheme 154, Table 19**). Similarly to the previous set of experiments, no conversion to the desired product was observed, despite a massive excess of 20 equivalents being employed.



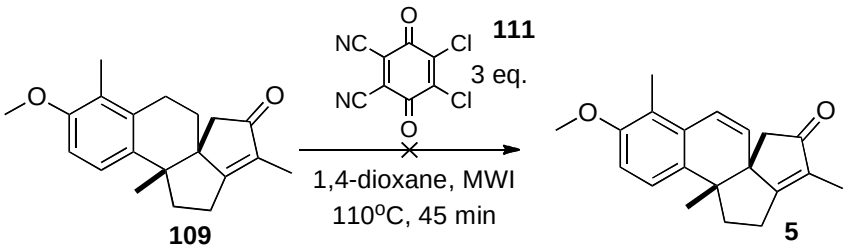
Scheme 154

Entry	Eq. DDQ	Comments
1	5	SM only
2	20	SM only

Table 19

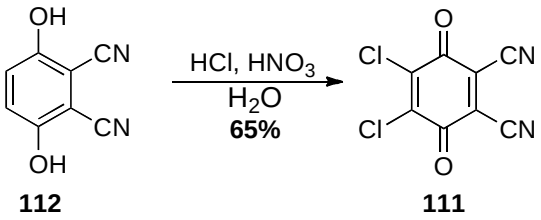
The final set of conditions to be investigated was those employing microwave irradiation

(**Scheme 155**); however, once again, this resulted in no conversion to the desired oxidised product.



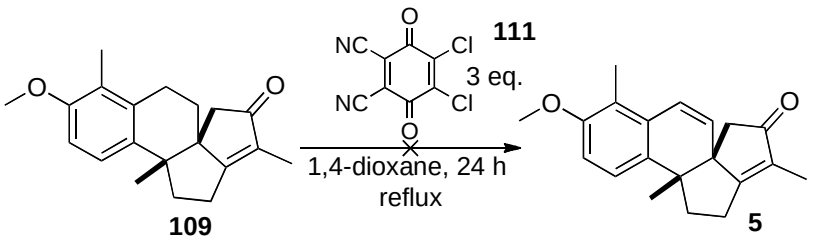
Scheme 155

Surprised by the outcome of the above reactions, the integrity of the oxidant was questioned. It was decided that, despite its commercial availability, 2,3-dichloro-5,6-dicyanobenzoquinone would be freshly prepared before use. To this end, a literature procedure was followed,[146] which involved the chlorination of compound **112** to furnish DDQ in an acceptable yield (**Scheme 156**).



Scheme 156

With this in-house prepared oxidant in hand, the transformation, in 1,4-dioxane, was re-attempted, along with repetition of the reactions using DDQ obtained from Sigma-Aldrich and Alfa Aesar suppliers (**Scheme 157, Table 20**). As can be seen from the results below, the variation in suppliers of 2,3-dichloro-5,6-dicyanobenzoquinone resulted in no difference in the reaction outcome; regrettably, still none of the desired product, **5**, was observed.

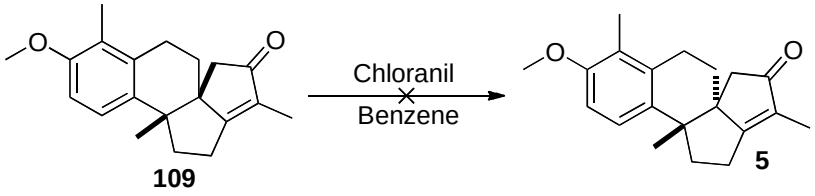


Scheme 157

Entry	Supplier	Comments
1	In-house preparation	SM only
2	Sigma-Aldrich	SM only
3	Alfa Aesar	SM only

Table 20

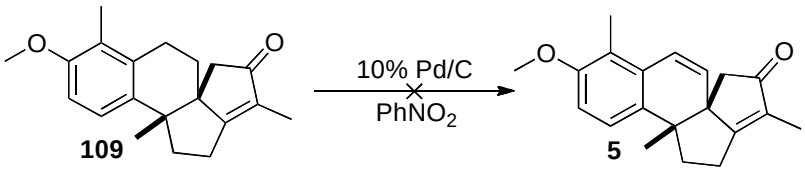
Disgruntled, yet not discouraged, by these results, it was decided to look an alternative oxidant. Sticking with a benzoquinone derivative, 2,3,5,6-tetrachlorobenzoquinone (Chloranil) was investigated. However, as before, it was frustrating to observe no success with our particular substrate (**Scheme 158**).



Scheme 158

Our next tactic involved the deployment of heterogeneous transition metal catalysis.[147] We considered the use of 10% palladium on carbon, in the presence of a hydrogen acceptor species, to generate the desired dehydrogenated product (**Scheme 159**). Our choice of hydrogen acceptor was nitrobenzene, which would, presumably, act to remove the hydrogen stripped from our

starting alkane. Again, various conditions were attempted including reactions under reduced pressure, as well as microwave irradiation (**Table 21**), none of which provided desired product **5**.

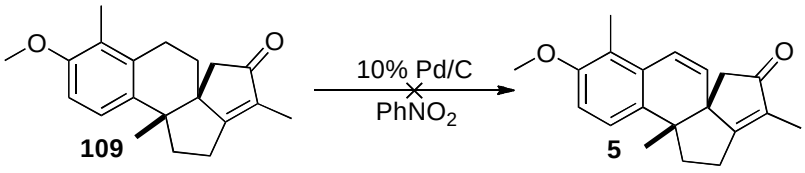


Scheme 159

Entry	Conditions	Yield
1	175°C, 16 h	SM only
2	224°C, 16 h	SM only
3	168°C, 135 mbar, 16 h	SM only
4	175°C, MWI, 10 min	SM only

Table 21

With the above experiments making use of standard grade palladium on carbon, it came to our attention that specific batches of catalysts may be required to effect our specific transformation. To this end, we acquired batches 487 and 87L, which were the recommended dehydrogenation catalysts by Johnson and Matthey (**Scheme 160, Table 22**).[148] When these were applied with subtrate **109**, exasperatingly, only starting material was observed in each case.

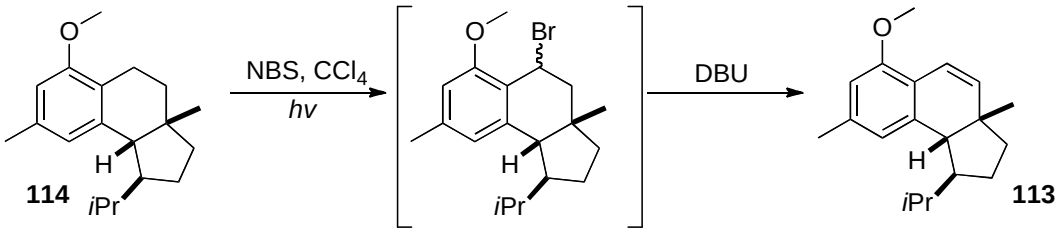


Scheme 160

Entry	Conditions	Yield
1	Cat. 487, 215°C, 16 h	SM only
2	Cat. 87L, 215°C, 16 h	SM only

Table 22

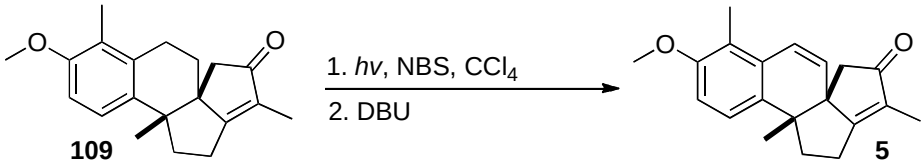
Undeterred by these frustrating results, attention turned to the use of a bromination/elimination sequence to introduce the required unsaturation. Pleasingly, upon reviewing the literature, a very similar example was reported by Clive and Wang, whereby *N*-bromosuccinimide and 1,8-diazabicycloundec-7-ene (DBU) were used to effect such a transformation (**Scheme 161**).[149] The authors note that further manipulation of compound **113** was required to separate unreacted starting material **114**.



Scheme 161

The initial set of conditions probed were those used in Clive and Wang's publication (**Scheme 162**).[149] Upon irradiation with ultraviolet light on substrate **109** in the presence of *N*-bromosuccinimide, followed by addition of the hindered tertiary amine base DBU, it was pleasing to observe a 20% conversion to the desired product (**Table 23, Entry 1**). Considering Clive and Wang's reaction conditions, it was noticed that the commonly used radical initiator, azobisisobutyronitrile (AIBN), was not included in Clive and Wang's protocol. With this in mind, it was wondered whether addition of such an initiator would have a beneficial effect upon the conversion. To probe this theory, the reaction was set up to include AIBN, and, pleasingly, an increase in conversion from 20% to 31% was observed (**Table 23, Entry 2**). With these

results in hand, it was decided that the reaction time should be investigated. Hence, a number of reactions were carried out with increased time under the ultra-violet light source, and, pleasingly after 7.5 h reaction time (**Table 23, Entry 4**) the conversion was increased to 63%. Whilst the increasing conversion is illustrated within **Table 23**, no mention of isolated yield is reported, in fact, in each case the recovery of inseparable **109** and **5** was poor with less than 50% mass balance being obtained.



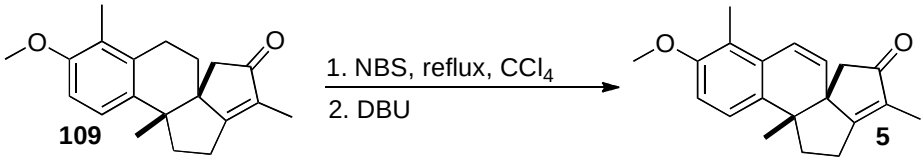
109 **5**

Scheme 162

Entry	Conditions	Conversion
1	10°C, 1 h, then DBU added at r.t.	20%
2	AIBN, 10°C, 1 h, then DBU added at r.t.	31%
3	AIBN, 10°C, 4 h, then DBU added at r.t.	54%
4	AIBN, 10°C, 7.5 h, then DBU added at r.t.	63%

Table 23

In addition to the ultraviolet protocol described above, a thermal variation of this reaction was also pursued. The initial set of thermal conditions attempted mimicked Clive and Wang's protocol, i.e. reacting substrate **109** with *N*-bromosuccinimide only, prior to the addition of DBU (**Scheme 163, Table 24, Entry 1**). This resulted in a moderate 45% conversion, however, as before, poor mass recovery was achieved. The protocol was repeated to include radical initiator AIBN, yet again, no improvement in conversion or chemical yield was observed (**Table 24, Entry 2**).

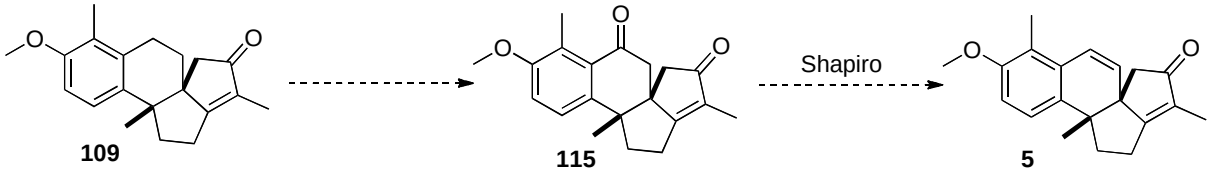


Scheme 163

Entry	Conditions	Comment
1	NBS, CCl_4, reflux, 16 h, then DBU added at r.t.	45% conversion
2	NBS, AIBN, CCl_4, reflux, 16 h, then DBU added at r.t.	42% conversion

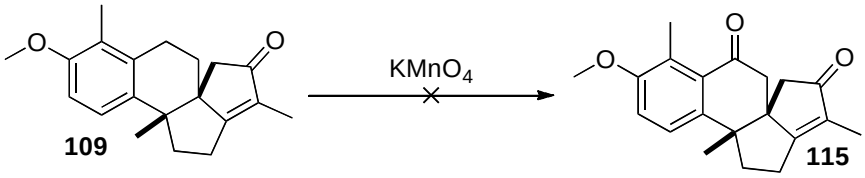
Table 24

Dismayed by the outcome of the reactions described above, an alternative derivative of the desired product was considered. It was envisaged that ketone **115** could be manipulated to give the required internal point of unsaturation *via* a Shapiro reaction,[150] as shown in **Scheme 164**.



Scheme 164

Turning to the chemical literature, it was pleasing to find that there were many established protocols already developed to effect the oxidative transformation of similar benzylic substrates.[151] Whilst, the use of potassium permanganate as an effective oxidant in organic chemistry has a long and extensive history,[152] initial attempts to oxidise **109** (**Scheme 165, Table 25**) delivered none of the desired benzylic ketone. As is depicted in **Table 25**, the outcome of this screen either resulted in complete destruction of the starting substrate or no reaction whatsoever.

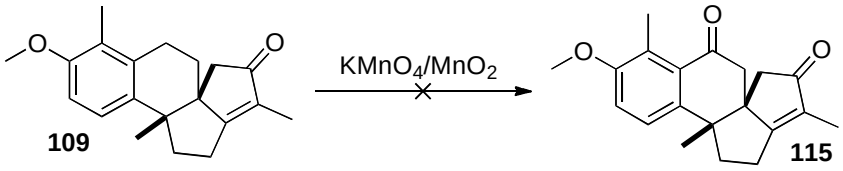


Scheme 165

Entry	Solvent	Eq. $KMnO_4$	Conditions	Comments
1	MeCN	2	r.t., 5 min	0% (no SM recovered)
2	MeCN	1	r.t., 6 h	SM only
3	MeCN	1	35°C, 16 h	SM only
4	MeCN	1	reflux, 16 h	SM only
5	DCM	2	r.t., 16 h	SM only

Table 25

Despite the above, we were also keen to explore a set of conditions developed by Shaabani *et al*.[153] These authors described the accelerating effect of manganese dioxide in oxidation reactions of alkyl arenes, sulfides, and allylic alcohols (with potassium permanganate) under solvent-free and heterogeneous conditions. The oxidant was prepared by grinding potassium permanganate with manganese dioxide, using a pestle and mortar, until a fine powder was obtained (*see experimental section for more detail*). In terms of practical benefits, if this reaction was successful, trivial purification would be required to isolate the desired organic compound. As shown in **Scheme 166**, **Table 26, Entries 1 and 2**, application of both the solvent-free and heterogeneous protocol described within Shaabani's publication to substrate **109** resulted in none of the desired product being observed. In fact, complete recovery of the starting material was achieved. In an attempt to attain some level of reactivity from our substrate with this catalyst, ultrasonication conditions were also applied (also detailed within Shaabani's report), however, neither the increased pressures nor temperatures that this method can provide resulted in any product being formed (**Table 26, Entry 3**).

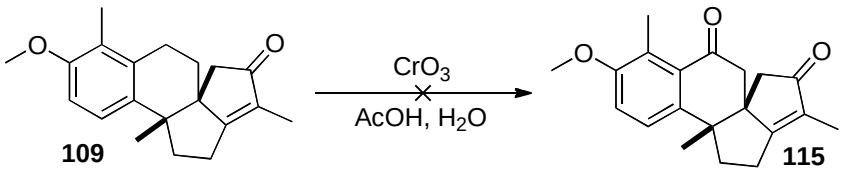


Scheme 166

Entry	Conditions	Comment
1	$KMnO_4/MnO_2$, r.t., 16 h	SM only
2	$KMnO_4/MnO_2$, DCM, r.t., 16 h	SM only
3	$KMnO_4/MnO_2$,))), r.t., 3 h	SM only

Table 26

Simultaneous to the above described experiments chromium-based oxidation protocols were investigated.[154] However, once again, the attempts made were fruitless with only starting material being observed after reaction with chromium trioxide in acidic media (**Scheme 167, Table 27**).



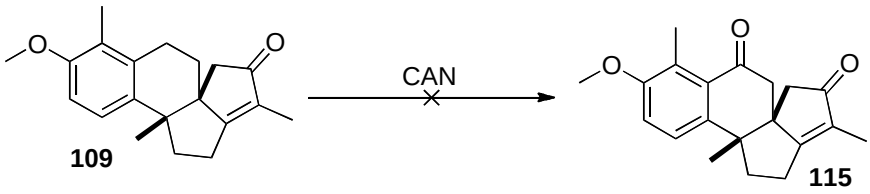
Scheme 167

Entry	CrO_3 (eq.)	Comment
1	1.3	SM only
2	5	SM only

Table 27

Attention now turned to the use of the known strong oxidant, ceric ammonium nitrate, to effect the oxidative transformation (**Scheme 168**).[155] A round of studies looked at the effect of reaction time, solvent, and varying equivalents of oxidant (**Table 28**). Initially, only starting material was observed after 20 min, when one equivalent of oxidant was used in a methanol/acetonitrile

co-solvent mixture (**Table 28, Entry 1**). However, altering the number of equivalents of oxidant (**Entries 2 and 3**), or reaction solvent system (**Entry 5**), resulted in an array of unidentifiable products being obtained.

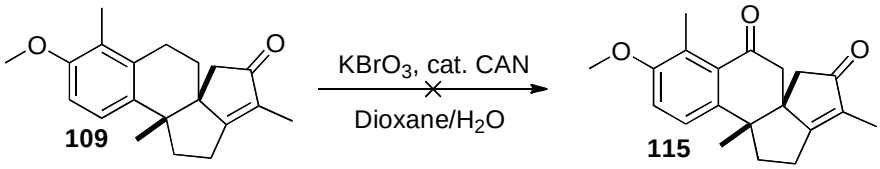


Scheme 168

Entry	Eq. CAN	Conditions	Comments
1	1	MeOH:MeCN (2:1), 20 min r.t.	SM only
2	2	MeOH:MeCN (2:1), 20 min r.t.	0%
3	4	MeOH:MeCN (2:1), 5 min r.t.	0%
4	2	MeCN, 20 min, r.t.	0%

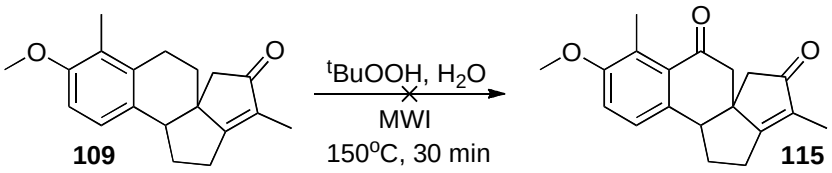
Table 28

Continuing with ceric ammonium nitrate as the chosen oxidant, consideration turned to a protocol published by Ganin and Amer,[156] which utilised this oxidant in catalytic quantities, along with bromate salts, to oxidise various alkyl aromatic compounds. Despite the authors being unable to oxidise any substrates bearing a methoxy (or nitro) moiety, substrate **109** was subjected to the described reaction conditions (**Scheme 169**). Unfortunately, and as somewhat expected, no oxidation product was observed. In fact, on analysis of the crude ^{1}H NMR, whilst a mixture of products was evident, the spectrum was suggestive of a reaction occurring on the aromatic ring with the disappearance of an aromatic proton.



Scheme 169

The next set of conditions investigated looked to react substrate **109** with *t*-butylhydroperoxide (TBHP) under microwave-promoted conditions (**Scheme 170**, **Table 29**).[157] With a lack of overall reactivity observed with compound **109** it was felt that the more forcing microwave irradiation conditions would effect the desired transformation. Once again, however, no product was observed, and a quantitative amount of starting material was returned.

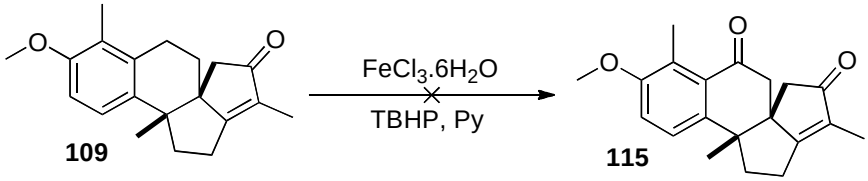


Scheme 170

Entry	Eq. ^{t}BuOOH	Yield
1	1	0%
2	2	0%

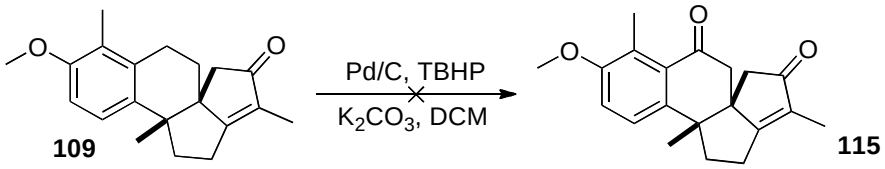
Table 29

Another set of conditions, reported by Bolm and Nakanishi,[158] utilised inexpensive iron(III)chloride and catalytic TBHP to effect the oxidation of benzylic centres under mild and convenient conditions. As shown in **Scheme 171**, however, this attempt to prepare ketone **115** was, frustratingly, unproductive.



Scheme 171

Despite the above, a further literature search revealed conditions published by Corey whereby the palladium-catalysed allylic oxidation of various olefins was carried out successfully using TBHP under slightly basic conditions.[159] At this stage, consideration was given to whether this protocol could be extended to benzylic substrates, and, as such, substrate **109** was treated under the conditions described in the Corey publication (**Scheme 172, Table 30, Entry 1**). With no product being obtained under these conditions, the temperature of the reaction was increased in an attempt to drive the reaction forward (**Table 30, Entry 2**). Regrettably, even at r.t., no reaction of substrate **109** occurred at all.

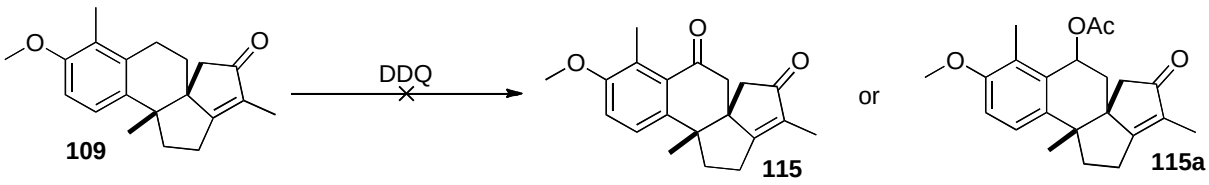


Scheme 172

Entry	Conditions	Outcome
1	-78°C, 24 h	SM only
2	r.t., 24 h	SM only

Table 30

At this stage, attention returned to the use of DDQ in a final attempt to gain access to the desired benzylic ketone **115**. Within the literature, the reaction of alkyl aromatic compounds with DDQ in acetone to furnish benzylic carbonyls has been reported.[160] Alternatively, it has been shown that these reactions, when performed in acetic acid, can give rise to acetate derivatives such as **115a** (**Scheme 173**).[161] Despite the target molecule being ketone **115**, acetate compound **115a** would certainly be of use within this research programme. As illustrated in **Table 31** various reaction conditions were attempted, once more, without success.



Scheme 173

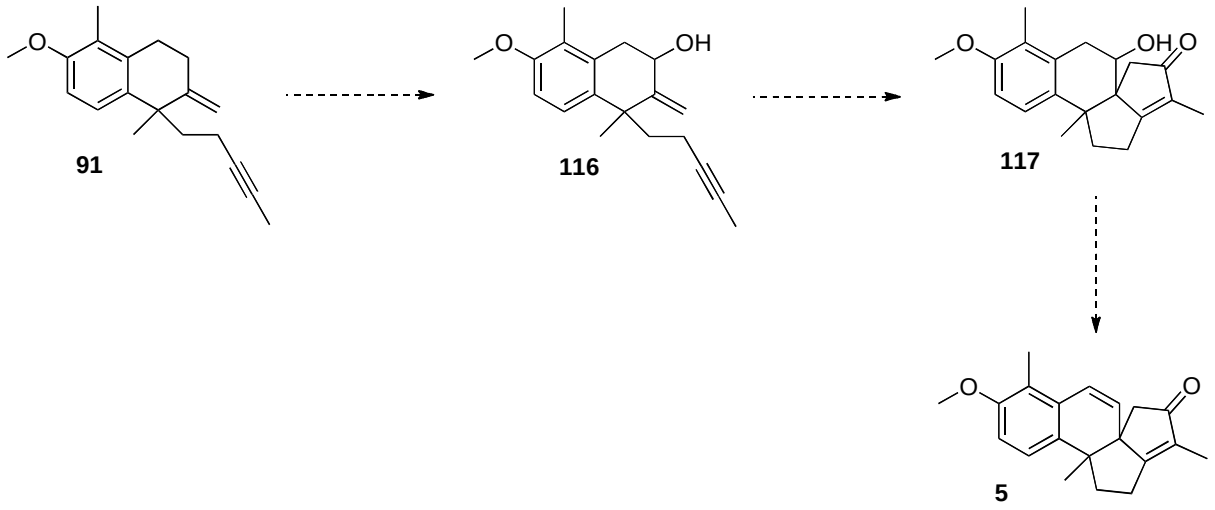
Entry	Conditions	Expected product	Comments
1	Acetone, 16 h, r.t.	**115**	SM only
2	AcOH, reflux, 16 h	**115a**	SM only
3	AcOH,))), 5h	**115a**	SM only
4	AcOH, MWI, 120^{o}C, 30 min	**115a**	SM only

Table 31

With respect to this section of the research programme, despite the tenacity, we were unable to embed the internal point of unsaturation from saturated counterpart **109**. Consequently, an alternative preparative plan was constructed.

3.2.9 Alternative Route Towards Compound 5: Allylic Oxidation Approach

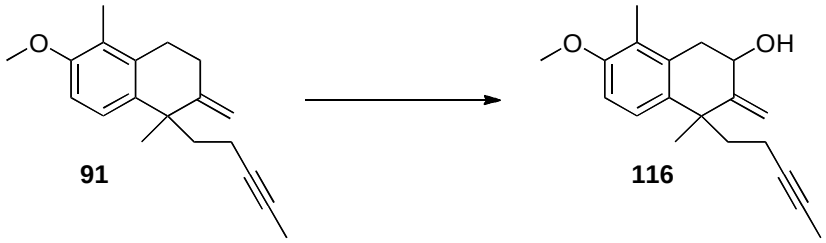
At this point in the project, it was clear that the reactivity of substrate **109** was extremely poor with respect to the introduction of the required (oxidative) internal point of unsaturation post-Pauson-Khand cyclisation. It was decided that an alternative route must be devised to embed this moiety. It was envisaged that the substrate **91** must be functionalised in a way so as to provide a handle for the introduction of the desired endocyclic olefin, however, at the same time, sustaining the established favourability of the P-K cyclisation. Towards this, **Scheme 174** illustrates the proposal for an allylic oxidation, which would install a hydroxyl moiety, which, could later be exploited as the desired masked olefin.



Scheme 174

The initial set of conditions attempted to prepare allylic alcohol **116** utilised stoichiometric selenium dioxide in ethanol. However, after 16 h, none of the oxidised product was observed (**Scheme 175, Table 32, Entry 1**). Additionally, performing the reaction in 1,4-dioxane also resulted in none of the desired alcohol product being formed (**Table 32, Entry 2**). In fact, with both protocols, there was no evidence of any appreciable reaction taking place; starting material was recovered in both cases. Fortunately, upon moving to a catalytic system (with respect to

selenium dioxide) involving the use of *tert*-butyl hydroperoxide as the oxidant the desired product **116** began to emerge, albeit in moderate yields. Initially, no success was achieved utilising *tert*-butyl hydroperoxide as a 70% solution in water (**Table 32, Entry 3**), however, moving to anhydrous systems (**Table 32, Entries 4 and 5**) compound **116** was obtained.



91 **116**

Scheme 175

Entry	Eq. SeO_2	Conditions	Yield
1	1	Ethanol, reflux, 16 h	0%
2	1	1,4-dioxane, reflux, 16 h	0%
3	0.5	*t*BuOOH (70% in H_2O), r.t. 16 h	0%
4	0.5	*t*BuOOH (3 M in DCM), r.t. 8 h	49%
5	0.5	*t*BuOOH (5.5 M in decane), r.t. 8 h	32%

Table 32

Pleased with these initial results, we sought to improve the isolated yield of the desired alcohol **116**. To this end, a further study set out to investigate the optimal number of equivalents with regards to selenium dioxide (**Table 33**). Somewhat surprisingly, no improvement in yield was observed when using stoichiometric selenium dioxide (**Table 33, Entry 1**). In addition to this, moving to 0.25 equivalents of selenium, disappointingly, provided the desired product in a much reduced 26% yield (**Table 33, Entry 2**).

Entry	Eq. SeO_2	Conditions	Yield
1	1	*t*BuOOH (3 M in DCM), r.t. 8 h	41%
2	0.25	*t*BuOOH (3 M in DCM), r.t. 8 h	26%

Table 33

Despite the optimal yield of the desired allylic alcohol being moderate (**Table 32, Entry 4**), little time was spent to optimise this further. In fact, we were, indeed, appreciative of this isolated yield given the presence of an alkyne functionality within the substrate. Indeed, one can imagine the possibility of oxidation on either sp^3 carbon adjacent to the triple bond (**Figure 9**).

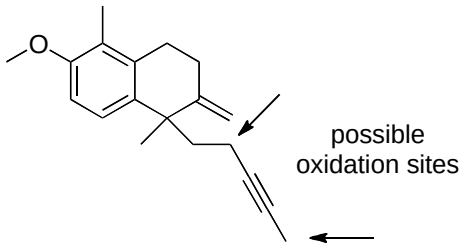
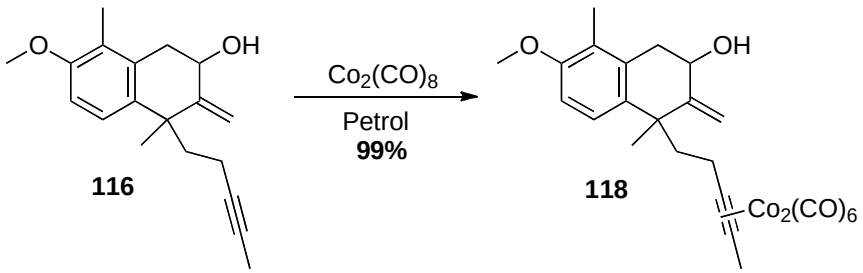


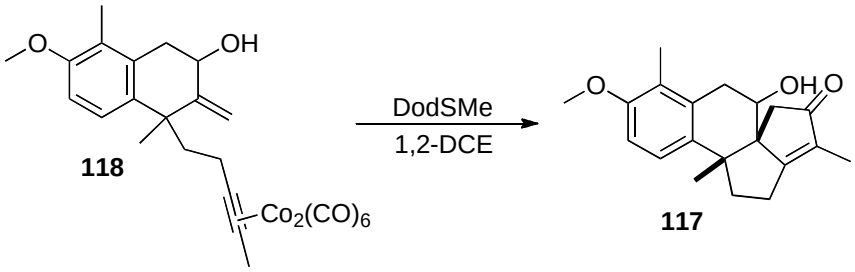
Figure 9

With oxygenated species **116** having been accessed, attention now turned to the key Pauson-Khand cyclisation of this new enyne substrate. With good quantities of **116** in hand, it was decided that the requisite dicobalt hexacarbonyl complex would be prepared and isolated. Therefore, under standard complex formation conditions desired compound **118** was furnished in an excellent 99% yield (**Scheme 176**).



Scheme 176

Employing the sulfide-promoted Pauson-Khand conditions,[94] previously successful within this programme of work, it was hugely disappointing to obtain only 26% of the desired tetracyclic product (**Scheme 177, Table 34, Entry 1**). Even more frustrating, was the fact that none starting complex (or decomplexed material) were recovered; this previously optimal protocol, unfortunately, seemed to favour decomposition of the reaction mixture. In an attempt to generate **117** under more mild conditions, the temperature of the reaction was reduced to 50°C (**Table 34, Entry 2**); however, this effort resulted in the slow decomposition of the starting material. Further annoyance was encountered upon repeating **Entry 1**; despite a 26% yield of the desired compound having been obtained, it was not possible to repeat this result.

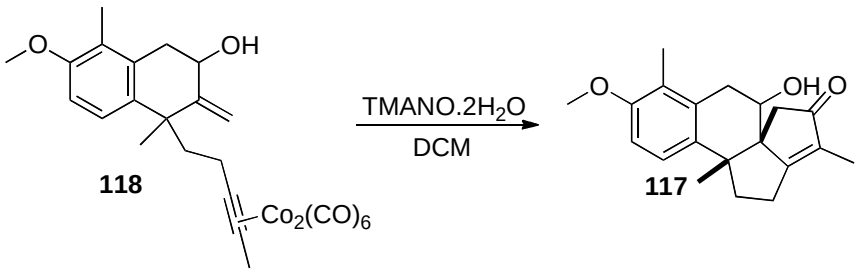


Scheme 177

Entry	Conditions	Yield
1	reflux (83°C), 16 h	26%
2	50°C, 24 h	0%

Table 34

Given the above failure, the next set of conditions investigated utilised trimethyl amine *N*-oxide dihydrate (TMANO.2H_2O) as an additive (**Scheme 178, Table 35**). The use of such amine *N*-oxides have shown to be excellent promotors within the Pauson-Khand reaction (*vide supra*), allowing cyclisations to occur incredibly efficiently at much lower temperatures.[85,86] As such, it was hoped that these more mild conditions would thwart the decomposition issue encountered with the sulfide-promoted protocols. Disappointingly, only trace amounts of the annulated product **117** were detected by ^{1}H NMR analysis. Again, decomposition of the reaction mixture occurred and no reusable starting material was isolated from this reaction.

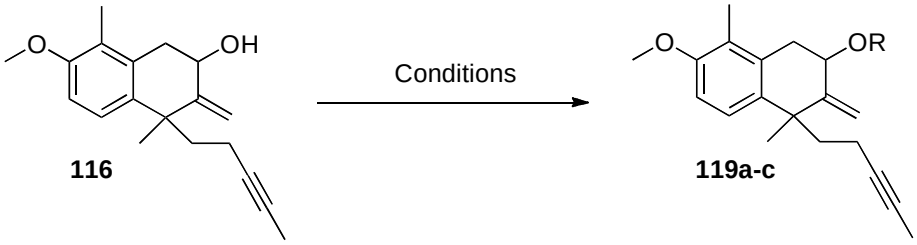


Scheme 178

Entry	Conditions	Yield
1	r.t., 16 h	trace
2	40^{o}C, 1 h	trace

Table 35

Undaunted by these results, it was decided that the free hydroxyl group should be protected to prevent any possible ligation to the metal centre, which may be hindering the cyclisation process. As such, a variety of protected alcohols were prepared in order to assess their reactivity within the Pauson-Khand process (**Scheme 179, Table 36**). The alcohol functionality was protected as the acetate, ethoxymethyl acetal, and *tert*-butyl dimethyl silylether group in 67%, 37%, and 100%, respectively (**Table 36, Entries 1, 2, and 3**).

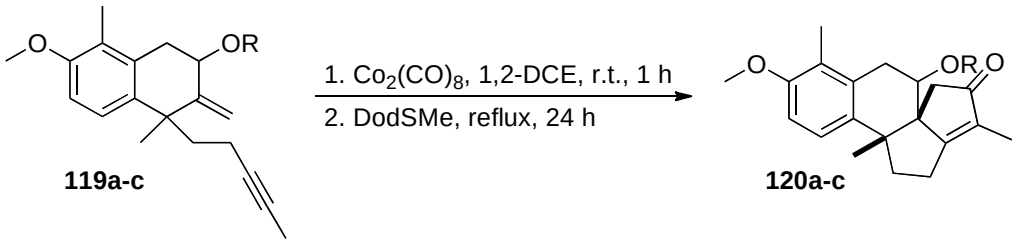


Scheme 179

Entry	R	Conditions	Yield
1	$COCH_3$	Ac_2O, pyridine, DCM	**119a**: 67%
2	CH_2OEt	$EtOCH_2Cl$, Et_3N, DCM	**119b**: 37%
3	TBS	TBSCl, Imidazole, DCM	**119c**: 100%

Table 36

With the above compounds in hand, we were keen to assess their reactivity within the Pauson-Khand reaction. It was decided that the required cobalt complex would be prepared *in situ*; the substrate was allowed to react for 1 hour with dicobalt octacarbonyl at room temperature before the addition of dodecylmethyl sulfide and warming to reflux (**Scheme 180, Table 37**).



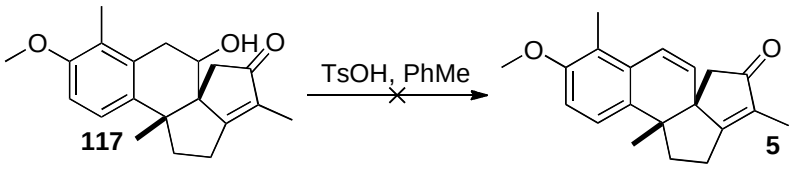
Scheme 180

Entry	R	Yield
1	$COCH_3$	**120a**: 0%
2	CH_2OEt	**120b**: 0%
3	TBS	**120c**: 0%

Table 37

Disappointly, and surprisingly, none of the protected allylic alcohols **119a-c** could be cyclised in an efficient manner. Perhaps the OR functionality is just too close to the reacting centre within the Pauson-Khand reaction, hindering the cyclisation of these particular substrates. Based on these outcomes, another strategy towards the preparation of the final natural product would have to be devised.

Nevertheless, with a small amount of tetracyclic compound **117** in hand, elimination of the hydroxyl group was attempted to furnish the desired internal point of unsaturation present in the final targeted natural product. The first set of conditions utilised tosic acid in toluene (**Scheme 181, Table 38**). Unfortunately, no elimination product was detected by ^{1}H NMR analysis after both thermal and microwave irradiation treatment.

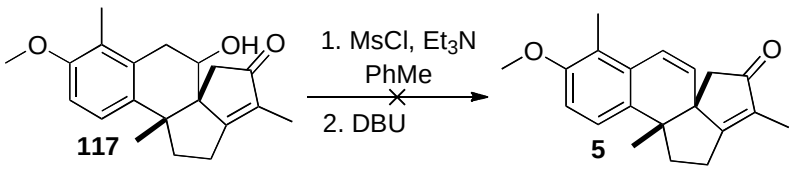


Scheme 181

Entry	Conditions	Yield
1	reflux, 16 h	0%
2	MWI, 125^{o}C, 10 min	0%

Table 38

At this juncture, it was decided to activate the alcohol, in the form of a mesylate, to facilitate the elimination process. As such, *in situ* preparation of the mesylate intermediate (followed by tlc analysis), and subsequent addition of DBU was carried out under, again, thermal and microwave irradiation conditions (**Scheme, 182, Table 39, Entries 1 and 2**). Unfortunately, as before, only starting material was observed from the reaction mixture, with none of the desired product being formed.

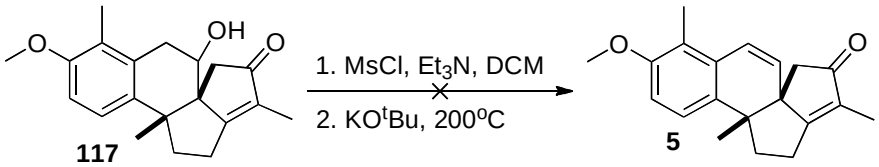


Scheme 182

Entry	Conditions	Yield
1	r.t., 2 h	0%
2	MWI, 125°C, 10 min	0%

Table 39

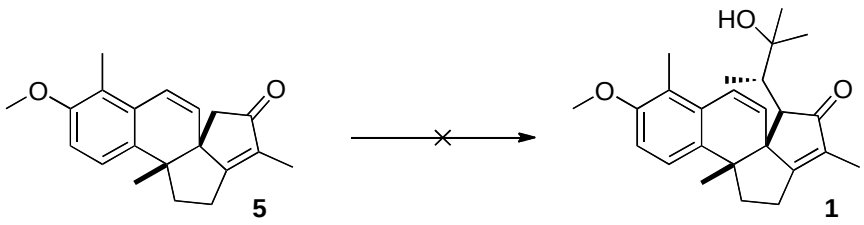
In addition to the above set of conditions, following mesylate formation, potassium *tert*-butoxide was added and the resulting mixture was heated in a sealed tube to 200°C. Unsurprisingly, these rather harsh conditions led to only decomposition of the starting material (**Scheme 183**).



Scheme 183

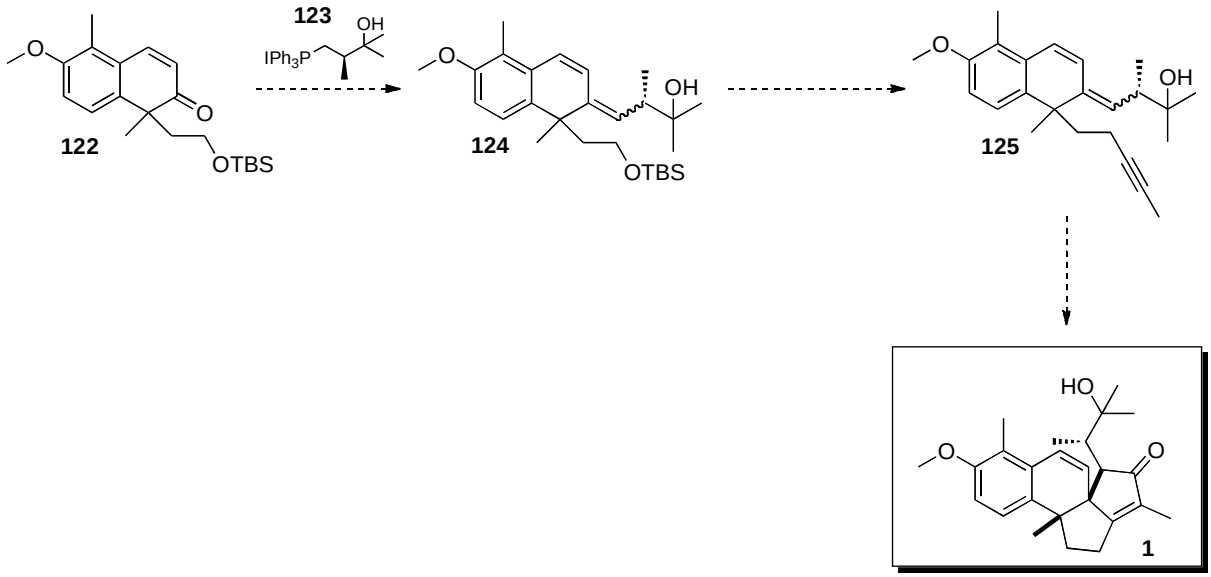
3.2.10 Final Strategy: Wittig Olefination Approach

Following the failures of the above described approaches, one last change of tact was pursued in attempts to complete the synthesis of the targeted natural product. As mentioned previously, compound **5** was prepared, albeit in more moderate yield, *via* a cobalt-mediated Pauson-Khand reaction. Simultaneous to this programme of work, efforts towards taking this intermediate to Agariblazeispriol C, i.e. introducing the oxygenated side chain, were being investigated within our laboratory. Despite many efforts however, it seemed that substrate **5** displayed an extreme lack of reactivity and, as such, no success was achieved in taking this molecule forward in this alkylation process (**Scheme 184**).[130]



Scheme 184

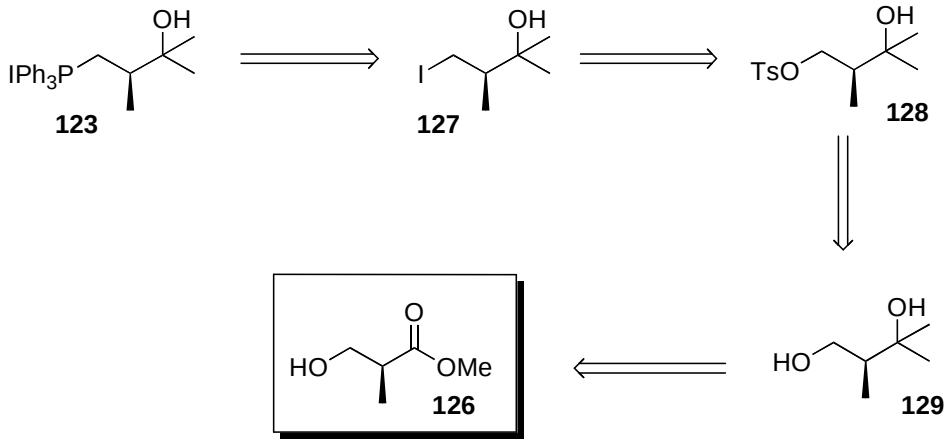
On revising the options, it was considered that the introduction of the oxygenated side chain earlier within the synthesis would provide an alternative, more convergent, pathway to the targeted molecule (**Scheme 185**). This would make the key Pauson-Khand annulation step the final transformation within this synthetic route, constructing the entire final structure during this ultimate cyclisation.



Scheme 185

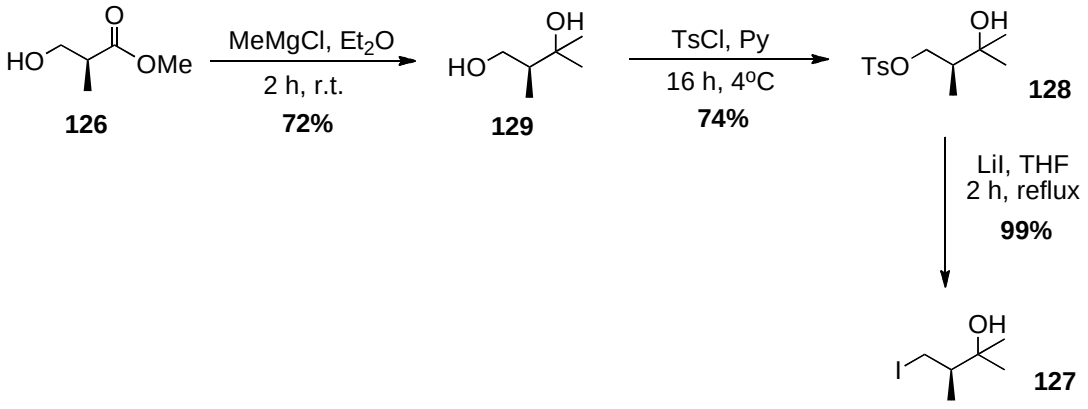
On closer inspection, this new synthetic sequence presented several challenging synthetic steps. Firstly, in order to pursue this revised route, enone **122** and chiral phosphine salt **123** would be required as key intermediates. In addition to this, the proposed Wittig olefination, utilising enone **122**, presented a difficult transformation in terms of both steric and electronic factors. Thirdly, and, perhaps, the most worrisome aspect was the newly proposed Pauson-Khand cyclisation. Not only does the starting substrate contain an internal alkyne and diene system, the olefin partner is now trisubstituted, which, of course, adds to the steric strain of this annulation process to build a quaternary carbon centre, as well as setting up the remaining contiguous stereocentres.

Despite the above reservations, the new synthetic sequence was embarked upon. Pleasingly, on searching the literature, phosphine salt **123** was readily accessible,[162] starting from the commercially available chiral ester **126**, as shown in Scheme **186**.



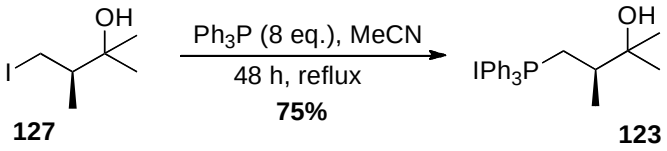
Scheme 186

Following the literature procedure,[162] treatment of compound **126** with excess methyl magnesium chloride yielded the desired diol product **129** in good yield, without prior protection of the primary hydroxyl functionality (**Scheme 187**). Following this, functionalisation of the primary alcohol as its tosylate was achieved in a 74% yield, with, pleasingly, no tosylation being observed at the tertiary alcohol. Subsequent iodination was facile, providing iodide **127** in an excellent 99% yield.



Scheme 187

With iodide **127** in hand, attention turned to the phosphonium salt formation. The authors note that this was the most challenging part of this short preparative pathway due to the formation of the dehydrated phosphonium salt. Nevertheless, after optimisation, the authors were able to selectively form salt **123** using eight equivalents of triphenylphosphine in refluxing acetonitrile. Indeed, repetition of this protocol resulted in the desired phosphine salt **123** being prepared in an appreciable 75% yield (**Scheme 188**).



Scheme 188

In order to confirm that complete retention of stereochemistry had been achieved throughout the above described synthetic transformations (**126→123**), the absolute stereochemistry of compound **123** was ascertained *via* X-ray crystallography. Suitable crystals were grown by slow diffusion of diethyl ether into a near saturated solution of **123** in dichloromethane at room temperature, and, as depicted in **Figure 11**, the stereochemistry at C2 represents the configuration that was initially provided in chiral starting ester **126**. The presence of the heavy iodine atom in compound **123** allowed the absolute configuration of the compound to be determined by analysis of the anomalous dispersion. This was done by the method of Flack,[163] giving a refined Flack parameter of -0.024 +/- 0.012 (where a value of 0 indicates the correct absolute configuration has been modelled, and 1 that the inverted structure has been modelled).

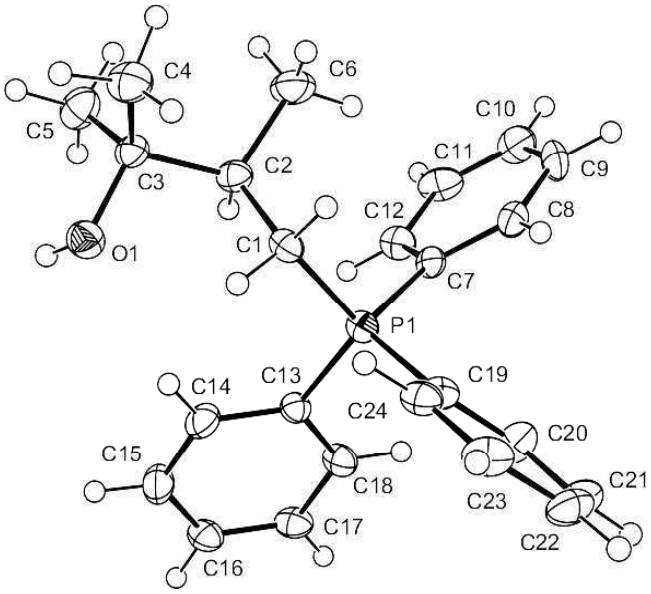
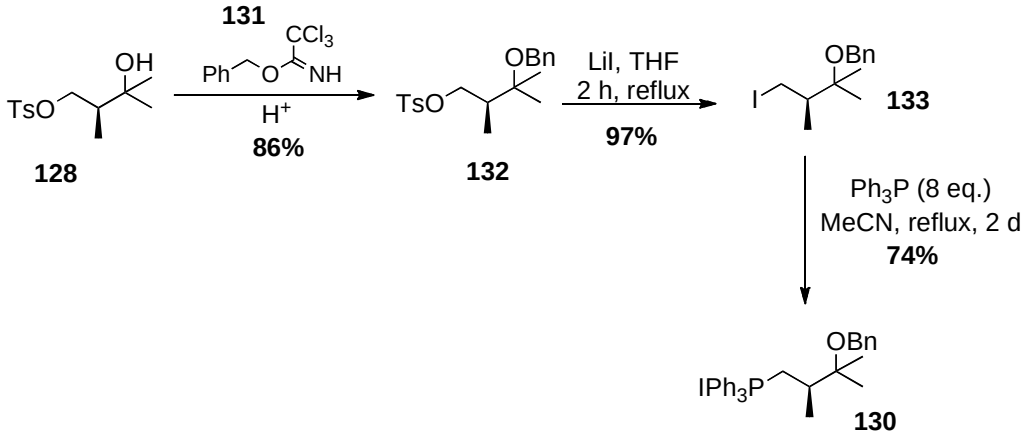


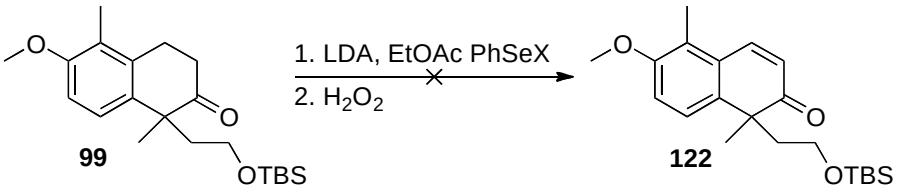
Figure 10

Simultaneous to the above described experiments, protected phosphine salt **130** was also targeted as an alternative substrate for the planned Wittig olefination. In this regard, tosylate **128** was reacted with benzylating agent **131**, in an acidic media, to furnish the desired benzyl protected compound **132** in 86% yield. Following this, iodide **133** was prepared in an excellent yield 97% yield prior to the reaction with excess triphenylphospine to prepare phosphine salt **130** (**Scheme 189**).



Scheme 189

With regards to the coupling partner for the proposed Wittig olefination, initial attempts looked to use selenium-based chemistry to achieve the transformation of previously prepared ketone **99** to enone **122** (**Scheme 190**). Unfortunately, deprotonation of ketone **99** followed by (external) quenching with phenylselenium chloride, afforded none of the desired product. Indeed, almost quantitative recovery of the starting material was achieved (**Table 40, Entry 1**). Given that no selenide intermediate was observed, the reaction seems to have failed due to lack of reactivity of the enolate with the selenium-based electrophile. As such, the more reactive phenylselenium bromide was employed. However, once again, only starting material was observed from this reaction (**Table 40, Entry 2**).

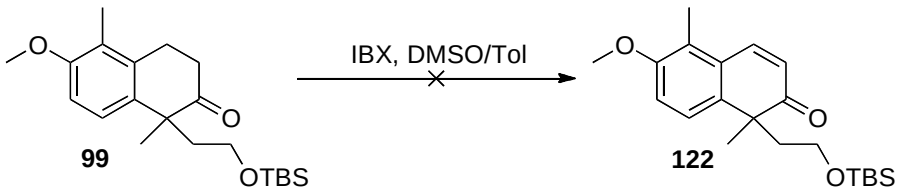


Scheme 190

Entry	X	Yield
1	Cl	0%
2	Br	0%

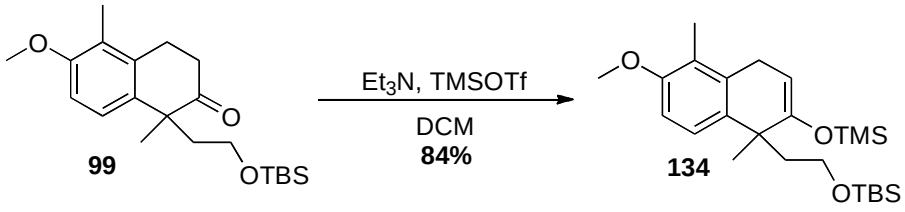
Table 40

Attention now turned to the use of 2-iodoxybenzoic acid (IBX) to perform this oxidative transformation (**Scheme 191**).[164] This material, fortunately, was available within our laboratory and so preparation of this reagent was not required. However, upon reacting IBX with ketone **99**, none of the desired product was observed. In fact, this protocol led to a complex mixture of products.



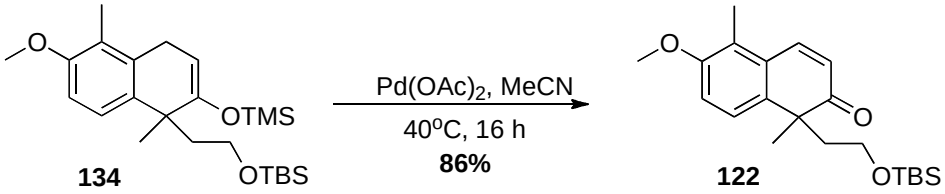
Scheme 191

Following these results, attention focused on the use of a palladium-mediated Saegusa oxidation[165] to introduce the enone functionality. This well known transformation, firstly, required the preparation of enol ether **134**, which, was achieved without incident in an 81% yield (**Scheme 192**).



Scheme 192

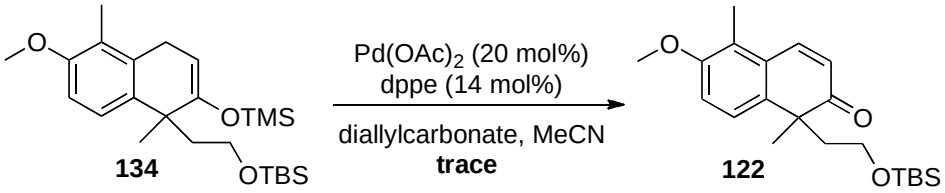
Enol ether **134** was then subjected palladium-mediated conditions to smoothly afford enone **122** (**Scheme 193**).



Scheme 193

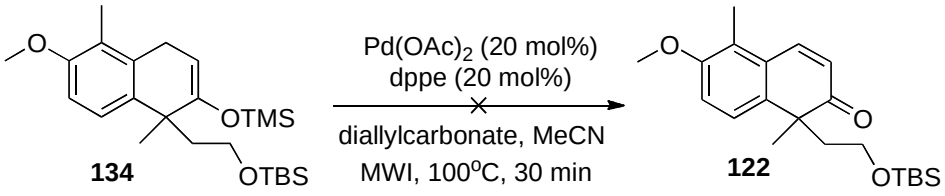
Initially, on a small scale, the above described conditions provided the desired compound in an excellent 86% yield. However, in the light of cost, we felt that employing catalytic Saegusa

conditions would be a more worthwhile pursuit. As such, a set of conditions previously successful within our research group[126] for such a transformation were considered (**Scheme 194**). Originally developed by Tsuji,[165b,c] this method relies on the use of diallylcarbonate as a reaction additive, which acts as a shuttle for the palladium throughout the process. However, on application of these reaction conditions, only a trace amount of the desired product was observed in the crude ^{1}H NMR after 40 h.



Scheme 194

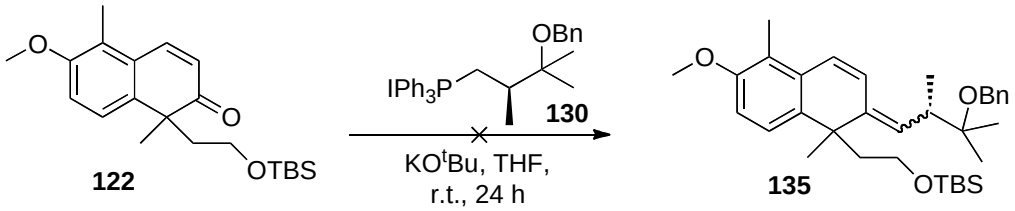
With mainly starting silyl enol ether present after such forcing conditions, the stability of this compound was evident. Therefore, to probe the reaction further, microwave irradiation was attempted. However, after 30 minutes at 100^{o}C, a mixture of products was observed by ^{1}H NMR analysis (**Scheme 195**).



Scheme 195

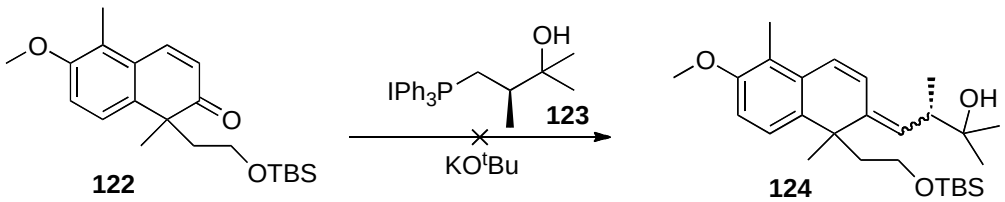
With a vein to advancing research progress at this stage in the project, it was decided that the stoichiometric Saegusa protocol would suffice until more time could be spent on the optimisation of this reaction. With both components for the required Wittig olefination prepared, initial attempts at this reaction began. Regrettably, initial attempts with protected salt **130**, utilising the protocol successful for methylenation of ketone **99** did not deliver the desired exocyclic alkene (**Scheme 196**). It is important to note that a colour change was expected upon reaction of the

base with the phosphonium salt, which would indicate the formation of the requisite phosphonium ylide. However, this expected observation did not occur in this reaction; hence, the outcome of this preliminary reaction was attributed to the failure to deprotonate phosphonium salt **130**.



Scheme 196

In a similar manner, phosphine salt **123** was also reacted under various conditions utilising potassium *tert*-butoxide as the base (**Scheme 197**). Indeed, in this case, considering the free hydroxyl unit, 2 equivalents of base relative to the phosphine salt may be required to form the required ylide species. **Table 41** details the results from this initial study. Once again, the expected colour change did, unfortunately, not occur in any of these reactions. As such, only starting enone was observed by crude ^{1}H NMR analysis.



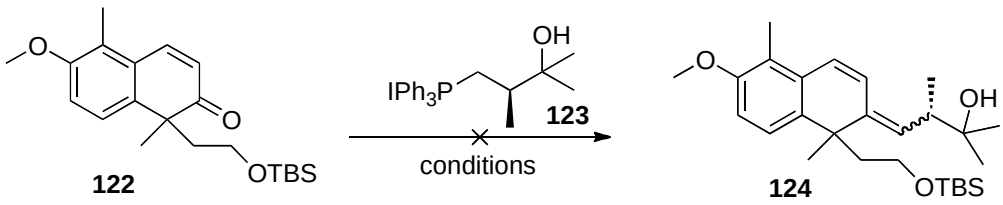
Scheme 197

Entry	Solvent	Salt (eq.)	Base (eq.)	Conditions	Yield
1	THF	4	8	A	0%
2	Et_2O	4	8	A	0%
3	THF	4	8	B	0%
4	THF	4	4	B	0%

Conditions A: base added to a solution of the salt, prior to the addition of **122**
Conditions B: base added to a solution of salt and **122**

Table 41

At this juncture, it was clear that a screen of alternative systems must be carried out. Imperative to such deprotonations is finding the correct aggregration state of the key molecules within the reaction. As such, we were sure that lithium chloride would play a key role; it has been well documented in the literature that inorganic halide salts can be employed in order to disrupt complex solution aggregates. In particular, lithium chloride has been shown to be highly effective[166] and has been used extensively as an additive in magnesium-enolate chemistry within our laboratory.[167] With this in mind, the initial experiment carried out made use of bismesitylmagnesium and lithium chloride, in THF; a protocol, which has been established as an efficient and convenient system within deprotonation reactions[167b,c] (**Scheme 198, Table 42, Entry 1**). Unfortunately, in this case, the expected colour change did not occur, and none of the desired olefin product was observed by ^{1}H NMR analysis. Following this result, attention turned to the use of methyllithium (**Table 42, Entries 2-4**). Reactions were carried both in the absence of lithium chloride (**Entry 2**) and with varying amounts of this inorganic additive (**Entries 3 and 4**). With regards to **Entries 2 and 3**, once again, the anticipated colour change did not occur, however, upon moving to 0.4 wt% lithium chloride in a 1.6 M methyllithium solution[162] (**Entry 4**) a distinct colour change from white to red was observed. Having said this, still none of the desired product was observed after a 24 h reaction time at room temperature. Nevertheless, it was incredibly pleasing to have achieved partial success in fact that now, seemingly, the required ylide species was being generated.



Scheme 198

Entry	Solvent	Salt (eq.)	Base (eq.)	Additive	Yield
1	THF	2.2	2.2 (Mes_2Mg)	LiCl (8.8 eq.)	0%
2	Et_2O	1.5	3 (MeLi)	none	0%
3	Et_2O	1.5	3 (MeLi)	LiCl (1.5 eq.)	0%
4	Et_2O	3	5.5 (MeLi)	*	0%

* MeLi as a stock solution (1.6 M in Et_2O with 0.4 wt.% LiCl)

Table 42

Despite the ylide formation now, seemingly, having been obtained, realising the conditions needed to execute the olefination with enone partner **122** would require further optimisation. Indeed, in terms of olefination reactions, such α,β-unsaturated ketones are not the most reactive substrate type. Unfortunately, this additionally required optimisation study could not be carried out as part of this research programme.

The following sections detail a summary of, and discuss proposed extensions to the research described throughout this chapter.

Chapter 4

Summary and Future Work

4.1 Summary *pg. 147*

4.2 Future Work *pg.149*

4.1 Summary

With regards to the originally proposed synthetic route towards Agariblazeispirol C, good quantities of Heck precursor **8** were prepared. With this material, the first key metal mediated cyclisation was carried out under optimised conditions, establishing the first all carbon quaternary centre present in the targeted compound. Nevertheless, with practical inefficiencies arising in relation to the preparation of required vinyl bromide **82**, an alternative route towards Agariblazeispirol C was proposed. As part of this new approach towards Agariblazeispirol C, alternative enyne substrate **91** was targeted. In comparison to the original Pauson-Khand substrate **6**, molecule **91** did not possess the additional (internal) point of unsaturation, conjugated to the exocyclic (reacting) alkene.

Regarding the newly developed synthetic pathway, excellent progress has been made. A much shorter and more robust pathway has been carried for the preparation of vinyl bromide **92**, as compared to the five step procedure originally employed to gain access to the one carbon homologue, intermediate **82**. With this compound, and Weinreb amide **78**, in hand, the newly targeted Heck reaction precursor **95** was prepared *via* an extremely efficient overall route. With regards to our first metal-mediated cyclisation reaction, extremely efficient microwave-assisted Heck conditions have been established, which generated the key bicyclic intermediate **94** in excellent yield after only 20 minutes reaction time. Following this, a series of established and optimised transformations have allowed access to the precursor for our cobalt-mediated, intramolecular Pauson-Khand reaction in gramme quantities. With this material, the tetracyclic core of Agariblazeispirol C has been synthesised now in a much improved 86% yield, as well as a dramatically reduced reaction time. Clearly, removal of the conjugated diene system, present in original precursor **6**, has a dramatic effect on the reactivity and efficiency of the cyclisation towards this key carbon skeleton. In addition to this, a catalytic protocol was also established, delivering tetracylic compound **109** in 65% yield using only 20 mol% of dicobalt octacbarbonyl. At this stage in the research project, advanced intermediate **109** has been furnished in an overall yield of 39% over 15 synthetic steps.

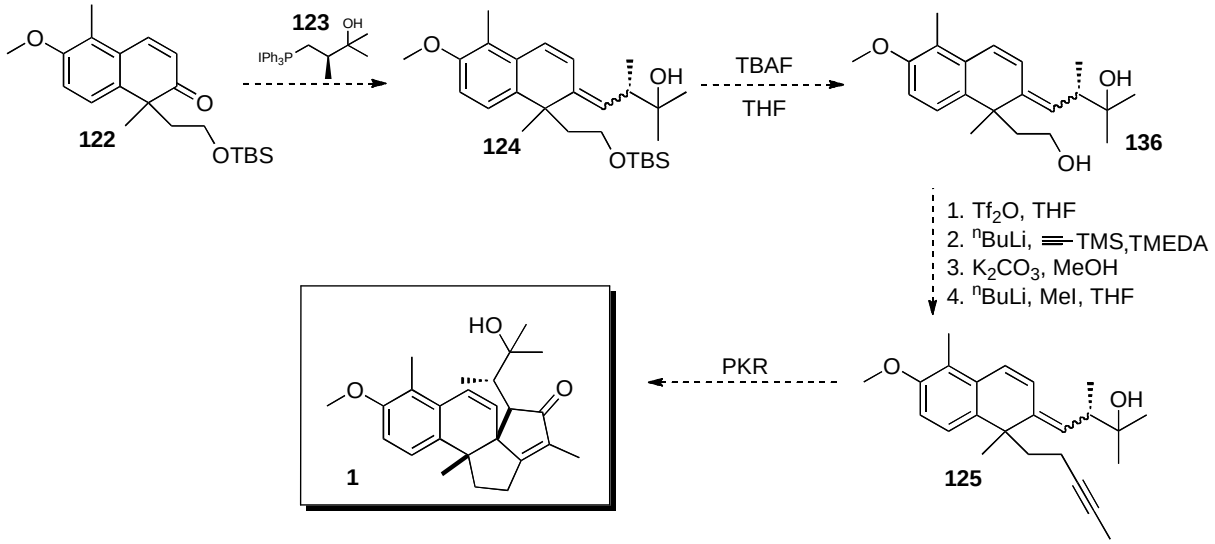
Following from this, numerous efforts were made to take advanced intermediate **109** towards

Agariblazeispirol C. Efforts included the attempted preparation of compounds **5** and **115**, which would have, potentially, allowed further manipulation to the desired natural target. In addition to this, an allylic oxidation/P-K sequence was attempted to potentially allow access to further intermediates without compromising the efficiency of the key Pauson-Khand cyclisation. Despite tenacious efforts, these endeavours were fruitless.

Due to the problems associated with the advancement of compounds **109**, **116**, and **5**, one last change of tact was pursued with a view to completing the synthesis of the targeted natural product. More specifically, it was envisioned that a more convergent pathway towards the natural target would involve the installment of the oxygenated side chain present in **1** at an earlier stage in this overall preparative pathway. In this regard, functionalised phosphine salt **123** and enone **122** were prepared and reacted under Wittig olefination conditions. Unfortunately, as yet, the desired olefination product has not been obtained. Having said this, initial problems involving the formation of the requisite phosphonium ylide species have, seemingly, been overcome.

4.2 Future Work

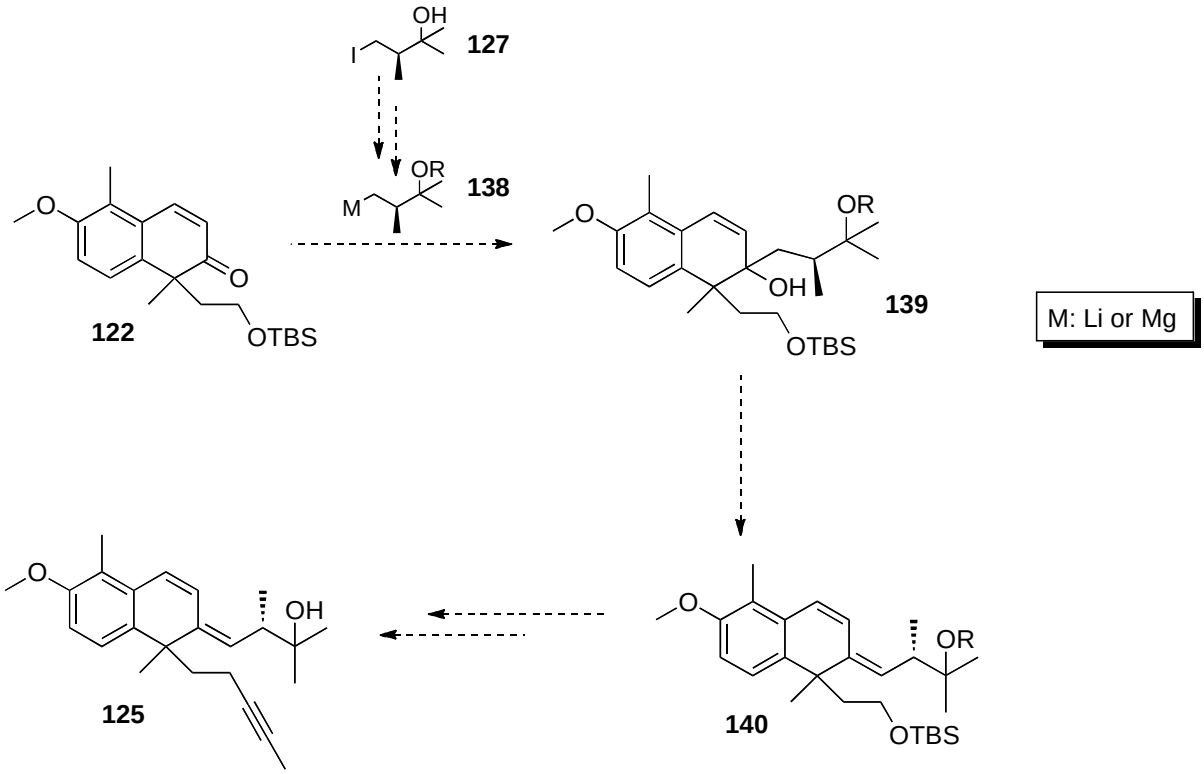
Undoubtedly, the primary goal of this project will be to complete the first total synthesis of the natural product, Agariblazeispirol C. In this regard, further optimisation of the newly proposed olefination of enone **122** should be investigated. If successful, it remains to embed the alkyne component of the molecule and attempt a novel Pauson-Khand reaction (**Scheme 199**). In this regard, transposition of already developed procedures within the research programme should generate compound **125**. Following this, the efficacy of compound **125** within the Pauson-Khand cyclistion reaction should be investigated. Indeed, substrate **125** presents itself as an incredibly challenging Pauson-Khand precursor, with both an internal alkyne and a trisubstituted alkene being present. Nevertheless, there are many avenues (*vide supra*), which can be followed in an attempt to execute this transformation.



Scheme 199

In addition to the above, an alternative pathway to compound **137** is illustrated in **Scheme 200**. An organometallic species, such as **138**, could be prepared from iodide **127** (previously synthesised within this programme of work), which, in turn, could be reacted with enone **122** to furnish the 1,2-addition product, **139**. From this molecule, dehydration would provide access to derivative **137**. Indeed, the dehydration reaction should occur to provide, exclusively, the

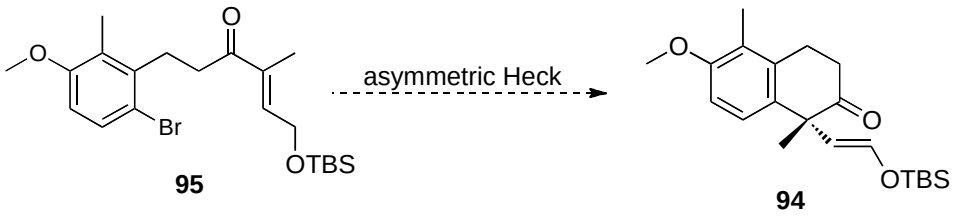
desired and thermodynamically more stable *E*-product, which would prevent the requirement to separate the possible mixture of *E*- and *Z*-isomers that may occur from the proposed olefination reaction shown in **Scheme 199**.



Scheme 200

On an alternative note, the synthetic chemistry described within this thesis has been focused on the preparation of Agariblazeispirol C in a racemic fashion. Indeed, the synthesis of Agariblazeispirol C in an enantio-enriched sense would be a natural extension to this piece of research. As alluded to earlier, in any development of an enantioselective synthesis the stereocentre present in compound **94** is crucial and must be controlled. It has already been shown within this thesis that this all-carbon, quaternary, stereocentre controls the diasteroselectivtity of the downstream Pauson-Khand cyclisation. In this regard, an asymmetric variant of the Heck reaction would, potentially, install this key centre in an enantio-enriched

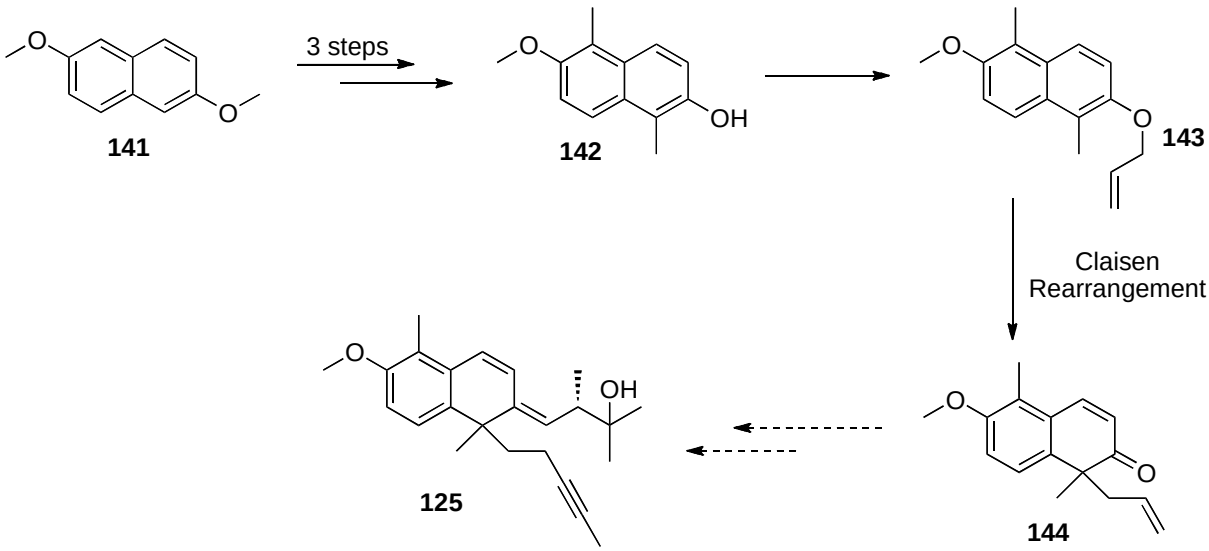
form (**Scheme 195**). Of course, within the literature, and as described within section 2.3, there are a vast number of examples of the Heck coupling being applied in an asymmetric fashion.



95 **94**

Scheme 201

In addition to the above, a further piece of research carried out within our laboratory has delivered compound **144** *via* a novel preparative pathway, which incorporates a Claisen rearrangement reaction as the key transformation (**Scheme 202**).[168] More specifically, compound **144** has been prepared in a good overall yield from the commercially available naphthalene **141**. It is envisaged that intermediate **144** could be further manipulated to deliver compound **125**, and in doing so could, potentially, present a more convergent pathway to the previously targeted dienyne **125**. Furthermore, one can envisage expanding this route into the asymmetric domain, whereby the employment of a chiral environment within the central Claisen rearrangement reaction should deliver enone **144** in an enantio-enriched form.



Scheme 202

Chapter 5

Experimental

5.1 General *pg. 154*

5.2 Synthetic Substrates and Intermediates *pg. 156*

5.1 General

Reagents

All reagents were obtained from commercial suppliers and used without further purification, unless otherwise stated. All reactions were carried out under an inert, dry nitrogen atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[169]

Tetrahydofuran, 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, and acetonitrile were dried by heating to reflux over calcium hydride then distilled under nitrogen.

Petrol refers to petroleum ether in the boiling point range of 40-60^{o}C.

^{n}BuLi, ^{t}BuLi, and MeLi were obtained as solutions in hexanes, pentanes, or diethyl ether, respectively, and standardised using salicylaldehyde phenylhydrazone.[170]

(*o*-tolyl)$_3$P and AIBN were recrystallised from ethanol before use.

N-Bromosuccinimide was recrystallised from water before use.

Instrumentation and Data

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

Reactions performed under ultrasonication were carried out using a Kerry low powered sonication bath.

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

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

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

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

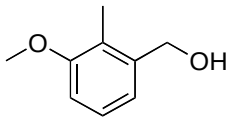
^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 100 MHz, respectively, or a Bruker DRX 500 spectrometer at 500 MHz and 125 MHz, respectively. ^{31}P NMR spectra were recorded on a Bruker DPX 400 spectrometer at 162 MHz. Chemical shifts are reported in ppm. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interections, unless otherwise stated.

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

Elemental analyses were obtained using a Carlo Ebra 1106 CHN analyser.

5.2 Synthetic Substrates and Intermediates

Preparation of (3-methoxy-2-methylphenyl)methanol.[171]



72

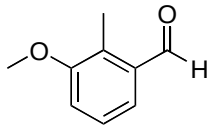
Scheme 96

A solution of 3-methoxy-2-methylbenzoic acid **9** (50.9 g, 306.3 mmol), in dry THF (500 ml), was cooled to 0°C in a previously flame dried and nitrogen cooled 3-neck round bottom flask, fitted with a condenser. To the solution was added borane dimethylsulfide complex (43.5 ml, 459.5 mmol) slowly. Upon addition an exotherm was observed. The resulting slurry was warmed to reflux and stirred for 16 h. After this time, the solution was cooled to 0^{o}C and quenched, carefully, with MeOH (100 ml). Following this, the solution was diluted with ether and washed with water (x 2). The organic solution was dried over sodium sulfate, filtered, and evaporated to give a pale brown oil. Purification by recrystallisation from hexane (x 3) provided **72** (46.6 g, 100% yield) as a white solid.

Melting Point: 60-61^{o}C.

IR (CH_2Cl_2): 3604 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.50 (t, *J* = 5.8 Hz, 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), 6.99 (d, *J* = 7.4 Hz, 1H, ArH), 7.19 ppm (t, *J* = 7.9 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 11.0, 55.6, 63.8, 109.9, 120.0, 124.8, 126.4, 140.0, 157.8 ppm.

Preparation of 3-methoxy-2-methylbenzaldehyde.[132]



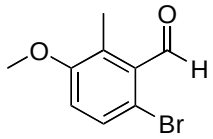
73

Scheme 97

A 3-neck round bottom flask was flame dried under vacuum prior to cooling under nitrogen. The cool, dry flask was charged with oxalyl chloride (7.4 ml, 85.4 mmol) and dry DCM (180 ml). The solution was cooled to -78°C prior to the slow addition of DMSO (10.7 ml, 151.1 mmol) *via* syringe. Stirring was continued at this temperature for 10 min prior to the addition of **72** (10.0 g, 65.7 mmol) as a solution in dry DCM (35 ml). Stirring of the reaction mixture was continued for 15 min before addition of triethylamine (45.7 ml, 328.5 mmol). Upon complete addition, the mixture was allowed to warm to room temperature. During the warming process, a pale yellow slurry formed that was difficult to stir. Stirring became easier after a time and the solution was left at ambient temperature for 16 h. The reaction was quenched with saturated ammonium chloride solution, washed with water ($\times$ 2), and brine. The organic solution was dried over sodium sulfate, filtered, and evaporated to yield **73** (9.90 g 100% yield) as a pale yellow oil.

IR (CH_2Cl_2): 1698 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 2.55 (s, 3H, $ArCH_3$), 3.88 (s, 3H, OCH_3), 7.09 (d, J = 8.0 Hz, 1H, ArH), 7.32 (t, J = 8.0 Hz, 1H, ArH), 7.44 (dd, J = 7.7 Hz, ^4J = 0.9 Hz, 1H, ArH), 10.34 ppm (s, 1H, aldehyde); ^{13}C NMR δ(100 MHz, $CDCl_3$): 10.4, 55.9, 115.3, 123.0, 126.5, 129.7, 135.1, 158.1, 192.7 ppm.

Preparation of 6-bromo-3-methoxy-2-methylbenzaldehyde.[132]



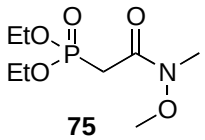
74

Scheme 98

An oven dried 1 L flask was charged with acetic acid (250 ml) and 3-methoxy-2-methylbenzaldehyde **73** (15.6 g, 103.9 mmol). To the stirred solution was added bromine (5.85 ml, 106.8 mmol) *via* a syringe. The reaction mixture was stirred at room temperature for 24 h prior to the addition of excess water. The resulting pale yellow slurry was extracted into DCM, washed with water and concentrated to a pale yellow solid. Purification by column chromatography (eluent: hexane) yielded **74** (23.05 g, 93% yield) as a pale yellow oil.

IR (CH_2Cl_2): 1697 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 2.43 (s, 3H, $ArCH_3$), 3.85 (s, 3H, OCH_3), 6.89 (d, *J* = 8.7 Hz, 1H, ArH), 7.44 (d, *J* = 8.7 Hz, 1H, ArH), 10.46 ppm (s, 1H, aldehyde); ^{13}C NMR δ(100 MHz, $CDCl_3$): 12.0, 56.0, 115.4, 117.1, 131.1, 131.3, 132.9, 157.6, 194.9 ppm.

Preparation of diethyl (N-methoxy-N-methylcarbamoyl)methylphosphonate.[134]



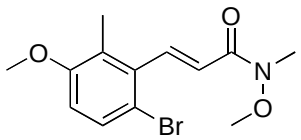
75

Scheme 99

An oven dried 500 ml flask fitted with a stirrer bar was charged with dry DCM (250 ml) and *N*-methoxymethylamine hydrochloride (19.5 g, 200 mmol). To the stirred slurry was added triethylamine (55.7 ml, 400 mmol) followed by chloroacetylchloride (16 ml, 200 mmol) in a dropwise fashion *via* a syringe. The reaction mixture was stirred at room temperature for 1 h prior to quenching with saturated sodium hydrogen carbonate solution. The organics were then washed sequentially with dilute hydrochloric acid and brine solutions prior to drying over sodium sulfate and filtering. Concentration of the organic solution yielded a brown oil. To this was added neat triethylphosphite (24 ml, 140 mmol) and this mixture was warmed to 80ºC and stirred for 24 h. After this time, excess triethylphosphite was removed *in vacuo* and the residue distilled (Kugelrohr, bulb-to-bulb; 150°C @ 0.03 mmHg) to yield **75** (35.9 g, 75% yield) as a colourless liquid.

IR (CH_2Cl_2): 1658 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, $CDCl_3$): 16.3 (d, J = 6.1 Hz), 31.4 (d, ^1J = 138.4 Hz), 32.1, 61.7, 62.5 (d, ^2J = 6.1 Hz), 166.1 ppm; ^{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.[129]



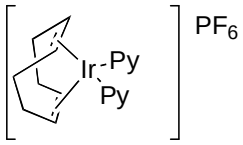
77

Scheme 100

A 500 ml 3-neck round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonate **75** (20.84 g, 87.1 mmol) and dry THF (450 ml) before being cooled to 0°C. The solution was treated with ^{n}BuLi (43.6 ml, 2 M in hexanes, 87.1 mmol) and allowed to stir for 10 mins. Aldehyde **74** (18.16 g, 79.27 mmol) was then slowly introduced as a solution in dry THF (50 ml). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, after which time it was quenched with saturated ammonium chloride. The mixture was diluted with diethyl ether, and washed with water and brine. Drying over sodium sulfate followed by filtration and evaporation yielded a pale yellow oil. Purification by filtration through a plug of silica gel (eluent: 0-30% diethyl ether in petrol) provided **77** (24.9 g, 100% yield) as a pale yellow oil.

IR (CH_2Cl_2): 1568, 1626, 1657 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 2.26 (s, 3H, $ArCH_3$), 3.33 (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), 7.73 ppm (d, *J* = 16.1 Hz, 1H, olefinic); ^{13}C NMR δ(100 MHz, $CDCl_3$): 14.0, 32.5, 55.8, 62.1, 111.2, 114.0, 123.7, 127.3, 130.3, 136.8, 141.8, 157.1, 166.2 ppm.

Preparation of (η^4-1,5-cyclooctadiene)bis(pyridine)iridium(I) hexafluorophosphate.[135]



80

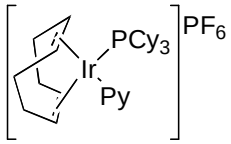
Scheme 101

An oven dried 250 ml flask, fitted with a stirrer bar, was charged with previously degassed acetone/water (75 ml:75 ml) and pyridine (8.4 ml, 104.2 mmol). To the stirred solution was added η^4-cycloocta-1,5-dieneiridium(I) chloride dimer, **79** (5.0 g, 7.4 mmol), and potassium hexafluorophosphate (4.15 g, 23.3 mmol). The resulting pale yellow solution was stirred at room temperature for 16 h during which time the solution turned to a bright yellow slurry. The slurry was concentrated under high vacuum and the yellow precipitate was filtered, washed with degassed water, and dried in a vacuum oven (40^{o}C, 0 mbar) overnight yielding the desired product **80** (8.36 g, 93% yield) as yellow powder.

Melting point: decomposed at > 190^{o}C.

IR (CH_2Cl_2): 838, 1448, 1606, 2983 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.81-1.87 (m, 4H, COD CH), 2.48-2.51 (m, 4H, COD CH), 3.85 (d, *J* = 2.4 Hz, 4H, olefinic CH), 7.49 (t, *J* = 7.2 Hz, 4H, ArH), 7.75 (t, *J* = 7.7 Hz, 2H, ArH), 8.72 ppm (d, *J* = 5.0 Hz, 4H, ArH); ^{31}P NMR δ(162 MHz, $CDCl_3$): -144.2 ppm (PF_6).

Preparation of Crabtree's Catalyst.[135]



81

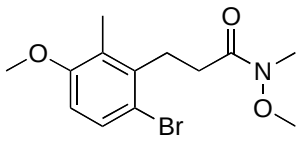
Scheme 102

An oven dried 250 ml flask, fitted with a stirrer bar, was charged with previously degassed methanol (175 ml) and (η^4-1,5-cyclooctadiene)*bis*(pyridine)iridium(I) hexafluorophosphate, **80** (7.40 g, 12.2 mmol). To the stirred solution was added tricyclohexylphosphine (4.13 g, 14.7 mmol), which resulted in an immediate colour change from yellow to bright orange. The orange slurry was stirred for 1 h at room temperature after which the solvent was reduced to ~30 ml *in vacuo*. The resulting mixture was diluted with diethyl ether and the precipitate filtered, washed with diethyl ether, and dried in a vacuum oven (40^{o}C, 0 mbar) for 16 h yielding the desired product **81** (9.51 g, 97% yield) as an orange powder.

Melting point: decomposed > 165^{o}C.

IR (CH_2Cl_2): 840, 1447, 2932 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.01-1.92 (m, 37H, Cy CH and COD CH), 2.31-2.39 (m, 4H, COD CH), 4.02 (d, *J* = 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 ppm (d, *J* = 5.1 Hz, 2H, ArH); ^{31}P NMR δ(162 MHz, $CDCl_3$): 10.2 (PCy_3), -144.2 ppm (PF_6).

Preparation of 3-(6-bromo-3-methoxy-2-methylphenyl)-N-methoxy-N-methylpropanamide.[129]



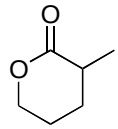
78

Scheme 103

A 250 ml round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with Crabtree's catalyst **81** (1.23 g, 1.53 mmol), dry DCM (50 ml) and **77** (4.79 g, 15.3 mmol) before being cooled to -78°C. The vessel was then evacuated and back filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. Upon the final refill, the mixture was allowed to warm to room temperature and stirred for 16 h. Removal of the reaction solvent *in vacuo* yielded a crude orange oil. Purification by column chromatography (eluent: 0-50% diethyl ether in petrol) provided **78** (4.69 g, 97% yield) as a pale yellow oil.

IR (CH_2Cl_2): 1569, 1653 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 2.26 (s, 3H, $ArCH_3$), 2.62 (t, *J* = 6.5 Hz, 2H, alkyl CH_2), 3.12-3.17 (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* = 9.0 Hz, 1H, ArH), 7.36 ppm (d, *J* = 9.0 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 12.3, 28.5, 30.9, 32.2, 55.7, 61.3, 109.9, 116.0, 127.1, 130.1, 139.5, 157.1, 173.8 ppm.

Preparation of tetrahydro-3-methylpyran-2-one.[136]



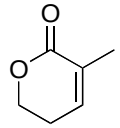
86

Scheme 105

A 3-neck round bottom flask, containing lithium chloride (8.48 g, 200 mmol), was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF (250 ml) and di-*iso*-propylamine (16.8 ml, 120 mmol) before cooling to 0^{o}C. To the solution was added ^{n}BuLi (44 ml, 2.5 M in hexanes, 110 mmol) slowly and the resulting mixture was stirred for 10 min before the addition of DMPU (6.03 mmol, 50 mmol). Following this, the reaction mixture was cooled to -78^{o}C and lactone **87** (9.28 ml, 100 mmol) was added. After 30 min, methyl iodide (8.09 ml, 130 mmol) was added dropwise and the reaction mixture stirred for a further 30 min before being warmed to room temperature and stirred for 16 h. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The ether extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to yield the desired product **86** (6.60 g, 58%) as a colourless liquid.

IR (CH_2Cl_2): 1727 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.26 (d, *J* = 7.0 Hz, 3H, CH_3), 1.51-1.59 (m, 1H, ring CH), 1.87-1.94 (m, 2H, ring CH_2), 2.06-2.14 (m, 1H, ring CH), 2.56-2.61 (m, 1H, CH_3CH), 4.30-4.34 ppm (m, 2H, OCH_2); ^{13}C NMR δ(100 MHz, $CDCl_3$): 16.7, 22.0, 27.1, 34.7, 68.6, 174.5 ppm.

Attempted preparations of 5,6-dihydro-3-methylpyran-2-one.[172]



85

Scheme 106

A 3-neck round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF (5 ml) and di-*iso*-propylamine (0.18ml, 1.41 mmol) before cooling to 0^{o}C. To the solution was added ^{n}BuLi (0.63 ml, 1.88 M in hexanes, 1.24 mmol) slowly and the resulting mixture was stirred for 10 min. Following this, the reaction mixture was cooled to -78^{o}C and lactone **86** (0.134 g, 1.17 mmol) was added. After 30 min PhSSPh (0.452 g, 1.98 mmol) was added and the reaction stirred for a further 30 min before being warmed to room temperature and stirred for 16 h. After this time, only starting material was observed by tlc analysis. The reaction was abandoned and the starting material (0.126 g, 95% yield) recovered *via* column chromatography (eluent: 0-20% diethyl ether in petrol).

Scheme 107

A 3-neck round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF (5 ml) and di-*iso*-propylamine (0.18 ml, 1.41 mmol) before cooling to 0^{o}C. To the solution was added ^{n}BuLi (0.63 ml, 1.88 M in hexanes, 1.24 mmol) slowly and the resulting mixture was stirred for 10 min. Following this, the reaction mixture was cooled to -78^{o}C and lactone **86** (0.134 g, 1.17 mmol) was added. After 30 min PhSeSePh (0.618 g, 1.98 mmol) was added and the reaction stirred for a further 30 min before being warmed to room temperature and stirred for 16 h. After this time, only starting material was observed by tlc analysis. The reaction was abandoned and the starting material recovered (0.123 g, 92% yield) recovered *via* column chromatography (eluent: 0-20% diethyl ether in petrol).

Preparation of N,N-dichloro-2-methylpropan-2-amine.[138]

$^{t}BuNCl_2$

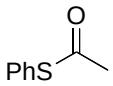
89

Scheme 108

A 1 L 3-neck flask was charged with DCM (400 ml) and cooled to 0°C. Calcium hypochlorite (175.15 g, 1.23 mol, tech. grade, 65% available Cl) was added followed by ^{t}butylamine (25.6 g, 350 mmol) as a solution in DCM (100 ml). 3 N HCl (900 ml) was added over a 1 h period and the resulting pale yellow solution was stirred for a further 3 h at 0°C. The organic layer was separated and the aqueous extracted with DCM (x 2). The organic extracts were dried over sodium sulfate, filtered, and concentrated (175 mmbar) to yield the desired product (49.72 g, 100%) as a pale yellow oil.

IR (CH_2Cl_2): 1390, 1480, 2990 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.39 ppm (s, 9H, N^{t}Bu); ^{13}C NMR δ(100 MHz, $CDCl_3$): 25.9, 72.6 ppm.

Preparation of S-phenyl ethanethioate.[173]



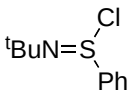
90

Scheme 108

To a stirred solution of triethylamine (51.2 ml, 367.5 mmol) in DCM (450 ml) was added thiophenol (35.9 ml. 350 mmol). The resulting solution was cooled to 0^{o}C and acetyl chloride (26.1 ml, 367.5 mmol) was added dropwise *via* syringe. A white precipitate formed immediately and stirring was continued for a further 4 hours at room temperature. After this time, the white precipitate was filtered and washed with DCM (x 3). The filtrate was collected, washed with saturated sodium bicarbonate solution, dried over sodium sulfate, filtered, and concentrated to give an orange liquid. The crude liquid was purified by distillation (10 mbar, 100^{o}C) to furnish the desired product (26.63 g, 50% yield) as a colourless liquid.

IR (CH_2Cl_2): 1720, 3060 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 2.43 (s, 3H, CH_3), 7.42 ppm (s, 5H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 30.2, 127.9, 129.2, 129.5, 134.5, 194.1 ppm.

Preparation of N-tert-butylbenzenesulfinimidoyl chloride.[138]



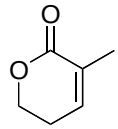
88

Scheme 109

N,*N*-Dichloro-2-methylpropan-2-amine **89** (13.0 g, 91.5 mmol) was dissolved in freshly distilled benzene (100 ml) in a pre-weighed 250 ml single necked round-bottom flask with a water condenser attached. *S*-Phenylthioacetate **90** (10.7 g, 70.4 mmol) was then added at room temperature, before the solution was refluxed for 1 h. Upon cooling, 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 and then under reduced pressure (~15 mmHg). The material was then subjected to high vacuum (<0.1 mmHg) at room temperature for 1 hour. An orange semi-solid was obtained which, upon standing, solidified to give the title compound **88** (14.9 g, 100% yield) as an oily orange solid. The product was kept under nitrogen and used without further purification.

IR (CH_2Cl_2): 1390, 1480, 2990 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.59 (s, 9H, N^{t}Bu), 7.50-7.63 (m, 3H, ArH), 8.13-8.15 ppm (m, 2H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 29.8, 64.4, 126.2, 129.3, 133.4, 142.9 ppm.

Preparation of 5,6-dihydro-3-methylpyran-2-one.[172]



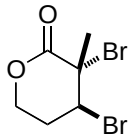
85

Scheme 110

A 3-neck round bottom flask, containing lithium chloride (5.68 g, 134 mmol), was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF (350 ml) and di-*iso*-propylamine (11.3 ml, 80.4 mmol) before cooling to 0^{o}C. To the solution was added ^{n}BuLi (73.7 ml, 2.2 M in hexanes, 33.5 mmol) slowly and the resulting mixture was stirred for 10 min before the addition of DMPU (4.04 ml, 33.5 mmol). Following this, the reaction mixture was cooled to -78^{o}C and lactone **86** (7.67 g, 66.0 mmol) was added. After 30 min *N*-^{t}butylbenzenesulfinimidoylchloride **88** (18.6 g, 87.1 mmol) was added dropwise and the reaction warmed to room temperature. The reaction mixture was strirred for 30 min before being quenched with saturated ammonium chloride solution and extracted with diethyl ether. The ether extracts were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-20% diethyl ether in petrol) to yield the desired product **85** (4.39 g) as a colourless liquid. This purification method delivered the desired product in an impure form, with sulfur residues remaining. Therefore, the yield of this reaction was estimated at 59%.

IR (CH_2Cl_2): 1719 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.93 (s, 3H, CH_3), 2.39-2.43 (m, 2H, ring CH_2), 4.38 (t, J = 6.3 Hz, 2H, OCH_2), 6.61-6.64 ppm (m, 1H, olefinic CH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 17.2, 24.3, 66.7, 128.8, 139.5, 165.5 ppm.

Preparation of trans-3,4-dibromotetrahydro-3-methylpyran-2-one.[174]



84

General Procedure

An oven-dried flask, containing a stirrer bar, was charged with dry DCM and lactone **85**. To the resulting solution was added bromine and the mixture stirred for 3 h. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (eluent: 0-10% ether in petrol) to yield the desired product **84** as a colourless liquid.

Following the ***General Procedure***, data are reported as (a) volume of DCM, (b) amount of lactone **85**, (c) amount of bromine, and (d) product yield.

Scheme 111, Table 7, Entry 1

(a) 10 ml, (b) 0.20 g, 1.8 mmol, (c) 0.1 ml, 1.8 mmol, and (d) 0.055 g, 11%.

Scheme 111, Table 7, Entry 2

(a) 5 ml, (b) 0.075 g, 0.7 mmol, (c) 0.05 ml, 1.0 mmol, and (d) 0.045 g, 22%.

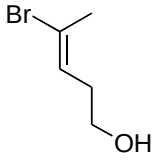
*The following entry used purified **85** (distilled at 140-142^{o}C, 15 mbar).*

Scheme 111, Table 7, Entry 3

(a) 10 ml, (b) 0.315 g, 2.81 mmol, (c) 0.29 ml, 5.62 mmol, and (d) 0.395 g, 52%.

IR (CH_2Cl_2): 1740 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 2.12-2.19 (m, 4H, CH_3 and ring CH_2), 3.26-3.34 (m, 1H, ring CH_2), 4.61-4.64 (m, 1H, OCH_2), 4.75-4.77 (m, 1H, CHBr), 4.88-4.94 ppm (td, ^{2}J =11.8 Hz, J = 4.9 Hz, 1H, OCH_2); ^{13}C NMR δ(100 MHz, $CDCl_3$): 29.6, 29.9, 54.6, 55.5, 67.3, 166.9 ppm.

Preparation of (E)-4-bromopent-3-en-1-ol.[174]



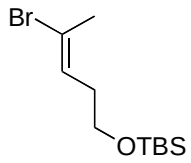
83

Scheme 112

To a stirred solution of lactone **84** (1.31 g, 4.82 mmol) in DMF/water (16 ml:4 ml) was added lithium hydroxide monohydrate (1.00 g, 24.1 mmol) and the resulting mixture stirred for 16 h at room temperature. After this time, the reaction mixture was diluted with brine and extracted five times with DCM (x 5). The organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Following this, column chromatography of the resulting residue (eluent: 0-30% diethyl ether in petrol) yielded the desired product **83** as a colourless liquid (0.36 g, 45% yield).

IR (CH_2Cl_2): 1629, 3426 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.43 (s, 1H, OH), 2.26-2.33 (m, 5H, CH_3 and CH_2), 3.67 (t, J = 6.5 Hz, 2H, OCH_2), 5.87-5.90 ppm (t, J = 7.7 Hz, 1H, olefinic CH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 23.9, 33.6, 62.1, 122.4, 128.7 ppm.

Preparation of (E)-2-bromo-5-(tert-butyldimethylsiloxyl)pent-2-ene.[129]



82

General Procedure

A 3-neck round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry DCM, **83**, and 2,6-lutidine. *Tert*-butyldimethylsilyltriflate was added slowly and the resulting solution was stirred at room temperature for 1 h. After this time, the reaction mixture was quenched with saturated sodium bicarbonate solution, the organic layer separated, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petrol) to yield the desired product **82** as a colourless liquid.

Following the ***General Procedure***, data are reported as (a) volume of DCM, (b) amount of alcohol **83**, (c) amount of 2,6-lutidine, (d) amount of TBSOTf, and (e) product yield.

Scheme 113, Table 8, Entry 1

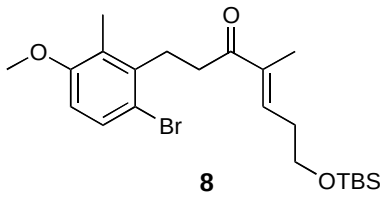
(a) 10 ml, (b) 0.242 g, 1.47 mmol, (c) 0.17 ml, 1.47 mmol, (d) 0.34 ml, 1.47 mmol, and (e) 0.279 g, 68%.

Scheme 113, Table 8, Entry 2

(a) 15 ml, (b) 0.992 g, 6.01 mmol, (c) 1.54 ml, 13.2 mmol, (d) 1.52 ml, 6.61 mmol, and (e) 1.56 g, 93%.

IR (CH_2Cl_2): 1653 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): -0.06 (s, 6H, $SiCH_3$), 0.90 (s, 9H, Si^tBu), 2.24-2.25 (m, 5H, CH_3 and CH_2), 3.63 (t, J = 6.7 Hz, 2H, OCH_2), 5.87 ppm (t, J = 6.7 Hz, 1H, olefinic CH); ^{13}C NMR δ(100 MHz, $CDCl_3$): -5.1, 18.5, 23.6, 26.1, 33.1, 62.2, 121.1, 129.0 ppm.

Preparation of (E)-1-(6-bromo-3-methoxy-2-methylphenyl)-7-(tert-butyldimethylsiloxy)-4-methylhept-4-en-3-one.[129]



8

Scheme 114

A 250 ml 3-neck round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with vinyl bromide **82** (0.640 g, 2.29 mmol) and dry diethyl ether (10 ml) before being cooled to -78°C. The solution was then treated with ^{t}BuLi (3.3 ml, 1.4 M in pentane, 4.58 mmol) and allowed to stir at this temperature for 1 h.

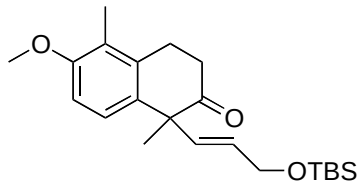
Simultaneously, a 100 ml 3-neck round bottom flask fitted with a condenser was charged with magnesium turnings (0.89 g, 36.8 mmol) and flame dried under vacuum. Following cooling under a blanket of nitrogen, the vessel was charged with dry diethyl ether (26 ml) and dry benzene (9 ml). To the stirred slurry was added dibromoethane (3.1 ml, 35 mmol) *via* syringe at such a rate as to ensure the mixture refluxed gently without external heating. Upon complete addition, the reaction vessel was warmed to a gentle reflux (50°C) and held at this temperature for 1 h. Stirring was then discontinued and the solution allowed to settle and cooled to r.t., providing an approximately 1 M solution of anhydrous $MgBr_2(OEt_2)$.

To the previously prepared vinyllithium species at -78^{o}C, was added the freshly generated anhydrous $MgBr_2(OEt_2)$ solution (2.4 ml, 1 M in Et_2O/benzene, 2.4 mmol). The mixture was stirred at this temperature for 10 min prior to warming to 0ºC. The colourless solution was stirred at this temperature for 30 min prior to the addition of Weinreb amide **78** (0.542 g, 1.72 mmol) as a solution in dry diethyl ether (10 ml). Stirring was continued at 0ºC for 30 min prior to warming to r.t. for a further 30 min. The reaction was quenched by addition of saturated ammonium chloride solution. The organics were washed with water, dried with sodium sulfate,

filtered, and concentrated to a crude yellow oil, which was purified by column chromatography (eluent: 0-3% diethyl ether in petrol) to provide **8** (0.570 g, 73% yield) as a colourless oil.

IR (CH_2Cl_2): 1573, 1666 cm^{-1}; ^1H NMR δ(500 MHz, $CDCl_3$): 0.20 (s, 6H, $SiCH_3$), 0.90 (s, 9H, Si^tBu), 1.83 (s, 3H, vinylic CH_3), 2.22 (s, 3H, $ArCH_3$), 2.45-2.49 (m, 2H, allylic CH_2), 2.83-2.87 (m, 2H, alkyl CH_2), 3.08-3.11 (m, 2H, alkyl CH_2), 3.70-3.73 (t, *J* = 6.5 Hz, 2H, OCH_2), 3.81 (s, 3H, OCH_3), 6.61 (d, *J* = 9.0 Hz, 1H, ArH), 6.67-6.71 (m, 1H, olefinic CH), 7.37 ppm (d, *J* = 9.0 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): -5.1, 11.6, 12.4, 18.3, 25.9, 28.6, 32.8, 36.1, 55.7, 61.7, 109.8, 115.9, 126.9, 130.1, 138.3, 139.4, 139.8, 157.1, 200.7 ppm.

Preparation of 1-(3-((E)-tert-butyldimethylsilyloxy)prop-1-enyl)-3,4-dihydro-6-methoxy-1,5-dimethyl)naphthalen-2(1H)-one.[129]



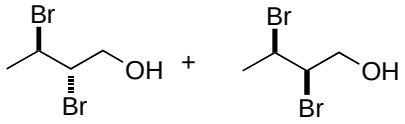
7

Scheme 115

To a microwave vial was added **8** (0.190 g, 0.42 mmol) as a solution in MeCN (0.42 ml). Palladium acetate (0.0047 g, 0.021 mmol), tri-*o*-tolylphosphine (0.025 g, 0.084 mmol), and triethylamine (0.06 ml, 0.42 mmol) were subsequently added and the resulting mixture was pre-stirred for 60 seconds prior to being heated under microwave irradiation (with cooling) for 20 minutes, at 100^{o}C. Following this, the solvent was removed *in vacuo* and the resulting residue filtered through a pad of celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo* and the residue purified *via* careful column chromatography (eluent: 0-8% diethyl ether in petrol) to provide the desired product **7** (0.118 g, 75% yield) as a pale yellow oil.

IR (CH_2Cl_2): 1586, 1666, 1713 cm^{-1}; ^{1}H NMR δ(500 MHz, $CDCl_3$): 0.03 (s, 6H, $SiCH_3$), 0.88 (s, 9H, Si^{t}Bu), 1.54 (s, 3H, alkyl CH_3), 2.20 (s, 3H, $ArCH_3$), 2.47-2.53 (m, 1H, ring CH), 2.76-2.82 (m, 1H, ring CH), 3.00-3.04 (m, 2H, ring CH_2), 3.84 (s, 3H, $ArOCH_3$), 4.12-4.14 (m, 2H, OCH_2), 5.35 (dt, J = 15.4 Hz and 5.0 Hz, 1H, olefinic CH), 5.68 (dt, J = 15.5 Hz, ^{4}J = 1.7 Hz, 1H, olefinic CH), 6.80 (d, J = 8.7 Hz, 1H, ArH), 7.08 ppm (d, J = 8.6 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): -5.1, 11.7, 18.5, 23.7, 25.4, 26.1, 37.1, 54.5, 55.7, 63.7, 109.3, 123.9, 125.9, 130.8, 133.3, 134.4, 136.3, 156.5, 211.5 ppm.

Preparation of 2,3-dibromobutan-1-ol.[140]



98a **98b**

Scheme 120

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry DCM (250 ml) and crotyl alcohol (4.27 ml, 50 mmol; *trans*:*cis* 96:4), before being cooled to -78^{o}C. Following this, bromine (2.6 ml, 50 mmol) was added in a dropwise fashion and stirred for 30 minutes at this temperature. After this time, the solution was allowed to warm to room temperature and stirred for a further 2 h. The solvent was removed *in vacuo* and the resulting red oil was purified *via* distillation (102-104^{o}C, 13 Torr) to give a mixture of diastereomers **98a** and **98b** (9.55 g, 82% yield; ratio 96:4) as a pale brown liquid.

*Data for major diastereomer **98a***:

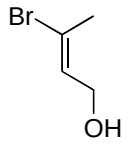
IR (CH_2Cl_2): 1448, 1593, 3379 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.91 (d, *J* = 6.8 Hz, 3H, CH_3), 2.06 (s, 1H, OH), 4.08-4.10 (m, 2H, OCH_2), 4.23-4.27 (m, 1H, CHBr), 4.35-4.42 ppm (m, 1H, CHBr); ^{13}C NMR δ(100 MHz, $CDCl_3$): 25.6, 47.6, 62.4, 66.1 ppm.

*Data for minor diastereomer **98b***:

Diagnostic peaks in ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.82 ppm (d, *J* = 6.8 Hz, CH_3).

Diagnostic peaks in ^{13}C NMR δ(100 MHz, $CDCl_3$): 23.3, 48.9, 60.8, 65.1 ppm.

Preparation of (E)-3-bromobut-2-en-1-ol.[140]



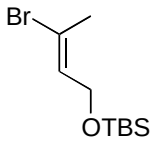
93

Scheme 121

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF (150 ml) and di-*iso*-propylamine (24.8 ml, 177.3 mmol) and the resulting solution cooled to 0^{o}C. To the solution was added ^{n}BuLi (67.9 ml, 2.5 M in hexanes, 169.9 mmol) slowly and the resulting mixture was stirred for 10 min before the addition of DMPU (4.45 ml, 36.9 mmol). Following this, the reaction mixture was cooled to -78^{o}C and a mixture (96:4) of **98a** and **98b** (17.14 g, 73.9 mmol) were added. After 30 minutes the reaction mixture was allowed to warm to room temperature and stirred for a further 3 h. After this time, the reaction was quenched with water and extracted with diethyl ether (x 2). The organic extracts were collected, dried over sodium sulfate, filtered, and concentrated to give a brown liquid. Purification *via* distillation (96-98^{o}C, 34 Torr) allowed the isolation of the desired alcohol **93** (8.58 g, 77% yield) as a pale brown liquid.

IR (CH_2Cl_2): 1527, 1629, 3426 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 2.30 (t, ^{4}J = 0.5 Hz, 3H, CH_3), 4.11 (d, J = 7.1 Hz, 2H, OCH_2), 6.10-6.13 ppm (m, 1H, vinyl CH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 23.6, 59.6, 124.2, 130.8 ppm.

Preparation of (E)-(3-bromobut-2-enyloxy)(tert-butyl)dimethylsilane. [175]



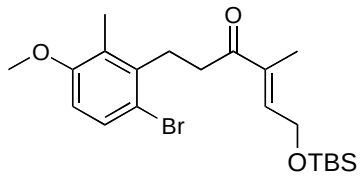
96

Scheme 122

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry DCM (200 ml), alcohol **93** (5.33 g, 35.3 mmol), and 2,6-lutidine (9.05 ml, 77.7 mmol). *Tert*-buyldimethylsilyl triflate (8.93 ml, 38.9 mmol) was added slowly and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated sodium bicarbonate solution, the organic layer separated, washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petrol) to yield the desired product **96** (9.18 g, 98% yield) as a colourless liquid.

IR (CH_2Cl_2): 1083, 1252, 1653 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 0.08 (s, 6H, $SiCH_3$), 0.91 (s, 9H, $^tBuCH_3$), 2.27 (s, 3H, CH_3), 4.14 (d, J = 5.9 Hz, 2H, OCH_2), 5.98-6.02 ppm (m, 1H, olefinic CH); ^{13}C NMR δ(100 MHz, $CDCl_3$): -5.2, 18.3, 23.7, 25.9, 60.4, 121.9, 131.7 ppm.

Preparation of (E)-1-(6-bromo-3-methoxy-2-methylphenyl)-6-(tert-butyldimethysilyloxy)-4-methylhex-4-ene-3-one.



95

Scheme 123

A 250 ml 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with vinyl bromide **96** (9.46 g, 35.7 mmol) and dry diethyl ether (150 ml) before being cooled to -78°C. The solution was treated with ^{t}BuLi (44.7 ml, 1.6 M in pentane, 71.4 mmol) and allowed to stir at this temperature for 1 h.

Simultaneously, a 100 ml 3-neck round bottom flask fitted with a condenser was charged with magnesium turnings (1.78 g, 73.6 mmol) and flame dried under vacuum. Following cooling under a blanket of nitrogen, the vessel was charged with dry diethyl ether (52 ml) and dry benzene (18 ml). To the stirred slurry was added dibromoethane (6.2 ml, 70 mmol) *via* syringe at such a rate as to ensure the mixture refluxed gently without external heating. Upon complete addition, the reaction vessel was warmed to a gentle reflux (50°C) and held at this temperature for 1 h. Stirring was then discontinued and the solution allowed to settle and cooled to r.t., providing an approximately 1 M solution of anhydrous $MgBr_2(OEt_2)$.

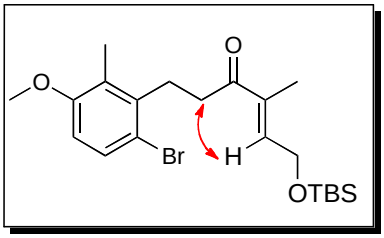
To the previously prepared vinyllithium species at -78^{o}C was added the freshly generated anhydrous $MgBr_2(OEt_2)$ solution (37.49 ml, 1 M in Et_2O/benzene, 37.49 mmol). The mixture was stirred at this temperature for 10 min prior to warming to 0^{o}C. The colourless solution was stirred at this temperature for 30 min prior to the addition of **78** (7.9 g, 25.0 mmol) as a solution in dry diethyl ether (20 ml). Stirring was continued at 0^{o}C for 30 min prior to warming to r.t. for a further 30 min. The reaction was quenched by addition of saturated ammonium chloride solution. The organics were washed with water, dried with sodium sulfate, filtered, and concentrated to a crude yellow oil, which was purified by column chromatography (eluent 0-3%

diethyl ether in petrol) to provide **95** (9.48 g, 86% yield) as a colourless oil.

IR (CH_2Cl_2): 1573, 1670 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 0.09 (s, 6H, $SiCH_3$), 0.92 (s, 9H, Si^tBu), 1.78 (s, 3H, vinylic CH_3), 2.23 (s, 3H, $ArCH_3$), 2.85-2.90 (m, 2H, alkyl CH_2), 3.08-3.13 (m, 2H, alkyl CH_2), 3.81 (s, 3H, $ArOCH_3$), 4.41 (d, *J* = 5.2 Hz, 2H, OCH_2), 6.62 (d, *J* = 8.8 Hz, 1H, ArH), 6.67-6.70 (m, 1H, olefinic CH), 7.36 (d, *J* = 8.8 Hz , 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): -5.3, 11.5, 12.4, 18.3, 25.9, 28.6, 35.9, 55.7, 60.9, 109.8, 115.9, 126.9, 130.1, 135.5, 139.7, 142.5, 157.1, 200.3 ppm; HRMS *m/z* (ESI) Calc. for $C_{21}H_{37}BrNO_3Si$ (M^++NH_4): 458.1721. Found: 458.1722; Elemental analysis calc. for $C_{21}H_{33}BrO_3Si$ required C, 57.13%; H, 7.53%; O, 18.10%. Found: C, 57.18%; H, 7.82%; O, 17.71%.

See appendix for relevant NOSEY spectrum (pg. 265).

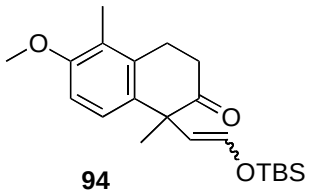
A correlation is evident between the methylene CH_2 α to the carbonyl group, and the olefinic proton; this confirms the *E*-configuration.



See appendix (pg. 266) for expansion in the aliphatic region of the proton NMR spectrum.

Second order spectra are observed with vicinal coupling constants (J_{ax} = 11.8 Hz, $J_{ax'}$ = 4.2 Hz) indicating a 70% preference for the *anti*-conformer as measured by the Gandour method.[179]

Preparation of 1-(2-(tert-butyldimethylsiloxy)ethenyl)-3,4-dihydro-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one.



94

General Procedure A:

To a microwave vial was added **95**, palladium acetate, (*o*-tolyl)$_3$P, solvent, and base. The resulting mixture was pre-stirred for 60 seconds prior to being heated under microwave irradiation (with cooling) for the allotted time, at the stated temperature. Following this, the solvent was removed *in vacuo* and the resulting residue filtered through a pad of celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo* and the residue purified *via* careful chromatography (eluent: 0-6% diethyl ether in petrol) providing the desired product, as a mixture of *E*/*Z* isomers.

General Procedure B:

To a microwave vial was added palladium acetate, (*o*-tolyl)$_3$P, and solvent. The resulting mixture was stirred for 5 minutes at room temperature prior to the addition of **95** and, finally, base. This mixture was heated under microwave irradiation for the allotted time, at the stated temperature. Following this, the solvent was removed *in vacuo* and the resulting residue filtered through a pad of celite (eluent: ethyl acetate). The resulting solution was concentrated *in vacuo* and the residue purified *via* careful chromatography (eluent: 0-6% diethyl ether in petrol) providing the desired product, as a mixture of *E*/*Z* isomers.

Following ***General Procedure A*** *or* ***B***, data are presented as (a) amount of substrate, **95**, (b) amount of Pd(OAc)$_2$, (c) amount of (*o*-tolyl)$_3$P, (d) volume of solvent, (e) amount of Et$_3$N, (f) reaction time, (g) temperature, and (h) product yield.

Scheme 124

Following ***General Procedure A:***

(a) 6.71 g, 15.19 mmol, (b) 0.340 g, 1.52 mmol, (c) 1.85 g, 6.08 mmol, (d) MeCN, 15.2 ml, (e) 4.23 ml, 30.4 mmol, (f) 20 min, (g) 100^{o}C, and (h) 3.37 g. 61% yield. The *E*/*Z* ratio was determined to be 1:0.6 by the ^{1}H NMR integration of signals at δ5.98 and δ6.13.

Scheme 125

Following ***General Procedure A:***

Table 9, Entry 1

(a) 0.116 g, 0.26 mmol, (b) 0.06 g, 0.026 mmol, (c) 0.032 g, 0.104 mmol, (d) DMF, 0.26 ml, (e) 0.07 ml, 0.52 mmol, (f) 20 min, (g) 100^{o}C, and (h) 0.048 g. 48% yield.

Table 9, Entry 2

(a) 0.104 g, 0.236 mmol, (b) 0.005 g, 0.0236 mmol, (c) 0.029 g, 0.094 mmol, (d) DMA, 0.24 ml, (e) 0.07 ml, 0.47 mmol, (f) 20 min, (g) 100^{o}C, and (h) trace.

Table 9, Entry 3

(a) 0.04 g, 0.091 mmol, (b) 0.002 g, 0.009 mmol, (c) 0.011 g, 0.036 mmol, (d) THF, 0.09 ml, (e) 0.025 ml, 0.18 mmol, (f) 20 min, (g) 100^{o}C, and (h) trace.

Scheme 126

Following ***General Procedure A:***

Table 10, Entry 1

(a) 0.717 g, 1.62 mmol, (b) 0.036 g, 0.162 mmol, (c) 0.198 g, 0.650 mmol, (d) MeCN, 1.62 ml, (e) 0.45 ml, 3.24 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.467 g, 80% yield.

Table 10, Entry 2

(a) 0.099 g, 0.224 mmol, (b) 0.005 g, 0.0224 mmol, (c) 0.027 g, 0.090 mmol, (d) MeCN, 0.224 ml, (e) 0.06 ml, 0.45 mmol, (f) 2 h, (g) 60^{o}C, and (h) trace.

Scheme 127

Following ***General Procedure A:***

Table 11, Entry 1

(a) 0.717 g, 1.62 mmol, (b) 0.036 g, 0.162 mmol, (c) 0.197 g, 0.648 mmol, (d) MeCN, 1.62 ml, (e) 0.45 ml, 3.24 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.467 g, 80% yield.

Table 11, Entry 2

(a) 1.01 g, 2.26 mmol, (b) 0.038 g, 0.226 mmol, (c) 0.275 g, 0.904 mmol, (d) MeCN, 2.26 ml, (e) 0.63 ml, 4.52 mmol, (f) 20 min, (g) 100^{o}C, and (h) 0.599 g, 74% yield.

Table 11, Entry 3

(a) 1.03 g, 2.32 mmol, (b) 0.052 g, 0.232 mmol, (c) 0.282 g, 0.928 mmol, (d) MeCN, 2.32 ml, (e) 0.65 ml, 4.64 mmol, (f) 20 min, (g) 100^{o}C, and (h) 0.45 g, 54% yield.

Table 11, Entry 4

(a) 3.67 g, 8.31 mmol, (b) 0.186 g, 0.831 mmol, (c) 1.01 g, 3.32 mmol, (d) MeCN, 8.31 ml, (e) 2.3 ml, 16.6 mmol, (f) 20 min, (g) 100^{o}C, and (h) 1.88 g, 63% yield.

Scheme 128

Following ***General Procedure B:***

Table 12, Entry 1

(a) 0.087 g, 0.197 mmol, (b) 0.004 g, 0.0197 mmol, (c) 0.024 g, 0.079 mmol, (d) MeCN, 0.2 ml, (e) 0.05 ml, 0.394 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.059 g, 83% yield.

Table 12, Entry 2

(a) 5.10 g, 11.71 mmol, (b) 0.263 g, 1.171 mmol, (c) 1.42 g, 4.680 mmol, (d) MeCN, 11.71 ml, (e) 3.26 ml, 23.42 mmol, (f) 60 min, (g) 80^{o}C, and (h) 2.07 g, 49% yield.

Table 12, Entry 3

(a) 0.20 g. 0.453 mmol, (b) 0.010 g, 0.045 mmol, (c) 0.055 g, 0.181 mmol, (d) MeCN, 0.45 ml,

(e) 0.13 ml, 0.906 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.134 g, 82% yield.

Table 13

Following ***General Procedure B:***

Entry 1 *(column chromatography performed at a fast rate)*

(a) 0.1 g, 0.230 mmol, (b) 0.005 g, 0.023 mmol, (c) 0.027 g, 0.092 mmol, (d) MeCN, 0.1 ml, (e) 0.06 ml, 0.460 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.067 g, 83% yield.

Entry 2 *(column chromatography performed at a slow rate)*

(a) 0.1 g, 0.230 mmol, (b) 0.005 g, 0.023 mmol, (c) 0.027 g, 0.092 mmol, (d) MeCN, 0.1 ml, (e) 0.06 ml, 0.460 mmol, (f) 60 min, (g) 80^{o}C, and (h) 0.049 g, 59% yield.

Scheme 129

Following ***General Procedure B:***

Table 14, Entry 1

(a) 0.1 g, 0.230 mmol, (b) 0.003 g, 0.012 mmol, (c) 0.014 g, 0.046 mmol, (d) MeCN, 0.1 ml, (e) 0.06 ml, 0.460 mmol, (f) 30 min, (g) 100^{o}C, and (h) 0.068 g, 82% yield; the conversion of this reaction was calculated to be 90% from the ^{1}H NMR integration of signals at δ6.67-6.70, δ6.13, and δ5.98.

Table 14, Entry 2

(a) 0.1 g, 0.230 mmol, (b) 0.004 g, 0.017 mmol, (c) 0.021g, 0.069 mmol, (d) MeCN, 0.1 ml, (e) 0.06 ml, 0.460 mmol, (f) 20 min, (g) 100^{o}C, and (h) 0.071 g, 86% yield.

IR (CH_2Cl_2): 1102, 1273, 1646, 1712 cm^{-1}.

E-isomer

^{1}H NMR δ(500 MHz, $CDCl_3$): 0.08 (s, 6H, $SiCH_3$), 0.8 (s, 9H, ^{t}BuSi), 1.51 (s, 3H, CH_3), 2.20 (s, 3H, $ArCH_3$), 2.45-2.51 (m, 1H, ring CH_2), 2.81-2.87 (m, 1H, ring CH_2), 2.98-3.06 (m, 1H, ring CH_2), 3.08-3.12 (m, 1H, CH_2), 3.85 (s, 3H, $ArOCH_3$), 5.07 (d, *J* = 12.0 Hz, 1H, olefinic CH), 5.98 (d, *J* = 12.0 Hz, 1H, olefinic CH), 6.80 (d, *J* = 8.5 Hz, 1H, ArH), 7.12 ppm (d, *J* = 8.5 Hz, 1H, ArH); ^{13}C δ(125 MHz, $CDCl_3$): -5.6, 18.0, 24.7, 25.2, 25.4, 25.6, 36.8, 50.9, 55.7, 108.9,

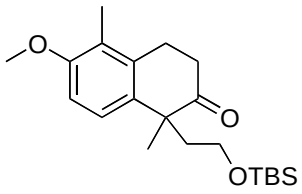
114.1, 123.2, 124.2, 135.8, 135.9, 139.0, 156.0, 213.2 ppm.

Z-isomer

^{1}H NMR δ(500 MHz, $CDCl_3$): 0.06 (s, 6H, $SiCH_3$), 0.81 (s, 9H, ^{t}Bu), 1.55 (s, 3H, CH_3), 2.19 (s, 3H, $ArCH_3$), 2.48-2.54 (m, 1H, ring CH_2), 2.82-2.89 (m, 1H, ring CH_2), 2.98-3.04 (m, 1H, ring CH_2), 3.16-3.22 (m, 1H, CH_2), 3.81 (s, 3H, $ArOCH_3$), 4.46 (d, *J* = 6.0 Hz, 1H, olefinic CH), 6.13 (d, *J* = 6.0 Hz, 1H, olefinic CH), 6.75 (d, *J* = 8.5 Hz, 1H, ArH), 7.13 ppm (d, *J* = 8.5 Hz, 1H, ArH).

HRMS *m/z* (ESI) Calc. for $C_{21}H_{33}O_3Si$ (M^++H): 361.2193. Found: 361.2191.

Preparation of 1-(2-(tert-butyldimethylsiloxy)ethyl)-3,4-dihydro-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one.



99

General Procedure:

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with enol ether, **94**, solvent, and 10% palladium on carbon catalyst before being cooled to -78°C. The vessel was then evacuated and back filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. Upon the final refill, the mixture was allowed to warm to room temperature and stirred for 16 h. Removal of the reaction solvent *in vacuo* yielded a crude oil. Direct purification *via* column chromatography (0-8% diethyl ether in petrol) provided **99** as a clear oil.

Following the ***General Procedure***, data are presented as (a) amount of **94**, (b) solvent, (c) amount of Pd/C, and (d) product yield.

Scheme 130, Table 15, Entry 1

(a) 0.396 g, 1.10 mmol, (b) MeOH, 15 ml, (c) 0.08 g, and (d) 0.210 g, 53% yield.

Scheme 130, Table 15, Entry 2

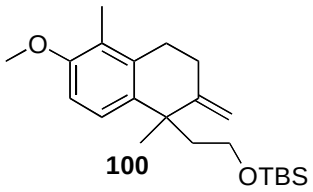
(a) 1.13 g, 3.14 mmol, (b) EtOAc, 30 ml, (c) 0.08 g, and (d) 1.14 g, 99% yield.

Scheme 131

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with Crabtree's catalyst, **81** (0.096 g, 0.119 mmol), dry DCM (40 ml) and enol ether **94** (0.429 g, 1.19 mmol) before being cooled to -78°C. The vessel was then evacuated and back filled (x 3) with hydrogen gas *via* a three way tap attached to a vacuum manifold and a hydrogen balloon. Upon the final refill, the mixture was allowed to warm to room temperature and stirred for 16 h. Removal of the reaction solvent *in vacuo* yielded a crude oil. Direct purification *via* column chromatography (eluent: 0-8% diethyl ether in petrol) provided **99** (0.417 g, 97% yield) as a clear oil.

IR (CH_2Cl_2): 1586, 1715 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): -0.04 (d, *J* = 2.2 Hz 6H, $SiCH_3$), 0.82 (s, 9H, ^{t}BuSi), 1.42 (s, 3H, alkyl CH_3), 1.87-1.93 (m, 1H, alkyl CH), 2.20 (s, 3H, $ArCH_3$), 2.34-2.41 (m, 1H, alkyl CH), 2.59-2.73 (m, 2H, ring CH_2), 3.00-3.03 (t, *J* = 7.5 Hz, 2H, ring CH_2), 3.25-3.36 (m, 2H, OCH_2), 3.84 (s, 3H, $ArOCH_3$), 6.81 (d, *J* = 8.7 Hz, 1H, ArH), 7.11 ppm (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): -5.5, 11.5, 18.3, 25.3, 25.9, 27.9, 37.6, 43.8, 49.1, 55.6, 59.9, 109.1, 123.4, 124.5, 134.1, 135.8, 155.7, 214.2 ppm; HRMS *m/z* (ESI) Calc. for $C_{21}H_{35}O_3Si$ (M^++H): 363.2350. Found: 363.2352.

Preparation of tert-butyl-(2-(-1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)ethoxy)dimethylsilane.



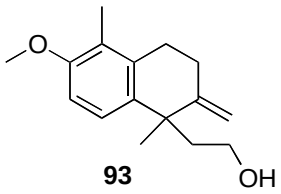
100

Scheme 132

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with methyltriphenylphosphonium bromide (1.50 g, 4.20 mmol), ketone **99** (0.244 g, 0.680 mmol), and dry THF (5 ml). To this solution was added potassium *tert*-butoxide solution in THF (5 ml, 0.82 M, 4.08 mmol) slowly *via* syringe and the resulting bright yellow solution was stirred for 16 h. After this time the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with diethyl ether. The organics were washed with brine, pooled, dried over sodium sulfate, filtered, and concentrated. The crude oil was purified by column chromatography (eluent: 0-5% diethyl ether in petrol) to yield the product **100** (0.240 g, 98% yield) as a colourless oil.

IR (CH_2Cl_2): 1653 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): -0.02 (s, 6H, $SiCH_3$), 0.85 (s, 9H, Si^tBu), 1.44 (s, 3H, alkyl CH_3), 2.07-2.12 (m, 5H, alkyl CH_2 and $ArCH_3$), 2.46-2.50 (t, J = 6.6 Hz, 2H, ring CH_2), 2.70 (t, J = 6.6 Hz, 2H, ring CH_2), 3.17-3.22 (m, 1H, OCH), 3.52-3.62 (m, 1H, OCH), 3.82 (s, 3H, $ArOCH_3$), 4.95 (d, ^2J =1.1 Hz, 1H, olefinic CH), 5.17 (d, ^2J = 1.1 Hz, 1H, olefinic CH), 6.78 (d, J = 8.8 Hz, 1H, ArCH), 7.21 ppm (d, J = 8.7 Hz, 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): -5.2, 11.4, 18.2, 25.9, 29.1, 30.4, 31.7, 41.6, 46.0, 55.6, 60.2, 107.5, 108.8, 123.3, 124.5, 136.7, 136.8, 152.5, 155.0 ppm; HRMS *m/z* (ESI) Calc. for $C_{22}H_{37}O_2Si$ (M^++H): 361.2557. Found: 362.2556.

Preparation of 2-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenapthalen-1-yl)ethanol.



93

General Procedure:

To a flame dried flask was added a solution of **100** in THF and the mixture was taken to the appropriate temperature. To this solution TBAF (1M in THF) was added and the resulting mixture stirred for 2 h. After this time, the reaction was quenched with saturated sodium bicarbonate solution and extracted with diethyl ether. The organics were washed with brine, pooled, dried over sodium sulfate, filtered, and concentrated to give a pale yellow oil. The crude oil was purified by column chromatography (eluent: 0-100% diethyl ether in petrol) to yield the desired product as colourless oil.

Following the ***General Procedure***, data are presented as (a) amount of **100**, (b) volume of THF, (c) temperature, (d) volume of TBAF, and (e) product yield.

Scheme 133, Table 16, Entry 1

(a) 0.82 mmol, 0.295 g, (b) 10 ml, (c) r.t., (d) 1.65 mmol, 1.65 ml, and (e) 0.133 g, 65% yield.

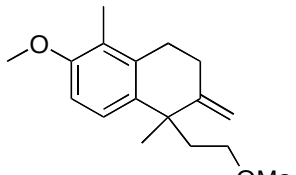
Scheme 133, Table 16, Entry 2

(a) 0.923 g, 2.56 mmol, (b) 15 ml, (c) 0^{o}C, (d) 3.85 ml, 8.85 mmol, and (e) 0.616 g, 98% yield.

IR (CH_2Cl_2): 1643, 3568 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.40 (s, 1H, OH), 1.47 (s, 3H, alkyl CH_3), 2.13-2.19 (m, 5H, $ArCH_3$ and alkyl CH_2), 2.51-2.54 (m, 2H, ring CH_2), 2.73-2.75 (m, 2H, ring CH_2), 3.34-3.38 (m, 1H, OCH), 3.55-3.59 (m, 1H, OCH), 3.82 (s, 3H, $ArOCH_3$), 4.95 (s, 1H, olefinic CH), 5.00 (s, 1H, olefinic CH), 6.79 (d, *J* = 8.8 Hz, 1H, ArH), 7.20 (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 11.4, 29.1, 30.6, 31.8, 41.8, 45.8, 55.6, 60.2, 107.7,

108.8, 123.5, 124.5, 136.3, 136.9, 153.3, 155.2 pm; HRMS *m/z* (ESI) Calc. for $C_{16}H_{26}NO_2$ (M^++NH_4): 264.1958. Found: 264.1957; Elemental analysis calc. for $C_{16}H_{22}O_2$ required C, 78.01%; H, 9.00%. Found: C, 77.96%; H, 9.06%.

Preparation of 2-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)ethyl methanesulfonate.



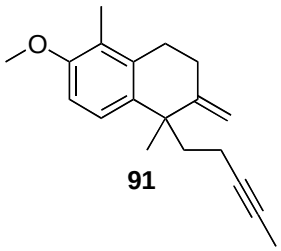
101

Scheme 134

To a solution of alcohol **93** (0.054 g, 0.22 mmol) in dry DCM (3 ml), was added triethylamine (0.04 ml, 0.308 mmol). The resulting mixture was cooled to -20^{o}C prior to the addition of mesyl chloride (0.02 ml, 0.264 mmol). After stirring for 1 h at this temperature the mixture was quenched with saturated sodium bicarbonate solution, and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification *via* column chromatography (eluent: 0-20% diethyl ether in petrol) afforded the desired product **101** (0.060 g, 84% yield) as a colourless oil.

IR (CH_2Cl_2): 1644 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.49 (s, 3H, alkyl CH_3), 2.13 (s, 3H, $ArCH_3$), 2.30-2.41 (m, 2H, ring CH_2), 2.46-2.55 (m, 2H, ring CH_2), 2.64-2.70 (m, 1H, alkyl CH), 2.76-2.82 (m, 1H, alkyl CH), 2.89 (s, 3H, SO_2CH_3), 3.75-3.80 (td, J = 5.7 Hz, ^{2}J = 9.7 Hz, 1H, OCH), 3.82 (s, 3H, $ArOCH_3$), 4.14-4.19 (td, J = 5.8 Hz, ^{2}J = 9.9 Hz, 1H, OCH), 4.96 (s, 1H, olefinic CH), 5.03 (d, J = 0.9 Hz, 1H, olefinic CH), 6.80 (d, J = 8.7 Hz, 1H, ArH), 7.20 ppm (d, J = 8.7 Hz , 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 11.4, 19.4, 29.0, 31.4, 37.2, 41.3, 41.6, 55.6, 67.7, 108.3, 109.1, 123.7, 124.4, 134.8, 137.0, 151.6, 155.4 ppm; HRMS *m/z* (ESI) Calc. for $C_{17}H_{28}NO_4S$ (M^++NH_4): 342.1734. Found: 342.1736.

Attempted preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)naphthalene.

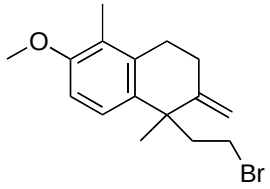


91

Scheme 135

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with mesylate **101** (0.05 g, 0.15 mmol) as a solution in THF (3 ml) and cooled to 0^{o}C. 1-Propynylmagnesium bromide (0.6 ml, 0.5 M in THF, 0.3 mmol) was added and the solution was allowed to warm to r.t. After 24 h reaction time, tlc analysis showed only starting material present, therefore, the reaction mixture was warmed to reflux and stirred for a further 24 h. After this time, the reaction was quenched with saturated ammonium chloride solution and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification *via* column chromatography (eluent: 0-100% diethyl ether in petrol) afforded three different components; starting material, **101**, alcohol **93**, and bromide **102**.

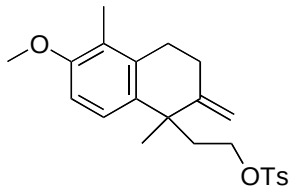
1-(2-Bromoethyl)-1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalene.



102

IR (CH_2Cl_2): 1595, 1646, 2946 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.45 (s, 3H, alkyl CH_3), 2.13 (s, 3H, $ArCH_3$), 2.40-2.50 (m, 4H, alkyl protons), 2.61-2.69 (m, 1H, alkyl proton), 2.73-2.88 (m, 2H, alkyl protons), 3.22-3.29 (m, 1H, alkyl proton), 3.82 (s, 3H, $ArOCH_3$), 4.91 (s, 1H, olefinic CH), 5.01 (s, 1H, olefinic CH), 6.79 (d, *J* = 8.7 Hz, 1H, ArH), 7.17 (d, *J* = 8.7 Hz , 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 11.6, 29.1, 29.5, 31.2, 31.9, 44.3, 46.6, 55.7, 108.1, 109.2, 123.8, 124.5, 135.1, 137.4, 151.7, 155.5 ppm; HRMS *m/z* (ESI) Calc. for $C_{16}H_{22}BrO$ (M^++H): 309.0849. Found: 309.0851.

Preparation of 2-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)ethyl 4-methylbenzenesulfonate.



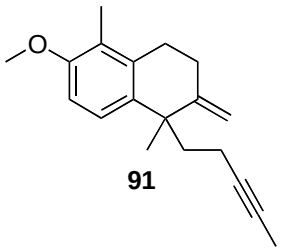
103

Scheme 136

To a solution of alcohol **93** (0.050 g, 0.203 mmol) in dry DCM (2 ml), was added triethylamine (0.11 ml, 0.810 mmol). The resulting mixture was cooled to -20^{o}C prior to the addition of tosylchloride (0.154 g, 0.810 mmol). After 16 h stirring at this temperature the mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification *via* column chromatography (eluent: 0-30% diethyl ether in petroleum ether) afforded the desired product **103** (0.076 g, 94% yield) as a colourless oil.

IR (CH_2Cl_2): 1360, 1643 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.27 (s, 3H, alkyl CH_3), 2.09 (s, 3H, $ArCH_3$), 2.16-2.29 (m, 2H, ring CH_2), 2.33-2.40 (m, 2H, ring CH_2), 2.43 (s, 3H, $ArCH_3$), 2.53-2.61 (m, 1H, chain CH), 2.67-2.65 (m, 1H, chain CH), 3.57-3.63 (m, 1H, OCH), 3.81 (s, 3H, $ArOCH_3$), 3.96-4.02 (m, 1H, OCH), 4.77 (s, 1H, olefinic CH), 4.91 (s, 1H, olefinic CH), 6.73 (d, *J* = 8.8 Hz , 1H, ArH), 7.08 (d, *J* = 8.7 Hz, 1H, ArH), 7.31 (d, *J* = 8.3 Hz, 2H, ArH), 7.68 ppm (d, *J* = 8.3 Hz, 2H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 154.3, 150.4, 143.5, 135.8, 133.9, 132.2, 128.7, 126.9, 123.3, 122.5, 107.9, 107.0, 67.0, 54.5, 40.5, 39.9, 30.4, 30.0, 27.9, 20.5, 10.3 ppm; HRMS *m/z* (ESI) Calc. for $C_{23}H_{32}NO_4S$ (M^++NH_4): 418.2047. Found: 418.2046.

Attempted preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl naphthalene.



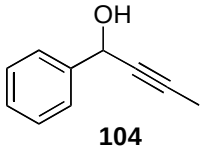
91

Scheme 136

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with tosylate **103** (0.091 g, 0.24 mmol) as a solution in THF (3 ml) and cooled to 0^{o}C. 1-Propynylmagnesium bromide (0.96 ml, 0.5 M in THF, 0.48 mmol) was added and the solution was allowed to warm to r.t. After 16 h, tlc analysis indicated only starting material present. The solution was heated to reflux and stirred for a further 16 h. After this time, tlc analysis indicated the formation of a new compound. The reaction was quenched with saturated ammonium chloride solution and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification *via* column chromatography afforded none of the desired product. Instead, bromide **102** was isolated as a colourless oil (0.081 g, 100% yield).

*See page 193 for analysis of compound **102**.*

Preparation of 1-phenylbut-2-yn-1-ol.[142]



104

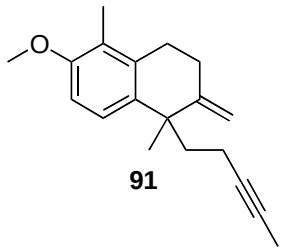
Scheme 137

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (5 ml) and cooled to -78^{o}C. Propyne gas was bubbled through the solution for 15 mins prior to the addition of ^{n}BuLi (3 ml, 2.5 M in hexanes, 12.5 mmol). After a further 10 minutes, TMEDA (1.13 ml, 7.5 mmol), and DMPU (0.9 ml, 7.5 mmol) were added.

Simultaneously, a flame dried flask was charged with THF (3 ml) and benzaldehyde (0.51 ml, 5 mmol) before being cooled to -78^{o}C. To this solution was added, *via* cannula, the previously prepared propynyl acetylide solution. The resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 10 minutes reaction time, tlc analysis showed the consumption of the starting material. The reaction mixture was quenched with a saturated solution of ammonium chloride and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated to give a pale yellow liquid. Purification *via* column chromatography (eluent: 0-20% diethyl ether in petrol) provided alcohol **104** (0.735 g, 100% yield) as a colourless liquid.

IR (CH_2Cl_2): 2231, 3432 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.92 (d, ^{5}J = 2.2 Hz, 3H, CH_3), 2.12 (s, 1H, OH), 5.44 (d, ^{5}J = 2.1 Hz, 1H, alkyl CH), 7.31-7.41 (m, 3H, ArH), 7.53-7.56 ppm (m, 2H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 3.3, 64.1, 79.1, 82.5, 126.3, 127.7, 128.1, 141.0 ppm.

Attempted preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)naphthalene.



91

Scheme 138

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (5 ml) and cooled to -78^{o}C. Propyne gas was bubbled through the solution for 15 mins prior to the addition of ^{n}BuLi (0.162 ml, 2.5 M in hexane, 0.406 mmol). After a further 10 minutes, TMEDA (0.06 ml, 0.406 mmol), and DMPU (0.059 ml, 0.406 mmol) were added.

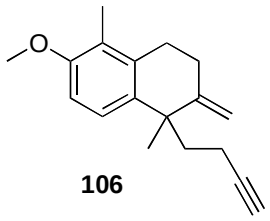
Simultaneously, a flame dried flask was charged with DCM (2 ml), **93** (0.050 g, 0.203 mmol), and pyridine (0.05 ml, 0.609 mmol) before being cooled to -78^{o}C. To this solution was added triflic anhydride (0.1 ml, 0.609 mmol). The resulting mixture was stirred for 5 minutes before being warmed to room temperature. After a further 5 minutes reaction time, tlc analysis showed the consumption of the starting material. The reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate and extracted with DCM. The organic layer washed with 1 M HCl (x 2) followed by brine before being dried over sodium sulfate, filtered and concentrated to give a pale yellow oil. The resulting oil was dissolved in dry THF (3 ml) and cooled to -78^{o}C whilst under an inert atmosphere. To this solution was added, *via* cannula, the previously prepared propynyl acetylide solution. The resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 5 minutes reaction time the solution turned a deep red colour. Tlc analysis showed no spot for either triflate intermediate **105** or starting alcohol **93**, therefore, the reaction was abandoned.

Scheme 139

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (4 ml) and cooled to -78^{o}C prior to the addition of (*Z*/*E*)-1-bromopropene (0.026 ml, 0.305 mmol) and ^{n}BuLi (0.27 ml, 2.5 M in hexanes, 0.671 mmol). After a further 10 minutes, TMEDA (0.10 ml, 0.671 mmol) and DMPU (0.08 ml, 0.671 mmol) were added and the resulting solution was stirred for 2 h.

Simultaneously, a flame dried flask was charged with DCM (2 ml), **93** (0.050 g, 0.203 mmol), and pyridine (0.05 ml, 0.609 mmol) before being cooled to -78^{o}C. To this solution was added triflic anhydride (0.1 ml, 0.609 mmol). The resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 5 minutes reaction time, tlc analysis showed the consumption of the starting material. The reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate and extracted with DCM. The organic layer washed with 1 M HCl (x 2), followed by brine, before being dried over sodium sulfate, filtered, and concentrated to give a pale yellow oil. The resulting oil was dissolved in dry THF (3 ml) and cooled to -78^{o}C whilst under an inert atmosphere. To this solution was added, *via* cannula, the previously prepared propynyl acetylide solution. The resulting mixture was stirred for an additional 1 h at -78^{o}C before being warmed to room temperature. Tlc analysis showed no spot for either triflate intermediate **105**, or starting alcohol **93**, therefore, the reaction was abandoned.

Attempted preparation of 1-(but-3-ynyl)-1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene naphthalene.



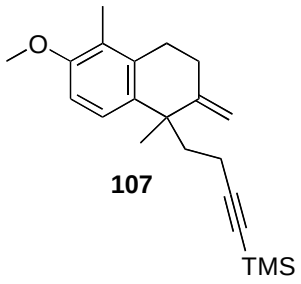
106

Scheme 140

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (4 ml) and cooled to -78^{o}C prior to the addition of sodium acetylide (0.24 ml, 18 wt.% slurry in xylene/light mineral oil, 0.813 mmol). After a further 10 minutes, TMEDA (0.05 ml, 0.407 mmol) and DMPU (0.06 ml, 0.407 mmol) were added.

Simultaneously, a flame dried flask was charged with DCM (6 ml), **93** (0.10 g, 0.407 mmol), and pyridine (0.1 ml, 1.22 mmol) before being cooled to -78^{o}C. To this solution was added triflic anhydride (0.2 ml, 1.22 mmol). The resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 5 minutes reaction time, tlc analysis showed the consumption of the starting material. The reaction mixture was quenched with a saturated solution of sodium hydrogen carbonate and extracted with DCM. The organic layer washed with 1 M HCl (x 2), followed by brine, before being dried over sodium sulfate, filtered, and concentrated to give a pale yellow oil. The resulting oil was dissolved in dry THF (3 ml) and cooled to -78^{o}C whilst under an inert atmosphere. To this solution was added, *via* cannula, the previously prepared solution. The resulting mixture was stirred for an additional 1 h at -78^{o}C before being warmed to room temperature. Tlc analysis showed no spot for either triflate intermediate **105** or starting alcohol **93**, therefore, the reaction was abandoned.

Attempted preparation of (4-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)but-1-ynyl)trimethylsilane.

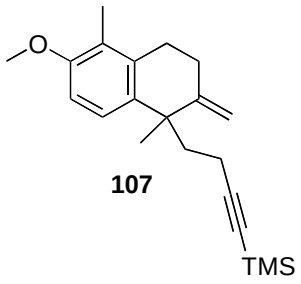


107

Scheme 141 (OMs reaction)

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (3 ml) and trimethylsilylacetylene (0.07 ml, 0.492 mmol) before being cooled to -78^{o}C. To this solution was added ^{n}BuLi (0.22 mmol, 2.2 M in hexane, 0.492 mmol). After a 10 minutes reaction time, TMEDA (0.07 ml, 0.492 mmol) and DMPU (0.06 ml, 0.492 mmol) were added. After a further 10 minutes mesylate **101** (0.053 g, 0.15 mmol) was added as a solution in THF (2 ml). The resulting mixture was stirred for 30 minutes before being warmed to r.t. After this time, tlc analysis showed only starting material present, therefore, the reaction mixture was left to stir at ambient temperature for a further 16 h. Tlc analysis, again, showed only starting material present, therefore the reaction was quenched with saturated ammonium chloride solution and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification *via* column chromatography (eluent: 0-20% diethyl ether in petrol) afforded mesylate **101** (0.050 g, 94% yield) as a colourless oil.

Attempted preparation of (4-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)but-1-ynyl)trimethylsilane.

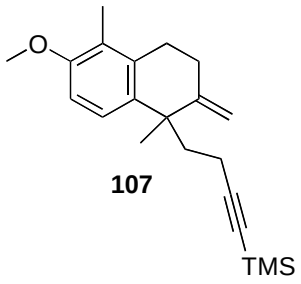


107

Scheme 141 (OTs reaction)

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (3ml) and trimethylsilylacetylene (0.08 ml, 0.570 mmol) before being cooled to -78^{o}C. To this solution was added ^{n}BuLi (0.26 ml, 2.2 M in hexane, 0.570 mmol). After a 10 minutes reaction time, TMEDA (0.09 ml, 0.570 mmol) and DMPU (0.07 ml, 0.570 mmol) were added. After a further 10 minutes tosylate **103** (0.076 g, 0.190 mmol) was added as a solution in THF (2 ml). The resulting mixture was stirred for 30 minutes before being warmed to r.t. After this time, tlc analysis showed only starting material present, therefore, the reaction mixture was left to stir at ambient temperature for a further 16 h. Tlc analysis, again, showed only starting material present, therefore the reaction was quenched with saturated ammonium chloride solution and extracted with ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. Purification *via* column chromatography (eluent: 0-20% diethyl ether in petrol) afforded tosylate **103** (0.069 g, 91% yield) as a colourless oil.

Preparation of (4-(1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalen-1-yl)but-1-ynyl)trimethylsilane.



107

***General Procedur*e:**

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF and trimethylsilylacetylene prior to being cooled to -78^{o}C. Following this, ^{n}BuLi was added to the solution *via* syringe. After 10 minutes reaction time, TMEDA and DMPU were added.

Simultaneously, a flame dried flask was charged with DCM, **93**, and pyridine before being cooled to -78^{o}C. To this solution was added triflic anhydride and the resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 5 minutes reaction time the mixture was quenched with a saturated solution of sodium hydrogen carbonate and extracted with DCM. The organic layer washed with 1 M HCl (x 2) followed by brine before being dried over sodium sulfate, filtered and concentrated to give a pale yellow oil. The resulting oil was dissolved in dry THF, placed under an inert atmosphere, and cooled to -78^{o}C. To this solution was added, *via* cannula, the previously prepared trimethylsilylacetylide solution at -78^{o}C. The resulting mixture was stirred for 5 mins before being warmed to room temperature. After a further 30 min reaction time, tlc analysis showed the absence of the triflate intermediate **105** and the presence of a new spot. The reaction was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organic layer was washed with water, dried over sodium sulfate, filtered, and concentrated to give a pale yellow oil. Purification *via* column chromatography (eluent: 0-5% diethyl ether in petrol) provided desired compound **107** as a colourless oil.

Following the ***General Procedure***, data are presented as (a) amount of THF, (b) amount of

trimethylsilylacetylene, (c) amount of ^{n}BuLi, (d) amount of TMEDA, (e) amount of DMPU, (f) volume of DCM, (g) amount of **93**, (h) amount of pyridine, (i) amount of triflic anhydride, (j) volume of THF, and (k) product yield.

Scheme 142, Table 17, Entry 1

(a) 1 ml, (b) 0.08 ml, 0.609 mmol, (c) 0.24 ml, 2.5 M in hexanes, 0.609 mmol, (d) 0.09 ml, 0.609 mmol, (e) 0.07 ml, 0.609 mmol, (f) 3 ml, (g), 0.05 g, 0.203 mmol, (h) 0.05 ml, 0.609 mmol, (i) 0.1 ml, 0.609 mmol, (j) 2 ml, and (k) 0.021 g, 31% yield.

Scheme 142, Table 17, Entry 2

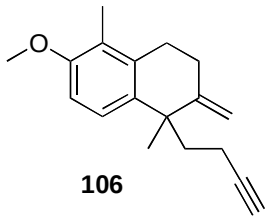
(a) 2 ml, (b) 0.16 ml, 1.22 mmol, (c) 0.48 ml, 2.5 M in hexanes, 1.22 mmol, (d) 0.18 ml, 1.22 mmol, (e) 0.14 ml, 1.22 mmol, (f) 3 ml, (g), 0.10 g, 0.406 mmol, (h) 0.1 ml, 1.22 mmol, (i) 0.2 ml, 1.22 mmol, (j) 4 ml, and (k) 0.06 g, 45% yield.

Scheme 142, Table 17, Entry 3 (Use of fresh Tf_2O)

(a) 2 ml, (b) 0.30 ml, 2.12 mmol, (c) 0.85 ml, 2.5 M in hexanes, 2.12 mmol, (d) 0.32 ml, 2.12 mmol, (e) 0.26 ml, 2.12 mmol, (f) 5 ml, (g), 0.174 g, 0.707 mmol, (h) 0.17 ml, 2.12 mmol, (i) 0.36 ml, 2.12 mmol, (j) 5 ml, and (k) 0.167 g, 72% yield.

IR (CH_2Cl_2): 1643, 2170 cm^{-1}; ^{1}H NMR δ(500 MHz, $CDCl_3$): 0.15 (s, 9H, $SiMe_3$), 1.42 (s, 3H, alkyl CH_3), 1.72-1.78 (m, 1H, alkyl CH), 2.04-2.11 (m, 6H, alkyl protons and $ArCH_3$), 2.47 (t, *J* = 6.5 Hz, 2H, alkyl CH_2), 2.65-2.76 (m, 2H, alkyl CH_2), 3.82 (s, 3H, OCH_3), 4.88 (s, 1H, olefinic CH), 5.00 (s, 1H, olefinic CH), 6.78 (d, *J* = 9.0 Hz, 1H, ArH), 7.16 ppm (d, *J* = 9.0 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 0.1, 11.4, 15.7, 29.0, 30.3, 31.7, 42.3, 43.0, 55.6, 83.8, 108.0, 108.1, 108.9, 123.4, 124.4, 135.9, 137.2, 151.8, 155.2 ppm; HRMS *m/z* (ESI) Calc. for $C_{21}H_{31}OSi$ (M^++H): 327.2143. Found: 327.2139.

Preparation of 1-(but-3-ynyl)-1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylenenaphthalene.



106

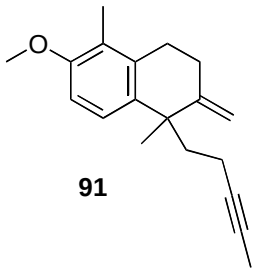
Scheme 143

A round bottomed flask was charged with alkyne **107** (0.152 g, 0.466 mmol) as a solution in MeOH (5 ml). To this was added potassium carbonate (0.064 g, 0.466 mmol) and the solution was stirred at room temperature for 16 h. After this time, the reaction mixture was extracted with ethyl acetate and the organic layer washed with water then brine. The organics were dried over sodium sulfate, filtered, and concentrated to give a pale yellow oil, which, on purification *via* column chromatography (0-5% diethyl ether in petrol) afforded the desired product (0.118 g, 99% yield) as a white solid.

Melting Point: 62-64^{o}C

IR (CH_2Cl_2): 1644, 2117 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.42 (s, 3H, alkyl CH_3), 1.65-1.72 (m, 1H, alkyl proton), 1.89 (t, ^{4}J = 2.5 Hz, 1H, alkyne proton), 2.01-2.17 (m, 6H, alkyl protons and $ArCH_3$), 2.45-2.48 (m, 2H, alkyl CH_2), 2.62-2.79 (m, 2H, alkyl CH_2), 3.81 (s, 3H, OCH_3), 4.87 (s, 1H, olefinic CH), 5.00 (s, 1H, olefinic CH), 6.78 (d, *J* = 8.7 Hz, 1H, ArH), 7.16 (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 11.4, 14.2, 29.0, 30.5, 31.6, 42.1, 43.0, 55.5, 67.6, 85.2, 107.9, 108.9, 123.2, 124.4, 135.8, 137.3, 151.8, 155.1 ppm; HRMS *m/z* (ESI) Calc. for $C_{18}H_{22}O$ (M^{+}): 254.1663. Found: 254.1665.

Preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)-naphthalene.



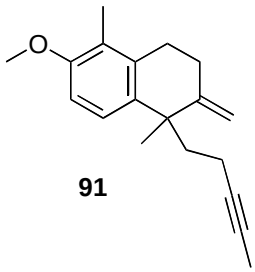
91

Scheme 144

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne **106** (0.356 g, 1.40 mmol) as a solution in dry THF (30 ml). The resulting solution was cooled to -78^{o}C before the addition of ^{n}BuLi (1.27 ml, 2.2 M in hexanes, 2.80 mmol). The reaction mixture was stirred for 30 minutes at this temperature before the addition of methyl iodide (0.17 ml, 2.80 mmol). The solution was then warmed to ambient temperature before being quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with water, then brine, and dried over sodium sulfate. After filtering, and concentrating under reduced pressure, the remaining residue was purified *via* column chromatography (eluent: 0-5% diethyl ether in petrol) to afford the desired product **91** (0.357 g, 95% yield) as a colourless oil.

IR (CH_2Cl_2): 1643, 2115 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.41 (s, 3H, alkyl CH_3), 1.61-1.69 (m, 1H, alkyl CH), 1.74 (s, 3H, alkynyl CH_3), 1.92-2.09 (m, 3H, alkyl protons), 2.11 (s, 3H, $ArCH_3$), 2.46 (t, J = 6.9 Hz, 2H, alkyl CH_2), 2.62-2.78 (m, 2H, alkyl CH_2), 3.81 (s, 3H, OCH_3), 4.86 (s, 1H, olefinic CH), 4.97 (s, 1H, olefinic CH), 6.77 (d, *J* = 8.7 Hz, 1H, ArH), 7.16 ppm (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 2.4, 10.4, 13.4, 28.0, 29.4, 30.7, 41.7, 42.0, 54.5, 73.9, 78.7, 106.7, 107.8, 122.3, 123.4, 134.9, 136.2, 150.9, 154.1 ppm; HRMS *m/z* (ESI) Calc. for $C_{19}H_{25}O$ (M^{+}+H): 269.1900. Found: 269.1907.

Attempted preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)naphthalene.

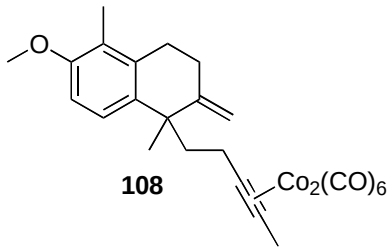


91

Scheme 145

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with THF (15 ml) and alkyne **107** (0.137 g, 0.420 mmol) prior to being cooled to -78^{o}C. To this solution was added ^{n}BuLi (0.34 ml, 2.5 M in hexanes, 0.840 mmol) and the resulting solution was stirred for 30 minutes prior to the addition of methyl iodide (0.05 ml, 0.84 mmol). After 15 minutes the reaction mixture was allowed to warm to room temperature before quenching with a saturated solution of ammonium chloride. The mixture was diluted with ether and the organic layer separated, washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification *via* column chromatography (eluent: 0-5% diethyl ether in petrol) returned starting material **107** (0.136 g, 100%) as the sole reaction component.

Preparation of 1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl) naphthalene dicobalthexacarbonyl complex.



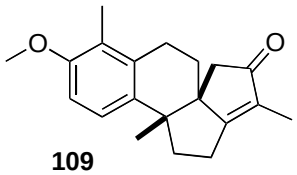
108

Scheme 147

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with petroleum ether (2 ml), alkyne **91** (0.03 g, 0.11 mmol), and dicobalt octacarbonyl (0.042 g, 0.12 mmol). The resulting red/brown solution was stirred at room temperature for 2 h. After this time, tlc analysis indicated the consumption of starting material **91**. The reaction was directly purified *via* column chromatography (eluent: petrol) to provide the desired cobalt complex **108** (0.057 g, 94% yield) as a red oil.

IR (CH_2Cl_2): 1644, 2013, 2044, 2087 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.48 (s, 3H, alkyl CH_3), 2.09-2.29 (m, 6H, alkyl protons and $ArCH_3$), 2.45-2.68 (m, 5H, alkyl protons and alkynyl CH_3), 2.70-2.85 (m, 3H, alkyl protons), 3.81 (s, 3H, OCH_3), 4.89 (s, 1H, olefinic CH), 5.01 (s, 1H, olefinic CH), 6.79 (d, *J* = 8.4 Hz, 1H, ArH), 7.18 ppm (d, *J* = 8.4 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 11.7, 20.5, 28.6, 29.2, 32.0, 32.1, 43.3, 44.3, 55.8, 94.1, 101.0, 107.7, 109.3, 123.7, 124.4, 136.1, 137.5, 152.7, 155.3, 200.4 ppm; HRMS *m/z* (ESI) Calc. for $C_{25}H_{28}Co_2NO_7$ (M^++NH_4): 572.0523. Found: 572.0524; Elemental analysis calc. for $C_{25}H_{24}Co_2O_7$ required C, 54.17% and H, 4.36%. Found: C, 54.17% and H, 4.69%.

Preparation of 5,6,7,11b-tetrahydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[a-a]naphthalene-4(2H)-one.



109

Scheme 148

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with cobalt complex **108** (0.175 g, 0.316 mmol) as a solution in 1,2-dichloroethane (15 ml). To this solution was added dodecylmethyl sulfide (0.29 ml, 1.106 mmol) and the resulting mixture was refluxed for 5 h before filtering through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was purified *via* column chromatography (eluent: 0-20% diethyl ether in petrol) to afford the desired tetracycle **109** (0.08 g, 86% yield) as a white solid.

Scheme 149

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne **91** (0.10 g, 0.37 mmol) as a solution in 1,2-dichloroethane (10 ml). To this solution was added dicobalt octacarbonyl (0.025 g, 0.074 mmol) followed by dodecylmethyl sulfide (0.12 ml, 0.44 mmol) and the resulting mixture was refluxed for 5 h before filtering through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was purified *via* column chromatography (eluent: 0-20% diethyl ether in petrol) to afford the desired tetracycle **109** (0.071 g, 65% yield) as a white solid.

Scheme 150

To a microwave vial was added enyne **91** (0.091 g, 0.340 mmol), dicobalt octacarbonyl (0.023 g, 0.068 mmol), dodecylmethyl sulfide (0.11 ml, 0.410 mmol) and toluene (2.5 ml). This mixture

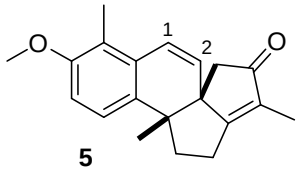
was reacted in the microwave (with cooling) at 100^{o}C for 20 min. Following this, the resulting solution was purified directly *via* column chromatography (eluent: 0-20% diethyl ether in petrol) to afford the desired tetracycle **109** (0.031 g, 31% yield) as a white solid.

Melting Point: 148-150^{o}C.

IR (CH_2Cl_2): 1664, 1701 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.15 (s, 3H, alkyl CH_3), 1.46 (ddd, ^{2}J = 13.3 Hz, J = 5.1 Hz, J = 2.0 Hz, 1H, alkyl CH_2), 1.75 (s, 3H, vinylic CH_3), 1.98-2.08 (m, 2H, alkyl CH_2), 2.14 (s, 3H, $ArCH_3$), 2.26-2.42 (m, 3H, alkyl protons), 2.54-2.71 (m, 3H, alkyl protons), 2.84 (ddd, ^{2}J = 14.0 Hz, J = 5.1 Hz, J = 2.0 Hz, 1H, alkyl CH_2), 3.82 (s, 3H, OCH_3), 6.77 (d, J = 8.6 Hz, 1H, ArH), 7.17 ppm (d. J = 8.6 Hz, 1H, ArH); ^{13}C NMR δ(100 MHz, $CDCl_3$): 8.4, 11.3, 23.6, 23.6, 25.4, 31.2, 42.8, 43.1, 43.4, 53.7, 55.6, 108.6, 124.1, 124.6, 132.1, 134.0, 135.7, 155.4, 186.8, 210.9 ppm; HRMS *m/z* (ESI) Calc. for $C_{20}H_{25}O_2$ (M^{+}+H): 297.1851. Found: 297.1849.

See appendix for X-ray crystallography data for this compound (pg. 267).

Attempted preparations of 5,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1-a]naphthalene-4(2H)-one.



5

General Procedure A:

A 10 ml round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen and charged with **109** and the appropriate solvent. To the solution was added 2,3-dichloro-5,6-dicyanobenzoquinone, **111**, and the reaction mixture was refluxed for the allotted time. The mixture was concentrated and analysed directly *via* ^{1}H NMR.

Following ***General Procedure A***, data are presented as (a) amount of substrate, **109**, (b) solvent, (c) amount of 2,3-dichloro-5,6-dicyanobenzoquinone, **111**, (d) reaction time, and (e) reaction outcome.

NOTE – ^{1}H NMR analysis of the crude reaction mixture saw the appearance of a doublet (J = 9.9 Hz) at δ5.58. Comparison with the previously acquired data for **5** showed this to be in good agreement with that structure, with the δ5.58 signal being attributed to the olefinic proton on carbon 2.[129] In all of the following reactions regarding compound **5** the ratio of starting material to product was determined using this signal at δ5.58 and the signal at δ2.84 from the starting material.

Scheme 152, Table 18, Entry 1

(a) 0.010 g, 0.034 mmol, (b) benzene, 1 ml, (c) 0.023 g, 0.102 mmol, (d) 24 h, and (e) 80:20 starting material:product by ^{1}H NMR.

Scheme 152, Table 18, Entry 2

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) 0.023 g, 0.102 mmol, (d) 24 h, and (e) 81:19 starting material:product by ^{1}H NMR.

Scheme 152, Table 18, Entry 3

(a) 0.010 g, 0.034 mmol, (b) MeOH, 1 ml, (c) 0.023 g, 0.102 mmol, (d) 24 h, and (e) only starting material observed by ^{1}H NMR.

Scheme 153

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) 0.023 g, 0.102 mmol, (d) 5 d, and (e) only starting material observed by ^{1}H NMR.

Scheme 154, Table 19, Entry 1

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) 0.039 g, 0.17 mmol, (d) 5 d, and (e) only starting material observed by ^{1}H NMR.

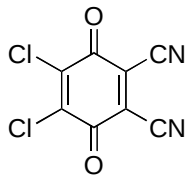
Scheme 154, Table 19, Entry 2

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) 0.154 g, 0.68 mmol, (d) 5 d, and (e) only starting material observed by ^{1}H NMR.

Scheme 155

To a microwave vial was added **109** (0.010 g, 0.034 mmol), 2,3-dichloro-5,6-dicyanobenzoquinone, **111**, (0.023 g, 0.102 mmol) and 1,4-dioxane (1 ml). The resulting mixture was heated in the microwave (with cooling) for 45 min at 110^{o}C. After this time, the reaction mixture was concentrated and analysed by ^{1}H NMR. The NMR spectrum obtained corresponded to starting material **109**.

Preparation of 2,3-dichloro-5,6-dicyanobenzoquinone.[146,178]



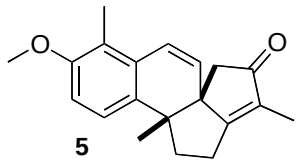
111

Scheme 156

To a three-necked round bottom flask, fitted with a thermometer, was added 2,3-dicyanohydroquinone (5.0 g, 31.0 mmol), water (35 ml), and concentrated hydrochloric acid (35 ml). To this solution was added concentrated nitric acid (9.4 ml, 70%, 150 mmol) dropwise, keeping the solution temperature below 35^{o}C by use of a water/ice bath. After complete addition, the resulting yellow suspension was stirred for 1 h before being filtered, washed with carbon tetrachloride, and dried in a vacuum oven (40^{o}C, 0 mbar) to yield the product (4.6 g, 65% yield) as a yellow solid.

Melting point: 210-212^{o}C. Lit melting point: 212-215^{o}C.[178]

Attempted preparations of 5,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1-a]naphthalene-4(2H)-one.



5

Following ***General Procedure A*** *(page 210):*

Scheme 157, Table 20, Entry 1

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) Prepared in-house, 0.023 g, 0.102 mmol, (d) 24 h, and (e) only starting material observed by ^{1}H NMR.

Scheme 157, Table 20, Entry 2

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) Sigma-Aldrich supplier, 0.023 g, 0.102 mmol, (d) 24 h, and (e) only starting material observed by ^{1}H NMR.

Scheme 157, Table 20, Entry 3

(a) 0.010 g, 0.034 mmol, (b) 1,4-dioxane, 1 ml, (c) Alfa Aesar supplier, 0.023 g, 0.102 mmol, (d) 24 h, and (e) only starting material observed by ^{1}H NMR.

Scheme 158

A 10 ml round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen and charged with **109** (0.01 g, 0.034 mmol) and benzene (1 ml). To the solution was added *p*-Chloranil (0.025 g, 0.102 mmol) and the reaction mixture was refluxed for 16 h. The mixture was concentrated and analysed directly *via* ^{1}H NMR, however, only starting material was observed.

General Procedure B:

10% palladium on carbon (0.005 g) was added to a stirred solution of **109** in nitrobenzene. The resulting solution was placed under the desired pressure, heated to the appropriate temperature (using a sand bath), and stirred for the allotted time. After this time, the reaction mixture was concentrated and analysed by ^{1}H NMR.

Following ***General Procedure B***, data are presented as (a) amount of substrate, **109**, (b) amount of nitrobenzene (c) pressure, (d) temperature, (e) reaction time, and (f) reaction outcome.

Scheme 159, Table 21, Entry 1

(a) 0.010 g, 0.034 mmol, (b) 1 ml, (c) atmospheric, (d) 175^{o}C, (e) 16 h, and (f) starting material only.

Scheme 159, Table 21, Entry 2

(a) 0.010 g, 0.034 mmol, (b) 1 ml, (c) atmospheric, (d) 224^{o}C, (e) 16 h, and (f) starting material only.

Scheme 159, Table 21, Entry 3

(a) 0.015 g, 0.051 mmol, (b) 1 ml, (c) 135 mbar, (d) 168^{o}C, (e) 16 h, and (f) starting material only.

Scheme 159, Table 21, Entry 4

To a microwave vial was added **109** (0.010 g, 0.034 mmol), nitrobenzene (1 ml), and 10% palladium on carbon (0.005 g). The resulting solution was heated in the microwave at 175^{o}C for 10 minutes. After this time, the reaction mixture was concentrated and analysed by ^{1}H NMR. The NMR spectrum obtained corresponded to starting material **109**.

Scheme 160, Table 22, Entry 1

Palladium on carbon, 487, (0.005 g) was added to a stirred solution of **109** (0.011 g, 0.037 mmol) in nitrobenzene 1 ml. The resulting solution was heated to 215^{o}C (using a sand bath), and stirred

for the 16 h. After this time, the reaction mixture was concentrated and analysed by ^{1}H NMR. The NMR spectrum obtained corresponded to starting material **109**.

Scheme 160, Table 22, Entry 2

Palladium on carbon, 87L, (0.005 g) was added to a stirred solution of **109** (0.011 g, 0.037 mmol) in nitrobenzene (1 ml). The resulting solution was heated to 215^{o}C (using a sand bath), and stirred for the 16 h. After this time, the reaction mixture was concentrated and analysed by ^{1}H NMR. The NMR spectrum obtained corresponded to starting material **109**.

General Procedure C:

A 10 ml round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with a solution of **109** in CCl_4. To the solution was added NBS and AIBN (when employed) and the reaction mixture was cooled to -20^{o}C. The reaction mixture was irradiated with ultraviolet light for the allotted time, keeping the reaction temperature below 10^{o}C. After this time, the solution was warmed to room temperature and DBU added. The resulting mixture was stirred at room temperature for 16 h. The mixture was concentrated filtered through a pad of silica (eluent: 0-20% diethyl ether in petrol) and analysed by ^{1}H NMR.

Following ***General Procedure C***, data are presented as (a) amount of substrate, **109**, (b) volume of CCl_4, (c) amount of NBS, (d) amount of AIBN, (e) reaction time, (f) amount of DBU, and (g) reaction outcome.

Scheme 162, Table 23, Entry 1

(a) 0.025 g, 0.084 mmol, (b) 0.5 ml, (c) 0.023 g, 0.13 mmol, (d) none, (e) 1 h, (f) 0.04 ml, 0.25 mmol, and (g) inseparable mixture of **109** and **5** (12 mg), 20% conversion.

Scheme 162, Table 23, Entry 2

(a) 0.020 g, 0.068 mmol, (b) 0.5 ml, (c) 0.018 g, 0.10 mmol, (d) 0.001 g, 0.0068 mmol, (e) 1 h, (f) 0.03 ml, 0.20 mmol, and (g) inseparable mixture of **109** and **5** (7 mg), 31% conversion.

Scheme 162, Table 23, Entry 3

(a) 0.020 g, 0.068 mmol, (b) 0.5 ml, (c) 0.018 g, 0.10 mmol, (d) 0.001 g, 0.0068 mmol, (e) 4 h, (f) 0.03 ml, 0.20 mmol, and (g) inseparable mixture of **109** and **5** (6 mg), 54% conversion.

Scheme 162, Table 23, Entry 4

(a) 0.020 g, 0.068 mmol, (b) 0.5 ml, (c) 0.018 g, 0.10 mmol, (d) 0.001 g, 0.0068 mmol, (e) 7.5 h, (f) 0.03 ml, 0.20 mmol, and (g) inseparable mixture of **109** and **5** (8 mg), 63% conversion.

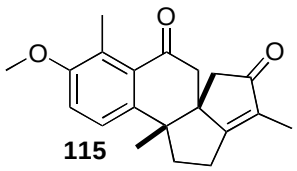
Scheme 163, Table 24, Entry 1

A round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with NBS (0.018 g, 0.102 mmol), **109** (0.02 g, 0.068 mmol), and CCl_4 (1 ml). The resulting mixture was heated to reflux and stirred for 16 h. After this time, the reaction mixture was cooled to room temperature, DBU (0.03 ml, 0.204 mmol) was added, and the resulting solution was stirred for 3 h before being concentrated (6 mg) and analysed by ^{1}H NMR. The NMR spectrum obtained showed a 45% conversion.

Scheme 163, Table 24, Entry 2

A round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with NBS (0.018 g, 0.102 mmol), AIBN (0.001 g, 0.0068 mmol), **30** (0.02 g, 0.068 mmol), and CCl_4 (1 ml). The resulting mixture was heated to reflux and stirred for 16 h. After this time, the reaction mixture was cooled to room temperature, DBU (0.03 ml, 0.204 mmol) was added, and the resulting solution was stirred for 3 h before being concentrated (7 mg) and analysed by ^{1}H NMR. The NMR spectrum obtained showed a 42% conversion.

Attempted preparation of 6,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-a]naphthalene-4,7(2H,5H)-dione.



115

General Procedure A:

A 10 ml round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with **109** and the appropriate solvent. To the solution was added potassium permanganate and the reaction mixture was stirred at the allocated temperature for the allotted time. The mixture was filtered through celite (eluent: DCM), concentrated, and analysed directly *via* ^{1}H NMR.

Following ***General Procedure A***, data are presented as (a) amount of substrate, **109**, (b) solvent, (c) amount of potassium permanganate, (d) reaction temperature, (e) reaction time, and (f) reaction outcome.

Scheme 165, Table 25, Entry 1

(a) 0.005 g, 0.017 mmol, (b) MeCN, 0.5 ml, (c) 0.0054 g, 0.034 mmol, (d) r.t., (e) 5 min, and (f) 0% yield (no starting material recovered).

Scheme 165, Table 25, Entry 2

(a) 0.005 g, 0.017 mmol, (b) MeCN, 0.5 ml, (c) 0.0027 g, 0.017 mmol, (d) r.t., (e) 6 h, and (f) starting material only.

Scheme 165, Table 25, Entry 3

(a) 0.005 g, 0.017 mmol, (b) MeCN, 0.5 ml, (c) 0.0027 g, 0.017 mmol, (d) 35^{o}C, (e) 16 h, and (f) starting material only.

Scheme 165, Table 25, Entry 4

(a) 0.005 g, 0.017 mmol, (b) MeCN, 0.5 ml, (c) 0.0027 g, 0.017 mmol, (d) reflux, (e) 16 h, and (f) starting material only.

Scheme 165, Table 25, Entry 5

(a) 0.005 g, 0.017 mmol, (b) DCM, 0.5 ml, (c) 0.0054 g, 0.034 mmol, (d) r.t., (e) 16 h, and (f) starting material only.

Scheme 166

Preparation of the oxidant:

The oxidant was prepared by grinding potassium permanganate (1.0 g, 6.3 mmol) and active manganese dioxide (3.0 g, 34.5 mmol) in a mortar until a homogeneous powder was obtained. This reagent was used for all of the experiments described in **Table 26**.

Scheme 166, Table 26, Entry 1

An oven-dried round bottom flask was charged with compound **109** (0.01 g, 0.034 mmol) and oxidant (0.068 g). The resulting mixture was stirred at room temperature for 16 h. After this time, DCM (5 ml) was added and the mixture filtered. The filtrate was evaporated *in vacuo* and the residue (0.01 g) was analysed by ^{1}H NMR, showing only starting material.

Scheme 166, Table 26, Entry 2

An oven-dried round bottom flask was charged with compound **109** (0.01 g, 0.034 mmol), oxidant (0.068 g), and DCM (5 ml). The resulting solution was stirred at room temperature for 16 h. After this time, the reaction mixture was filtered and the filtrate evaporated *in vacuo*. The resulting residue (0.01 g) was analysed by ^{1}H NMR and showed only starting material.

Scheme 166, Table 26, Entry 3

An oven-dried round bottom flask was charged with compound **109** (0.01 g, 0.034 mmol) and oxidant (0.068 g). The resulting mixture was stirred at room temperature for 5 min before being irradiated in a sonication bath for 3 h. After this time, DCM (5 ml) was added and the mixture filtered. The filtrate was evaporated *in vacuo* and the residue (0.01 g) was analysed by ^{1}H NMR, showing only starting material.

General Procedure B:

To a stirred solution of **109** in glacial acetic acid at 0^{o}C was added a solution of CrO_3 in glacial acetic acid/water solution dropwise. The reaction mixture was then allowed to warm to room temperature and stirred for 24 h. After this time, the reaction mixture was diluted with water, neutralised with a solution of saturated sodium bicarbonate, and extracted with diethyl ether (x 2). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was analysed by ^{1}H NMR.

Following ***General Procedure B***, data are presented as (a) amount of substrate, **109**, (b) volume of acetic acid, (c) amount of CrO_3, (d) volume of acetic acid, (e) volume of water, and (f) reaction outcome.

Scheme 167, Table 27, Entry 1

(a) 0.006 g, 0.020 mmol, (b) 0.6 ml, (c) 0.003 g, 0.026 mmol, (d) 0.16 ml, (e) 0.04 ml, and (f) SM only.

Scheme 167, Table 27, Entry 2

(a) 0.005 g, 0.017 mmol, (b) 0.6 ml, (c) 0.008 g, 0.08 mmol, (d) 0.16 ml, (e) 0.04 ml, and (f) SM only.

General Procedure C:

To a stirred solution of **109** in a MeOH/MeCN solution was added ceric ammonium nitrate (CAN) in one portion. After stirring at room temperature for the allotted time the reaction mixture was concentrated and the residue diluted with DCM. The organic solution was washed with water and then brine, dried over sodium sulfate, filtered, and concentrated. The resultant oil was analysed using ^{1}H NMR.

Following ***General Procedure C***, data are presented as (a) amount of substrate, **109**, (b) volume of MeOH, (c) volume of MeCN, (d) amount of CAN, (e) reaction time, and (f) reaction outcome.

Scheme 168, Table 28, Entry 1

(a) 0.005 g, 0.017 mmol, (b) 0.1 ml, (c) 0.05 ml, (d) 0.01 g, 0.017 mmol, (e) 20 min, and (f) only starting material was observed.

Scheme 168, Table 28, Entry 2

(a) 0.005 g, 0.017 mmol, (b) 0.1 ml, (c) 0.05 ml, (d) 0.019 g, 0.034 mmol, (e) 20 min, and (f) a complex mixture of products was observed.

Scheme 168, Table 28, Entry 3

(a) 0.005 g, 0.017 mmol, (b) 0.1 ml, (c) 0.05 ml, (d) 0.037 g, 0.068 mmol, (e) 5 min, and (f) a complex mixture of products was observed.

Scheme 168, Table 28, Entry 4

(a) 0.005 g, 0.017 mmol, (b) 0.15 ml, (c) none, (d) 0.019 g, 0.034 mmol, (e) 20 min, and (f) a complex mixture of products was observed.

Scheme 169

A 10 ml flask, fitted with a condenser, was charged with **109** (0.01 g, 0.034 mmol), 1,4-dioxane (0.75 ml), water (0.5 ml), potassium bromate (0.003 g, 0.017 mmol), and CAN (0.001 g, 0.0017 mmol). The resulting mixture was heated to 95^{o}C and stirred for 48 h. After this time, the reaction mixture was diluted with diethyl ether (10 ml) and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed using ^{1}H NMR, whereby no product or starting material was observed. The ^{1}H NMR spectrum showed a disappearance of one of the aromatic protons from the starting materials (6.77 ppm), suggesting substitution on the aromatic ring.

General Procedure D:

To a microwave vial was added **109**, water, and TBHP. The resulting solution was heated in the microwave at 150^{o}C for 30 minutes. After this time, the reaction mixture was diluted with DCM, and the organic layer separated, dried over sodium sulfate, filtered, and concentrated. The

resulting residue was analysed by ^{1}H NMR.

Following ***General Procedure D***, data are presented as (a) amount of substrate, **109**, (b) volume of water, (c) volume of TBHP, and (d) reaction outcome.

Scheme 170, Table 29, Entry 1

(a) 0.010 g, 0.034 mmol, (b) 1 ml, (c) 4.4 µl, 70% in H_2O, 0.034 mmol, and (d) starting material only (0.01 g, 100%)

Scheme 170, Table 29, Entry 2

(a) 0.010 g, 0.034 mmol, (b) 1 ml, (c) 8.8 µl, 70% in H_2O, 0.068 mmol, and (d) starting material only (0.08 g, 80%)

Scheme 171

Substrate **109** (0.02 g, 0.068 mmol) was added to a solution of iron(III)chloride hexahydrate (0.001 g, 0.004 mmol) in pyridine (1 ml). Following the addition of TBHP (0.03 ml, 70% H_2O, 0.204 mmol) the reaction mixture was heated to 82^{o}C and stirred for 24 h. After this time, the reaction mixture was allowed to cool to room temperature, diluted with DCM, and poured into a 1 M solution of HCl (10 ml). The organic phase was separated, washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR and showed only starting substrate **109** to be present (0.017 g, 85% yield).

General Procedure E:

A 10 ml round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with **109**, DCM, TBHP, potassium carbonate, and palladium on charcoal catalyst. The resulting solution was held at the appropriate temperature for 24 h. After this time, the reaction mixture was concentrated to a residue and analysed *via* ^{1}H NMR.

Following ***General Procedure E***, data are presented as (a) amount of substrate, **109**, (b) volume of DCM, (c) volume of TBHP, (d) amount of potassium carbonate, (e) amount of Pd/C, (f) reaction temperature, and (g) reaction outcome.

Scheme 172, Table 30, Entry 1

(a) 0.021 g, 0.071 mmol, (b) 0.6 ml, (c) 0.06 ml, 5.5 M in decane, 0.355 mmol, (d) 0.0025 g, 0.018 mmol, (e) 0.002 g, 0.0018 mmol, (f) -78^{o}C, and (g) starting material only.

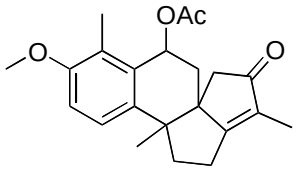
Scheme 172, Table 30, Entry 2

(a) 0.021 g, 0.071 mmol, (b) 0.6 ml, (c) 0.06 ml, 5.5 M in decane, 0.355 mmol, (d) 0.0025 g, 0.018 mmol, (e) 0.002 g, 0.0018 mmol, (f) r.t., and (e) starting material only.

Scheme 173, Table 31 Entry 1

A 10 ml round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with **109** (0.005 g, 0.017 mmol) and acetone (1 ml). To the solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.006 g, 0.03 mmol) and the reaction mixture was stirred at room temperature for 16 h. After this time, the mixture was concentrated and analysed directly *via* ^{1}H NMR, which showed only starting material to be present.

Attempted preparation of 2,4,5,6,7,11b-hexahydro-9-methoxy-3,8,11b-trimethyl-4-oxo-1H-pentaleno[1,6a-a]naphthalen-7-yl acetate.



115a

Scheme 173, Table 31, Entry 2

A 10 ml round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen and charged with **109** (0.005 g, 0.017 mmol) and dry acetic acid (1 ml). To the solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.006 g, 0.03 mmol) and the reaction mixture was heated to reflux. After 16 h the mixture was diluted with DCM and washed with water. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. Analysis *via* ^{1}H NMR spectroscopy showed only starting material to be present.

Scheme 173, Table 31, Entry 3

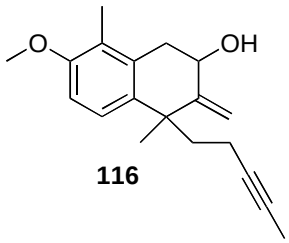
A 10 ml round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with **109** (0.006 g, 0.02 mmol) and dry acetic acid (1 ml). To the solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (0.006 g, 0.03 mmol) and the reaction mixture was sonicated, using a low power sonication bath, for 5 h. After this time, the mixture was diluted with DCM and washed with water. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. Analysis *via* ^{1}H NMR spectroscopy showed only starting material to be present.

Scheme 173, Table 31, Entry 4

To a microwave vial was added **109** (0.005 g, 0.017 mmol), 2,3-dichloro-5,6-dicyanobenzoquinone (0.006 g, 0.03 mmol) and dry acetic acid (1 ml). The resulting mixture was heated in the microwave (with cooling) for 30 min at 120^{o}C. After this time, the mixture was diluted with DCM and washed with water. The organic layer was washed with brine, dried over

sodium sulfate, filtered, and concentrated. The NMR spectrum obtained corresponded to starting material **109**.

Preparation of 1,2,3,4-tetrahydro-7-methoxy-4,8-dimethyl-3-methylene-4-(pent-3-ynyl)naphthalen-2-ol.



116

Scheme 175, Table 32, Entry 1

A round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen and charged with a solution of enyne **91** (0.012 g, 0.045 mmol) in ethanol (2 ml). To this solution was added selenium dioxide (0.005 g, 0.045 mmol) and the resultant mixture refluxed for 16 h. After this time, tlc analysis indicated the presence of starting material only and, therefore, the reaction was concentrated and analysed *via* ^{1}H NMR to confirm this.

Scheme 175, Table 32, Entry 2

A round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen and charged with a solution of enyne **91** (0.010 g, 0.037 mmol) in 1,4-dioxane (2 ml). To this solution was added selenium dioxide (0.004 g, 0.037 mmol) and the resultant mixture refluxed for 16 h. After this time, tlc analysis indicated the presence of starting material only and, therefore, the reaction was concentrated and analysed *via* ^{1}H NMR to confirm this.

Scheme 175, Table 32, Entry 3

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged selenium dioxide (0.011 g, 0.0095 mmol), DCM (5 ml), and *tert*-butyl hydroperoxide (1ml, 70% in water). The resulting solution was stirred at room temperature for 15 minutes prior to the addition of enyne **91** (0.050 g, 0.019 mmol) in DCM (5 ml). After a further 16 h at room temperature, tlc analysis indicated the presence of starting material only and, therefore, the reaction was subsequently terminated.

NOTE: The crude mixtures from ***Scheme 179, Table 32, Entries 1-3*** were combined and the starting material recovered (0.065 g, 90% yield) *via* column chromatography (eluent: 0-40% diethyl ether in petrol).

Scheme 175, Table 32, Entry 4

Preparation of 3 M TBHP in DCM[176]

In an oven-dried separating funnel, *tert*-butyl hydroperoxide (85 ml, 70% H_2O) was mixed with DCM (140 ml). The resulting milky mixture was allowed to stand until complete separation of the phases had occurred. The organic layer was separated and used without further drying.

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with selenium dioxide (0.048 g, 0.44 mmol), DCM (2 ml), and *tert*-butyl hydroperoxide (0.87 ml, 3 M in DCM, 2.61 mmol). The resulting solution was stirred at room temperature for 15 minutes prior to the addition of enyne **91** (0.234 g, 0.87 mmol) in DCM (2 ml). After a further 8 h at room temperature, tlc analysis indicated the consumption of the starting material and, therefore, the reaction mixture was concentrated and directly purified *via* column chromatography (eluent: 0-40% diethyl ether in petrol) to yield the desired product (0.121 g, 49% yield) as a colourless oil.

Scheme 175, Table 32, Entry 5

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with selenium dioxide (0.006 g, 0.054 mmol), DCM (0.5 ml), and *tert*-butyl hydroperoxide (0.06 ml, 5.5 M in decane, 0.324 mmol). The resulting solution was stirred at room temperature for 15 minutes prior to the addition of enyne **91** (0.029 g, 0.11 mmol) in DCM (0.5 ml). After a further 8 h at room temperature, tlc analysis indicated the consumption of the starting material and, therefore, the reaction mixture was concentrated and directly purified *via* column chromatography (eluent: 0-40% diethyl ether in petrol) to yield the desired product (0.01 g, 32% yield) as a colourless oil.

Table 33, Entry 1

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with

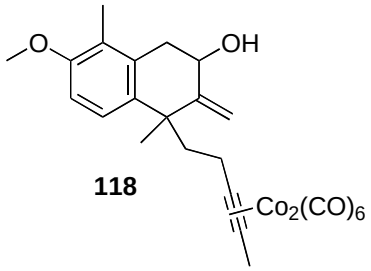
selenium dioxide (0.021 g, 0.19 mmol), DCM (0.5 ml), and *tert*-butyl hydroperoxide (0.19 ml, 3 M in DCM, 0.57 mmol). The resulting solution was stirred at room temperature for 15 minutes prior to the addition of enyne **91** (0.05 g, 0.19 mmol) in DCM (0.5 ml). After a further 8 h at room temperature, tlc analysis indicated the consumption of the starting material and, therefore, the reaction mixture was concentrated and directly purified *via* column chromatography (eluent: 0-40% diethyl ether in petrol) to yield the desired product (0.022 g, 41% yield) as a colourless oil.

Table 33, Entry 2

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with selenium dioxide (0.005 g, 0.045 mmol), DCM (0.5 ml), and *tert*-butyl hydroperoxide (0.19 ml, 3 M in DCM, 0.57 mmol). The resulting solution was stirred at room temperature for 15 minutes prior to the addition of enyne **91** (0.05 g, 0.19 mmol) in DCM (0.5 ml). After a further 8 h at room temperature, tlc analysis indicated the consumption of the starting material and, therefore, the reaction mixture was concentrated and directly purified *via* column chromatography (eluent: 0-40% diethyl ether in petrol) to yield the desired product (0.014 g, 26% yield) as a colourless oil.

IR (CH_2Cl_2): 1596, 3370 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.46 (s, 3H, CH_3), 1.73-1.85 (m, 5H, alkyl protons and CH_3), 1.96-2.01 (m, 2H, CH_2), 2.14 (s, 3H, $ArCH_3$), 2.65 (dd, ^2J = 15.8 Hz, J = 9.2 Hz, 1H, benzylic CH_2), 3.12 (dd, ^2J = 15.8 Hz, J = 5.2 Hz, 1H, benzylic CH_2), 3.81 (s, 3H, OCH_3), 4.51-4.56 (broad m, 1H, OCH), 5.06 (s, 1H, olefinic CH), 5.36 (s, 1H, olefinic CH), 6.79 (d, J = 8.7 Hz, 1H, ArH), 7.16 ppm (d, J = 8.7 Hz, 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 3.4, 11.5, 14.6, 29.3, 37.5, 43.5, 44.3, 55.6, 69.8, 75.3, 79.3, 106.7, 109.2, 124.0, 124.2, 133.5, 135.5, 154.1, 155.6 ppm; HRMS *m/z* (ESI) Calc. for $C_{19}H_{28}NO_2$ (M^++NH_4): 302.2114. Found: 302.2119.

Preparation of 1,2,3,4-tetrahydro-7-methoxy-4,8-dimethyl-3-methylene-4-(pent-3-ynyl)naphthalen-2-ol dicobalt hexacarbonyl complex.



118

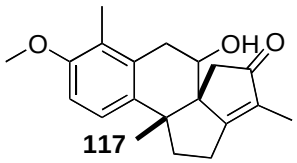
Scheme 176

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with petroleum ether (3 ml), alkyne **116** (0.085 g, 0.30 mmol), and dicobalt octacarbonyl (0.143 g, 0.42 mmol). The resulting red/brown solution was stirred at room temperature for 2 h. After this time, tlc analysis indicated the consumption of starting material **116**. The reaction was directly purified *via* column chromatography (eluent: petrol) to provide the desired cobalt complex **118** (0.169 g, 99% yield) as a red oil.

IR (CH_2Cl_2): 1644, 2013, 2044, 3352 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 1.52 (s, 3H, CH_3), 2.04-2.22 (m, 5H, alkyl CH_2 and CH_3), 2.38-2.50 (m, 1H, alkyl CH), 2.53-2.79 (m, 5H, alkyl CH_2 and CH_3), 3.09-3.22 (m, 1H, alkyl CH), 3.82 (s, 3H, OCH_3), 4.48-4.61 (m, 1H, OCH), 5.12 (s, 1H, olefinic CH), 5.41 (s, 1H, olefinic CH), 6.81 (d, J = 8.1 Hz, 1H, ArH), 7.18 ppm (d, J = 8.1 Hz, 1H, ArH); HRMS *m/z* (ESI) Calc. for $C_{25}H_{28}Co_2NO_8$ (M^++NH_4): 558.0473. Found: 588.0471.

^{13}C analysis was not obtained for this molecule.

Preparation of 5,6,7,11b-tetrahydro-6-hydroxy-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one.



117

General Procedure A;

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with cobalt complex **118** as a solution in 1,2-dichloroethane. To this solution was added dodecylmethyl sulfide and the resulting mixture was heated to the appropriate temperature for the allotted time. Following this, the reaction mixture was filtered through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was purified *via* column chromatography (eluent: 0-100% diethyl ether in petrol).

Following ***General Procedure A***, data are presented as (a) amount of cobalt complex, (b) volume of 1,2-DCE, (c) amount of DodSMe, (d) temperature, (e) reaction time, and (f) reaction outcome.

Scheme 177, Table 34, Entry 1

(a) 0.028 g, 0.049 mmol, (b) 2 ml, (c) 0.05 ml, 0.17 mmol, (d) 83^{o}C, (e) 16 h, and (f) 0.004 g, 26% yield.

Scheme 177, Table 34, Entry 2

(a) 0.186 g, 0.33 mmol, (b) 13 ml, (c) 0.31 ml, 1.15 mmol, (d) 50^{o}C, (e) 24 h, and (f) 0% yield.

General Procedure B:

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with cobalt complex **118** as a solution in DCM. To this solution was added TMANO.2H_2O in two portions and the resulting mixture was stirred at the appropriate temperature for the allotted time. Following this, the reaction mixture was filtered through a

plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue analysed *via* ^{1}H NMR spectrometry.

Following ***General Procedure B***, data are presented as (a) amount of cobalt complex, (b) volume of DCM, (c) amount of TMANO.2H_2O, (d) temperature, (e) reaction time, and (f) reaction outcome.

Scheme 178, Table 35, Entry 1

(a) 0.030 g, 0.053 mmol, (b) 2 ml, (c) 0.035 g, 0.32 mmol, (d) r.t., (e) 16 h, and (f) trace amounts of desired product **117** were observed in the crude ^{1}H NMR spectrum.

Scheme 178, Table 35, Entry 2

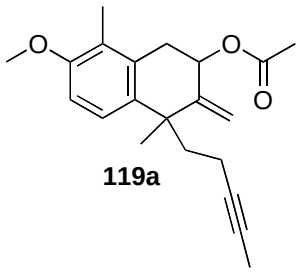
(a) 0.030 g, 0.053 mmol, (b) 2 ml, (c) 0.035 g, 0.32 mmol, (d) 40^{o}C, (e) 1 h, and (f) trace amounts of desired product **117** were observed in the crude ^{1}H NMR spectrum.

IR (CH_2Cl_2): 1670, 1704, 3369 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.19 (s, 3H, alkyl CH_3), 1.81 (s, 3H, vinylic CH_3), 2.07-2.16 (m, 5H, alkyl protons and $ArCH_3$), 2.30-2.39 (m, 1H, alkyl proton), 2.50-2.71 (m, 4H, alkyl protons), 3.14 (dd, J = 5.3 Hz, ^{2}J = 16.4 Hz, 1H, benzylic CH), 3.82 (s, 3H, OCH_3), 4.10-4.15 (m, 1H, OCH), 6.79 (d, J = 8.7 Hz, 1H, ArH), 7.14 ppm (d, J = 8.7 Hz, 1H, ArH); HRMS *m/z* (ESI) Calc. for $C_{20}H_{25}O_3$ (M^++H): 313.1798. Found: 313.1803.

Due to the small quantity of this material obtained, the ^{13}C spectrum was very weak. Diagnostic peaks include:

^{13}C δ(125 MHz, $CDCl_3$): 8.8, 11.7, 23.6, 24.9, 33.7, 38.0, 43.1, 55.8, 60.6, 67.8, 109.3, 124.7, 132.6, 210.5 ppm.

Preparation of 1,2,3,4-tetrahydro-7-methoxy-4,8-dimethyl-3-methylene-4-(pent-3-ynyl)naphthalen-2-yl acetate.



119a

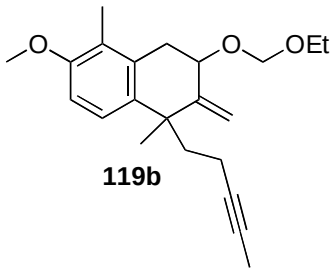
Scheme 179, Table 36, Entry 1

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with alcohol **116** (0.074 g, 0.26 mmol) as a solution in DCM (2 ml) and pyridine (0.06 ml, 0.78 mmol). The resulting solution was cooled to 0^{o}C before the dropwise addition of acetic anhydride (0.075 ml, 0.78 mmol). After addition, the reaction was warmed to reflux and stirred for 48 h. After this time, the reaction mixture was quenched with saturated sodium bicarbonate solution, the organic layer separated, washed with 1 M HCl (x 2) followed by brine. The organic layer was then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-10% diethyl ether in petrol) to yield the desired product **119a** (0.057 g, 67% yield) as a colourless liquid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.46 (s, 3H, CH_3), 1.72-1.73 (m, 3H, alkyl protons), 1.84-1.90 (m, 1H, alkyl proton), 1.95-2.07 (m, 3H, alkyl protons), 2.11-2.12 (m, 6H, 2 x CH_3), 2.77 (dd, ^{2}J = 15.8 Hz, J = 9.2 Hz, 1H, benzylic CH_2), 3.10 (dd, ^{2}J = 15.8 Hz, J = 5.2 Hz, 1H, benzylic CH_2), 3.82 (s, 3H, OCH_3), 5.06 (s, 1H, olefinic CH), 5.24 (s, 1H, olefinic CH), 5.58-2.62 (broad m, 1H OCH), 6.80 (d, J = 8.7 Hz, 1H, ArH), 7.16 ppm (d, J = 8.7 Hz, 1H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 3.4, 11.5, 14.5, 21.3, 29.1, 34.5, 43.6, 44.0, 55.5, 71.7, 75.2, 79.2, 108.2, 109.3, 123.8, 124.1, 132.9, 135.3, 149.1, 155.5, 170.1 ppm.

IR and accurate mass analyses were not obtained for this compound.

Preparation of 3-(ethoxymethoxy)-1,2,3,4-tetrahydro-6-methoxy-1,5-dimethyl-2-methylene-1-(pent-3-ynyl)naphthalene.



119b

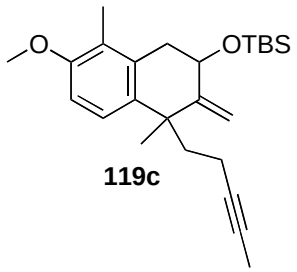
Scheme 179, Table 36, Entry 2

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with alcohol **116** (0.018 g, 0.063 mmol) as a solution in DCM (2 ml). To this solution was added triethylamine (0.03 ml, 0.21 mmol) followed by chloromethyl ethyl ether (0.02 ml, 0.19 mmol). The resulting solution was stirred at room temperature for 16 h. After this time, the reaction mixture was quenched with water, the organic layer separated, and washed with 1 M HCl (x 2) followed by brine. The organic layer was then dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: 0-50% diethyl ether in petrol) to yield the desired product **119b** (0.008 g, 37% yield) as a colourless liquid.

^{1}H NMR δ(400 MHz, $CDCl_3$): 1.23 (t, *J* = 7.1 Hz, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.64-1.74 (m, 4H, alkyl proton and alkyne CH_3), 1.91-2.10 (m, 3H, alkyl protons), 2.13 (s, 3H, CH_3), 2.81 (dd, ^{2}J = 15.8 Hz, *J* = 7.6 Hz, 1H, benzylic CH_2), 2.98 (dd, ^{2}J = 15.8 Hz, *J* = 4.5 Hz, 1H, benzylic CH_2), 3.51-3.59 (m, 1H, OCH_2), 3.69-3.77 (m, 1H, OCH_2), 3.81 (s, 3H, OCH_3), 4.45-4.49 (m, 1H, OCH), 4.73 (d, ^{2}J = 15.5 Hz, 1H, OCH_2O), 4.75 (d, ^{2}J = 15.5 Hz, 1H, OCH_2O), 5.11 (s, 1H, olefinic CH), 5.32 (s, 1H, olefinic CH), 6.78 (d, *J* = 8.6 Hz, 1H, ArH), 7.14 ppm (d, *J* = 8.6 Hz, 1H, ArH).

IR, ^{13}C, and accurate mass analyses were not obtained for this molecule.

Preparation of tert-butyl-1,2,3,4-tetrahydro((7-methoxy-4,8-dimethyl-3-methylene-4-(pent-3-yn-1-yl)naphthalen-2-yl)oxy)dimethylsilane.



119c

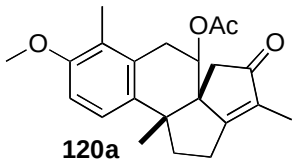
Scheme 179, Table 36, Entry 3

A round bottom flask was flame dried under vacuum, cooled under nitrogen, and charged with alcohol **116** (0.01 g, 0.035 mmol) as a solution in DCM (1 ml). To this solution was added imidazole (0.006 g, 0.088 mmol) followed by *tert*-butyldimethylsilyl chloride (0.008 g, 0.053 mmol). The resulting solution was stirred at room temperature for 5 h. After this time, the reaction mixture was quenched with saturated sodium bicarbonate solution, the organic layer separated, washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petrol) to yield the desired product **119c** (0.014 g, 100% yield) as a colourless liquid.

IR (CH_2Cl_2): 1189, 1652, 2110 cm^{-1}; ^1H NMR δ(400 MHz, $CDCl_3$): 0.05 (s, 6H, $SiCH_3$), 0.97 (s 9H, ^tBuSi), 1.41 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.92-2.01 (m, 4H, alkyl protons), 2.14 (s, 3H, $ArCH_3$), 2.53-2.61 (m, 1H, alkyl CH), 3.04-2.09 (m, 1H, alkyl CH), 3.83 (s, 3H, $ArOCH_3$), 4.39-4.43 (m, 1H, OCH), 5.00 (s, 1H, olefinic CH), 5.45 (s, 1H, olefinic CH), 6.80 (d, J = 8.7 Hz, 1H, ArH), 7.16 ppm (d, J = 8.7 Hz, 1H, ArH); HRMS *m/z* (ESI) Calc. for $C_{25}H_{39}O_2Si$ (M^++H): 399.2714. Found: 399.2716.

^{13}C analysis was not carried out on this compound.

Attempted preparation of 2,4,5,6,7,11b-hexahydro-9-methoxy-3,8,11b-trimethyl-4-oxo-1H-pentaleno[1,6a-a]naphthalen-6-yl acetate.

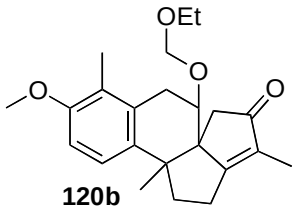


120a

Scheme 180, Table 37, Entry 1

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne **119a** (0.038 g, 0.12 mmol) as a solution in 1,2-dichloroethane (1 ml). To this solution was added dicobalt octacarbonyl (0.048 g, 0.14 mmol) and the resulting red solution was stirred for 1 h. After this time, tlc analysis showed consumption of the starting alkyne and a spot indicative of the cobalt complex. Dodecylmethyl sulfide (0.11 ml, 0.42 mmol) was added and the resulting mixture was heated to reflux. Following this, the reaction mixture was filtered through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was purified *via* column chromatography (eluent: 0-100% diethyl ether in petrol). None of the desired product was isolated from this reaction; in fact, no identifiable product was obtained.

Attempted preparation of 6-(ethoxymethoxy)-5,6,7,11b-tetrahydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one.

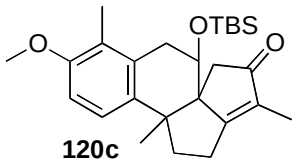


120b

Scheme 180, Table 37, Entry 2

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne **119b** (0.007 g, 0.02 mmol) as a solution in 1,2-dichloroethane (1 ml). To this solution was added dicobalt octacarbonyl (0.011 g, 0.03 mmol) and the resulting red solution was stirred for 1 h. After this time, tlc analysis showed consumption of the starting alkyne and a spot indicative of the cobalt complex. Dodecylmethyl sulfide (0.02 ml, 0.07 mmol) was added and the resulting mixture was heated to reflux. Following this, the reaction mixture was filtered through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was analysed *via* ^{1}H NMR. None of the desired product was observed in this spectrum; in fact, no identifiable product was observed.

Attempted preparation of 6-((tert-butyldimethylsilyl)oxy)-5,6,7,11b-tetrahydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1,6a-a]naphthalen-4(2H)-one.

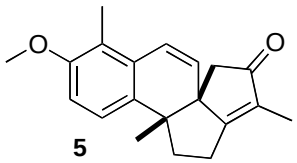


120c

Scheme 180, Table 37, Entry 3

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alkyne **119c** (0.073 g, 0.18 mmol) as a solution in 1,2-dichloroethane (9 ml). To this solution was added dicobalt octacarbonyl (0.086 g, 0.25 mmol) and the resulting red solution was stirred for 1 h. After this time, tlc analysis showed consumption of the starting alkyne and a spot indicative of the cobalt complex. Dodecylmethyl sulfide (0.17 ml, 0.63 mmol) was added and the resulting mixture was heated to reflux. Following this, the reaction mixture was filtered through a plug of celite (eluent: EtOAc). The filtrate was concentrated under reduced pressure, and the resulting residue was analysed *via* ^{1}H NMR. None of the desired product was isolated from this reaction; in fact, no identifiable product was isolated.

Attempted preparations of 5,11b-dihydro-9-methoxy-3,8,11b-trimethyl-1H-pentaleno[1-a]naphthalene-4(2H)-one.



5

Scheme 181, Table 38, Entry 1

A round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with **117** (0.003 g, 0.01 mmol) as a solution in toluene (1 ml). After the addition of tosic acid (0.001 g, 0.005 mmol) the reaction mixture was headed to reflux and stirred for 16 h. After this time, tlc analysis indicated only starting material to be present. The reaction mixture was concentrated under reduced pressure, diluted with DCM, washed with water, dried and filtered. The filtrate was evaporated to return compound **117** (0.003 g, 100% yield.)

Scheme 181, Table 38, Entry 2

A microwave vial was charged with **117** (0.003 g, 0.01 mmol), toluene (1 ml), and tosic acid (0.001 g, 0005 mmol). The resulting mixture was heated in the microwave (with cooling) at 125^{o}C for 10 minutes. After this time, tlc analysis indicated only starting material to be present. The reaction mixture was concentrated under reduced pressure, diluted with DCM, washed with water, dried and filtered. The filtrate was evaporated to return compound **117** (0.003 g, 100% yield.)

Scheme 182, Table 39, Entries 1 and 2

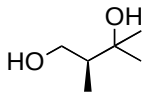
A round bottom flask, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with **117** (0.003 g, 0.01 mmol) as a solution in toluene (1 ml), mesyl chloride (1.4µl, 0.018 mmol), and triethylamine (2.5µl, 0.019 mmol). After 10 mins stirring at room temperature, tlc analysis indicated no starting material to be present and a new spot indicative of the mesylate derivative. DBU (3.0 µl, 0.02 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. After this time, tlc analysis indicated only the

mesylate spot to be present, therefore, the reaction mixture was transferred to a microwave vial and heated in the microwave (with cooling) at 125^{o}C for 10 minutes. After this time, no change was observed by tlc analysis. This crude reaction mixture was used in the following experimental procedure (**Scheme 178**).

Scheme 183

To the crude mixture obtained from the reaction described above (***Scheme 177, Table 39, Entries 1 and 2***) was added potassium *tert*-butoxide (0.006 g, 0.05 mmol) and the resulting mixture was heated, under a sealed system, to 200^{o}C (using a sand bath) for 16 h. After this time, the reaction mixture was concentrated and analysed directly *via* ^{1}H NMR. The spectrum obtained showed no indication of the desired product; in fact no identifiable product was observed.

Preparation of (S)-2,3-dimethylbutan-1,3-diol.[162,177]



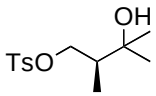
129

Scheme 187

A round bottom flask was flame dried under vacuum, cooled under nitrogen and charged with diethyl ether (2 ml) and methylmagnesium chloride (7.45 ml, 3 M in THF, 22.35 mmol). To this solution was added methyl (*S*)-(+)-3-hydroxy-2-methylpropionate **126** (0.80 g, 6.77 mmol), in diethyl ether (2 ml), dropwise, keeping the reaction temperature between 20-25^{o}C (an ice bath was necessary). The mixture was stirred at room temperature for 2 hours before being quenched with saturated ammonium chloride solution and extracted thoroughly with diethyl ether (x 5). The organics were washed with brine, dried over sodium sulfate, and concentrated to yield the desired diol **129** (0.574 g, 72% yield) as a colourless liquid. This material was used in subsequent reactions without further purification.

IR (CH_2Cl_2): 3346 cm^{-1}; ^{1}H NMR δ(500 MHz, $CDCl_3$): 0.87 (d, *J* = 7.1 Hz, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.79-1.86 (m, 1H, CH), 2.37 (bs, 2H, OH), 3.68-376 ppm (m, 2H, OCH_2); ^{13}C δ(100 MHz, $CDCl_3$): 13.3, 24.6, 30.1, 44.4, 66.6, 74.0 ppm.

Preparation of (S)-3-hydroxy-2,3-dimethylbutyl-4-methylbenzene sulfonate.[162,177]



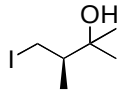
128

Scheme 187

An oven-dried round bottom flask was charged with diol **129** (0.117 g, 0.99 mmol) and pyridine (0.99 ml, 1 M). The resulting solution was cooled to 0^{o}C and 4-toluenesulfonyl chloride (0.189 g, 0.99 mmol) was added before the flask was placed in a refrigerator at 4^{o}C for 16 h. After this time, the mixture was poured into iced water and extracted with diethyl ether. The organics were sequentially washed with water (x 2), 1 M HCl (x 2), and brine before being dried with sodium sulfate and concentrated. The resulting clear residue was purified *via* column chromatography (eluent: 0-50% diethyl ether in petrol) to yield tosylate **128** (0.199 g, 74% yield) as a colourless oil.

IR (CH_2Cl_2): 1176, 3546 cm^{-1}; ^{1}H NMR δ(500 MHz, $CDCl_3$): 0.97 (d, J = 7.0 Hz, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.82-1.90 (m, 1H, CH), 2.46 (s, 3H, $ArCH_3$), 3.94 (dd, ^{2}J = 9.7, J = 7.5 Hz, 1H, OCH), 4.24 (dd, ^{2}J = 9.7, J = 7.5 Hz, 1H, OCH), 7.35 (d, J = 8.1 Hz, 2H, ArH), 7.80 ppm (d, J= 8.3 Hz, 2H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 12.9, 21.9, 26.3, 28.9, 43.6, 72.2, 72.8, 128.1, 130.1, 133.3, 145.0 ppm.

Preparation of (R)-4-iodo-2,3-dimethylbutan-2-ol.[162]



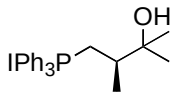
127

Scheme 187

A round bottom flask, fitted with a condenser, was flame dried under vacuum, cooled under nitrogen, and charged with tosylate **128** (0.197 g, 0.723 mmol) and THF (1.5 ml). Anhydrous lithium iodide (0.116 g, 0.87 mmol) was added and the resulting solution was refluxed for 2 h. After this time, the solution was allowed to cool and diethyl ether was added resulting in the precipitation of a pale yellow solid. After filtration, the resulting filtrate was washed with saturated ammonium chloride solution, dried over sodium sulfate, and concentrated *in vacuo*. The resulting residue was purified *via* column chromatography (eluent: 0-50% diethyl ether in petrol) to deliver iodide **127** (0.177 g, 99% yield) as colourless oil.

IR (CH_2Cl_2): 3360 cm^{-1}; ^1H NMR δ(500 MHz, $CDCl_3$): 1.12 (d, J = 6.9 Hz, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.83-1.90 (m, 1H, CH), 2.93 (dd, ^2J = 10.7 Hz , J = 9.5 Hz , 1H, CH_2I), 3.67-3.69 ppm (m, 1H, CH_2I); ^{13}C δ(100 MHz, $CDCl_3$): 11.1, 16.3, 25.5, 28.8, 47.9, 73.4 ppm.

Preparation of (R)-(3-hydroxy-2,3-dimethylbutyl)triphenylphosphonium iodide.[162]



123

Scheme 188

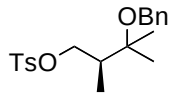
An oven-dried round bottom flask, fitted with a condenser, was charged with iodide **127** (0.433 g, 1.90 mmol), MeCN (13 ml), and triphenylphosphine (3.98 g, 15.2 mmol). The resulting mixture was warmed to reflux and stirred for 48 h. After this time the solvent was removed *in vacuo* and the resulting residue was taken up in diethyl ether, which resulted in the precipitation of a white solid. This mixture was stirred for 20 min before filtration. The white solid obtained was taken up in diethyl ether (30 ml) and stirred for a further 20 min. After further filtration, the white solid was dried under vacuum for 10 min to yield pure **123** (0.699 g, 75% yield). Note: the addition of diethyl ether and filtration steps were repeated until no excess triphenyphosphine was observed in the ^{1}H NMR spectrum of the white solid.

Melting point: 165-167^{o}C

IR (CH_2Cl_2): 3417 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 0.55 (d, J = 6.9 Hz, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 2.09-2.17 (m, 1H, CH), 2.83-2.93 (m, 1H, CH_2PPh_3), 3.69 (s, 1H, OH), 4.59 (t, J = 15.6 Hz, 1H, CH_2PPh_3), 7.69-7.73 (m, 6H, ArH), 7.78-7.81 (m, 3H, ArH), 7.95-8.00 ppm (m, 6H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 17.2, 23.7, 25.7 (d, $^{1}J_{P\text{-}C}$ = 51.4 Hz), 29.5, 39.8 (d, $^{2}J_{P\text{-}C}$ = 4.0 Hz), 73.7 (d, $^{3}J_{P\text{-}C}$ = 12.0 Hz), 119.1 (d, $^{1}J_{P\text{-}C}$ = 85.7 Hz), 130.6, (d, $^{2}J_{P\text{-}C}$ = 12.4 Hz), 134.0 (d, $^{3}J_{P\text{-}C}$ = 9.9 Hz), 135.1 ppm (d, $^{4}J_{P\text{-}C}$ = 3.0 Hz); ^{31}P NMR δ(162 MHz, $CDCl_3$): 23.7 ppm; HRMS *m/z* (ESI) Calc. for $C_{24}H_{28}OP$ (M^{+}-I^{-}): 363.1872. Found: 363.1870.

See appendix for X-ray crystallography data for this compound (pg. 277).

Preparation of (S)-3-(benzyloxy)-2,3-dimethylbutyl-4-methylbenzenefulfonate.



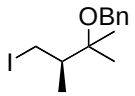
132

Scheme 189

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with alcohol **128** (0.051 g, 0.19 mmol), DCM (0.25 ml), and cyclohexene (0.50 ml). The resulting solution was cooled to 0^{o}C prior to the dropwise addition of benzyl-2,2,2-trichloroacetimidate (0.04 ml, 0.22 mmol) and trifluoromethanesufonic acid (1.7 µl, 0.019 mmol). The mixture was then allowed to warm to room temperature and stirred for 5 h. After this time, the reaction mixture was diluted with DCM and washed with 1 M NaOH solution. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified via column chromatography (eluent: 0-30% diethyl ether in petrol) to yield the desired product (0.056 g, 86% yield) as a colourless oil.

IR (CH_2Cl_2): 1360, 3031 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 1.02 (d, *J* = 6.9 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.06-2.13 (m, 1H, CH), 2.44, (s, 3H, $ArCH_3$), 3.92 (dd, ^{2}J = 9.4 Hz, *J* = 8.6 Hz, 1H, CH_2), 3.71 ppm (dd, ^{2}J = 9.5 Hz, *J* = 3.8 Hz, 1H, CH_2), 4.35 (s, 2H, OCH_2), 7.21-7.32 (m, 7H, ArH), 7.78 ppm (d, *J* = 8.3 Hz, 2H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 12.8, 21.8, 22.2, 24.0, 41.7, 63.4, 72.8, 76.6, 127.2, 127.9, 128.1, 129.2, 129.9, 133.2, 139.5, 144.7 ppm; HRMS *m/z* (ESI) Calc. for $C_{20}H_{30}NO_4S$ (M^{+}+NH_4): 380.1890. Found: 380.1888.

Preparation of (R)-(((4-iodo-2,3-dimethylbutan-2-yl)oxy)methyl)benzene.



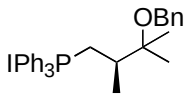
133

Scheme 189

An oven-dried round bottom flask, fitted with a condenser, was charged with tosylate **132** (0.050 g, 0.14 mmol), THF (1 ml), and anhydrous lithium iodide (0.028 g, 0.21 mmol). The resulting mixture was warmed to reflux and stirred for 2 h. After this time, the reaction mixture was allowed to cool to room temperature prior to the addition of diethyl ether (10 ml), which, resulted in the formation of a pale yellow precipitate. After filtration of the solid, the filtrate was evaporated *in vacuo*. The resulting residue was purified *via* column chromatography (eluent: 0-10% diethyl ether in petrol) to furnish iodide **133** (0.043 g, 97% yield) as a colourless oil.

IR (CH_2Cl_2): 1496, 2976, 3030 cm^{-1}; ^1H NMR δ(500 MHz, $CDCl_3$): 1.15 (d, J = 6.9 Hz, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.12-2.19 (m, 1H, CH), 2.93 (dd, ^2J = 11.0 Hz, J = 9.4 Hz, 1H, CH_2), 3.72-3.75 (m, 1H, CH_2), 4.43 (s, 2H, OCH_2), 7.26-7.29 (m, 1H, ArH), 7.33-7.37 ppm (m, 4H, ArH); ^{13}C δ(125 MHz, $CDCl_3$): 11.5, 16.0, 21.7, 24.0, 45.8, 63.7, 78.0, 127.5 (2xC), 128.6, 139.6 ppm; HRMS *m/z* (ESI) Calc. for $C_{13}H_{23}INO$ (M^++NH_4): 336.0819. Found: 336.0820.

Preparation of (R)-(3-(benzyloxy)-2,3-dimethylbutyl)triphenylphosphonium iodide.



130

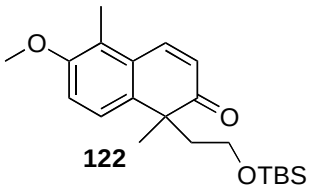
Scheme 189

An oven-dried round bottom flask, fitted with a condenser, was charged with iodide **133** (0.089 g, 0.28 mmol), MeCN (2 ml), and triphenylphosphine (0.584 g, 2.23 mmol). The resulting mixture was warmed to reflux and stirred for 48 h. After this time the solvent was removed *in vacuo* and the resulting reside was taken up in diethyl ether, which resulted in the precipitation of a white solid. This mixture was stirred for 20 min before filtration. The white solid obtained was taken up in diethyl ether (30 ml) and stirred for a further 20 min. After further filtration, the white solid was dried under vacuum for 10 min to yield pure **130** (0.115 g, 74% yield). Note: the addition of diethyl ether and filtration steps were repeated until no excess triphenyphosphine was observed in the ^{1}H NMR spectrum of the white solid.

Melting point: 174-176^{o}C.

IR (CH_2Cl_2): 1438, 2979, 3055cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): 0.69 (d, J = 6.9 Hz, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 3.57-3.66 (m, 1H, CH), 3.80-3.88 (m, 1H, CH), 4.44 (d, ^{2}J = 10.4 Hz, 1H, CH), 4.53 (d, ^{2}J = 10.4 Hz, 1H, CH), 7.51-7.56 (m, 7H, ArH), 7.66-7.88 (m, 13H, ArH); ^{13}C δ(100 MHz, $CDCl_3$): 16.6, 19.1, 23.7, 24.4 (d, $^{1}J_{P\text{-}C}$ = 51.6 Hz), 39.4 (d, $^{2}J_{P\text{-}C}$ = 4.1 Hz), 64.6, 79.3, 118.9 (d, $^{1}J_{P\text{-}C}$ = 85.5 Hz), 127.9, 128.8, 130.4, 130.5 (d, $^{2}J_{P\text{-}C}$ = 12.5 Hz), 134.2 (d, $^{3}J_{P\text{-}C}$ = 10.1 Hz), 135.0 (d, $^{4}J_{P\text{-}C}$ = 3.0 Hz), 139.0 ppm; ^{31}P NMR δ(162 MHz, $CDCl_3$): 23.8 ppm; HRMS *m/z* (ESI) Calc. for $C_{31}H_{34}OP$ (M^{+}-I^{-}): 453.2342. Found: 453.2338.

Attempted preparations of 1-(2-(tert-butyldimethylsiloxy)ethyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one.



122

General Procedure A:

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with dry THF and di-*iso*-propylamine before cooling to 0^{o}C. To the solution was added ^{n}BuLi slowly and the resulting mixture was stirred for 10 min. Following this, the reaction mixture was cooled to -78^{o}C and ketone **99** was added. After 30 min PhSeX was added and the reaction warmed to room 0^{o}C. After a further 20 minutes the solution was washed with 1 M HCl, water, and saturated sodium bicarbonate. The organics were dried with sodium sulfate and concentrated. Following this, the crude oil was taken up in DCM and the solution was cooled to 0^{o}C prior to addition of H_2O_2. After 10 minutes at this temperature the reaction was quenched with water and the organics separated, dried, and concentrated to afford a pale yellow oil.

Following ***General Procedure A***, data are reported as (a) volume of THF, (b) volume of di-*iso*-propylamine, (c) volume of ^{n}BuLi, (d) amount of ketone **99**, (e) amount of PhSeX, (f) volume of DCM, (g) volume of H_2O_2, and (h) product yield.

Scheme 190, Table 40, Entry 1

(a) 5 ml, (b) 0.04 ml, 0.3 mmol, (c) 0.11 ml, 2.5 M in hexanes, 0.275 mmol, (d) 0.091 g, 0.25 mmol, (e) PhSeCl, 0.058 g, 0.3 mmol, (f) 2 ml, (g) 0.06 ml, 0.88 mmol, and (h) 0%.

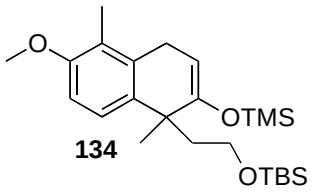
Scheme 190, Table 40, Entry 2

(a) 5 ml, (b) 0.06 ml, 0.4 mmol, (c) 0.14 ml, 2.5 M in hexanes, 0.35 ml, (d) 0.11 g, 0.3 mmol, (e) PhSeBr, 0.078 g, 0.36 mmol, (f) 2 ml, (g) 0.07 ml, 1.03 mmol, and (h) 0%.

Scheme 191

A 3-necked round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with ketone **99** (0.10 g, 0.28 mmol), DMSO (0.9 ml), toluene (1.7 ml), and IBX (0.157 g, 0.56 mmol). The resultant solution was heated to 70^{o}C for 16 h, after which, the reaction mixture was quenched with a saturated solution of sodium bicarbonate. The mixture was extracted with DCM, washed with water, then brine, and the organics separated. The organics were dried over sodium sulfate, filtered, concentrated *in vacuo*, and analysed directly *via* ^{1}H NMR. The spectrum obtained showed no indication of the desired product; in fact no identifiable product was observed at all.

Preparation of tert-butyl(2-(1,4-dihydro-6-methoxy-1,5-dimethyl-2-((trimethylsilyl)oxy)naphthalen-1-yl)ethoxy)dimethylsilane.



134

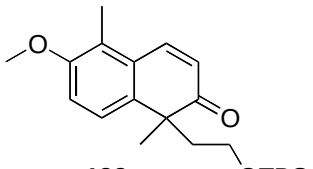
Scheme 192

A 3-necked round bottom flask, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with a solution of ketone **99** (0.606 g, 1.67 mmol) in dry DCM (18 ml) and triethylamine (0.70 ml, 5.02 mmol) before being cooled to -5^{o}C. To this solution was added TMSOTf (0.45 ml, 2.51 mmol) dropwise and the resulting mixture was stirred for 30 minutes. After this time, the solution was quenched with saturated sodium bicarbonate solution and extracted with DCM. The organic extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (eluent: petroleum ether) to yield the desired product **134** (0.610 g, 84% yield) as a colourless liquid.

IR (CH_2Cl_2): 1687 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): -0.05 (s, 6H, $SiCH_3$), 0.25 (s, 9H, $SiCH_3$), 0.82 (s, 9H, Si ^{t}Bu), 1.35 (s, 3H, alkyl CH_3), 1.85-1.91 (m, 1H, alkyl CH), 2.11 (s, 3H, $ArCH_3$), 2.19-2.26 (m, 1H, alkyl CH), 3.06-3.12 (m, 1H, OCH), 3.26 (t, *J* = 3.8 Hz, 2H, ring CH_2), 3.41-3.47 (m, 1H, OCH), 3.82 (s, 3H, $ArOCH_3$), 4.93 (t, *J* = 3.8 Hz, 1H, olefinic CH), 6.79 (d, *J* = 8.8 Hz, 1H, ArH), 7.19 ppm (d, *J* = 8.7 Hz, 1H, ArH); ^{13}C δ(125 MHz, $CDCl_3$): -5.0, 0.6, 11.3, 18.5, 26.2, 28.2, 30.0, 40.5, 43.5, 55.8, 61.1, 98.8, 109.3, 123.0, 124.6, 133.1, 134.1, 152.1, 155.3 ppm.

Due to the sensitive nature of this compound, high resolution mass spectrometry data could not be obtained.

Preparation of 1-(2-(tert-butyldimethylsiloxy)ethyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-one.



122

Scheme 193

A 3-necked round bottom flask, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged a solution of enol ether **134** (0.610 g, 1.40 mmol) in acetonitrile (6 ml) and palladium acetate (0.347 g, 1.54 mmol). The resulting mixture was gently heated (40^{o}C) for 16 h before being concentrated *in vacuo* and purified directly by column chromatography (eluent: 0-5% diethyl ether in petrol) to furnish the desired enone (0.434 g, 86% yield) as a colourless oil.

Scheme 194

A 3-necked round bottom flask, fitted with a condenser, was flame dried under vacuum prior to cooling under a blanket of nitrogen. To the vessel was added palladium acetate (0.01 g, 0.045 mmol) as a solution in acetonitrile (3 ml) and 1,2-bis(diphenylphosphino)ethane (0.013 g, 0.032 mmol) prior to being heated to reflux. After 10 minutes, diallylcarbonate (0.04 ml, 0.31 mmol) was added slowly down the condenser followed by silyl enol ether **134** (0.097 g, 0.22 mmol) as a solution in acetonitrile (1 ml). The resulting mixture was stirred for 40 h before being concentrated *in vacuo* and analysed directly *via* ^{1}H NMR spectroscopy. The spectrum obtained showed only trace amounts of the desired enone **122**.

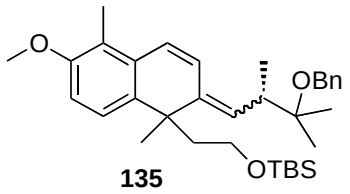
Scheme 195

To a microwave vial was added **134** (0.087 g, 0.2 mmol), palladium acetate (0.009 g, 0.04 mmol), 1,2-bis(diphenylphosphino)ethane (0.016 g, 0.04 mmol), diallylcarbonate (0.09 ml, 0.6 mmol), and MeCN (1 ml). The resulting mixture was pre-stirred for 60 seconds prior to being

heated under microwave irradiation (with cooling) for 30 minutes at 100^{o}C. After this time, the resulting mixture was concentrated *in vacuo* and analysed directly *via* ^{1}H NMR spectroscopy. The spectrum obtained showed a complex mixture of products.

IR (CH_2Cl_2): 1573, 1661 cm^{-1}; ^{1}H NMR δ(400 MHz, $CDCl_3$): -0.13 (s, 6H, $SiCH_3$), 0.76 (s, 9H, Si ^{t}Bu), 1.39 (s, 3H, alkyl CH_3), 2.04-2.09 (m, 1H, alkyl CH), 2.35 (s, 3H, $ArCH_3$), 2.52-2.58 (m, 1H, alkyl CH), 3.21-3.24 (m, 2H, OCH_2), 3.85 (s, 3H, $ArOCH_3$), 6.17 (d, *J* = 10.3 Hz, 1H, olefinic H), 6.92 (d, *J* = 8.6 Hz, 1H, ArH), 7.22 (d, *J* = 8.6 Hz, 1H, ArH), 7.76 ppm (d, *J* = 10.5 Hz, 1H, olefinic H); ^{13}C δ(125 MHz, $CDCl_3$): -5.3, 10.9, 18.4, 26.0, 29.9, 44.8, 49.1, 56.0, 59.9, 112.1, 124.7, 125.1, 125.4, 128.9, 138.1, 140.5, 156.1, 203.8 ppm; HRMS *m/z* (ESI) Calc. for $C_{21}H_{33}O_3Si$ (M^{+}+H): 361.2193. Found 361.2192.

Attempted preparation of (2-(2-((S)-3-(benzyloxy)-2,3-dimethylbutylidene)-1,2-dihydro-6-methoxy-1,5-dimethylnaphthalen-1-yl)ethoxy)(tert-butyl)dimethylsilane.

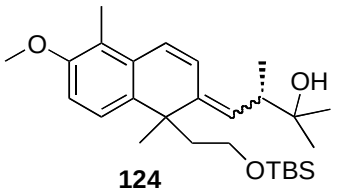


135

Scheme 196

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonium salt **130** (0.083 g, 0.15 mmol) and dry THF (2 ml). To this solution was added potassium *tert*-butoxide (0.016 g, 0.14 mmol) and the white solution was stirred for 2 h. After this time, enone **122** (0.018 g, 0.05 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR spectroscopy, which showed that none of the desired product had been formed.

Attempted preparations of (3S)-4-(1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-6-methoxy-1,5-dimethylnaphthalen-2(1H)-ylidene)-2,3-dimethylbutan-2-ol.



124

General Procedure A

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonium salt **123** and the appropriate solvent. To this solution was added base and the resulting mixture was stirred the appropriate time. After this time, enone **122** was added as a solution and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR spectroscopy.

Following ***General Procedure A***, the data are presented as (a) amount of **123**, (b) solvent, (c) base, (d) time, (e) amount of **122** in volume of solvent, and (f) reaction outcome.

Scheme 197, Table 41, Entry 1

(a) 0.10 g, 0.20 mmol, (b) THF, 1 ml, (c) KO^{t}Bu, 0.046 g, 0.41 mmol, (d) 2 h, (e) 0.018 g, 0.051 mmol in 0.5 ml of THF, and (f) only starting material observed.

Scheme 197, Table 41, Entry 2

(a) 0.10 g, 0.20 mmol, (b) Et_2O, 1 ml, (c) KO^{t}Bu, 0.046 g, 0.41 mmol, (d) 2 h, (e) 0.018 g, 0.051 mmol in 0.5 ml of Et_2O, and (f) only starting material observed.

General Procedure B

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonium salt **123**, enone **122**, and the appropriate solvent. To this solution was added base and the resulting mixture was stirred for 24 h. After this time the reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR spectroscopy.

Following ***General Procedure B***, the data are presented as (a) amount of **123**, (b) amount of enone **122**, (c) solvent, (d) base, and (e) reaction outcome.

Scheme 197, Table 41, Entry 3

(a) 0.10 g, 0.20 mmol, (b) 0.018 g, 0.051 mmol, (c) THF, 1 ml, (d) KO^{t}Bu, 0.046 g, 0.41 mmol, and (e) only starting material observed.

Scheme 197, Table 41, Entry 4

(a) 0.10 g, 0.20 mmol, (b) 0.018 g, 0.051 mmol, (c) THF, 1 ml, (d) KO^{t}Bu, 0.023 g, 0.205 mmol, and (e) only starting material observed.

General Procedure C

A round bottom flask, containing lithium chloride, was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonium salt **123**, the appropriate solvent, and held at the appropriate temperature. To this solution was added base and the resulting mixture was stirred for the appropriate time. After this time, enone **122** was added and the reaction mixture was kept at the appropriate temperature for 24 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with brine, dried over sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR spectroscopy.

Following ***General Procedure C***, the data are presented as (a) amount of LiCl, (b) amount of

123, (c) solvent, (d) temperature, (e) base, (f) time, (g) amount of **122**, (h) temperature, and (i) reaction outcome.

Scheme 198, Table 42, Entry 1

(a) 0.026 g, 0.62 mmol, (b) 0.076 g, 0.15 mmol, (c) THF, 1 ml, (d) 0°C, (e) $(Mes)_2Mg$, 0.32 ml, 0.48 M in THF, 0.15 mmol, (f) 30 min, (g) 0.025 g, 0.07 mmol, (h) 4°C (refrigerator), and (i) only starting material observed.

Scheme 198, Table 42, Entry 2

(a) none, (b) 0.054 g, 0.11 mmol, (c) Et_2O, 1 ml, (d) r.t., (e) MeLi, 0.14 ml, 1.6 M in Et_2O, 0.22 mmol, (f) 2 h, (g) 0.026 g, 0.072 mmol, (h) r.t., and (i) only starting material observed.

Scheme 198, Table 42, Entry 3

(a) 0.004 g, 0.09 mmol, (b) 0.045 g, 0.09 mmol, (c) Et_2O, 1 ml, (d) r.t., (e) MeLi, 0.11 ml, 1.6 M in Et_2O, 0.18 mmol, (f) 2 h, (g) 0.022 g, 0.061 mmol, (h) r.t., and (i) only starting material observed.

Scheme 198, Table 42, Entry 4

Preparation of the 1.6 M MeLi solution in Et_2O containing 0.4 wt% LiCl

An oven-dried Schlenk tube was flame dried under vacuum prior to cooling under a blanket of nitrogen. Lithium chloride (0.029 g, previously flame dried) and MeLi (10 ml, 1.6 M in Et_2O) was added to the Schlenk tube. This solution was kept under an inert atmosphere and used within the subsequent reaction.

A round bottom flask was flame dried under vacuum prior to cooling under a blanket of nitrogen. The vessel was charged with phosphonium salt **123** (0.206 g, 0.42 mmol) and dry diethyl ether (2 ml). To this solution was added the previously prepared MeLi solution (0.48 ml, 1.6 M in Et_2O (0.4 wt% LiCl), 0.77 mmol) and the resulting bright red solution was stirred for 15 mins. After this time, enone **122** (0.05 g, 0.14 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with diethyl ether. The organics were washed with brine, dried over

sodium sulfate, filtered, and concentrated. The resulting residue was analysed *via* ^{1}H NMR spectroscopy, which showed none of the desired product **124**.

Chapter 6

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Appendix

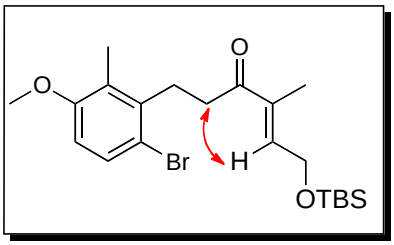
*1. NOSEY spectrum for compound **95*** *pg. 265*

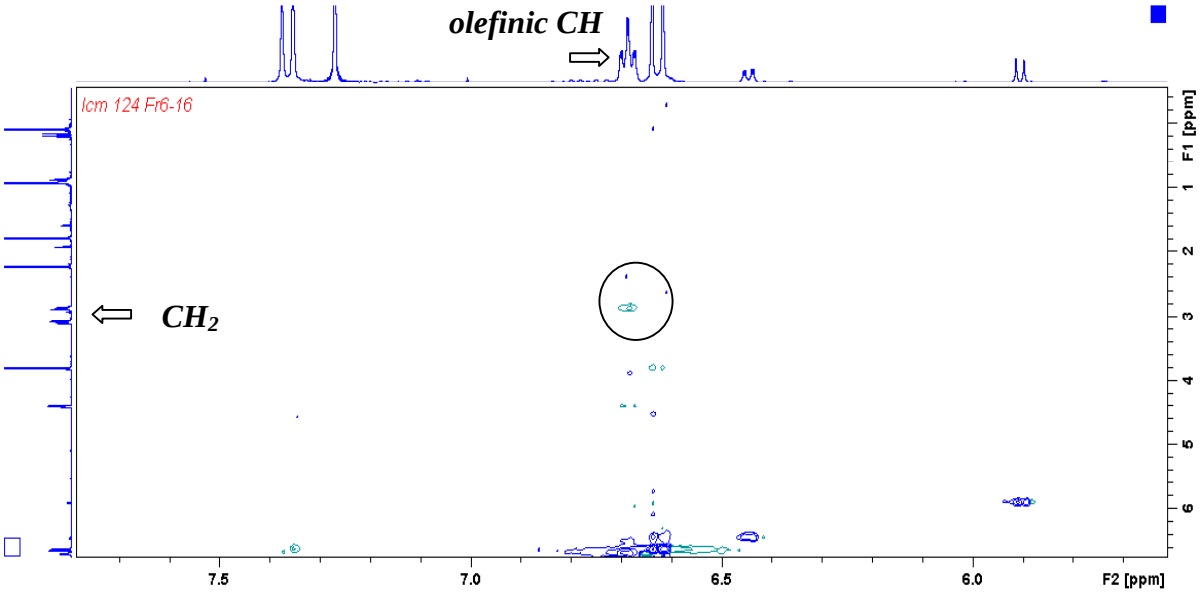
*2. ^{1}H NMR spectrum of compound **95** (expansion of the aliphatic region)* *pg. 266*

*3. X-ray crystallography data for compound **109*** *pg. 267*

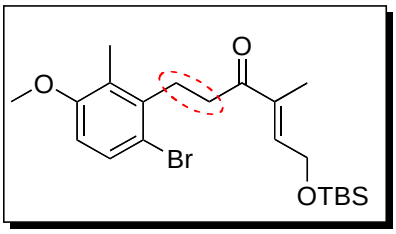
*4. X-ray crystallography data for compound **123*** *pg 277*

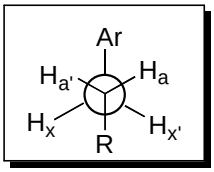
1. NOSEY spectrum for compound ***95***



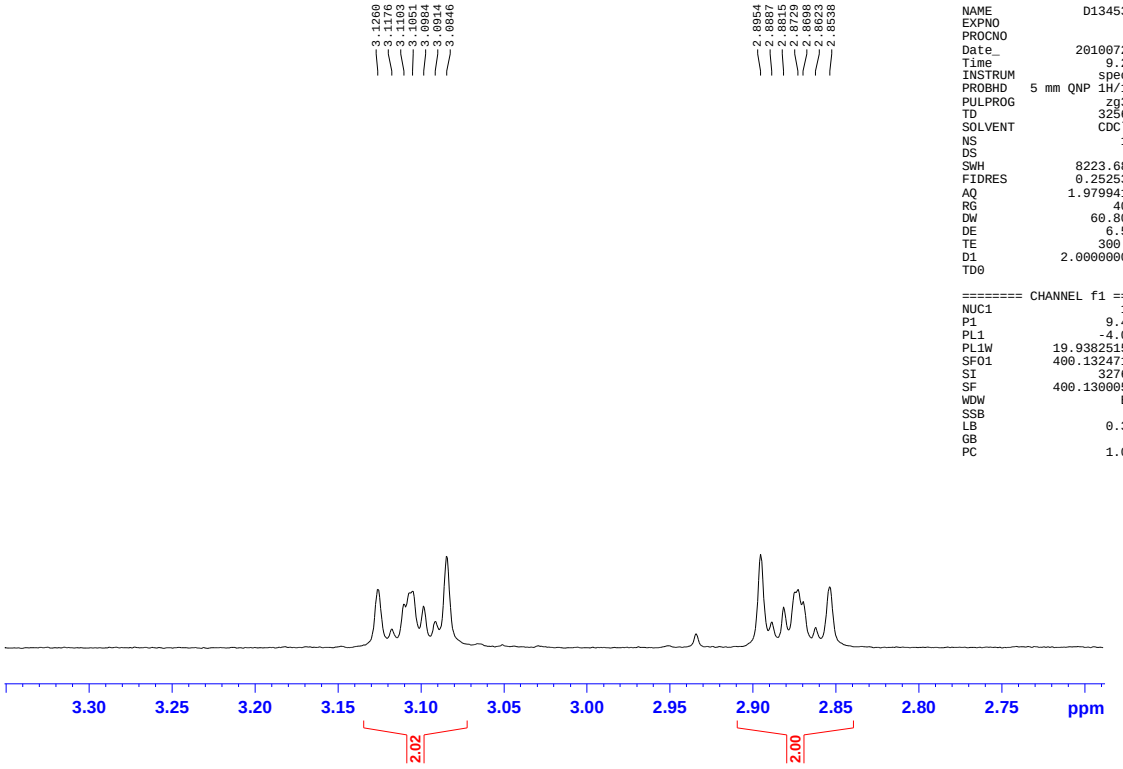


*2. ^{1}H NMR spectrum of compound **95** (expansion of the aliphatic region)*

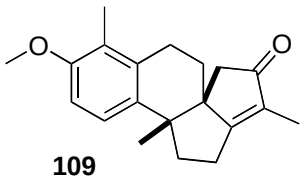




J_{ax} = 11.2 Hz, $J_{ax'}$ = 4.2 Hz



*3. X-ray crystallography data for compound **109***



109

Table 1. Crystal data and structure refinement for bk_28jan09.

Identification code	bk_28jan09	
Empirical formula	C20 H24 O2	
Formula weight	296.39	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 10.4995(4) Å	□= 90°.
	b = 15.4913(5) Å	□= 101.117(3)°.
	c = 9.8227(3) Å	□ = 90°.
Volume	1567.69(9) $Å^3$	
Z	4	
Density (calculated)	1.256 Mg/m^3	
Absorption coefficient	0.079 mm^{-1}	
F(000)	640	
Crystal size	0.25 x 0.22 x 0.22 mm^3	
Theta range for data collection	2.49 to 29.77°.	
Index ranges	-14<=h<=14, -21<=k<=18, -12<=l<=12	
Reflections collected	11038	
Independent reflections	3962 [R(int) = 0.0375]	
Completeness to theta = 27.50°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.99872	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3962 / 0 / 203	
Goodness-of-fit on F^2	0.933	
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.0925	
R indices (all data)	R1 = 0.0925, wR2 = 0.1022	
Largest diff. peak and hole	0.298 and -0.257 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for bk_28jan09. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5066(1)	-1171(1)	2829(1)	26(1)
O(2)	11925(1)	1740(1)	-402(1)	20(1)
C(1)	5522(2)	-455(1)	2730(1)	19(1)
C(2)	6840(2)	-276(1)	2368(2)	19(1)
C(3)	6851(1)	707(1)	2153(1)	16(1)
C(4)	5769(2)	1001(1)	2855(1)	16(1)
C(5)	4956(2)	371(1)	3061(1)	18(1)
C(6)	3738(2)	422(1)	3629(2)	24(1)
C(7)	5967(2)	1917(1)	3336(2)	21(1)
C(8)	7309(2)	2151(1)	3017(2)	21(1)
C(9)	8006(2)	1282(1)	2832(1)	16(1)
C(10)	9031(1)	1409(1)	1935(1)	15(1)
C(11)	8862(2)	1125(1)	551(1)	16(1)
C(12)	7611(2)	703(1)	-136(1)	18(1)
C(13)	6499(1)	915(1)	595(1)	17(1)
C(14)	8631(2)	936(1)	4271(2)	24(1)
C(15)	10175(2)	1834(1)	2493(2)	20(1)
C(16)	11146(2)	1966(1)	1747(2)	20(1)
C(17)	10988(1)	1651(1)	407(2)	16(1)
C(18)	9853(2)	1231(1)	-214(1)	16(1)
C(19)	9688(2)	906(1)	-1685(1)	19(1)
C(20)	13107(2)	2147(1)	205(2)	29(1)

Table 3. Bond lengths [Å] and angles [°] for bk_28jan09.

O(1)-C(1)	1.2203(17)
O(2)-C(17)	1.3855(16)
O(2)-C(20)	1.4170(18)
C(1)-C(5)	1.473(2)
C(1)-C(2)	1.519(2)
C(2)-C(3)	1.5377(19)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.509(2)
C(3)-C(13)	1.5379(19)
C(3)-C(9)	1.548(2)
C(4)-C(5)	1.337(2)
C(4)-C(7)	1.498(2)
C(5)-C(6)	1.4928(19)
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(7)-C(8)	1.544(2)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.560(2)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(10)	1.5293(19)
C(9)-C(14)	1.536(2)
C(10)-C(15)	1.386(2)
C(10)-C(11)	1.407(2)
C(11)-C(18)	1.4060(19)
C(11)-C(12)	1.506(2)
C(12)-C(13)	1.5198(19)
C(12)-H(12A)	0.9900
C(12)-H(12B)	0.9900
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800

C(14)-H(14C)	0.9800
C(15)-C(16)	1.3809(19)
C(15)-H(15)	0.9500
C(16)-C(17)	1.383(2)
C(16)-H(16)	0.9500
C(17)-C(18)	1.391(2)
C(18)-C(19)	1.5081(19)
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800

C(17)-O(2)-C(20)	117.66(11)
O(1)-C(1)-C(5)	126.21(14)
O(1)-C(1)-C(2)	125.02(14)
C(5)-C(1)-C(2)	108.56(12)
C(1)-C(2)-C(3)	104.12(12)
C(1)-C(2)-H(2A)	110.9
C(3)-C(2)-H(2A)	110.9
C(1)-C(2)-H(2B)	110.9
C(3)-C(2)-H(2B)	110.9
H(2A)-C(2)-H(2B)	109.0
C(4)-C(3)-C(2)	102.11(11)
C(4)-C(3)-C(13)	109.51(12)
C(2)-C(3)-C(13)	109.65(11)
C(4)-C(3)-C(9)	103.10(11)
C(2)-C(3)-C(9)	122.47(12)
C(13)-C(3)-C(9)	109.06(11)
C(5)-C(4)-C(7)	134.26(13)
C(5)-C(4)-C(3)	114.09(12)
C(7)-C(4)-C(3)	111.00(12)
C(4)-C(5)-C(1)	107.67(13)
C(4)-C(5)-C(6)	129.49(14)
C(1)-C(5)-C(6)	122.67(13)
C(5)-C(6)-H(6A)	109.5
C(5)-C(6)-H(6B)	109.5

H(6A)-C(6)-H(6B)	109.5
C(5)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(4)-C(7)-C(8)	103.60(11)
C(4)-C(7)-H(7A)	111.0
C(8)-C(7)-H(7A)	111.0
C(4)-C(7)-H(7B)	111.0
C(8)-C(7)-H(7B)	111.0
H(7A)-C(7)-H(7B)	109.0
C(7)-C(8)-C(9)	106.77(12)
C(7)-C(8)-H(8A)	110.4
C(9)-C(8)-H(8A)	110.4
C(7)-C(8)-H(8B)	110.4
C(9)-C(8)-H(8B)	110.4
H(8A)-C(8)-H(8B)	108.6
C(10)-C(9)-C(14)	110.61(12)
C(10)-C(9)-C(3)	113.97(11)
C(14)-C(9)-C(3)	110.82(12)
C(10)-C(9)-C(8)	110.76(11)
C(14)-C(9)-C(8)	108.71(12)
C(3)-C(9)-C(8)	101.55(12)
C(15)-C(10)-C(11)	117.96(13)
C(15)-C(10)-C(9)	119.07(13)
C(11)-C(10)-C(9)	122.96(13)
C(18)-C(11)-C(10)	120.73(14)
C(18)-C(11)-C(12)	118.88(12)
C(10)-C(11)-C(12)	120.40(12)
C(11)-C(12)-C(13)	112.19(11)
C(11)-C(12)-H(12A)	109.2
C(13)-C(12)-H(12A)	109.2
C(11)-C(12)-H(12B)	109.2
C(13)-C(12)-H(12B)	109.2
H(12A)-C(12)-H(12B)	107.9
C(12)-C(13)-C(3)	111.46(12)
C(12)-C(13)-H(13A)	109.3
C(3)-C(13)-H(13A)	109.3
C(12)-C(13)-H(13B)	109.3

C(3)-C(13)-H(13B)	109.3
H(13A)-C(13)-H(13B)	108.0
C(9)-C(14)-H(14A)	109.5
C(9)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
C(9)-C(14)-H(14C)	109.5
H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
C(16)-C(15)-C(10)	122.19(14)
C(16)-C(15)-H(15)	118.9
C(10)-C(15)-H(15)	118.9
C(15)-C(16)-C(17)	119.15(14)
C(15)-C(16)-H(16)	120.4
C(17)-C(16)-H(16)	120.4
C(16)-C(17)-O(2)	122.84(14)
C(16)-C(17)-C(18)	121.19(13)
O(2)-C(17)-C(18)	115.96(12)
C(17)-C(18)-C(11)	118.69(13)
C(17)-C(18)-C(19)	120.46(12)
C(11)-C(18)-C(19)	120.85(13)
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(2)-C(20)-H(20A)	109.5
O(2)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
O(2)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for bk_28jan09. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	17(1)	30(1)	1(1)	6(1)	-7(1)
O(2)	14(1)	24(1)	23(1)	1(1)	5(1)	-1(1)
C(1)	23(1)	19(1)	14(1)	1(1)	0(1)	-4(1)
C(2)	22(1)	14(1)	22(1)	0(1)	5(1)	2(1)
C(3)	16(1)	13(1)	18(1)	1(1)	4(1)	-1(1)
C(4)	18(1)	17(1)	14(1)	1(1)	0(1)	3(1)
C(5)	19(1)	20(1)	15(1)	1(1)	2(1)	0(1)
C(6)	23(1)	28(1)	22(1)	1(1)	6(1)	-3(1)
C(7)	23(1)	16(1)	26(1)	-2(1)	6(1)	0(1)
C(8)	22(1)	16(1)	24(1)	-6(1)	5(1)	-3(1)
C(9)	15(1)	18(1)	16(1)	-1(1)	2(1)	-1(1)
C(10)	16(1)	13(1)	17(1)	1(1)	2(1)	2(1)
C(11)	17(1)	12(1)	17(1)	2(1)	1(1)	1(1)
C(12)	19(1)	18(1)	14(1)	-1(1)	1(1)	-3(1)
C(13)	16(1)	16(1)	18(1)	-1(1)	1(1)	-3(1)
C(14)	22(1)	33(1)	17(1)	2(1)	3(1)	-3(1)
C(15)	20(1)	20(1)	17(1)	-4(1)	2(1)	-1(1)
C(16)	15(1)	21(1)	22(1)	-2(1)	0(1)	-2(1)
C(17)	15(1)	15(1)	20(1)	4(1)	5(1)	4(1)
C(18)	18(1)	13(1)	17(1)	2(1)	2(1)	3(1)
C(19)	17(1)	21(1)	19(1)	-1(1)	4(1)	0(1)
C(20)	19(1)	39(1)	31(1)	-1(1)	6(1)	-9(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for bk_28jan09.

	x	y	z	U(eq)
H(2A)	6935	-585	1510	23
H(2B)	7550	-455	3132	23
H(6A)	3796	907	4278	36
H(6B)	3621	-117	4115	36
H(6C)	2996	508	2866	36
H(7A)	5968	1965	4341	26
H(7B)	5281	2297	2821	26
H(8A)	7819	2488	3790	25
H(8B)	7207	2500	2158	25
H(12A)	7735	69	-139	21
H(12B)	7383	898	-1113	21
H(13A)	5723	577	169	20
H(13B)	6281	1535	470	20
H(14A)	9122	410	4166	36
H(14B)	7951	804	4797	36
H(14C)	9218	1373	4768	36
H(15)	10294	2041	3419	23
H(16)	11914	2268	2149	24
H(19A)	10511	964	-2007	29
H(19B)	9017	1244	-2285	29
H(19C)	9430	297	-1717	29
H(20A)	12931	2740	462	44
H(20B)	13689	2155	-464	44
H(20C)	13517	1827	1035	44

Table 6. Torsion angles [°] for bk_28jan09.

O(1)-C(1)-C(2)-C(3)	171.34(14)
C(5)-C(1)-C(2)-C(3)	-13.68(15)
C(1)-C(2)-C(3)-C(4)	17.60(14)
C(1)-C(2)-C(3)-C(13)	-98.46(13)
C(1)-C(2)-C(3)-C(9)	131.89(13)
C(2)-C(3)-C(4)-C(5)	-17.56(17)
C(13)-C(3)-C(4)-C(5)	98.60(15)
C(9)-C(3)-C(4)-C(5)	-145.41(13)
C(2)-C(3)-C(4)-C(7)	154.60(12)
C(13)-C(3)-C(4)-C(7)	-89.24(14)
C(9)-C(3)-C(4)-C(7)	26.74(15)
C(7)-C(4)-C(5)-C(1)	-160.44(16)
C(3)-C(4)-C(5)-C(1)	9.31(17)
C(7)-C(4)-C(5)-C(6)	14.8(3)
C(3)-C(4)-C(5)-C(6)	-175.46(14)
O(1)-C(1)-C(5)-C(4)	178.19(15)
C(2)-C(1)-C(5)-C(4)	3.29(16)
O(1)-C(1)-C(5)-C(6)	2.6(2)
C(2)-C(1)-C(5)-C(6)	-172.34(13)
C(5)-C(4)-C(7)-C(8)	164.75(17)
C(3)-C(4)-C(7)-C(8)	-5.23(16)
C(4)-C(7)-C(8)-C(9)	-18.48(15)
C(4)-C(3)-C(9)-C(10)	-155.24(12)
C(2)-C(3)-C(9)-C(10)	90.97(15)
C(13)-C(3)-C(9)-C(10)	-38.94(16)
C(4)-C(3)-C(9)-C(14)	79.22(14)
C(2)-C(3)-C(9)-C(14)	-34.57(17)
C(13)-C(3)-C(9)-C(14)	-164.48(12)
C(4)-C(3)-C(9)-C(8)	-36.11(13)
C(2)-C(3)-C(9)-C(8)	-149.90(12)
C(13)-C(3)-C(9)-C(8)	80.19(13)
C(7)-C(8)-C(9)-C(10)	155.68(12)
C(7)-C(8)-C(9)-C(14)	-82.59(15)
C(7)-C(8)-C(9)-C(3)	34.29(14)
C(14)-C(9)-C(10)-C(15)	-47.49(17)
C(3)-C(9)-C(10)-C(15)	-173.13(13)

C(8)-C(9)-C(10)-C(15)	73.11(17)
C(14)-C(9)-C(10)-C(11)	133.51(15)
C(3)-C(9)-C(10)-C(11)	7.86(19)
C(8)-C(9)-C(10)-C(11)	-105.89(15)
C(15)-C(10)-C(11)-C(18)	3.2(2)
C(9)-C(10)-C(11)-C(18)	-177.79(13)
C(15)-C(10)-C(11)-C(12)	-176.70(13)
C(9)-C(10)-C(11)-C(12)	2.3(2)
C(18)-C(11)-C(12)-C(13)	-159.65(12)
C(10)-C(11)-C(12)-C(13)	20.24(18)
C(11)-C(12)-C(13)-C(3)	-53.27(16)
C(4)-C(3)-C(13)-C(12)	174.99(11)
C(2)-C(3)-C(13)-C(12)	-73.74(15)
C(9)-C(3)-C(13)-C(12)	62.85(14)
C(11)-C(10)-C(15)-C(16)	-1.5(2)
C(9)-C(10)-C(15)-C(16)	179.49(13)
C(10)-C(15)-C(16)-C(17)	-1.2(2)
C(15)-C(16)-C(17)-O(2)	-178.66(13)
C(15)-C(16)-C(17)-C(18)	2.1(2)
C(20)-O(2)-C(17)-C(16)	2.1(2)
C(20)-O(2)-C(17)-C(18)	-178.65(13)
C(16)-C(17)-C(18)-C(11)	-0.4(2)
O(2)-C(17)-C(18)-C(11)	-179.68(12)
C(16)-C(17)-C(18)-C(19)	179.01(14)
O(2)-C(17)-C(18)-C(19)	-0.25(19)
C(10)-C(11)-C(18)-C(17)	-2.3(2)
C(12)-C(11)-C(18)-C(17)	177.61(13)
C(10)-C(11)-C(18)-C(19)	178.28(13)
C(12)-C(11)-C(18)-C(19)	-1.8(2)

Symmetry transformations used to generate equivalent atoms:

*4. X-ray crystallography data for compound **123***

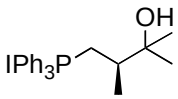


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Table 1. Crystal data and structure refinement for kerr_laurasept10.

Identification code	kerr_laurasept10	
Empirical formula	C24 H28 I O P	
Formula weight	490.33	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 10.0260(2) Å	α= 90∞.
	b = 17.0325(3) Å	β= 90∞.
	c = 26.4796(5) Å	γ = 90∞.
Volume	4521.86(15) $Å^3$	
Z	8	
Density (calculated)	1.441 Mg/m^3	
Absorption coefficient	1.498 mm^{-1}	
F(000)	1984	
Crystal size	0.49 x 0.32 x 0.23 mm^3	
Theta range for data collection	3.07 to 29.20°.	
Index ranges	-13<=h<=13, -22<=k<=18, -25<=l<=35	
Reflections collected	23202	
Independent reflections	10885 [R(int) = 0.0317]	
Completeness to theta = 27.00∞	99.8 %	
Absorption correction	Analytical	
Max. and min. transmission	0.776 and 0.652	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10885 / 2 / 501	
Goodness-of-fit on F^2	1.028	
Final R indices [I>2sigma(I)]	R1 = 0.0372, wR2 = 0.0609	
R indices (all data)	R1 = 0.0480, wR2 = 0.0641	
Absolute structure parameter	-0.024(12)	
Largest diff. peak and hole	0.741 and -0.378 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\approx^2$x 10^3) for kerr_laurasept10. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	7712(1)	2147(1)	1819(1)	28(1)
I(2)	16161(1)	-874(1)	660(1)	29(1)
P(1)	10892(1)	-724(1)	-1604(1)	21(1)
P(1A)	10604(1)	156(1)	1083(1)	19(1)
O(1)	12179(3)	1341(2)	-931(1)	30(1)
O(1A)	7848(3)	294(2)	-204(1)	28(1)
C(1)	11554(3)	-239(2)	-1055(1)	23(1)
C(1A)	9246(3)	655(2)	778(1)	21(1)
C(2)	13007(3)	35(2)	-1106(1)	24(1)
C(2A)	9548(3)	1013(2)	250(1)	22(1)
C(3)	13267(3)	815(2)	-820(1)	25(1)
C(3A)	8248(4)	1072(2)	-68(1)	25(1)
C(4)	13240(4)	698(2)	-248(1)	35(1)
C(4A)	8514(4)	1488(2)	-566(1)	33(1)
C(5)	14574(4)	1175(2)	-986(2)	35(1)
C(5A)	7124(4)	1478(2)	214(1)	32(1)
C(6)	13980(4)	-615(2)	-937(2)	40(1)
C(6A)	10266(4)	1795(2)	291(2)	37(1)
C(7)	12042(3)	-1467(2)	-1797(1)	21(1)
C(7A)	11939(3)	838(2)	1211(1)	21(1)
C(8)	12010(3)	-2204(2)	-1552(1)	29(1)
C(8A)	11599(4)	1457(2)	1532(1)	28(1)
C(9)	13017(4)	-2735(2)	-1637(2)	39(1)
C(9A)	12532(4)	2028(2)	1650(1)	31(1)
C(10)	14055(4)	-2547(2)	-1954(2)	39(1)
C(10A)	13808(4)	1980(2)	1458(1)	29(1)
C(11)	14101(4)	-1828(3)	-2197(2)	34(1)
C(11A)	14136(4)	1371(2)	1147(1)	30(1)
C(12)	13080(4)	-1289(2)	-2121(1)	28(1)
C(12A)	13212(3)	798(2)	1014(1)	24(1)
C(13)	10660(3)	-43(2)	-2115(1)	21(1)
C(13A)	11088(3)	-676(2)	704(1)	21(1)
C(14)	10684(4)	759(2)	-2039(1)	29(1)

C(14A)	12345(4)	-1028(2)	750(2)	33(1)
C(15)	10420(4)	1265(2)	-2433(2)	34(1)
C(15A)	12659(4)	-1678(2)	456(2)	38(1)
C(16)	10086(4)	976(2)	-2905(1)	30(1)
C(16A)	11734(4)	-1986(2)	130(2)	33(1)
C(17)	10054(4)	180(2)	-2981(1)	28(1)
C(17A)	10496(4)	-1652(2)	92(1)	32(1)
C(18)	10347(4)	-334(2)	-2594(1)	27(1)
C(18A)	10157(4)	-998(2)	370(1)	26(1)
C(19)	9313(3)	-1174(2)	-1451(1)	23(1)
C(19A)	10065(3)	-175(2)	1694(1)	21(1)
C(20)	8769(4)	-1719(2)	-1782(2)	32(1)
C(20A)	10996(4)	-540(2)	2011(1)	25(1)
C(21)	7545(4)	-2053(2)	-1676(1)	35(1)
C(21A)	10644(4)	-768(2)	2491(1)	31(1)
C(22)	6878(4)	-1859(2)	-1239(1)	34(1)
C(22A)	9376(4)	-623(2)	2666(2)	37(1)
C(23)	7409(4)	-1306(2)	-910(1)	31(1)
C(23A)	8445(4)	-267(3)	2358(1)	38(1)
C(24)	8633(3)	-959(2)	-1017(1)	27(1)
C(24A)	8777(4)	-46(2)	1873(1)	29(1)

Table 3. Bond lengths [≈] and angles [∞] for kerr_laurasept10.

P(1)-C(7)	1.787(3)
P(1)-C(13)	1.798(3)
P(1)-C(1)	1.799(4)
P(1)-C(19)	1.804(4)
P(1A)-C(1A)	1.796(3)
P(1A)-C(19A)	1.799(4)
P(1A)-C(13A)	1.803(3)
P(1A)-C(7A)	1.805(3)
O(1)-C(3)	1.441(4)
O(1)-H(1H)	0.828(18)
O(1A)-C(3A)	1.430(4)
O(1A)-H(2H)	0.837(18)
C(1)-C(2)	1.535(5)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(1A)-C(2A)	1.554(5)
C(1A)-H(1A1)	0.9900
C(1A)-H(1A2)	0.9900
C(2)-C(6)	1.542(5)
C(2)-C(3)	1.552(5)
C(2)-H(2)	1.0000
C(2A)-C(6A)	1.518(5)
C(2A)-C(3A)	1.555(5)
C(2A)-H(2A)	1.0000
C(3)-C(5)	1.513(5)
C(3)-C(4)	1.526(5)
C(3A)-C(5A)	1.519(5)
C(3A)-C(4A)	1.521(5)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(4)-H(4C)	0.9800
C(4A)-H(4A1)	0.9800
C(4A)-H(4A2)	0.9800
C(4A)-H(4A3)	0.9800
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800

C(5)-H(5C)	0.9800
C(5A)-H(5A1)	0.9800
C(5A)-H(5A2)	0.9800
C(5A)-H(5A3)	0.9800
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(6)-H(6C)	0.9800
C(6A)-H(6A1)	0.9800
C(6A)-H(6A2)	0.9800
C(6A)-H(6A3)	0.9800
C(7)-C(12)	1.382(5)
C(7)-C(8)	1.414(5)
C(7A)-C(12A)	1.380(5)
C(7A)-C(8A)	1.396(5)
C(8)-C(9)	1.374(5)
C(8)-H(8)	0.9500
C(8A)-C(9A)	1.385(5)
C(8A)-H(8A)	0.9500
C(9)-C(10)	1.374(6)
C(9)-H(9)	0.9500
C(9A)-C(10A)	1.379(5)
C(9A)-H(9A)	0.9500
C(10)-C(11)	1.384(6)
C(10)-H(10)	0.9500
C(10A)-C(11A)	1.364(5)
C(10A)-H(10A)	0.9500
C(11)-C(12)	1.389(5)
C(11)-H(11)	0.9500
C(11A)-C(12A)	1.392(5)
C(11A)-H(11A)	0.9500
C(12)-H(12)	0.9500
C(12A)-H(12A)	0.9500
C(13)-C(14)	1.382(5)
C(13)-C(18)	1.396(5)
C(13A)-C(18A)	1.398(5)
C(13A)-C(14A)	1.400(5)
C(14)-C(15)	1.379(5)
C(14)-H(14)	0.9500

C(14A)-C(15A)	1.390(5)
C(14A)-H(14A)	0.9500
C(15)-C(16)	1.385(5)
C(15)-H(15)	0.9500
C(15A)-C(16A)	1.372(5)
C(15A)-H(15A)	0.9500
C(16)-C(17)	1.370(5)
C(16)-H(16)	0.9500
C(16A)-C(17A)	1.369(5)
C(16A)-H(16A)	0.9500
C(17)-C(18)	1.380(5)
C(17)-H(17)	0.9500
C(17A)-C(18A)	1.378(5)
C(17A)-H(17A)	0.9500
C(18)-H(18)	0.9500
C(18A)-H(18A)	0.9500
C(19)-C(24)	1.384(5)
C(19)-C(20)	1.389(5)
C(19A)-C(24A)	1.392(5)
C(19A)-C(20A)	1.399(5)
C(20)-C(21)	1.381(5)
C(20)-H(20)	0.9500
C(20A)-C(21A)	1.376(5)
C(20A)-H(20A)	0.9500
C(21)-C(22)	1.378(5)
C(21)-H(21)	0.9500
C(21A)-C(22A)	1.375(5)
C(21A)-H(21A)	0.9500
C(22)-C(23)	1.389(5)
C(22)-H(22)	0.9500
C(22A)-C(23A)	1.380(5)
C(22A)-H(22A)	0.9500
C(23)-C(24)	1.392(5)
C(23)-H(23)	0.9500
C(23A)-C(24A)	1.377(5)
C(23A)-H(23A)	0.9500
C(24)-H(24)	0.9500
C(24A)-H(24A)	0.9500

C(7)-P(1)-C(13)	108.92(17)
C(7)-P(1)-C(1)	108.61(16)
C(13)-P(1)-C(1)	111.08(17)
C(7)-P(1)-C(19)	109.26(16)
C(13)-P(1)-C(19)	109.25(16)
C(1)-P(1)-C(19)	109.69(16)
C(1A)-P(1A)-C(19A)	108.99(16)
C(1A)-P(1A)-C(13A)	109.04(16)
C(19A)-P(1A)-C(13A)	109.56(16)
C(1A)-P(1A)-C(7A)	110.06(16)
C(19A)-P(1A)-C(7A)	104.76(16)
C(13A)-P(1A)-C(7A)	114.27(16)
C(3)-O(1)-H(1H)	111(3)
C(3A)-O(1A)-H(2H)	116(3)
C(2)-C(1)-P(1)	114.8(2)
C(2)-C(1)-H(1A)	108.6
P(1)-C(1)-H(1A)	108.6
C(2)-C(1)-H(1B)	108.6
P(1)-C(1)-H(1B)	108.6
H(1A)-C(1)-H(1B)	107.5
C(2A)-C(1A)-P(1A)	116.2(2)
C(2A)-C(1A)-H(1A1)	108.2
P(1A)-C(1A)-H(1A1)	108.2
C(2A)-C(1A)-H(1A2)	108.2
P(1A)-C(1A)-H(1A2)	108.2
H(1A1)-C(1A)-H(1A2)	107.4
C(1)-C(2)-C(6)	110.9(3)
C(1)-C(2)-C(3)	112.1(3)
C(6)-C(2)-C(3)	111.6(3)
C(1)-C(2)-H(2)	107.3
C(6)-C(2)-H(2)	107.3
C(3)-C(2)-H(2)	107.3
C(6A)-C(2A)-C(1A)	111.9(3)
C(6A)-C(2A)-C(3A)	112.3(3)
C(1A)-C(2A)-C(3A)	110.4(3)
C(6A)-C(2A)-H(2A)	107.3
C(1A)-C(2A)-H(2A)	107.3

C(3A)-C(2A)-H(2A)	107.3
O(1)-C(3)-C(5)	110.1(3)
O(1)-C(3)-C(4)	105.7(3)
C(5)-C(3)-C(4)	111.0(3)
O(1)-C(3)-C(2)	107.7(3)
C(5)-C(3)-C(2)	110.5(3)
C(4)-C(3)-C(2)	111.6(3)
O(1A)-C(3A)-C(5A)	109.7(3)
O(1A)-C(3A)-C(4A)	105.2(3)
C(5A)-C(3A)-C(4A)	110.2(3)
O(1A)-C(3A)-C(2A)	108.1(3)
C(5A)-C(3A)-C(2A)	112.7(3)
C(4A)-C(3A)-C(2A)	110.7(3)
C(3)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(3A)-C(4A)-H(4A1)	109.5
C(3A)-C(4A)-H(4A2)	109.5
H(4A1)-C(4A)-H(4A2)	109.5
C(3A)-C(4A)-H(4A3)	109.5
H(4A1)-C(4A)-H(4A3)	109.5
H(4A2)-C(4A)-H(4A3)	109.5
C(3)-C(5)-H(5A)	109.5
C(3)-C(5)-H(5B)	109.5
H(5A)-C(5)-H(5B)	109.5
C(3)-C(5)-H(5C)	109.5
H(5A)-C(5)-H(5C)	109.5
H(5B)-C(5)-H(5C)	109.5
C(3A)-C(5A)-H(5A1)	109.5
C(3A)-C(5A)-H(5A2)	109.5
H(5A1)-C(5A)-H(5A2)	109.5
C(3A)-C(5A)-H(5A3)	109.5
H(5A1)-C(5A)-H(5A3)	109.5
H(5A2)-C(5A)-H(5A3)	109.5
C(2)-C(6)-H(6A)	109.5

C(2)-C(6)-H(6B)	109.5
H(6A)-C(6)-H(6B)	109.5
C(2)-C(6)-H(6C)	109.5
H(6A)-C(6)-H(6C)	109.5
H(6B)-C(6)-H(6C)	109.5
C(2A)-C(6A)-H(6A1)	109.5
C(2A)-C(6A)-H(6A2)	109.5
H(6A1)-C(6A)-H(6A2)	109.5
C(2A)-C(6A)-H(6A3)	109.5
H(6A1)-C(6A)-H(6A3)	109.5
H(6A2)-C(6A)-H(6A3)	109.5
C(12)-C(7)-C(8)	119.8(3)
C(12)-C(7)-P(1)	120.6(3)
C(8)-C(7)-P(1)	118.8(3)
C(12A)-C(7A)-C(8A)	119.5(3)
C(12A)-C(7A)-P(1A)	125.6(3)
C(8A)-C(7A)-P(1A)	114.8(3)
C(9)-C(8)-C(7)	119.5(4)
C(9)-C(8)-H(8)	120.3
C(7)-C(8)-H(8)	120.3
C(9A)-C(8A)-C(7A)	120.2(3)
C(9A)-C(8A)-H(8A)	119.9
C(7A)-C(8A)-H(8A)	119.9
C(8)-C(9)-C(10)	120.3(4)
C(8)-C(9)-H(9)	119.9
C(10)-C(9)-H(9)	119.9
C(10A)-C(9A)-C(8A)	120.1(4)
C(10A)-C(9A)-H(9A)	119.9
C(8A)-C(9A)-H(9A)	119.9
C(9)-C(10)-C(11)	121.0(4)
C(9)-C(10)-H(10)	119.5
C(11)-C(10)-H(10)	119.5
C(11A)-C(10A)-C(9A)	119.4(4)
C(11A)-C(10A)-H(10A)	120.3
C(9A)-C(10A)-H(10A)	120.3
C(10)-C(11)-C(12)	119.5(4)
C(10)-C(11)-H(11)	120.2
C(12)-C(11)-H(11)	120.2

C(10A)-C(11A)-C(12A)	121.7(3)
C(10A)-C(11A)-H(11A)	119.2
C(12A)-C(11A)-H(11A)	119.2
C(7)-C(12)-C(11)	120.0(4)
C(7)-C(12)-H(12)	120.0
C(11)-C(12)-H(12)	120.0
C(7A)-C(12A)-C(11A)	119.0(3)
C(7A)-C(12A)-H(12A)	120.5
C(11A)-C(12A)-H(12A)	120.5
C(14)-C(13)-C(18)	119.3(3)
C(14)-C(13)-P(1)	121.7(3)
C(18)-C(13)-P(1)	118.9(3)
C(18A)-C(13A)-C(14A)	119.2(3)
C(18A)-C(13A)-P(1A)	118.7(3)
C(14A)-C(13A)-P(1A)	122.1(3)
C(15)-C(14)-C(13)	120.2(3)
C(15)-C(14)-H(14)	119.9
C(13)-C(14)-H(14)	119.9
C(15A)-C(14A)-C(13A)	119.8(4)
C(15A)-C(14A)-H(14A)	120.1
C(13A)-C(14A)-H(14A)	120.1
C(14)-C(15)-C(16)	120.6(4)
C(14)-C(15)-H(15)	119.7
C(16)-C(15)-H(15)	119.7
C(16A)-C(15A)-C(14A)	120.2(4)
C(16A)-C(15A)-H(15A)	119.9
C(14A)-C(15A)-H(15A)	119.9
C(17)-C(16)-C(15)	119.3(4)
C(17)-C(16)-H(16)	120.4
C(15)-C(16)-H(16)	120.4
C(17A)-C(16A)-C(15A)	120.0(4)
C(17A)-C(16A)-H(16A)	120.0
C(15A)-C(16A)-H(16A)	120.0
C(16)-C(17)-C(18)	121.0(4)
C(16)-C(17)-H(17)	119.5
C(18)-C(17)-H(17)	119.5
C(16A)-C(17A)-C(18A)	121.4(4)
C(16A)-C(17A)-H(17A)	119.3

C(18A)-C(17A)-H(17A)	119.3
C(17)-C(18)-C(13)	119.7(4)
C(17)-C(18)-H(18)	120.1
C(13)-C(18)-H(18)	120.1
C(17A)-C(18A)-C(13A)	119.4(3)
C(17A)-C(18A)-H(18A)	120.3
C(13A)-C(18A)-H(18A)	120.3
C(24)-C(19)-C(20)	120.4(3)
C(24)-C(19)-P(1)	120.4(3)
C(20)-C(19)-P(1)	119.1(3)
C(24A)-C(19A)-C(20A)	119.0(3)
C(24A)-C(19A)-P(1A)	122.4(3)
C(20A)-C(19A)-P(1A)	118.5(3)
C(21)-C(20)-C(19)	119.8(4)
C(21)-C(20)-H(20)	120.1
C(19)-C(20)-H(20)	120.1
C(21A)-C(20A)-C(19A)	120.5(4)
C(21A)-C(20A)-H(20A)	119.7
C(19A)-C(20A)-H(20A)	119.7
C(22)-C(21)-C(20)	120.2(4)
C(22)-C(21)-H(21)	119.9
C(20)-C(21)-H(21)	119.9
C(22A)-C(21A)-C(20A)	119.8(4)
C(22A)-C(21A)-H(21A)	120.1
C(20A)-C(21A)-H(21A)	120.1
C(21)-C(22)-C(23)	120.3(4)
C(21)-C(22)-H(22)	119.9
C(23)-C(22)-H(22)	119.9
C(21A)-C(22A)-C(23A)	120.4(4)
C(21A)-C(22A)-H(22A)	119.8
C(23A)-C(22A)-H(22A)	119.8
C(22)-C(23)-C(24)	119.9(3)
C(22)-C(23)-H(23)	120.1
C(24)-C(23)-H(23)	120.1
C(24A)-C(23A)-C(22A)	120.4(4)
C(24A)-C(23A)-H(23A)	119.8
C(22A)-C(23A)-H(23A)	119.8
C(19)-C(24)-C(23)	119.4(4)

C(19)-C(24)-H(24)	120.3
C(23)-C(24)-H(24)	120.3
C(23A)-C(24A)-C(19A)	119.8(4)
C(23A)-C(24A)-H(24A)	120.1
C(19A)-C(24A)-H(24A)	120.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (≈^{2}x 10^3)for kerr_laurasept10. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	27(1)	30(1)	26(1)	-2(1)	-1(1)	6(1)
I(2)	26(1)	30(1)	30(1)	-2(1)	7(1)	-3(1)
P(1)	23(1)	22(1)	18(1)	-2(1)	1(1)	3(1)
P(1A)	18(1)	18(1)	22(1)	-1(1)	-4(1)	1(1)
O(1)	30(1)	29(2)	31(2)	-1(1)	-1(1)	3(1)
O(1A)	35(2)	26(2)	24(2)	-2(1)	1(1)	-5(1)
C(1)	27(2)	22(2)	20(2)	1(2)	0(2)	5(1)
C(1A)	17(2)	20(2)	26(2)	0(1)	-2(1)	2(1)
C(2)	24(2)	28(2)	21(2)	-2(2)	-2(2)	2(2)
C(2A)	20(2)	19(2)	28(2)	1(2)	2(2)	1(1)
C(3)	26(2)	25(2)	23(2)	-6(2)	-4(1)	2(2)
C(3A)	26(2)	25(2)	23(2)	-1(2)	-2(2)	2(2)
C(4)	38(2)	41(3)	25(2)	-6(2)	-2(2)	6(2)
C(4A)	38(2)	31(2)	29(2)	10(2)	-2(2)	2(2)
C(5)	32(2)	39(3)	35(2)	-10(2)	1(2)	-2(2)
C(5A)	30(2)	37(2)	30(2)	4(2)	-6(2)	12(2)
C(6)	29(2)	43(3)	47(3)	-8(2)	-13(2)	10(2)
C(6A)	37(2)	30(2)	44(3)	8(2)	-7(2)	-11(2)
C(7)	23(2)	20(2)	21(2)	-6(2)	-1(2)	2(1)
C(7A)	19(2)	20(2)	25(2)	-3(2)	-5(1)	-1(2)
C(8)	25(2)	23(2)	40(2)	0(2)	-3(2)	-5(2)
C(8A)	21(2)	31(2)	31(2)	-5(2)	4(2)	-2(2)
C(9)	39(2)	15(2)	62(3)	-2(2)	-8(2)	1(2)
C(9A)	34(2)	31(2)	29(2)	-4(2)	-3(2)	-5(2)
C(10)	31(2)	32(2)	53(3)	-19(2)	-5(2)	11(2)
C(10A)	26(2)	31(2)	29(2)	7(2)	-7(2)	-9(2)
C(11)	21(2)	51(3)	31(2)	-8(2)	3(2)	7(2)
C(11A)	18(2)	38(3)	34(2)	10(2)	4(2)	-2(2)
C(12)	29(2)	30(2)	24(2)	-3(2)	1(2)	4(2)
C(12A)	26(2)	25(2)	20(2)	2(2)	0(1)	2(2)
C(13)	21(2)	21(2)	20(2)	2(1)	0(2)	0(1)
C(13A)	23(2)	15(2)	26(2)	-1(1)	0(2)	-1(1)
C(14)	33(2)	29(2)	24(2)	-2(2)	-7(2)	-5(2)

C(14A)	32(2)	22(2)	46(2)	-4(2)	-7(2)	2(2)
C(15)	47(3)	23(2)	31(2)	2(2)	-9(2)	-5(2)
C(15A)	27(2)	26(2)	59(3)	-10(2)	-1(2)	9(2)
C(16)	32(2)	30(2)	28(2)	9(2)	-7(2)	1(2)
C(16A)	43(2)	16(2)	40(2)	-8(2)	7(2)	4(2)
C(17)	29(2)	36(2)	18(2)	-3(2)	-4(2)	6(2)
C(17A)	38(2)	23(2)	35(2)	-3(2)	-8(2)	-5(2)
C(18)	30(2)	26(2)	23(2)	-5(2)	-1(2)	8(2)
C(18A)	26(2)	26(2)	28(2)	-1(2)	-5(2)	5(2)
C(19)	22(2)	30(2)	19(2)	3(2)	1(2)	2(2)
C(19A)	25(2)	16(2)	22(2)	1(1)	-6(1)	-1(1)
C(20)	27(2)	39(2)	31(2)	-10(2)	4(2)	-4(2)
C(20A)	24(2)	25(2)	27(2)	1(2)	-5(2)	-1(2)
C(21)	28(2)	45(3)	32(2)	-7(2)	-4(2)	-2(2)
C(21A)	32(2)	29(2)	32(2)	10(2)	-15(2)	-7(2)
C(22)	19(2)	46(3)	36(2)	4(2)	-2(2)	-5(2)
C(22A)	42(2)	46(3)	21(2)	7(2)	-4(2)	-9(2)
C(23)	25(2)	46(3)	23(2)	0(2)	4(2)	7(2)
C(23A)	31(2)	55(3)	27(2)	7(2)	4(2)	0(2)
C(24)	27(2)	31(2)	22(2)	0(2)	-3(2)	5(2)
C(24A)	26(2)	35(2)	27(2)	4(2)	-1(2)	5(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\approx^2$x 10^3) for kerr_laurasept10.

	x	y	z	U(eq)
H(1A)	10989	223	-979	28
H(1B)	11491	-602	-764	28
H(1A1)	8498	279	741	25
H(1A2)	8939	1082	1003	25
H(2)	13176	136	-1472	29
H(2A)	10160	642	71	27
H(4A)	13281	1209	-80	52
H(4B)	14009	379	-146	52
H(4C)	12415	428	-152	52
H(4A1)	9303	1258	-727	49
H(4A2)	8670	2047	-504	49
H(4A3)	7741	1425	-789	49
H(5A)	14529	1301	-1347	53
H(5B)	15300	801	-927	53
H(5C)	14740	1656	-794	53
H(5A1)	6339	1515	-5	48
H(5A2)	7408	2007	313	48
H(5A3)	6899	1175	517	48
H(6A)	13799	-755	-585	60
H(6B)	14899	-425	-968	60
H(6C)	13860	-1079	-1151	60
H(6A1)	10510	1979	-47	55
H(6A2)	11074	1731	495	55
H(6A3)	9677	2180	452	55
H(8)	11298	-2332	-1330	35
H(8A)	10725	1487	1669	33
H(9)	12997	-3233	-1476	46
H(9A)	12293	2453	1864	38
H(10)	14751	-2917	-2007	46
H(10A)	14453	2367	1542	34
H(11)	14827	-1704	-2413	41
H(11A)	15019	1338	1018	36

H(12)	13096	-799	-2292	33
H(12A)	13453	385	791	28
H(14)	10883	963	-1713	35
H(14A)	12980	-822	981	40
H(15)	10468	1816	-2380	40
H(15A)	13518	-1911	482	45
H(16)	9881	1325	-3174	36
H(16A)	11953	-2431	-70	39
H(17)	9827	-20	-3304	34
H(17A)	9858	-1875	-131	38
H(18)	10335	-884	-2653	32
H(18A)	9298	-769	336	32
H(20)	9238	-1862	-2080	39
H(20A)	11878	-630	1893	30
H(21)	7163	-2418	-1906	42
H(21A)	11275	-1025	2702	37
H(22)	6051	-2104	-1162	40
H(22A)	9140	-768	3000	44
H(23)	6937	-1166	-612	38
H(23A)	7568	-175	2480	45
H(24)	8999	-577	-795	32
H(24A)	8130	194	1662	35
H(2H)	7340(30)	70(20)	1(12)	34(12)
H(1H)	12430(40)	1699(18)	-1120(12)	36(13)

Table 6. Torsion angles [∞] for kerr_laurasept10.

C(7)-P(1)-C(1)-C(2)	49.8(3)
C(13)-P(1)-C(1)-C(2)	-70.0(3)
C(19)-P(1)-C(1)-C(2)	169.1(3)
C(19A)-P(1A)-C(1A)-C(2A)	177.6(2)
C(13A)-P(1A)-C(1A)-C(2A)	-62.8(3)
C(7A)-P(1A)-C(1A)-C(2A)	63.3(3)
P(1)-C(1)-C(2)-C(6)	-89.2(3)
P(1)-C(1)-C(2)-C(3)	145.4(3)
P(1A)-C(1A)-C(2A)-C(6A)	-80.2(3)
P(1A)-C(1A)-C(2A)-C(3A)	154.0(2)
C(1)-C(2)-C(3)-O(1)	-44.8(4)
C(6)-C(2)-C(3)-O(1)	-169.9(3)
C(1)-C(2)-C(3)-C(5)	-165.1(3)
C(6)-C(2)-C(3)-C(5)	69.8(4)
C(1)-C(2)-C(3)-C(4)	70.9(4)
C(6)-C(2)-C(3)-C(4)	-54.2(4)
C(6A)-C(2A)-C(3A)-O(1A)	164.2(3)
C(1A)-C(2A)-C(3A)-O(1A)	-70.3(4)
C(6A)-C(2A)-C(3A)-C(5A)	-74.4(4)
C(1A)-C(2A)-C(3A)-C(5A)	51.1(4)
C(6A)-C(2A)-C(3A)-C(4A)	49.5(4)
C(1A)-C(2A)-C(3A)-C(4A)	175.0(3)
C(13)-P(1)-C(7)-C(12)	33.9(3)
C(1)-P(1)-C(7)-C(12)	-87.2(3)
C(19)-P(1)-C(7)-C(12)	153.2(3)
C(13)-P(1)-C(7)-C(8)	-156.5(3)
C(1)-P(1)-C(7)-C(8)	82.4(3)
C(19)-P(1)-C(7)-C(8)	-37.2(3)
C(1A)-P(1A)-C(7A)-C(12A)	-117.6(3)
C(19A)-P(1A)-C(7A)-C(12A)	125.3(3)
C(13A)-P(1A)-C(7A)-C(12A)	5.4(4)
C(1A)-P(1A)-C(7A)-C(8A)	61.1(3)
C(19A)-P(1A)-C(7A)-C(8A)	-56.0(3)
C(13A)-P(1A)-C(7A)-C(8A)	-175.9(3)
C(12)-C(7)-C(8)-C(9)	0.2(5)
P(1)-C(7)-C(8)-C(9)	-169.5(3)

C(12A)-C(7A)-C(8A)-C(9A)	0.1(6)
P(1A)-C(7A)-C(8A)-C(9A)	-178.7(3)
C(7)-C(8)-C(9)-C(10)	0.7(6)
C(7A)-C(8A)-C(9A)-C(10A)	-1.1(6)
C(8)-C(9)-C(10)-C(11)	-0.7(6)
C(8A)-C(9A)-C(10A)-C(11A)	0.7(6)
C(9)-C(10)-C(11)-C(12)	-0.4(6)
C(9A)-C(10A)-C(11A)-C(12A)	0.5(6)
C(8)-C(7)-C(12)-C(11)	-1.2(5)
P(1)-C(7)-C(12)-C(11)	168.3(3)
C(10)-C(11)-C(12)-C(7)	1.3(6)
C(8A)-C(7A)-C(12A)-C(11A)	1.1(5)
P(1A)-C(7A)-C(12A)-C(11A)	179.7(3)
C(10A)-C(11A)-C(12A)-C(7A)	-1.5(5)
C(7)-P(1)-C(13)-C(14)	-134.2(3)
C(1)-P(1)-C(13)-C(14)	-14.6(4)
C(19)-P(1)-C(13)-C(14)	106.5(3)
C(7)-P(1)-C(13)-C(18)	50.8(3)
C(1)-P(1)-C(13)-C(18)	170.4(3)
C(19)-P(1)-C(13)-C(18)	-68.5(3)
C(1A)-P(1A)-C(13A)-C(18A)	-23.3(3)
C(19A)-P(1A)-C(13A)-C(18A)	95.9(3)
C(7A)-P(1A)-C(13A)-C(18A)	-146.9(3)
C(1A)-P(1A)-C(13A)-C(14A)	159.4(3)
C(19A)-P(1A)-C(13A)-C(14A)	-81.4(3)
C(7A)-P(1A)-C(13A)-C(14A)	35.8(4)
C(18)-C(13)-C(14)-C(15)	-0.9(6)
P(1)-C(13)-C(14)-C(15)	-175.9(3)
C(18A)-C(13A)-C(14A)-C(15A)	1.4(6)
P(1A)-C(13A)-C(14A)-C(15A)	178.7(3)
C(13)-C(14)-C(15)-C(16)	2.1(6)
C(13A)-C(14A)-C(15A)-C(16A)	-1.3(6)
C(14)-C(15)-C(16)-C(17)	-1.7(6)
C(14A)-C(15A)-C(16A)-C(17A)	0.0(6)
C(15)-C(16)-C(17)-C(18)	0.1(6)
C(15A)-C(16A)-C(17A)-C(18A)	1.2(6)
C(16)-C(17)-C(18)-C(13)	1.0(6)
C(14)-C(13)-C(18)-C(17)	-0.6(5)

P(1)-C(13)-C(18)-C(17)	174.5(3)
C(16A)-C(17A)-C(18A)-C(13A)	-1.0(6)
C(14A)-C(13A)-C(18A)-C(17A)	-0.3(5)
P(1A)-C(13A)-C(18A)-C(17A)	-177.6(3)
C(7)-P(1)-C(19)-C(24)	135.0(3)
C(13)-P(1)-C(19)-C(24)	-105.9(3)
C(1)-P(1)-C(19)-C(24)	16.1(4)
C(7)-P(1)-C(19)-C(20)	-47.1(3)
C(13)-P(1)-C(19)-C(20)	72.0(3)
C(1)-P(1)-C(19)-C(20)	-166.0(3)
C(1A)-P(1A)-C(19A)-C(24A)	0.4(4)
C(13A)-P(1A)-C(19A)-C(24A)	-118.9(3)
C(7A)-P(1A)-C(19A)-C(24A)	118.1(3)
C(1A)-P(1A)-C(19A)-C(20A)	-176.2(3)
C(13A)-P(1A)-C(19A)-C(20A)	64.5(3)
C(7A)-P(1A)-C(19A)-C(20A)	-58.5(3)
C(24)-C(19)-C(20)-C(21)	-0.4(6)
P(1)-C(19)-C(20)-C(21)	-178.4(3)
C(24A)-C(19A)-C(20A)-C(21A)	0.1(5)
P(1A)-C(19A)-C(20A)-C(21A)	176.8(3)
C(19)-C(20)-C(21)-C(22)	-1.3(6)
C(19A)-C(20A)-C(21A)-C(22A)	-1.4(6)
C(20)-C(21)-C(22)-C(23)	2.2(6)
C(20A)-C(21A)-C(22A)-C(23A)	1.6(6)
C(21)-C(22)-C(23)-C(24)	-1.3(6)
C(21A)-C(22A)-C(23A)-C(24A)	-0.7(7)
C(20)-C(19)-C(24)-C(23)	1.3(5)
P(1)-C(19)-C(24)-C(23)	179.2(3)
C(22)-C(23)-C(24)-C(19)	-0.5(5)
C(22A)-C(23A)-C(24A)-C(19A)	-0.6(6)
C(20A)-C(19A)-C(24A)-C(23A)	0.8(5)
P(1A)-C(19A)-C(24A)-C(23A)	-175.8(3)

Symmetry transformations used to generate equivalent atoms: