Applications of the Pauson-Khand Reaction in the Synthesis of Tricyclic Sesquiterpene Natural Products

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

By

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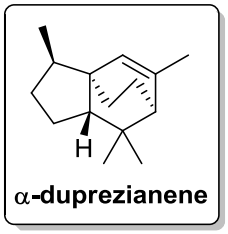
Abstract

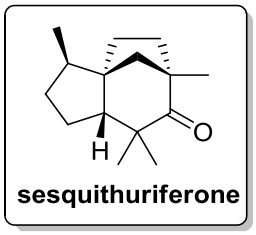
Within our laboratory, the syntheses of several related tricyclic sesquiterpene natural products have been completed, and, in all cases, the synthetic route employed the Pauson-Khand reaction (PKR) to generate the complex tricyclic core of each target. To further extend our studies within this area, we embarked upon synthesis of the [5,6,6]-fused tricyclic natural product α-duprezianene. Two main synthetic strategies towards construction of this complex and challenging target molecule have been investigated, and are described within.



The first of these strategies focussed on direct formation of the central [5,6,6]-fused skeleton structure in a rapid and efficient fashion through the PKR. Initial synthetic endeavour thus focussed on the generation of suitable enyne intermediates to allow investigation of this key PKR. Towards this aim, a series of novel routes were proposed and investigated, ultimately delivering the requisite enyne intermediates. Regrettably, PKR of these enynes was unsuccessful and an alternative approach towards the target molecule was thus required.

The second strategy towards formation of α-duprezianene involved initial construction of the related natural target sesquithuriferone. Indeed, formation of this target would provide a formal route to not only α-duprezianene, but also to a series of related sesquiterpene products. Once again, the PKR was employed in attempts to generate the [5,6,5]-fused tricyclic core of this target. In this regard, following investigation of several potential synthetic pathways, a robust and high yielding route

was developed providing a formal total synthesis of sesquithuriferone. Key to this strategy was an extremely efficient PKR which furnished the [5,6,5]-skeletal core of sesquithuriferone in rapid fashion. In establishing this route, the original target α-duprezianene was also accessed in a formal manner. The success of this work serves to further reinforce the utility of the PKR within organic synthesis.



sesquithuriferone

Acknowledgements

First and foremost I would like to thank Professor Billy Kerr, without whom none of the work described herein would have been possible. On welcoming me into your research group it was clear that I could not ask for a better supervisor. Your drive to motivate and further train your students is exceptional, and I am all the better for the experience. I would also like to extend my sincere gratitude to the group's research administrators, Dr. Laura Paterson and Dr. David Lindsay. Your continual aid throughout my tenure was essential to the success of the project. For the help each of you provided I am forever grateful.

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Having spent 9 years within its halls I also have a great deal of affection for the Thomas Graham Building within the University of Strathclyde. This is due to the high quality of both its academic and support staff. My thanks goes to all who helped me throughout my time, and will, no doubt, help many more in the years to come. A special word of thanks goes to Dr John Parkinson who provided invaluable insight in the final stages of the project.

I would like to thank my friends and family, chiefly my parents, who have been unendingly supportive throughout this long period of further education. I dedicate this thesis to you and the wealth of opportunities you have provided me with throughout my life. Lastly, I reserve my deepest and most enduring thanks to Alex, while all others have helped you have been closest to my side. With your superhuman patience, optimism and often a cold beer you have continually lifted my spirits when they were at their lowest point. For this I thank you from the bottom of my heart.

Abbreviations

)))	Ultrasonication
4 Å MS	4 Å molecular sieves
AcCl	Acetyl chloride
AcOH	Acetic acid
atm.	Atmospheres
BAIB	(Diacetoxyiodo)benzene
b.p.	Boiling point
n-BuLi	*n*-butyllithium
n-BuSMe	*n*-butyl methyl sulfide
d	Days
d.r.	Diastereomeric ratio
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DIPA	Di*iso*propylamine
DMS	Dimethyl sulfide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DodSMe	*n*-dodecyl methyl sulfide
DSAC	Dry state adsorption conditions
EDG	Electron donating group

EWG	Electron withdrawing group
Eq.	Equivalents
IR	Infrared
h	Hours
HCl	Hydrochloric acid
HRMS	High resolution mass spectrometry
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
min	Minutes
MWI	Microwave irradiation
NHC	*N*-heterocyclic carbene
NMO	*N*-methylmorpholine *N*-Oxide
NMR	Nuclear magnetic resonance
s	Singlet
d	Doublet
t	triplet
q	quartet
br	broad
NOE	Nuclear overhauser effect
OPP	Pyrophosphate
p-TsOH	*p*-toluenesulfonic acid
PEG	poly(ethylene glycol)

PG	Protecting group
Ph	Phenyl
PhH	Benzene
PhMe	Toluene
Piv	Pivaloyl
PKR	Pauson-Khand reaction
PPTS	Pyridinium *p*-tolunesulfonate
Quant.	Quantitative
r.t.	Room temperature
TBAI	Tetrabutylammonium iodide
TBAF	tetrabutylammonium flouride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl triflate
TES	triethylsilane
TESOTf	triethylsilane triflate
temp.	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TLC	Thin layer chromatography
TMANO	Trimethylamine *N*-oxide
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
TPAP	Tetrapropylammonium perruthenate

Contents

Chapter 1

The Pauson-Khand Reaction

1 Introduction

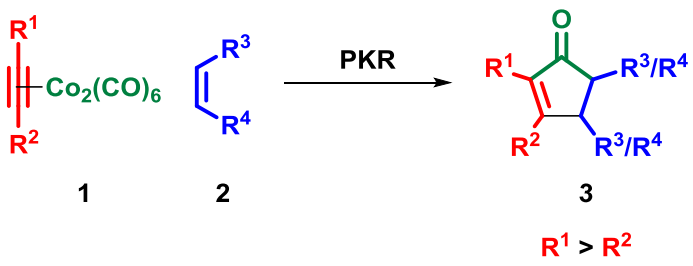
The desire to artificially generate naturally occurring molecules is longstanding within the scientific community. This aspiration led, in the mid-19th century, to the establishment of organic synthesis as a scientific discipline.[1] From these early forays the field has greatly enhanced to the mature, and prolific, area of research we know today, with the 20th century seeing significant advancements of both our understanding and accomplishments within synthetic organic chemistry. Both producing and showcasing this advancement were numerous landmark syntheses of complex natural products, which were established and reported to the community at large, providing benefits in many areas of scientific research.[2] These syntheses often arose from relatively simple and available precursors which through careful transformation, over multiple steps, successfully led to the intended target. The overall value of these syntheses and yielded compounds, coupled with the significant challenge encountered throughout their construction, has led the field of total synthesis to be described as both art and science.

To date, the pursuit of natural products remains a driving force in the development of synthetic organic research. The difficulty involved has in no way decreased. However, the organic chemist is now presented with a much expanded toolkit of transformations with which construction can be accomplished. From the 1950's onwards, one of the greatest developments in the field has been the employment of a variety of metal-mediated methods, which have significantly escalated both the profile and the preparative potential of organic synthesis.

Amongst these developed synthetic procedures were a number of novel methods for organic cyclisations, often employing organometallic complexes, which have been prominently utilised in numerous intricate syntheses. A noteworthy example is the Pauson-Khand reaction (PKR), which has found great favour within the synthetic community due to both its flexibility and atom economy, with numerous reviews having been written on the subject.[3–25] Our laboratory has focused on the advancement of this exciting methodology and its subsequent employment towards numerous complex challenging natural product targets (*vide infra*). Indeed, the programme of work contained in this thesis is centred on the PKR. As such, the following chapter shall provide a non-exhaustive discussion of the current state of this reaction methodology along with its development, scope, and applications within synthesis.

1.1 The Pauson-Khand reaction

Since its inception, the PKR has seen increasing employment in many fields of organic chemistry, with the efficiently generated cyclopentenone products of the PKR being highly sought after due to their ubiquitous value as building blocks in natural products, pharmaceuticals, and fine chemicals. The PKR was first reported in 1971 by I. U. Khand and P. L. Pauson, and is formally a [2+2+1] cycloaddition which utilises an alkyne, as its hexacarbonyldicobalt complex **1**, an alkene **2**, and carbon monoxide, present as a ligand within the complex, to generate cyclopentenone products **3** (**Scheme 1.1**).[26,27,]

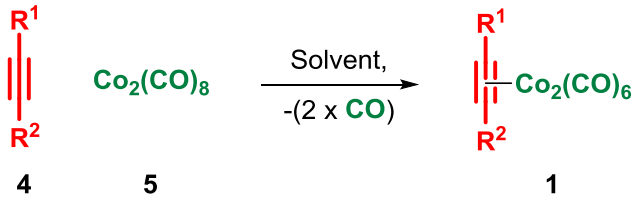


Scheme 1.1

As shown above, the more sterically bulky group (R^1) present on the alkyne substrate is typically installed at the α-position of the cyclopentenone product. In contrast, with respect to incorporation of the alkene component, regioselectivity within the final cyclopentenone product is often variable and particularly challenging to predict.

1.2 The alkyne-cobalt complex

While the PKR employs an alkyne moiety, it requires that this alkyne, **4**, first be converted to the requisite alkyne hexacarbonyldicobalt complex **1**. Fortunately, the preparation of complexes such as species **1** is a simple and robust procedure (**Scheme 1.2**). Typically, the desired complex is generated by reaction of the appropriate alkyne **4** with octacarbonyldicobalt **5** through stirring at room temperature (r.t.) in an inert solvent such as dichloromethane (DCM), petrol or ether.[28] During this time, displacement of the two bridging carbon monoxide ligands present in octacarbonyldicobalt **5** by the alkyne **4** furnishes the desired alkyne-cobalt complex **1**.[29,30] These reactions typically require a trivial purification *via* column chromatography through silica gel or alumina and are generally found to proceed in either quantitative or high yields. Furthermore, an extensive range of alkyne functionality is found to be tolerated, and, dependant on the alkyne substitution, these complexes tend to be relatively air stable at r.t. Indeed, storage under argon at low temperature allows the complexes to be retained indefinitely without degradation.



Scheme 1.2

X-Ray analysis of the alkyne-cobalt complex **1** has been successfully achieved, allowing far greater understanding of the structural and electronic arrangement of

this key intermediate. Knowledge of the subtle changes encountered on moving from the free alkyne, **4**, to the complexed state, **1**, has provided the basis for rationalisation of the complex reactivity observed during final cyclopentenone formation. With regards to structure, crystallographic studies have shown that complexes of this type contain two η^2 bridging bonds between the cobalt and carbon atoms of the alkyne (**Figure 1.1**).[28] Within this complex, the carbon atoms of the alkyne are observed to possess distorted tetrahedral geometry, while each cobalt atom shows distorted octahedral geometry. Further to this, the C_2Co_2 core of the complex, as a whole, appears to exhibit a *pseudo*-tetrahedral geometry, in which, the coordinated alkyne is observed to sit both perpendicular to and above the Co-Co bond. This is of fundamental importance with regards to the asymmetric PKR, as generation of a complex from an unsymmetrical alkyne would render the two $Co(CO)_3$ units enantiotopic, thus affording a prochiral complex.[31]

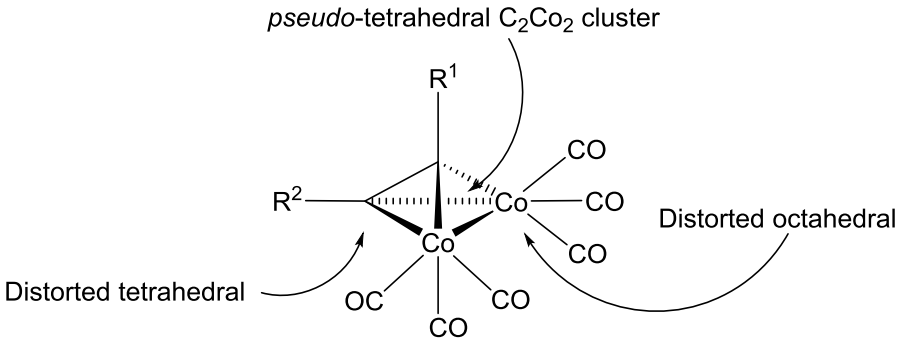


Figure 1.1

These crystallographic studies have also revealed that bond lengths of the alkyne differ before and after complexation. Prior to complexation, a distance of ~ 1.2 Å is observed compared to ~ 1.35 Å post complexation, indicating an increase in sp^2 rather than sp character in the complexed species.[28,32] The change in bond length observed is most likely a result of the complex metal-alkyne bonding orbital overlap. It has been suggested that as the alkyne bonds to the dicobalt species, σ-donation from the alkyne into the metal centres promotes the complexation. However, at the same time back donation from the metal to the alkyne ($d \rightarrow \pi^*$) ensues to further stabilise the complex. As the back donation occurs through the π*-orbitals of the

alkyne an overall lengthening of the carbon-carbon reflects the increased occupancy of the π*-orbital.[28,33]

Further analysis of the alkyne-cobalt complex has also been carried out through employment of infrared (IR) spectroscopy.[34,35] This research clearly displayed not only that the alkyne component is altered through complexation, cobalt, and its bound carbon monoxide units are also subtly changed. These IR studies showed C≡O stretches which had become non-equivalent post complexation. This appears to be a direct reflection of their relative position within the complex. When the complex is redrawn it can be seen that there are actually two distinct carbon monoxide environments, that of axial or equatorial (**Figure 1.2**). These two distinct environments arise from the distorted octahedral geometry of each cobalt atom within the complex. This differentiation in carbon monoxide environment is thought to be greatly involved in the observed regioselectivity of the reaction (*vide infra*).

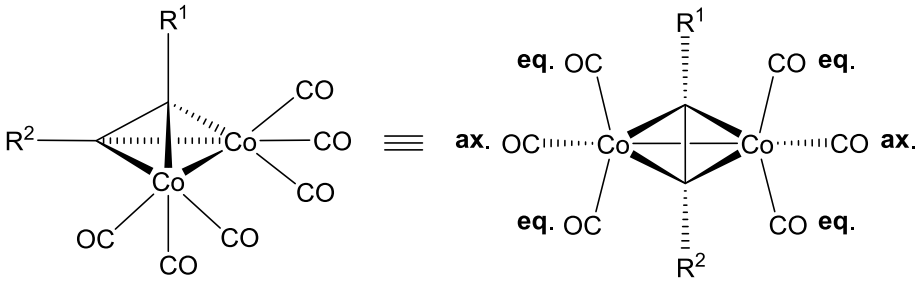
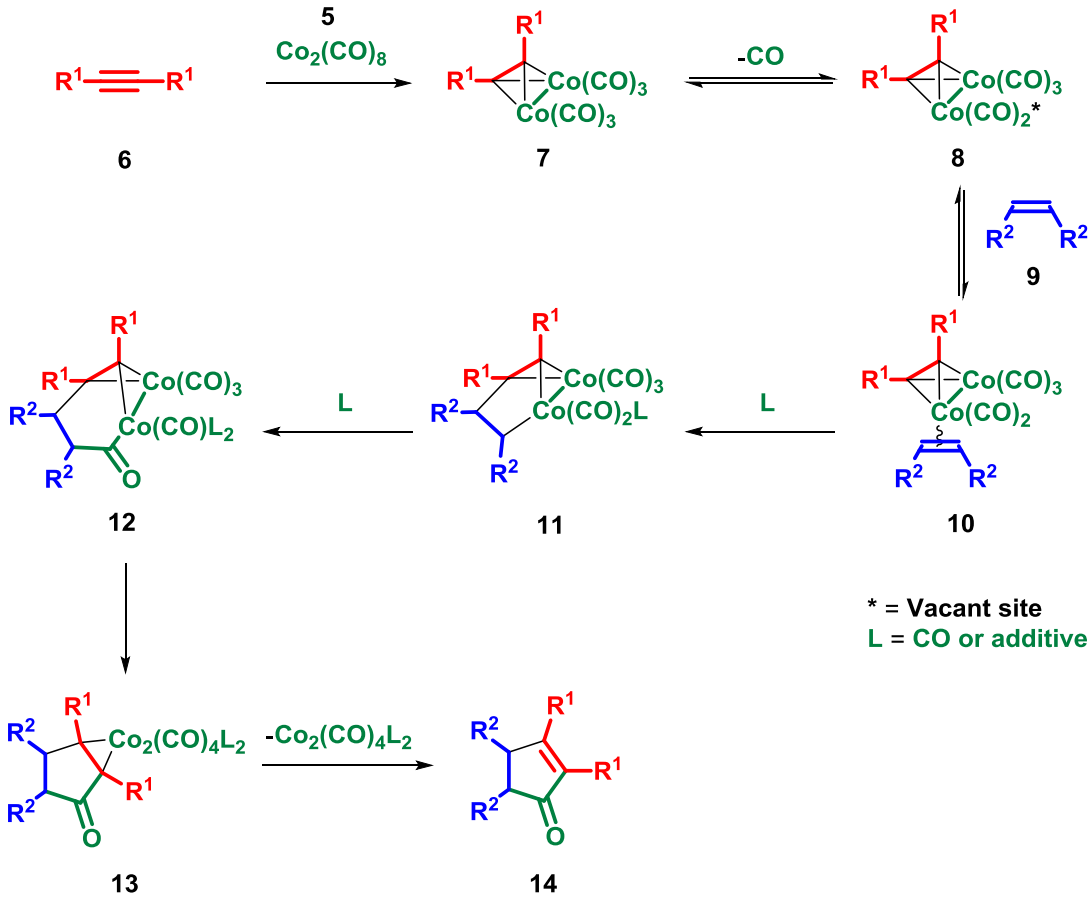


Figure 1.2

1.3 Reaction mechanism

To date, the mechanism of the PKR is yet to be fully elucidated, however, in 1985, Magnus and co-workers proposed a mechanism which remains generally accepted (**Scheme 1.3**).[36,37] The proposed mechanistic sequence was postulated with the intention of rationalising the diastereoselectivity observed in a series of experiments. The first step in Magnus' proposed PKR mechanism is the formation of the alkyne hexacarbonyldicobalt complex **7**. This occurs as previously discussed through

displacement of the two bridging carbon monoxide ligands in octacarbonyl dicobalt **5** by the alkyne **6**. The reaction then proceeds *via* a reversible carbon monoxide dissociation to produce the coordinatively unsaturated dicobalt pentacarbonyl species **8**. The vacant site present on alkyne pentacarbonyl dicobalt species **8** allows reversible coordination of the alkene **9** in a *trans* orientation to the alkyne carbon holding the sterically larger substituent, in turn yielding species **10**. Subsequent irreversible alkene insertion into the least hindered cobalt-carbon bond occurs to produce the cobaltacycle **11**. Following this, a molecule of carbon monoxide can insert itself into the newly formed cobalt-carbon bond to generate intermediate **12**. Two successive reductive elimination steps complete the mechanism generating intermediate **13** and the product cyclopentenone **14**, respectively.



Scheme 1.3

Having examined the proposed mechanism, it can be observed that there are four main events within the pathway that require further consideration:

i) Loss of carbon monoxide
ii) Alkene insertion
iii) Carbon monoxide insertion
iv) Reductive elimination

1.3.1 Loss of carbon monoxide

With respect to ligand substitution, experimental observation has demonstrated that performing the PKR under a carbon monoxide overpressure produces an inferior reaction rate. Indeed, this is considered to result from prevention of carbon monoxide dissociation and the subsequent formation of intermediate **8** (**Scheme 1.3**). In addition, it has been noted that when solvents with Lewis base character, or Lewis base additives are included the reaction, rate accelerates.[38] This likely occurs due to increased stabilisation of the coordinatively unsaturated intermediate **8**, which leads to more facile dissociation of the carbon monoxide ligands present. In PKRs performed under thermal conditions, with no nucleophilic additives, it is believed that the ligand substitution step is the rate-determining step of the reaction. With this in mind, numerous efforts to develop the reaction have focused on strategies which promote the loss of carbon monoxide; these methodologies will be discussed in a further section.

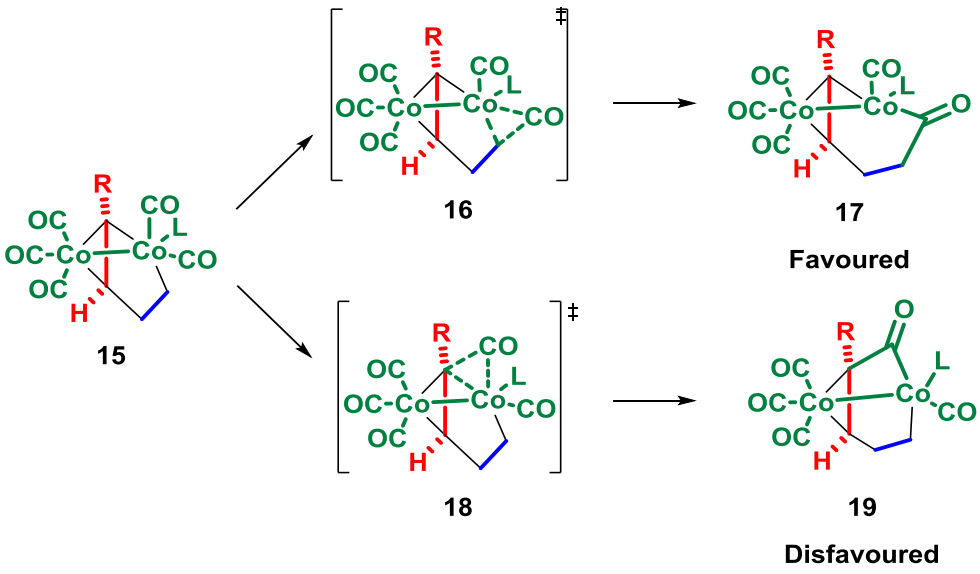
1.3.2 Alkene insertion

Alkene insertion is of particular importance within the PKR's mechanistic pathway as it is in this step that both the regio- and stereochemistry of the final cyclopentenone products are determined.[21] It has been observed that the alkene-substituted complex **10** readily transforms into cobaltacycle **11** (**Scheme 1.3**). In order for this step of the mechanistic pathway to successfully proceed, a *syn*-

periplanar arrangement between the carbon-cobalt bond and the carbon-carbon double bond of the participating alkene must be achieved. With respect to the control of regio- and stereochemistry that this step enforces, further discussion will be presented, in a later section.

1.3.3 Carbon monoxide insertion

On considering carbon monoxide insertion in the proposed mechanism it can be seen that insertion could occur between either of the two carbon-cobalt sigma bonds present in cobaltacycle **15** (**Scheme 1.4**). Generally, insertion of carbon monoxide has been considered to occur into the C(sp^3)-Co bond, i.e. into the newly formed C-Co bond, as can be seen in transition state **16**.[21] Further theoretical studies aimed towards elucidation of the PKR's mechanistic subtleties were performed by Yamanaka and Nakamura. From these investigations it was suggested that the insertion producing transition state **16**, leading to intermediate **17**, is favoured.[39] It was as such discerned that the alternative insertion, into the C(sp)-Co bond, leading to intermediate **19,** exhibits a marginally higher energy transition state. The difference between transition states **16** and **18** being 4 kcal mol^{-1}.

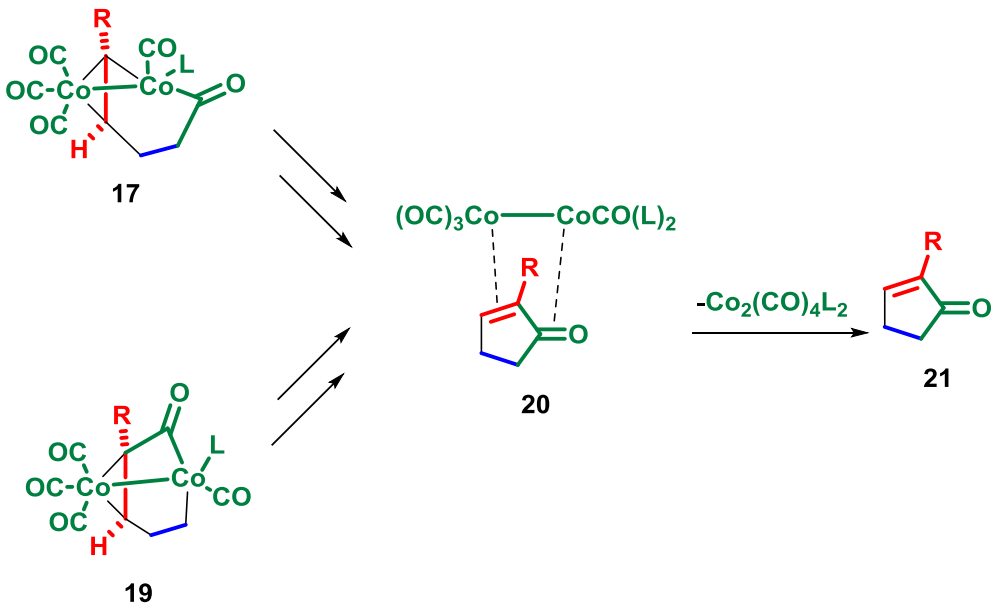


Scheme 1.4

Regardless of which bond experiences carbon monoxide insertion the nature of the final product remains unchanged. The subsequent reductive elimination steps of both **17** & **19** will lead to the same cyclopentenone product.

1.3.4 Reductive elimination

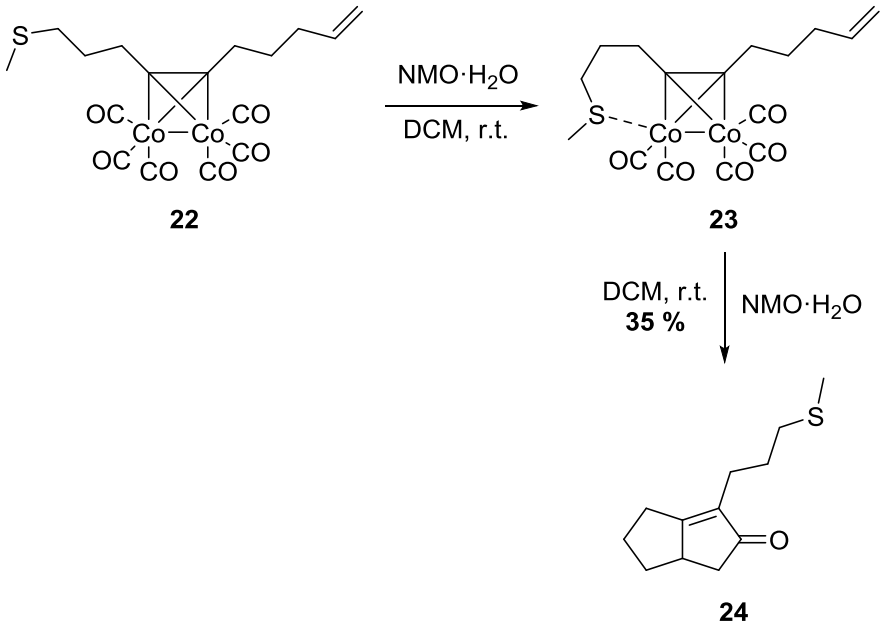
In a similar fashion to many of the intermediate species suggested by Magnus in his proposed PKR mechanism, acylcobaltacycles, such as intermediates **17** and **19**, are generally not observed experimentally (**Scheme 1.5**). It is considered that as soon as such intermediates are formed a double reductive elimination process will transpire leading to weakly bound cyclopentenone dicobalt complexes such as species **20**.[21,39] These complexes are expected to readily decompose generating the desired cyclopentenone product **21** and unstable cobalt residues. This step is of crucial importance with respect to the catalytic PKR, as the catalytic cycle's proliferation will depend on successful transfer of the dicobalt carbonyl moiety to new starting materials entering the reaction cycle.



Scheme 1.5

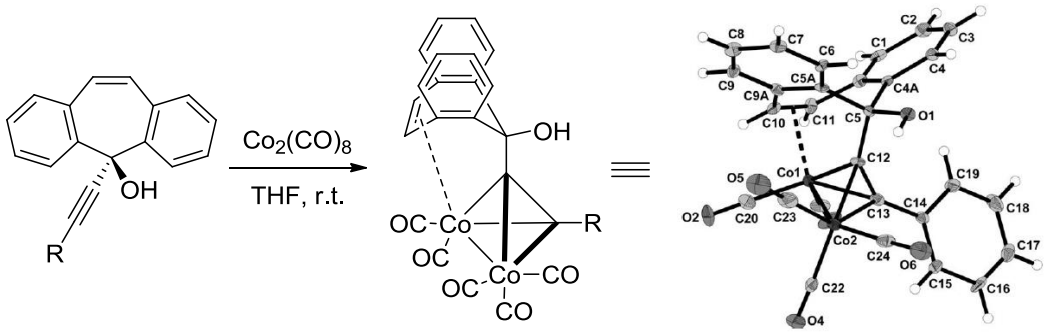
1.3.5 Evidence for the proposed mechanism

Since its original proposal in 1985, substantial research has been undertaken in an attempt to provide evidence which validates Magnus's PKR mechanism. While many of the suggested intermediates in this mechanistic pathway have not been observed experimentally, derivatives of the alkyne pentacarbonyldicobalt species, **8** have been successfully identified through low temperature IR spectroscopy.[34,40] Analogues of this alkyne pentacarbonyldicobalt species have also been successfully characterised in independent studies by Krafft, and Pericàs and Riera.[41,42,43] In these cases, the vacant coordination site of cobalt is occupied and stabilised by a sulfur atom present on an alkyl side chain. The first example, **23**, presented by Krafft and co-workers, was found to form during studies on the directed intramolecular PKR (**Scheme 1.6**).[41] In this case, it was found that reacting substrate **22** with *N*-methylmorpholine *N*-oxide (NMO) monohydrate, at ambient temperatures, generated the stabilised intermediate **23**. This intermediate could then be further transformed into cyclopentenone product **24**, albeit requiring 10 equivalents of NMO·H_2O and a reaction time of 5 days.



Scheme 1.6

Additional experimental evidence for the proposed mechanism has been obtained *via* X-ray crystallography, an example of such are the compounds **26a-e**, which were prepared by Evans and McGlinchey (**Scheme 1.7**).[35,44] The observation of these structures provided validation for coordination of alkenes to the alkyne pentacarbonyldicobalt intermediate prior to migratory insertion. Interestingly, compounds **26a-e**, while providing structural validation for the alkyne pentacarbonyldicobalt intermediate, do not in fact proceed through the PKR to yield cyclopentenone products. The authors believed that this lack of reactivity is a result of prohibitive molecular strain.

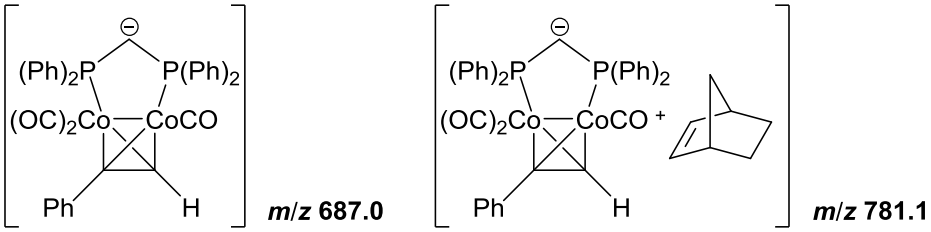


25a-e **26a-e** **26a**

26a: R = Ph, **26b**: R = TMS, **26c**: R = *p*-C_6H_4CN
26d: R = *p*-C_6HF, **26e**: R = *p*-C_6CF_3

Scheme 1.7

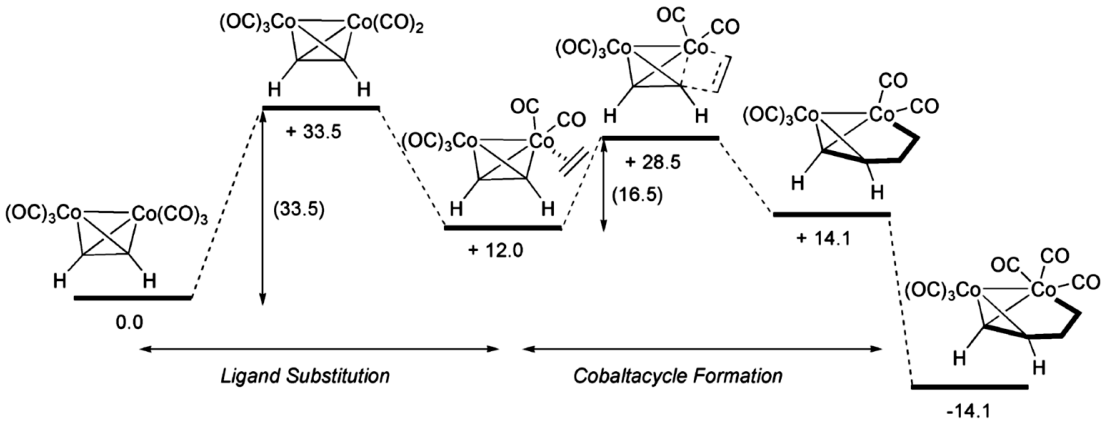
The reaction mechanism has been further probed through electrospray ionisation mass spectrometry. Employment of this method by Gimbert and co-workers allowed mass spectrometry conformation of two intermediates within the reaction pathway.[45] In order to achieve this, suitable substrates were generated featuring the easily deprotonated bridging ligand bis(diphenylphosphino)methane. Thus, the mass ion of intermediate **27**, correlating to the alkyne pentacarbonyldicobalt species, and intermediate **28** were detected (**Scheme 1.8**).



Scheme 1.8

With regards to intermediate **28**, it was proposed that this mass ion could correspond to either coordination of the alkene or the more advanced intermediate resulting from migratory insertion (**Scheme 1.8**). To further elucidate this observation, density functional theory (DFT) studies were conducted which strongly suggested that the observed ion resulted from the more advanced cobaltacycle intermediate. This provided the first observation of such an intermediate and yet more evidence for the proposed mechanistic pathway. Following this initial work, Fox and co-workers were able to isolate and further characterise a similar cobaltacycle intermediate which followed migratory insertion of the alkene.[46]

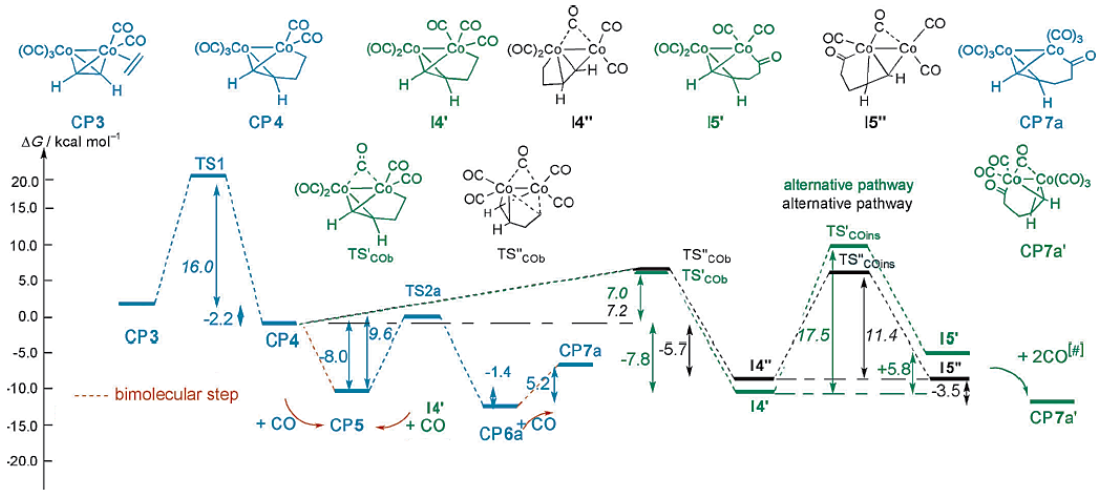
Computational experiments have also been employed to provide further validation of the proposed mechanism, with the first fully comprehensive theoretical study of the thermally promoted PKR reported in 2001 by Yamanaka and Nakamura.[39] This study was performed through the use of DFT calculations of simple substrates, and confirmed the feasibility of Magnus's proposed PKR mechanism. Shortly after, Pericàs and co-workers performed a complimentary DFT, study which further highlighted some of the reaction mechanisms key points (**Scheme 1.9**).[47]



Scheme 1.9[13]

It can be observed from these studies that overall the PKR is thermodynamically favourable. The PKR mechanism can be essentially split into two parts in terms of enthalpy. Throughout the ligand substitution process, from starting materials to coordination of the alkene, the reaction is essentially endothermic. However, the cobaltacycle formation onwards is found to be strongly exothermic and irreversible leading to the final cyclopentenone products. It was also concluded that loss of carbon monoxide is the most energy-demanding step in the entire reaction and thus the rate-determining step when the reaction is performed under thermal promotion. It should be noted however that the use of additives may alter the equilibrium and thus change the rate-determining step to that of the alkene insertion. In addition to validation of the proposed pathway, theoretical studies have also been of great importance to the elucidation of further aspects of the PKR such as its variations in substrate reactivity and the potential regio- and stereochemistry of the reaction.[48–55]

One such theoretical study was very recently performed by Gimbert and co-workers.[55] Following the group's previous investigations using mass spectrometry, further studies were performed in regard to the installation of carbon monoxide within the cobaltacycle. Their findings, made through a combination of mass spectrometry, and theoretical and kinetic calculations, have led them to publish further insight into the PKR mechanism (**Scheme 1.10**).



Scheme 1.10[55]

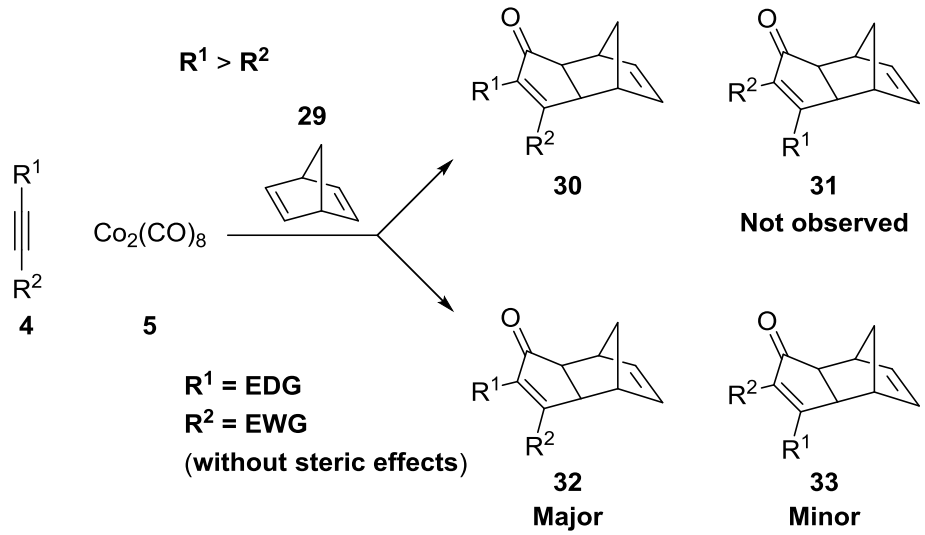
Gimbert and co-workers proposed that insertion of carbon monoxide, in the complex of type **CP4**, could occur through bridged transfer of CO between cobalt atoms (**Scheme 1.10**). To compare this proposed pathway to that previously disclosed additional calculations were performed based on Yamanaka and Nakamura's model (**blue pathway**). Since it was considered that CO insertion into the Co-C bond would likely involve a fully coordinated Co atom, an intramolecular migration of CO in the complex **CP4** was the first considered alternative, (**green pathway**). This pathway showed that such a structure could be formed through a bridged transfer of CO between cobalt atoms. It was observed that the transition state, **TS'COb**, was only 7.0 kcal mol^{-1} above intermediate **CP4** and thus could be easily accessed. This pathway could then lead to exothermic formation of the newly proposed intermediate **I4'**. CO insertion from **I4'** to form **I5'** can be seen to be the most energetically challenging step of this new pathway, however, it is still comparable to the energy required for formation of **CP4**. Another possible pathway has also been described, in which translocation of the cobaltacycle occurs through switching from one Co atom to the other, *via* **TS''COb**, (**black pathway**). This pathway would involve initial formation of a CO bridge between the two Co atoms, as shown in **I4''**. This migration allows the CO insertion to proceed at lower energy. Theoretical calculations thus suggest that alternative, potentially higher energy but intramolecular pathways, involving transfer or bridging of CO between cobalt atoms, are possible. This study clearly shows that while our understanding of the mechanism has advanced greatly from its initial postulation, further investigation

continues to be of a major concern and will be required to fully understand this transformation.

1.4 Regioselectivity in the intermolecular PKR

1.4.1 Alkyne regioselectivity

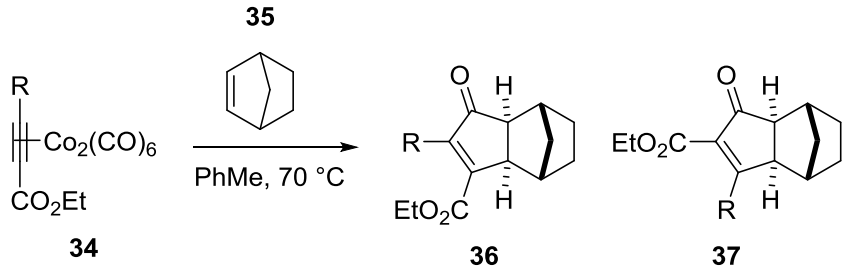
Classically, the PKR has been found to be highly regioselective with respect to alkyne incorporation.[5,21] In general, steric interactions during the course of the reaction lead the bulkier alkyne substituent to occupy the carbonyl's α-position in the final cyclopentenone product, **30**, with the opposite regioisomer, **31**, often not observed (**Scheme 1.11**).[56] It has however been indicated that in the absence of steric effects, substituents possessing electron donating groups (EDGs) will preferentially occupy the α-position, as in product **32**, whereas those with electron withdrawing groups (EWGs) will occupy the β-position.[57,49]



Scheme 1.11

It is the case for many PKRs employing nonsymmetrical alkynes, that the regiochemistry is often dependent on a combination of both steric and electronic

effects leading to products which can be problematic to predict.[49,53,58] An excellent example of this was reported by Krafft and co-workers (**Scheme 1.12 & Table 1.1**).[59] When the alkyne is terminal (R = H) its steric effect is much less than that of the ester group and, as such, electronic factors of the EWG do not significantly influence regiochemistry, i.e. sterics prevail and compound **37** dominates the product mixture. However, when the R group is switched to a methyl its steric effect is closer to that of the ester, and as such, electronic effects take over and the EWG occupies the β-position exclusively, as in compound **36**.

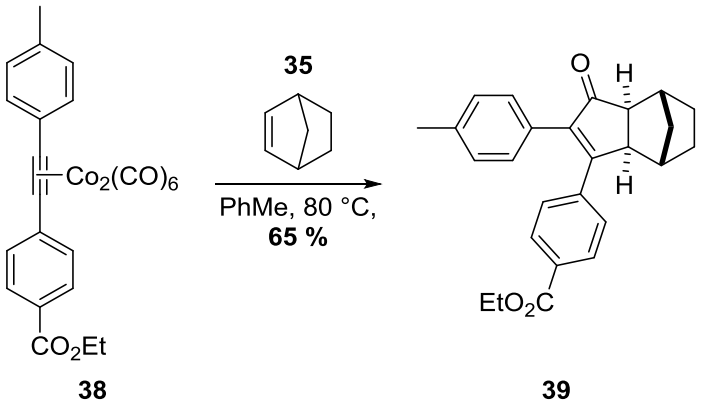


Scheme 1.12

Entry	R group	Yield (%)	Ratio 36:37
1	H	43	1:10
2	Me	78	1:0

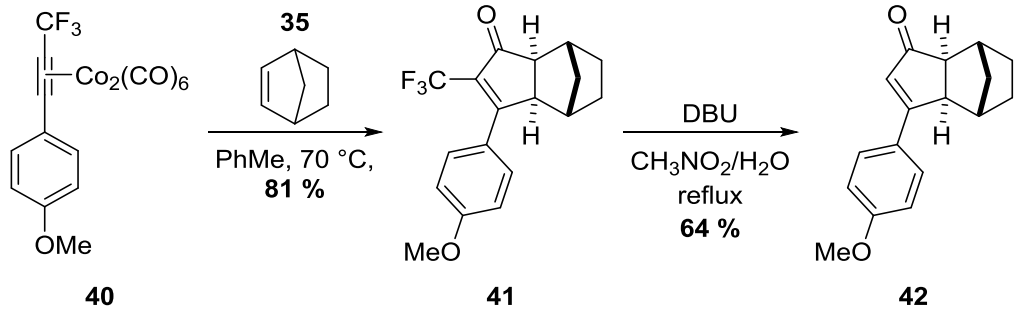
Table 1.1

Gimbert and Greene provided another excellent illustration of electronic effects versus steric effects on regioselectivity (**Scheme 1.13**).[48] In this instance, substrate **38** is an alkyne possessing two substituents which are electronically distinct but sterically similar. This difference in electronics leads to the substituent bearing the EWG occupying the β-position exclusively in the final cyclopentenone product **39**.



Scheme 1.13

While these examples show that electronics of the substrates play a large role in determining the product regiochemistry, recent research appears to show that such electronic effects can be overcome by steric effects.[53,54] An interesting example, which highlights this point is the incorporation of trifluoromethyl featuring alkynes such as compound **40**, performed by Riera and co-workers.[60,61] In this case, reaction with norbornene, **35**, resulted in cyclopentenone **41**, wherein the EWG is incorporated at the α-position (**Scheme 1.14**).[56] This is attributed to its large steric effect, despite its electronic nature. Interestingly, an efficient procedure to remove the trifluoromethyl group, following PKR, was also developed. Reaction of product **41** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in nitromethane, mixed with a small amount of water, was found to successfully yield novel β-substituted PK adducts such as product **42**.



Scheme 1.14

Interestingly, and in relation to alkyne substituents, it was theorised that electronic difference between the two alkyne termini may influence the position from which the CO ligand is lost, and thus, affect the regioselectivity of the reaction. Gimbert and Greene proposed that a *trans*-effect is in action producing differentiation in CO ligands surrounding the cobalt (**Figure 1.3**).[48] It was thought to arise from back donation to the alkyne component which weakens bonding to the pseudo-equatorial CO ligands leading these CO ligands to become more labile. This overall effect may explain the electronic bias determining the reversal in product regioselectivity when EWGs are present on the alkyne moiety.

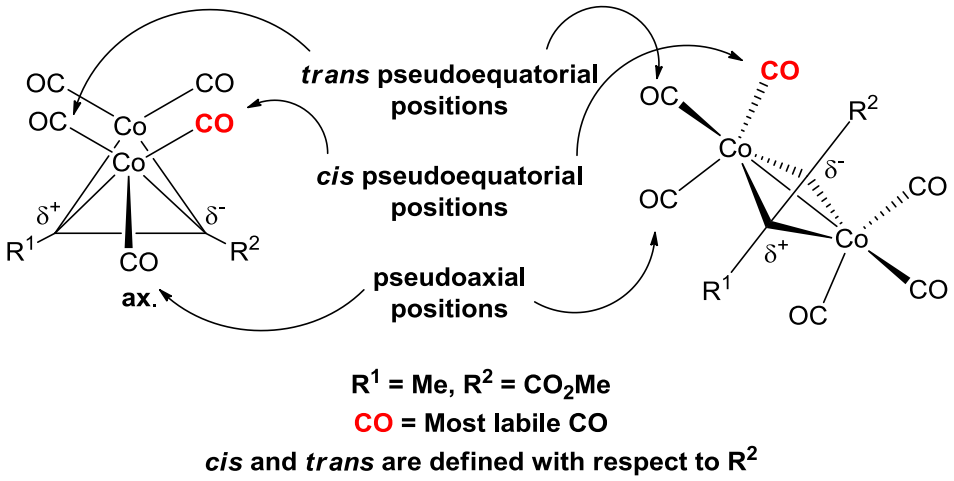


Figure 1.3

DFT studies have also shown that, energetically, the two equatorial CO ligands incur a lower energy barrier to removal than the axial CO ligand within the complex.[48] This results in the equatorial CO ligands becoming more available towards substitution by an alkene. Further to this, these DFT studies showed that the *trans* equatorial CO ligand is the most labile of the two equatorial positions, although the energy difference in comparison to the *cis* equatorial CO ligand is minimal.[50] At this stage in the mechanistic pathway, steric effects are able to reinforce the proposed electronic factors in determining the regioselectivity of the alkyne, ultimately (**Figure 1.4**). Thus, alkene co-ordination and insertion is favoured adjacent to the alkyne carbon containing least steric hindrance.

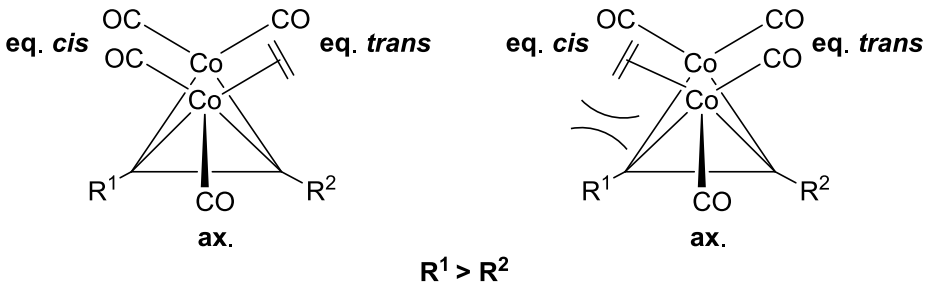
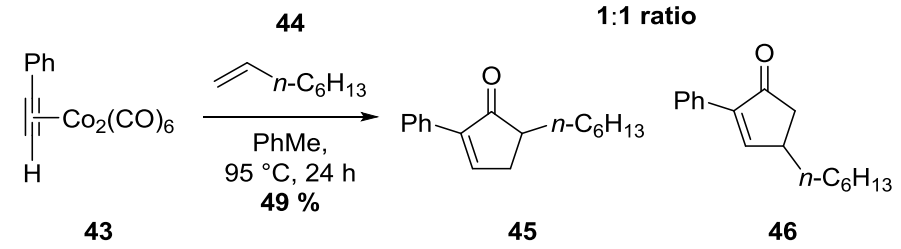


Figure 1.4

Following this work, Milet and Gimbert performed a study which suggested an alternative axial pathway.[49] This work showed that while the CO ligands are more labile when equatorial, the barrier to pseudo-rotation in the complex is also approachable, suggesting subsequent alkene insertion could occur from both axial and equatorial positions. It was suggested that in certain cases a near-equilibrium distribution among equatorial and axial positions could be established rapidly. However, the acetylinic carbon which carried the greater electron density would, in general, be that involved in C-C bond formation.[52] These reports serve to highlight the complex regiochemistry of the PKR and the challenges present in its understanding.

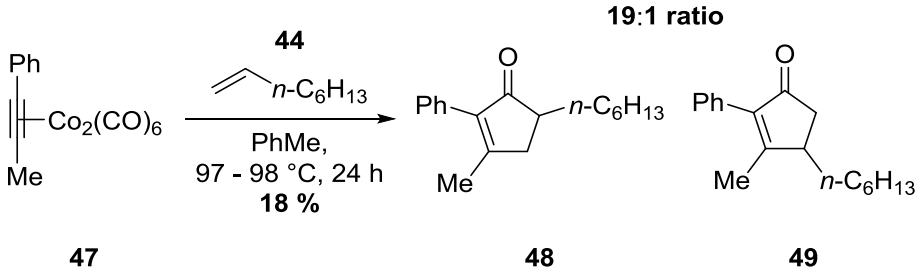
1.4.2 Alkene regioselectivity

With regards to insertion of the alkene component, it became apparent throughout development of the PKR that regioselectivity was much harder to predict.[5,21] Initially, it was believed that the alkene substrate's sterics and substitution pattern should provide insight to the regiochemical outcome. However, the regioselectivity for insertion is not dependent on just the alkene but also the alkyne's substitution further complicating prediction. An example of this poor regioselectivity was provided in early studies by Pauson and Khand (**Scheme 1.15**).[62] It was observed that the use of acyclic alkene substrates, such as **43**, yielded cyclopentenone products in which there was little to no regioselectivity with relation to incorporation of the alkene.



Scheme 1.15

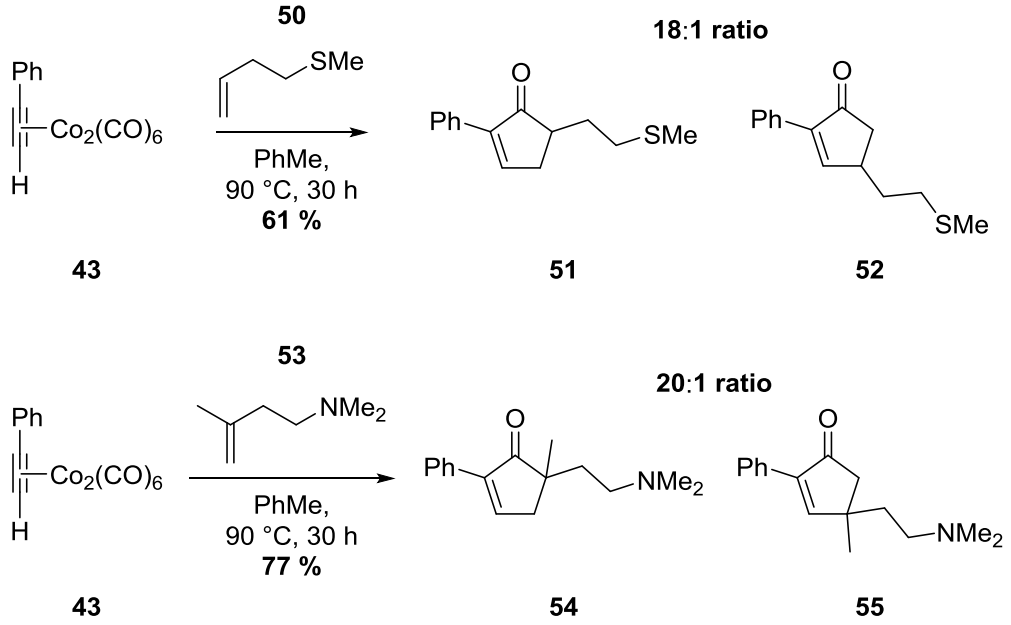
In contrast to this result, Krafft and co-workers showed that when the internal alkyne cobalt complex **47** was employed with the same alkene **44**, a remarkable improvement in regioselectivity could be observed (**Scheme 1.16)**.[63] This lead to the generation of cyclopentenone product **48**, albeit in a reduced chemical yield, in which the alkene's larger substituent occupied the α-position, in a 19:1 ratio.



Scheme 1.16

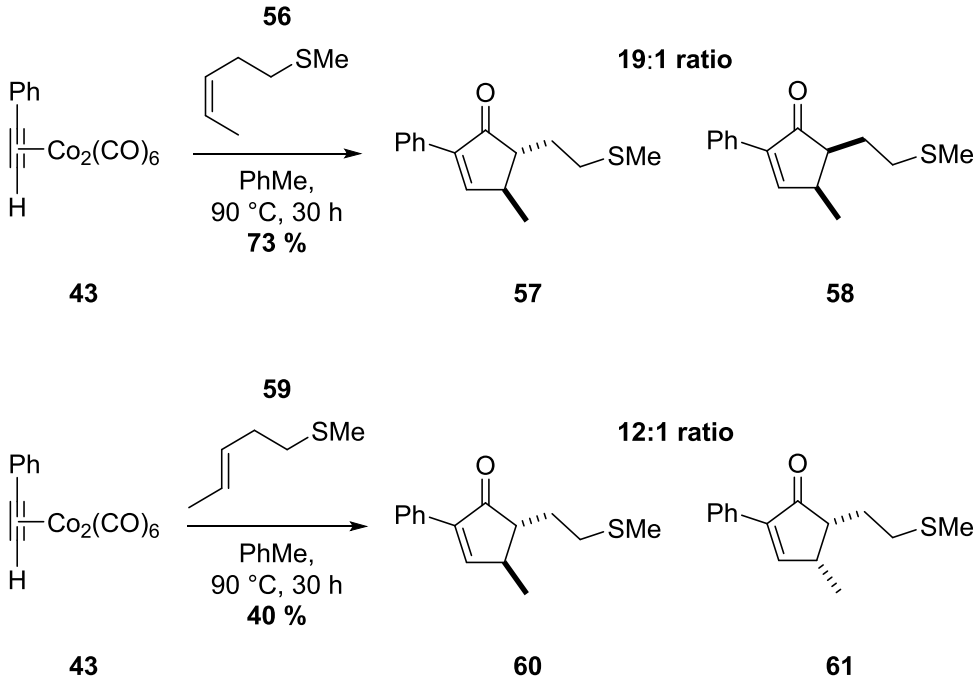
Further to this, Krafft and co-workers discovered that in the case of alkenes which are aryl-substituted, or substituted with heteroatom containing units, high regioselectivity could be achieved when the reaction was performed with terminal alkynes. In these experiments, homoallylic or bishomoallyic sulfides and amines were employed to increase both the efficiency and regioselectivity of the intermolecular PKR in what have come to be known as directed intermolecular PKRs.[41,63–65] These enhancements are believed to result from the tethered heteroatom units acting as soft donor ligands for the cobalt centre throughout the reaction pathway. This donor effect also restricts the conformational flexibility of the alkene in the complex, leading to more favourable insertion of the heteroatom substituent at the α-position of the cyclopentenone product. The effect is illustrated

in the reaction of phenylacetylene cobalt complex **43** with the sulfide containing olefin **50** to generate product **51** in an extremely selective manner (**Scheme 1.17**).[63,64] A further example is the reaction of the same alkyne complex **43** with amine containing olefin **53** to generate the final product, **54**, with even greater regiochemical control. The improved efficiency of these reactions should also be noted, with both showing significantly higher yields than the previously described examples (*vide supra*).



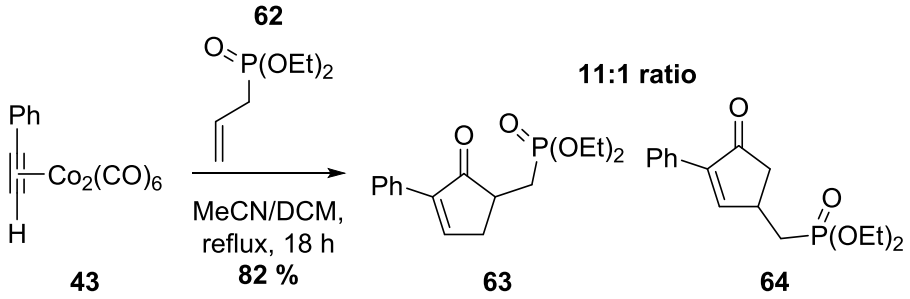
Scheme 1.17

It was noted by Kraft and co-workers that when performing these experiments the products formed from reaction with internal alkenes, such as **56** and **59**, a highly favoured a *trans* stereochemical relationship was observed (**Scheme 1.18**).[64] As can be seen, reaction of complex **43** with *Z*-olefin **56** provided the final products **57** and **59** in a 19:1 *trans* to *cis* ratio, while reaction with *E*-olefin yielded products **60** and **61** in a slightly lesser 12:1 *trans* to *cis* ratio. It was proposed that this occurred as the result of epimerisation of the product cyclopentenones to the most thermodynamically stable product, that of the *trans* orientation. This shows that these directed intermolecular PKR condition are able to confer both excellent regiocontrol and a high level of stereocontrol.



Scheme 1.18

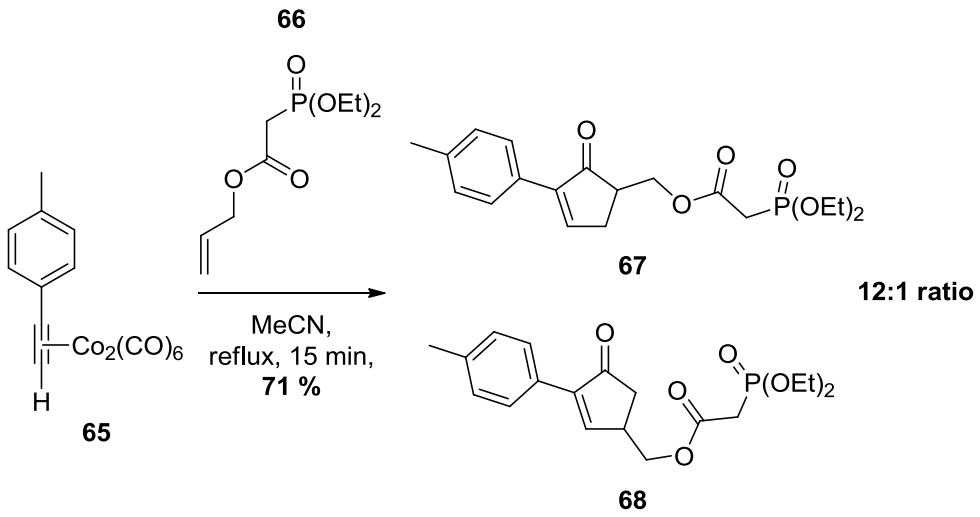
Following on from Krafft's establishment of the directed PKR, research within our own laboratory led to development of a similar system in which allylphosphonates were employed to induce a significantly high level of regiocontrol.[66] When diethyl allylphosphonate **62** was reacted with phenylacetylene cobalt complex **43** the resulting cyclopentenone **63** was produced in excellent yield and high regioselectivity (**Scheme 1.19**).



Scheme 1.19

Further studies within this area led to an extended class of alkenes containing a phosphonate ester moiety, such as **66**, which could be successfully employed in the

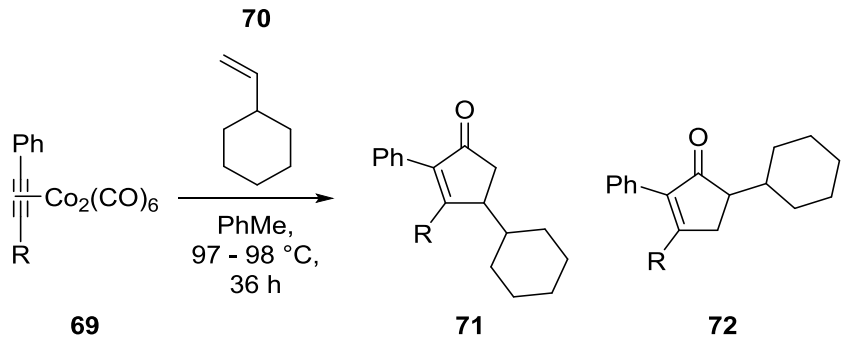
PKR (**Scheme 1.20**).[67] An illustrative example is the reaction of alkene **66** with complex **65** yielding product **67** in high yield and excellent regiochemical control. This phosphonate ester substrate class provides the added benefit of increased potential for further synthetic elaboration.



Scheme 1.20

1.5 General substrate reactivity

Since its initial development, the PKR has been shown to possess a substantially wide scope and tolerance for a variety of substrate structures and functionalities. With regards to the alkyne component it has been found that terminal substrates provided the highest degree of reactivity, with internal alkynes often displaying reduced yields.[5,21] An illustrative example of this was provided by Krafft, wherein it was observed that on moving from a terminal alkyne complex to the corresponding internal variant a significant reduction in yield, from 45 % to 22 % resulted (**Scheme 1.21 & Table 1.2**).[63] It should also be noted that the previously discussed regioselectivity trends can be observed within this substrate change. While this loss of reactivity on moving to internal alkynes would appear to limit the reaction scope, several methods of promotion have been developed which allow seemingly unreactive substrates to proceed through the PKR very efficiently (*vide infra*).



Scheme 1.21

Entry	R group	Yield (%)	Ratio 71:72
1	H	45	1:2.5
2	Me	22	0:1

Table 1.2

The alkene component shows a somewhat similar reactivity pattern with the least substituted alkenes generally being the most reactive. In relation to this trend, it is noteworthy that ethylene has been successfully employed in numerous PKRs, though elevated temperatures and high pressures of ethylene are typically required.[68–74] In addition to the above, it has been observed, under classical conditions, that strained cyclic species provide the best reactivity within the PKR. A theoretical study was performed by Milet, Gimbert and co-workers which provided some rationalisation for this tendency.[50] They noted that the reactivity of the alkene component is associated with back donation of electrons from the metal centre to the π* orbital, the lowest unoccupied molecular orbital (LUMO), of the olefin. It was also noted that a relationship exists between the C=C-C bond angle and the energy of the LUMO, wherein the smaller the angle the lower the LUMO energy. This discovery translates well to the previous experimental observations of olefin reactivity, where norbornene > cyclopentene >> cyclohexene (in the following table [a]angle refers to the C=C-C angle. [b]$LUMO_{coord}$ refers to the calculated energy of the olefin's LUMO when coordinated to the metal centre) (**Scheme 1.22 & Table 1.3**).[27,62,75,76]

43 **73** **74**

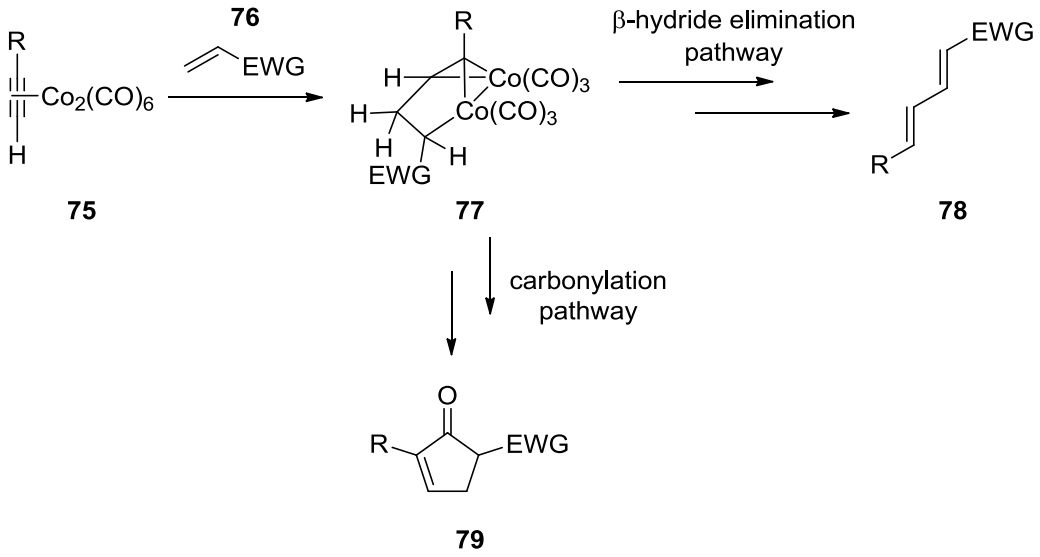
Scheme 1.22

Entry	Alkene	Angle[a]	$LUMO_{coord}$[b]	Conditions	Yield (%)
1	norbornene	107 °	-0.087 eV	mesitylene, 60-70 °C, 4 h	59
2	cyclopentene	112 °	+0.203 eV	PhMe, 160 °C, 80 atm, 7 h	47
3	cyclohexene	128 °	+0.336 eV	PhMe, reflux, 6 h	3

Table 1.3

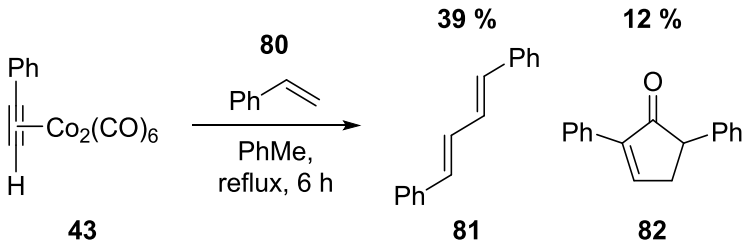
1.5.1 Conjugate alkenes

One distinct limitation within the PKR's substrate scope is olefins with conjugated EWG's and dienes, which often undergo alternative side reactions.[77] It has been observed that such substrates can yield complex mixtures of which conjugated alkenes are the largest component. It is believed that this occurs through a competing β-hydride elimination pathway. As such, following alkene insertion to provide **77**, β-hydride elimination generates the conjugated diene **78** instead of the normal pathway of carbonyl insertion (**Scheme 1.23**). This appears to be significantly faster than the desired carbonylation pathway which would ultimately form cyclopentenones of type **79**.



Scheme 1.23

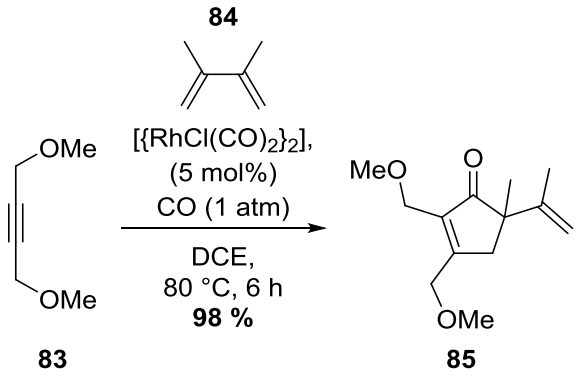
This competing pathway was noted by Pauson and Khand who provided a suitable example in the reaction of complex **43** with styrene **80** (**Scheme 1.24**).[62] Here, it can be seen that styrene appears to display intermediate behaviour with the conjugated diene **81** forming as the main product, however, some of the cyclopentenone **82** is also formed.



Scheme 1.24

While these results suggest that conjugated alkenes cannot be employed effectively within the PKR, much synthetic effort has been performed to develop suitable conditions for this class of substrate. Indeed, to this end, Wender and co-workers have been able to significantly increase the selectivity for the desired cyclopentenone product using a variety of conjugated diene substrates.[78–82] In order to accomplish this, rhodium-catalysed conditions, performed under an atmosphere of CO, were

developed and employed. An illustrative example of these conditions is the reaction of alkyne **83** and conjugated diene **84** to generate the desired cyclopentenone **85** in excellent yield (**Scheme 1.25**).[79] This efficiency of this protocol is remarkable when considering the challenges previously discussed with both conjugated alkenes and intermolecular PKR's, in general, however, it should be noted that up to 10 equivalents of the diene **90** was required. This example also serves to highlight the use of alternative metals and catalytic systems which have helped to expand the potential scope and applicability of the PKR (*vide infra*).



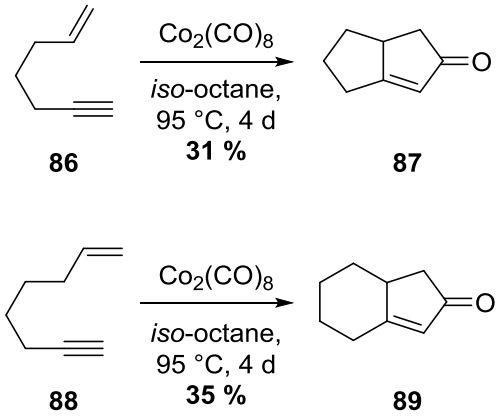
Scheme 1.25

1.6 The intramolecular PKR

With the observed challenges in regioselectivity for the intermolecular PKR, an intramolecular variant was sought. In this case, all issues of regioselectivity could be solved through tethering of the alkyne component to the alkene, with only one regioisomer having the possibility to form. This variation would not only allow regiochemical control it would also allow reversal of typically observed trends through initial synthesis of a suitable substrate.

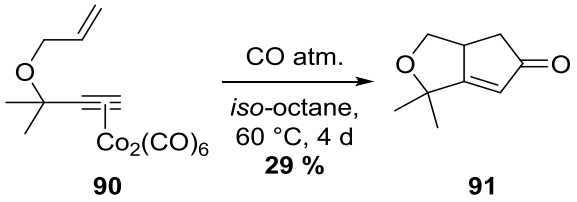
With this goal in mind, in the early 1980's the first example of an intramolecular PKR was reported by Schore and co-workers.[83] Within the original publication, the intramolecular reaction of hept-6-en-1-yne **86** and oct-7-en-1-yne **88** was shown to

successfully generate the bicyclopentenone products **87** and **89**; respectively (**Scheme 1.26**). It should, however, be noted that these initial reactions required a lengthy 4 days and proceeded in low yields.



Scheme 1.26

A notable development of the intramolecular PKR was the successful reaction of heteroatom tethered enynes to generate their respective bicyclopentenone products. An example of this is the fruitful, although low yielding, reaction of oxygen tethered complexed enyne **90** to generate the bicyclopentenone product **91** (**Scheme 1.27**).[84]



Scheme 1.27

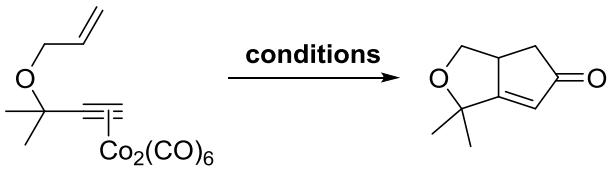
Since this time, the intramolecular PKR has been further developed and has found increasing use within organic synthesis, particularly in the field of natural product synthesis (*vide infra*). Indeed, the following sections will highlight some of the most impressive intramolecular examples to date.

1.7 Reaction promotion

Classically, the PKR required relatively harsh conditions, such as elevated temperatures and pressures, which often facilitated transformations of low efficiency. Additionally, many organic and organometallic by-products were also formed, which commonly led to challenging purifications and isolations of the desired cyclopentenones. These practical limitations considerably hindered the potential of this synthetically desirable reaction and, as such, a great deal of effort has been invested into the development of improved procedures for the PKR. Throughout the years since its inception, a number of research groups have attained this goal, reporting numerous methodologies which have enhanced the PKR through milder and more reliable reaction conditions, successfully transforming the PKR into a robust reaction with widespread synthetic use.

1.7.1 Dry state adsorption

In the mid 1980's a new PKR methodology was reported by Smit & Caple, which provided significant enhancements over the previously ubiquitous conditions.[85–88] This protocol required adsorption of the alkyne complex onto a solid support such as silica, alumina, or zeolite, coming to be known as dry state adsorption conditions (DSAC). It was observed that when these milder DSAC were employed the PKR became largely more efficient, with reaction yields generally increasing and the required reaction time decreasing considerably. An illustrative example comparing DSAC with the more classical thermal conditions is presented, wherein the intramolecular PKR reaction of enyne complex **90** generates bicyclopentenone product **91** (**Scheme 1.28 & Table 1.4**).[84,87] In this case, the benefits of DSAC can clearly be seen as a substantial yield increase and reaction duration decrease are found.



90 **91**

Scheme 1.28

Entry	Promotion	Conditions	Yield (%)
1	Thermal	CO atm., *iso*-octane, 60 °C, 24 h	29
2	DSAC	O_2 atm., SiO_2, 45 °C, 30 min	75

Table 1.4

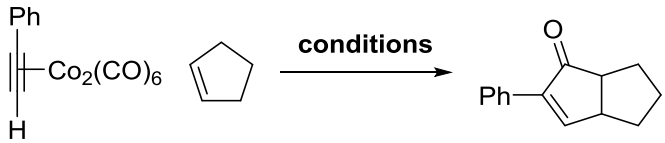
The promotional effects of DSAC are proposed to derive from nucleophilic donor sites on the solid support surface, which are able to facilitate decarbonylative ligand exchange in the PKR pathway.[87,86] It is also believed that these donor sites can effectively stabilise any electron-deficient intermediates, which may be produced throughout the reaction pathway. With particular reference to silica adsorption, the solid support may also serve to restrict conformational movement of the complex, in a similar manner to the restricted rotamer effect, encouraging the cyclisation reaction. DSAC have been observed to function best with enynes bearing heteroatoms, as it is proposed the heteroatoms can better interact with this solid support. Following the initial report of these DSAC, Smit, and other researchers, continued development of this methodology, leading eventually to much greater substrate scope for both intra- and intermolecular versions.[89,90]

1.7.2 Ultrasound

As previously discussed, within the PKR's mechanistic pathway it has been determined that formation of the coordinatively unsaturated dicobalt pentacarbonyl species is the most energy-demanding step in the reaction process.[39] As such, it was theorised that conditions which could enhance this decarbonylative step would provide a boost in efficiency to the PKR. One method which was proposed to achieve this was the use of ultrasonication))), which had previously been suggested

to promote metal-carbonyl bond cleavage.[91,92] It was thought that this occurred through the formation of transient, localised areas of high pressure and temperature.

Initial use of these conditions employed an ultrasonic cleaning bath to generate low intensity ultrasonication in order to promote reactions. It was revealed that while these conditions were effective in decreasing the required reaction duration, they had little general effect on yields. These conditions were however successfully applied to both inter- and intramolecular variants of the PKR.[74,93] An example of low intensity ultrasonication promotion is shown below (**Scheme 1.29 & Table 1.5)**. When the ultrasonication promoted reaction conditions, to generate PKR product **93**, is compared to that under thermal promotion it can be seen that a significant reduction in required reaction duration and a substantial increase in yield is provided.[74]



43 **92** **93**

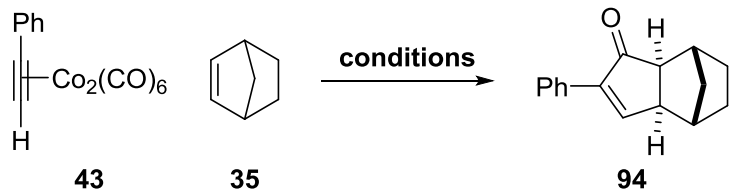
Scheme 1.29

Entry	Promotion	Conditions	Yield (%)
1	Thermal	PhMe, 70 °C, 48 h	23
2	Low intensity)))	PhMe, 70 °C, 3 h	59

Table 1.5

Following this initial advancement, further work within our own laboratory revealed that use of high intensity ultrasonication, such as that provided by an ultrasonic probe, could be extremely effective in enhancing the cyclisation efficiency.[94] As illustrated below, reaction duration is monumentally reduced when compared to a thermally promoted PKR performed on the same substrates (**Scheme 1.30 & Table 1.6**). Additionally, high intensity ultrasonication combined with an amine *N*-oxide promoter (*vide infra*) provided further enhancement to both reaction time and overall cyclopentenone yields. It has been suggested that the higher intensity sonication

delivers greater pressures within the reaction solution; potentially leading to faster metal-carbonyl bond cleavage.



43 **35** **94**

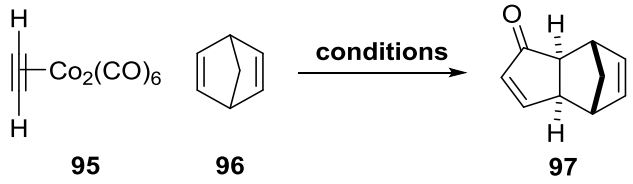
Scheme 1.30

Entry	Promotion	Conditions	Yield (%)
1	Thermal	PhMe, 60 – 70 °C, 4 h	75
2	High intensity)))	PhMe, r.t., 10 min,	84
3	High intensity)))	PhMe, r.t., TMANO·2H_2O, 6 min	95

Table 1.6

1.7.3 Microwave irradiation

Microwave irradiation (MWI) has, over recent years, become an extremely common alternative to thermal heating in synthetic organic chemistry.[95,96] Numerous organic reactions have been subjected to microwave irradiation, with generally observed enhanced efficiencies with significantly reduced reaction times. In 2002, the first example of a PKR promoted by microwave irradiation was presented by Evans and co-workers.[97] Within the publication, a variety of substrates underwent PKRs promoted by MWI, with the cyclopentenone products commonly delivered in good to excellent yields. Both inter- and intramolecular examples were presented, however, it should be noted that only highly strained, and thus more reactive, olefins could be employed in this protocol. An illustrative comparison of these microwave promoted reactions is presented below (**Scheme 1.31 & Table 1.7**). In this instance, while the cyclopentenone product yield is increased over that provided by thermal promotion, the true enhancement is the greatly reduced reaction time. Further to this, it was also noted that diastereoselectivity was improved when MWI was employed.



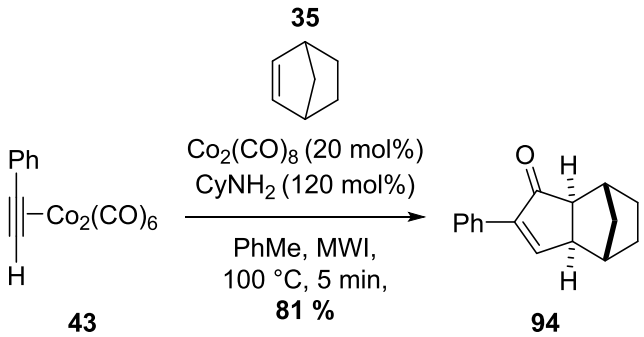
95 **96** **97**

Scheme 1.31

Entry	Promotion	Conditions	Yield (%)	*Exo*:*Endo*
1	Thermal	PhMe, reflux, 16 h	70	80:20
2	Microwave	DCE, 90 °C, 20 min	89	95:5

Table 1.7

In the same year, the first example of a catalytic PKR promoted by MWI was presented by Groth and co-workers.[98] This publication described the inter- and intramolecular PKR of various substrates through use of sub stoichiometric amounts of $Co_2(CO)_8$ with cyclohexylamine as an additive. Optimisation led to good yields for product **94** in as little as 5 minutes, and notably, no additional CO gas was required, as the reaction was performed in a closed system (**Scheme 1.32**). This example also serves to highlight the possibilities of the catalytic PKR which shall be further discussed in a subsequent section.



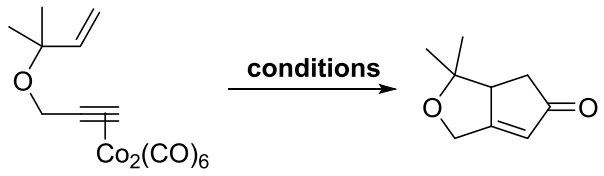
43 **94**

Scheme 1.32

1.7.4 Amine *N*-oxides

A major advancement in methodology for the promotion of the PKR came with the discovery of chemical additives that could exert an enhancing effect on the reaction efficiency. It could be argued that the significant improvement these additives provided, and their general ease of use, has led in a large part to the organic community's endorsement of the PKR and its subsequent widespread synthetic application. The first group of such additives to be identified were amine *N*-oxides, which were divulged by Crowe and co-workers in 1990.[99] Their use initiated from the known ability of amine *N*-oxides to remove carbon monoxide ligands from metal complexes by oxidation to carbon dioxide.[100–102]

When applied to the PKR, oxidation of carbon monoxide renders the initial decarbonylation irreversible, thus preventing re-association of carbon monoxide and forcing the reaction to progress. It was believed that by facilitating this key step significantly milder reaction conditions could be employed. To illustrate the effectiveness of amine *N*-oxides, a reaction using *N*-methylmorpholine *N*-oxide (NMO) is shown with a reaction under DSAC (**Scheme 1.33 & Table 1.8**).[99] While the time required to generate cyclopentenone **99** is increased with NMO promotion, the reaction proceeds at room temperature and in a far greater yield overall.



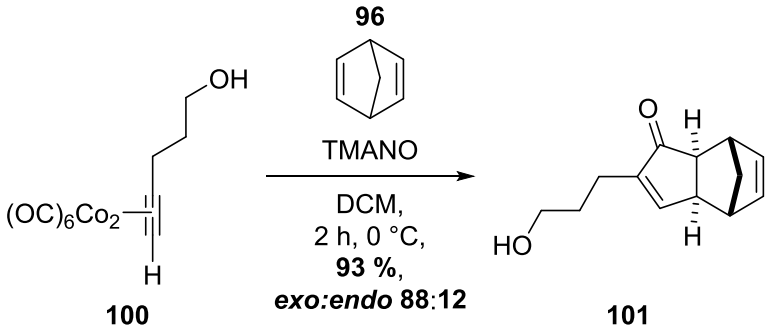
98 **99**

Scheme 1.33

Entry	Promotion	Conditions	Yield (%)
1	DSAC	O_2 atm., SiO_2, 55 °C, 1.5 h	59
2	*N*-oxide	NMO, DCM, r.t., 12 h	92

Table 1.8

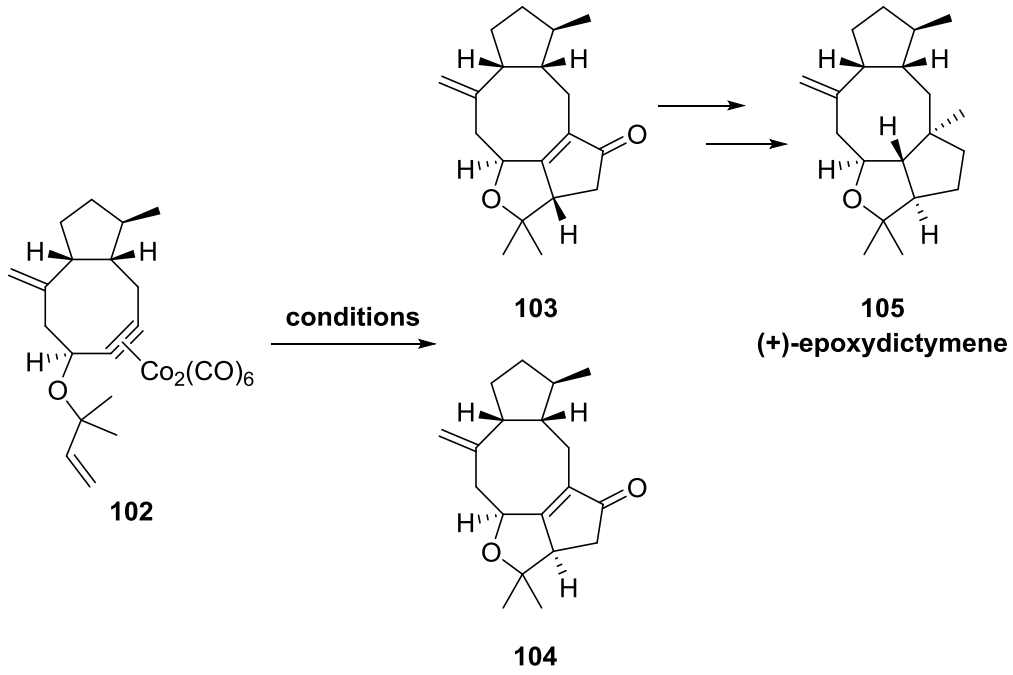
Following this initial work with NMO promotion, Jeong and co-workers published a report detailing the use of trimethylamine *N*-oxide (TMANO) as a similarly effective additive for the PKR, allowing reactions to proceed efficiently under mild conditions.[103] While Schreiber's research had focused on the promotion of intramolecular PKRs, Jeong expanded the scope with TMANO to include several successful intermolecular PKRs and the use of some substrates with typically sensitive functional groups. An excellent example of this functional group tolerance is the TMANO-promoted intermolecular PKR of alkynol **100**, which furnished cyclopentenone product **101** in excellent yield within 2 hours (**Scheme 1.34**).



Scheme 1.34

A noteworthy advantage of amine *N*-oxide additives is that PKRs which they promote are generally significantly cleaner than those promoted through thermal means. The final cyclopentenone products can often be isolated through a rather trivial filtration or short silica column purification.[21] One often overlooked point is the hydration state of the amine *N*-oxide additives. Within our own laboratory and in the laboratories of others it has been observed that, in general, the monohydrate species of NMO and the dihydrate species of TMANO provide the best yields when employed as additives.[57,104–111] The equivalent anhydrous *N*-oxides often have been found to lead to some degree of alkyne decomplexation or decomposition.[112] However, in the case of less reactive alkyne complexes the anhydrous, and more active *N*-oxides, may be the correct choice.

The enhancement provided through the use of amine *N*-oxide additives has led to increasing use within the synthetic organic community, including its application as a key step in numerous natural product syntheses. An excellent example of this is the synthesis of the diterpene natural product (+)-epoxydictymene **105** by Schreiber and co-workers (**Scheme 1.35 & Table 1.9)**.[93,99,113] With NMO promotion, the key PKR within the synthesis proceeded in slightly lower yields than under thermal promotion, however the desired cyclopentenone product, **103**, was generated with enhanced selectivity allowing progression to the final product.



Scheme 1.35

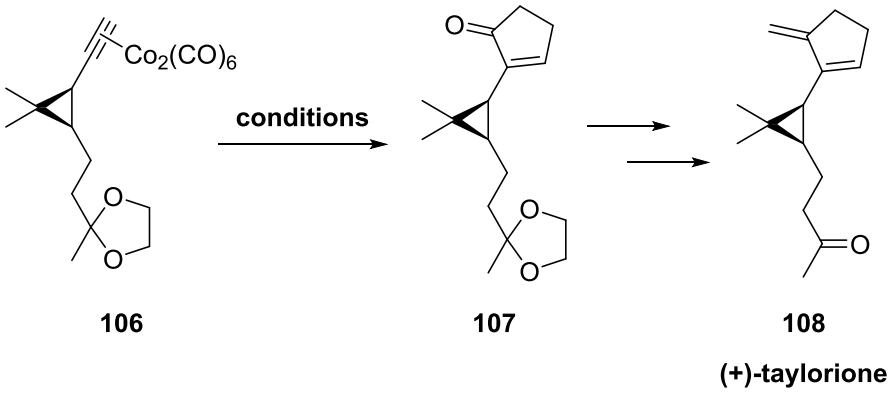
Entry	Promotion	Conditions	Yield (%)	103:104
1	Thermal	MeCN, reflux, 15 min	85	5:1
2	*N*-oxide	NMO, DCM, r.t., 12 h	70	11:1

Table 1.9

One of the major challenges of the PKR is the use of gaseous olefinic substrates. Reactions employing gaseous olefins generally require forcing conditions and often poor yields of the product cyclopentenone result.[21,74] In an attempt to advance this field, work within our own laboratory has led to optimised conditions for the use of

ethylene as the alkene component in PKRs with *N*-oxide promotion under relatively mild conditions.[105–107] It was discovered that mild autoclave pressures (25 - 30 atm.) and temperatures (40 °C) could be applied to provide excellent yields in most instances. Significantly, it was found that the desired cyclopentenone could be generated from ethylene at atmospheric pressure and room temperature.

With these enhanced protocols in hand the total synthesis of the sesquiterpene (+)-taylorione **108** was efficiently completed (**Scheme 1.36 & Table 1.10**).[105,106] Utilising TMANO dihydrate as the *N*-oxide promoter, under a autoclave generated pressure of ethylene, the desired cyclopentenone product **107** was generated in high yield and optical purity. When compared to the product yield generated through thermal conditions, and the high pressures of ethylene required, the benefit of *N*-oxide promotion is clear. Further to this, when the reaction was performed with *N*-oxide promotion at r.t. and atmospheric pressure, a moderate yield, but still greater than that produced by thermal conditions, was produced.

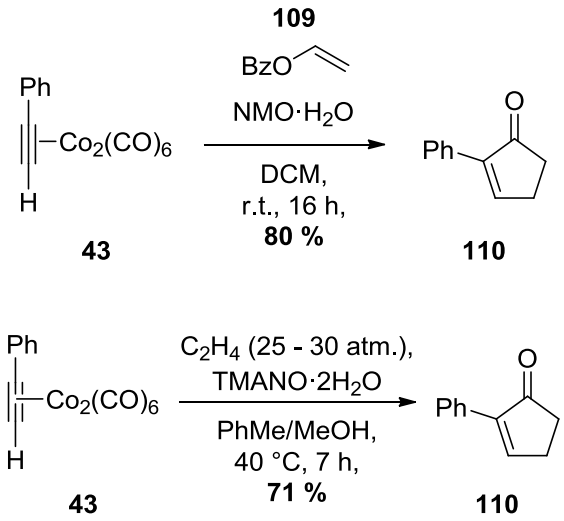


Scheme 1.36

Entry	Promotion	Conditions	Yield (%)
1	Thermal	C_2H_4 (50 atm.), PhMe, 80 °C, 5 h	38
2	*N*-oxide	C_2H_4 (25 – 30 atm.) PhMe/ MeOH, TMANO·$2H_2O$, 40 °C, 24 h	81
3	*N*-oxide	C_2H_4 (bubbling) PhMe/ MeOH, TMANO·$2H_2O$, r.t., 18 h	41

Table 1.10

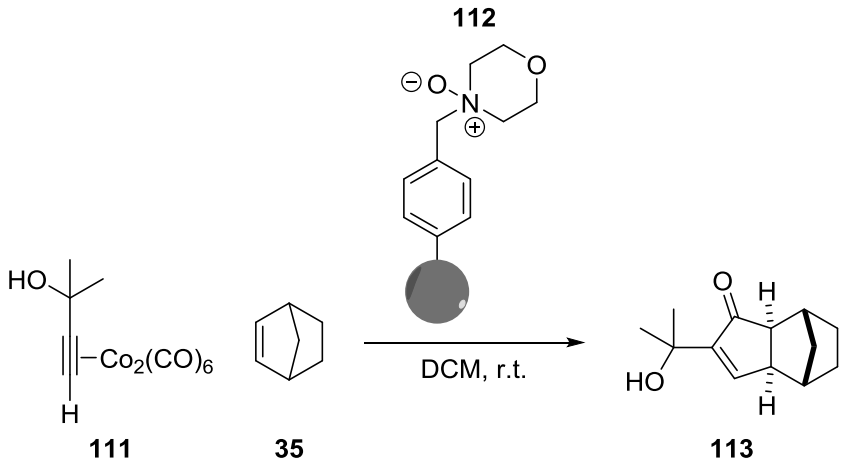
Within our laboratory, further efforts were made to generate cyclopentenone products derived from ethylene incorporation. To this end, it was discovered that when vinyl esters were employed in PKRs with *N*-oxide promotion the resultant products were those in which the ester had been cleaved, essentially producing the product of ethylene incorporation.[108–110] This ester cleavage is believed to result from an *in situ* reduction process with low valent cobalt. An example of this methodology is shown below, wherein benzoate **109** acts as an ethylene surrogate in the NMO monohydrate promoted cyclisation to generate cyclopentenone **110** in excellent yield (**Scheme 1.37**). It can be seen that this ethylene surrogate method produces similar yield of product **110** when compared to a reaction employing ethylene gas, with the added benefit of far milder and more practically accessible conditions.



Scheme 1.37

The *N*-oxide promotion of PKRs has been further advanced to include solid supported variants, such as a highly user friendly polymer supported amine-*N*-oxide methodology, which was also developed within our laboratory.[114,115] It was discovered that commercially available NMO resin could be activated for promotion of PKRs through *in situ* oxidation. An added advantage was found in the fact that the resins employed sequestered the cobalt by-products leading to particularly clean reaction profiles. An illustrative example is provided below which serves to

highlight not only the efficiency of this solid supported *N*-oxide **112** but also its ability to be recycled, up to five times, with little loss in reactivity (**Scheme 1.38 & Table 1.11**).



Scheme 1.38

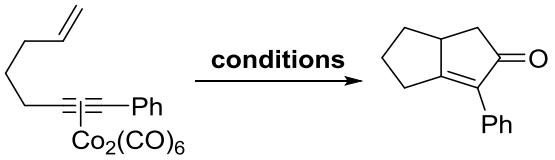
Run	Time (h)	Yield (%)
1	2.5	100
2	5	97
3	5	95
4	6	94
5	5	90

Table 1.11

1.7.5 Amines

Following the discovery of the enhancing effect of amine-*N*-oxides, a report in 1997 by Sugihara, Yamaguchi, and co-workers disclosed the potential of primary amines, and, in particular, amines containing secondary alkyl functionalities to function as PKR promoters.[116] It was theorised that ligands which contained a nitrogen or oxygen atom could facilitate olefin insertion through a coordination effect, allowing stabilisation of any coordinatively unsaturated intermediates produced throughout the reaction. Experimental results showed that amines did indeed enhance the PKR,

with cyclohexylamine found to be the most efficient of all amines tested. This amine was applied successfully to both intra- and intermolecular PKRs, with, in some cases, generation of quantitative yields in as little as 5 min (**Scheme 1.39 & Table 1.12**). Interestingly, ammonia was also shown to be an effective promoter, delivered to the reaction through use of a biphasic mixture of ammonium hydroxide and 1,4-dioxane.



114 **115**

Scheme 1.39

Entry	Conditions	Yield (%)
1	3.5 eq. $CyNH_2$, DCE, reflux, 5 min	100
2	2 M NH_4OH/1,4-dioxane (3:1), 100 °C, 15 min	93

Table 1.12

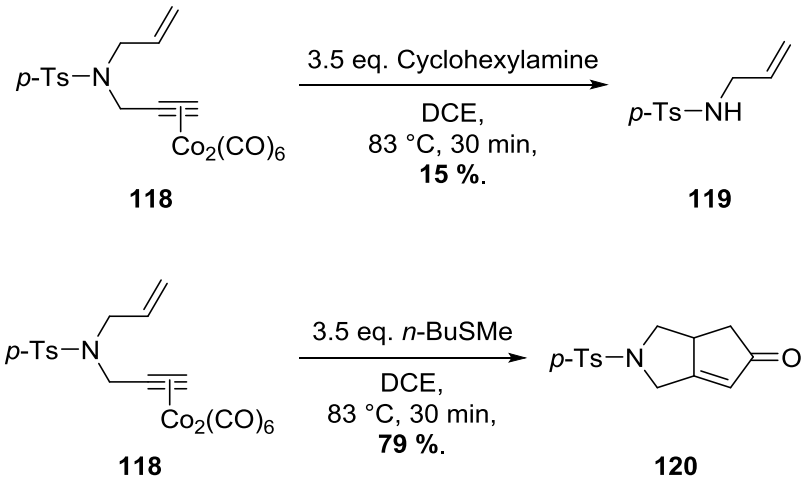
It should be noted that in order to generate the high yields and short reaction times observed, far more forcing conditions were required than those utilised in *N*-oxide promotion, with refluxing solvents generally essential. A further limitation of this methodology was the fact that less reactive alkenes commonly performed poorly, with cleavage of carbon-heteroatom bonds also observed in some cases.

1.7.6 Sulfides and sulfoxides

In a short study conducted by Chung and Lee, it was found that sulfoxides provided a beneficial effect on reaction yields in the PKR, albeit, extended reaction times were often required.[38] Shortly after this, Jeong and co-workers described the use of a dimethyl sulfide (DMS)/dimethyl sulfoxide (DMSO) additive mixture, which delivered improved yields when applied to several allylpropargyl sulfide substrates, such as **116** (**Scheme 1.40**).[117]

Scheme 1.40

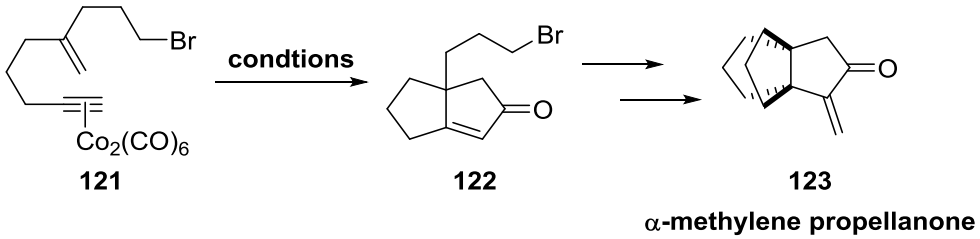
Following this report, further advances were achieved with the development and employment of a variety of sulfide-based methodologies.[118] Sugihara, Yamaguchi, and co-workers proposed that alkyl methyl sulfides were the most efficient of these sulfide-based promoters, with the most effective being those which possessed primary or secondary alkyl groups. The authors particularly recommended *n*-butyl methyl sulfide (*n*-BuSMe); the advantages of this sulfide-promoted PKR method are apparent when compared to an equivalent amine-promoted example (**Scheme 1.41)**. When substrate **118** was subjected to a PKR with cyclohexylamine promotion, cleavage of the alkyne cobalt complex was observed and compound **119** was isolated in 15 % yield. Conversely, when *n*-BuSMe was employed no cleavage was observed and the reaction quickly proceeded to furnish product, **120**, in a very good yield.



Scheme 1.41

Within our laboratories, we have employed *n*-BuSMe as a promoter in the key step in our synthesis of the biologically active compound α-methylene propellanone **123**.[119]

In this instance, *N*-oxide promotion was initially employed to furnish desired product **122**, and pleasingly the cyclopentenone product was yielded in 28 % (**Scheme 1.42 & Table 1.13**). In an attempt to improve upon this result, *n*-BuSMe was trialled, however, a slight reduction in yield was observed. Following this, a concentration study was performed which determined that a concentration of 0.02 M was optimal. To our delight, this alteration produced the desired compound **121** in 70 % yield and in far shorter time. This result, achieved through judicious choice of promoter and concentration, allowed us to proceed through the synthesis generating the target molecule, α-methylene propellanone, **122**, in 12 steps and an overall yield of 11 %.

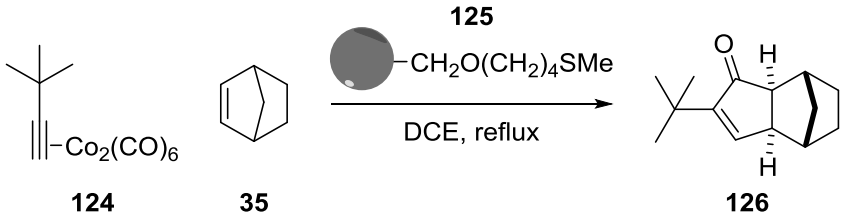


Scheme 1.42

Entry	Promoter	Conditions	Conc. (M)	Yield (%)
1	*N*-oxide	NMO·H_2O, DCM, r.t., 15 h	0.012	28
2	Sulfide	*n*-BuSMe, DCE, reflux, 15 h	0.2	26
3	Sulfide	*n*-BuSMe, DCE, reflux, 4 h	0.02	70

Table 1.13

While the *n*-BuSMe promotion methodology provides significant advantages, there are some substantial practical drawbacks to its use; relatively high temperatures are required and the low molecular weight sulfide possesses both an unpleasant smell and a lachrymator effect. It should also be noted that the reagent itself is relatively expensive and provides no potential for recyclability. With this in mind, research was carried out within our laboratory to establish a significantly more user friendly protocol. To this end, a suitably odourless, and reusable, polymer supported sulfide promoter was developed (**Scheme 1.43 & Table 1.14**).[120] This polymer supported sulfide, **125**, shows a similar promotional efficiency to *n*-BuSMe with the added benefit of retaining activity over a number of cycles.

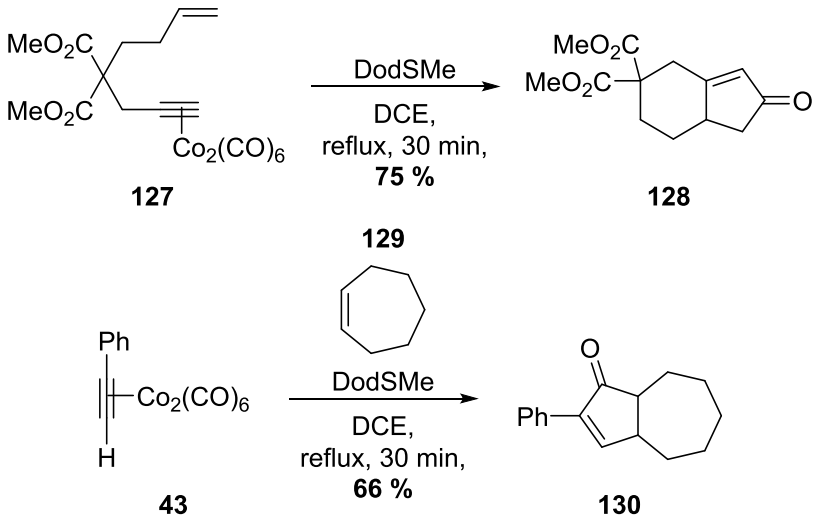


Scheme 1.43

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

Table 1.14

Further research within our laboratories led to the discovery of a suitably inexpensive and stench free solution phase sulfide alternative, *n*-dodecyl methyl sulfide (DodSMe), which displays exceedingly effective promotion in both intra- and intermolecular PKRs.[121] This promoter has been observed to provide at least comparable reaction efficiency with the less practical *n*-BuSMe, delivering products **128** and **130** in similarly short reaction times and good yields (**Scheme 1.44**).



Scheme 1.44

There has been a great deal of investigation into how such Lewis basic additives can effectively enhance the efficiency of the PKR. It was originally assumed that these species promoted the reaction through acceleration of the decarbonylative-Lewis base ligand exchange process; this would then promote loss of a CO ligand leading to a vacant coordination site allowing olefin coordination to occur.[21] More recently, however, an in depth theoretical study performed by Milet and Gimbert has led to the suggestion that Lewis base promoters force the olefin insertion step of the PK reaction pathway to become irreversible thus leading to enhanced efficiency.[51]

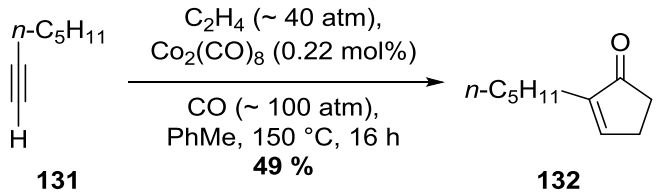
1.8 The catalytic PKR

While great synthetic diversity has been achieved through use of the stoichiometric cobalt-mediated PKR, advancement of the procedure to a robust catalytic variant would undoubtedly result in much greater application within the synthetic and industrial communities. The mechanism of the PKR is believed to proceed with regeneration of the hexacarbonyl dicobalt complex (*vide supra*) and, as such, it was originally theorised that a catalytic variant of the reaction could be achieved through supply of carbon monoxide. In reality, the development of the catalytic PKR has been problematic, most likely resulting from the fact that the coordinatively unsaturated $Co_2(CO)_6$ complex is unstable and will commonly undergo transformation into a more stable complex through an oligomerisation process.[21]

1.8.1 Homogeneous cobalt catalysis

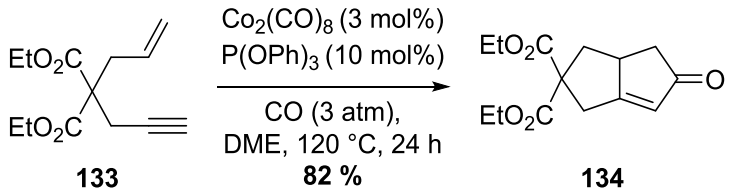
A catalytic approach to the PKR has been a goal since the reaction's discovery, with a version disclosed by Pauson and Khand in one of the original papers.[27] In this instance, acetylene-dicobalt hexacarbonyl was employed as a catalyst precursor and a reaction with norbornene was performed under a mixed gas system of acetylene and carbon monoxide. A subsequent example was reported in which a catalytic amount of $Co_2(CO)_8$ was employed to react alkyl acetylene **131** with ethylene under a highly

pressured carbon monoxide atmosphere to furnish cyclopentenone product **132** in moderate yield (**Scheme 1.45**).[122] This reaction suffered from requirements of both high temperature and high pressure. Both of these early examples had very narrow scope and significant practical challenges however, they did provide proof of concept for further investigation into the catalytic PKR.



Scheme 1.45

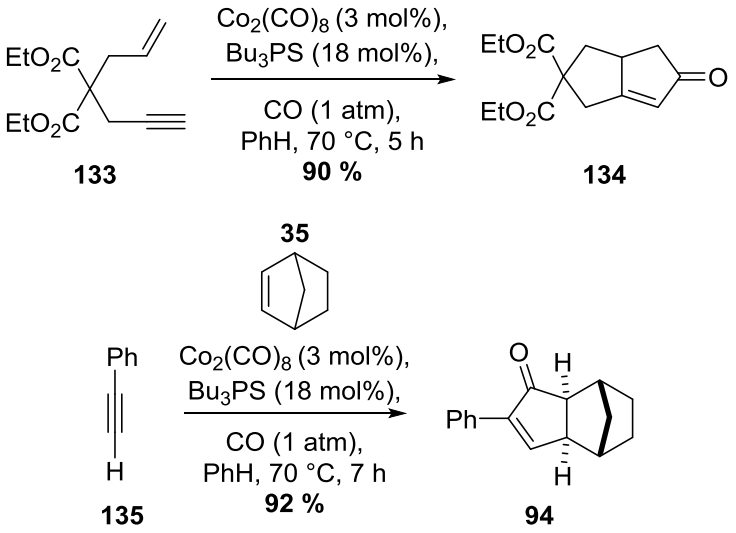
Stabilisation of the $Co_2(CO)_6$ complex formed within the PKR was thought essential in the development of an effective catalytic protocol. With respect to this, it was discovered that triarylphosphines could stabilise a cobalt carbonyl complex through displacement of a CO ligand.[21] Through the use of triphenylphosphite additives, Jeong and co-workers reported the first practical catalytic PKR.[123] With this protocol a number of 1,6-enynes, such as **133** could be efficiently transformed into their respective cyclopentenone products (**Scheme 1.46**). Product yields were generally excellent, however, relatively high temperatures and pressures of CO were required. The substrate scope was also limited with only intramolecular examples displayed.



Scheme 1.46

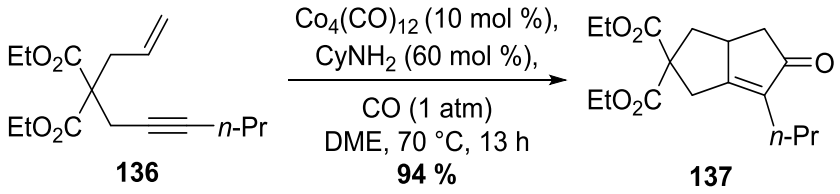
Following this work, Hashimoto, Saigo, and co-workers described the use of tributyl phosphine sulfide as an efficient ligand for the catalytic PKR.[124] Through use of this protocol, a variety of enynes could be successfully cyclised to their respective

bicyclic cyclopentenone products. Reactions typically proceeded in high yield, at the relatively low temperature of 70 °C, under atmospheric pressures of carbon monoxide (**Scheme 1.47**). Crucially, this protocol allowed the intermolecular PKR to be achieved catalytically, albeit with a reactive norbornene substrate, producing tricyclic enone **94** in excellent yield.



Scheme 1.47

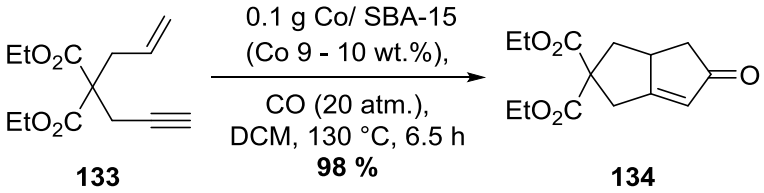
Whist many catalytic PKRs that employing the $Co_2(CO)_8$ complex have been reported a major problem is formation of stable and inactive oligomeric complexes. In order to combat this, attempts have been made to employ multinuclear cobalt carbonyl catalysts. An excellent example of this is the protocol reported by Krafft and co-workers, which made use of $Co_4(CO)_{12}$ as the catalyst coupled with catalytic cyclohexylamine as an additive.[125] Through this methodology, numerous 1,6-enynes could be successfully transformed into the corresponding bicyclic cyclopentenones in excellent yield under very mild conditions (**Scheme 1.48**).



Scheme 1.48

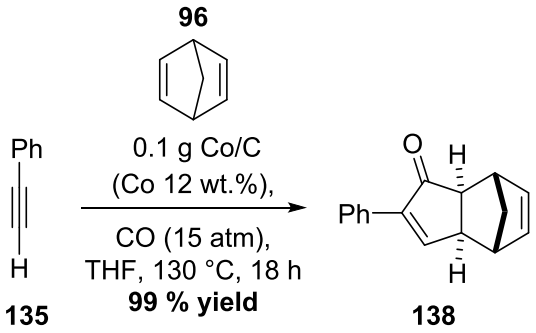
1.8.2 Heterogeneous cobalt catalysis

In addition to the use of homogeneous cobalt catalysis, several examples of the use of heterogeneous cobalt catalysis conditions for the PKR have been reported. Catalysis of this type was pioneered by Hyeon, Chung, and co-workers who used metallic cobalt supported on mesoporous silica (SBA-15).[126] Through use of this protocol, a variety of intramolecular enyne substrates were transformed into their corresponding cyclopentenone products in excellent yield (**Scheme 1.49**). A disadvantage to this methodology was the requirement of both high temperatures and high pressures of carbon monoxide, however, the heterogeneous nature of the catalyst allowed for recycling up to three times without loss of catalytic activity. Unfortunately, when this catalyst system was applied to the intermolecular PKRs of reactive norbornene derivatives and phenylacetylene, the reaction proved much less successful.



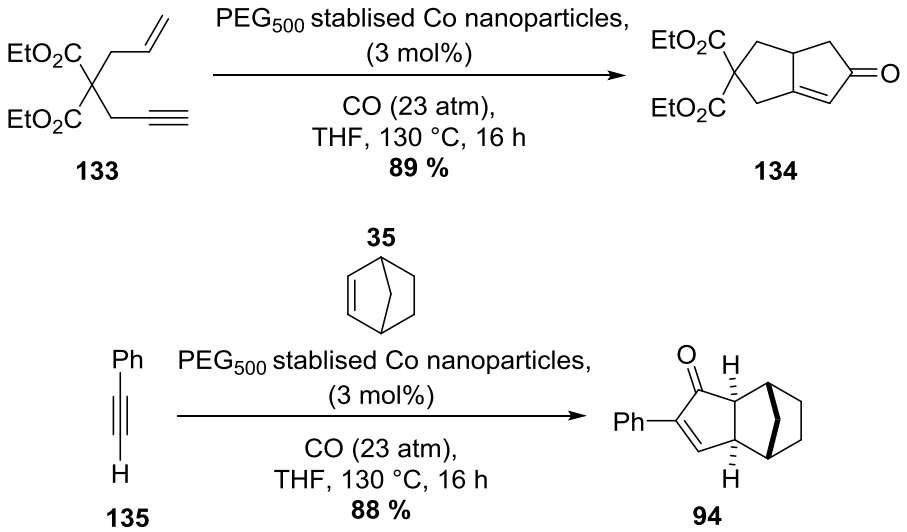
Scheme 1.49

Following on from this ground-breaking work, Chung and co-workers further disclosed a generally more convenient and cost effective heterogeneous cobalt catalyst system which employed cobalt nanoparticles supported on charcoal.[127] In comparison with their previously reported system, the reaction conditions still appeared relatively harsh, however, the catalyst could in this case be recycled up to nine times without loss of activity. Importantly, this methodology allowed for intra- and intermolecular PKRs (**Scheme 1.50**).



Scheme 1.50

Leitner and co-workers reported the use of cobalt nanoparticles stabilised on poly(ethylene glycol) (PEG) with the catalyst prepared through thermal decomposition of $Co_2(CO)_8$ in PEG.[128] This protocol, once again, required harsh conditions. However, both intra- and intermolecular substrates could efficiently undergo PKR to generate their respective cyclopentenone products (**Scheme 1.51**).



Scheme 1.51

This brief summary of cobalt-based catalytic methods shows that while research has led to a number of reasonably successful protocols, substrate scope is still a major challenge. Further development has been successfully attained through the introduction of alternative metals in a series of complementary catalytic techniques, which provide advantages in both an extended substrate scope and, in some cases,

elimination of the need for an external source of carbon monoxide. This area is however outside the scope of this review. Development of the catalytic PKR is still a major focus within the synthetic community, with the discovery of protocols which employ milder conditions and utilise less reactive substrates, a long sought-after goal.

1.9 Summary

Since its inception, the PKR has advanced to become a synthetic protocol of great value to the global chemistry community through research and development performed by numerous groups. As previously, discussed the reaction has been significantly enhanced through discovery of a variety of promoters, which have led to a more robust and widely applied reaction effective for both intra- and intermolecular substrates. As a result, the PKR has seen increasing utilisation as a key step in numerous natural product syntheses. Further to this, a variety of methods which induce asymmetry in the PKR have been developed; these include the use of chiral additives, or a chiral C_2Co_2 core. This area has understandably received much interest and, as such, a vast number of reports are available.

While the PKR has been greatly advanced, there still remain areas which require further investigation. With regards to the mechanistic understanding, while much has been determined, continuing attempts for further elucidation will provide a better understanding of the transformation and, as such, allow for better overall control. The intermolecular variant of the reaction also continues to suffer from a limited substrate scope, with only the more strained and reactive olefins providing elevated levels of efficiency. Continuing research will hopefully deliver methodologies which will successfully expand this substrate scope and further improve the PKR's applicability.

Chapter 2

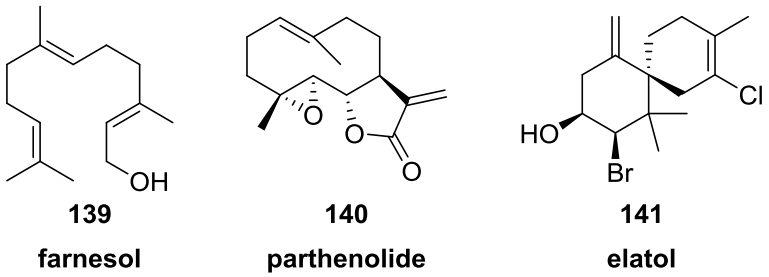
Investigations towards the total synthesis of α-duprezianene

1 Introduction

1.1 Sesquiterpenes and the cedrene family of natural products

Sesquiterpenes are a naturally occurring class of terpene compounds that contain 15 carbon and 24 hydrogen atoms.[129] Biochemical modifications of these sesquiterpene skeletons, through, for example, oxidation or rearrangement, yields the related sesquiterpenoid products. Owing to their structural similarities, sesquiterpenoid compounds are also often referred to as sesquiterpenes. Sesquiterpenes have been isolated from a variety of organisms such as marine organisms, fungi, and flowering plants. They have been found to participate in numerous biological functions such as acting as insect attractants, phytoalexins, pheromones, juvenile hormones, and as components of essential oils.[130] Their structural diversity and pharmacological activity have generated great interest within the synthetic community.

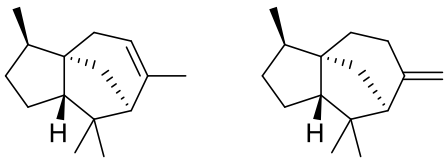
To illustrate the structural variation found throughout the sesquiterpene class, three biologically active sesquiterpenes are shown below (**Figure 2.1**). Acyclic sesquiterpene farnesol, **139**, has been found to possess anti-cancer activities against pancreatic cancers.[131] Bicyclic sesquiterpene parthenolide, **140**, also shows anti-cancer properties, along with reports of anti-inflammatory behaviour.[132–134] Finally, the bicyclic sesquiterpene elatol, **141**, has been reported to show anti-bacterial, anti-fungal, and anti-cancer activities.[135–139]



139 **farnesol** **140** **parthenolide** **141** **elatol**

Figure 2.1

One such subset of these compounds, which has received much interest from the synthetic community, is the cedrene family of sesquiterpenes. These compounds have been identified as major components within the essential oils of ceder wood. Cedrene was first isolated in 1841 by Walter, from the essential oil of *Juniperus cedrus*, as a mixture of both α-cedrene **142** and β-cedrene **143** (**Figure 2.2**).[140] The compounds were successfully characterised in 1953, by Stork and Breslow, revealing that they possessed a complex, tricyclic carbon skeleton.[141] Cedrene, like many sesquiterpenes, has been found to exert various biological activities, such as antiseptic, anti-inflammatory, antispasmodic, tonic, astringent, diuretic, sedative, insecticidal, and antifungal effects.[142–147]



142 **α-cedrene** **143** **β-cedrene**

Figure 2.2

Since this initial characterisation, with improved isolation and analysis techniques, many more structurally related members of the cedrene family of sesquiterpenes have been positively identified. Indeed, Barrero and co-workers isolated and characterised several previously unknown related natural products from the essential oil of *Juniperus thurifera* (**Figure 2.3**).[148,149] It was also noted that eight previously

characterised natural products, including α-cedrene **142** and β-cedrene **143**, were present in these oils.

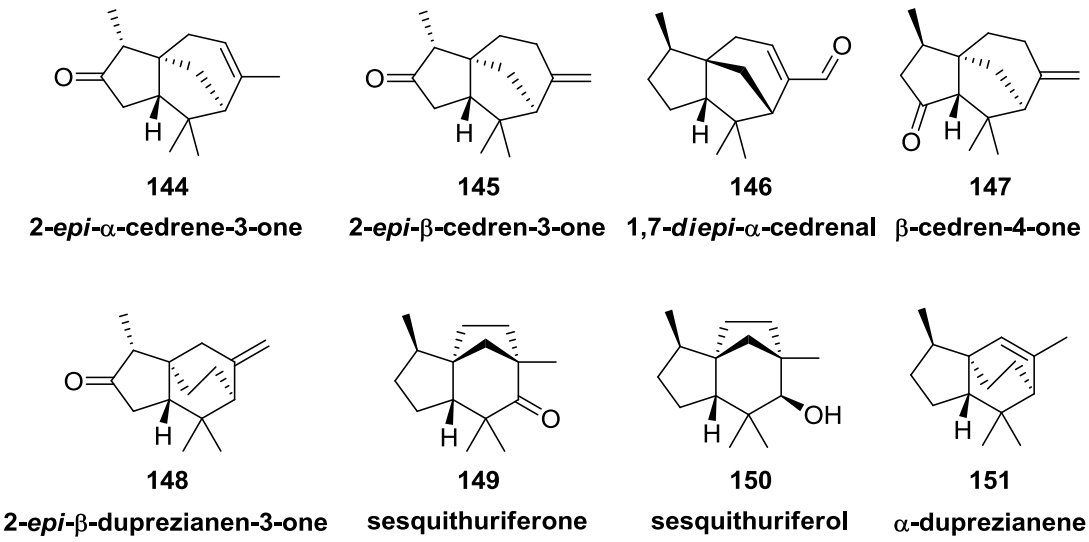
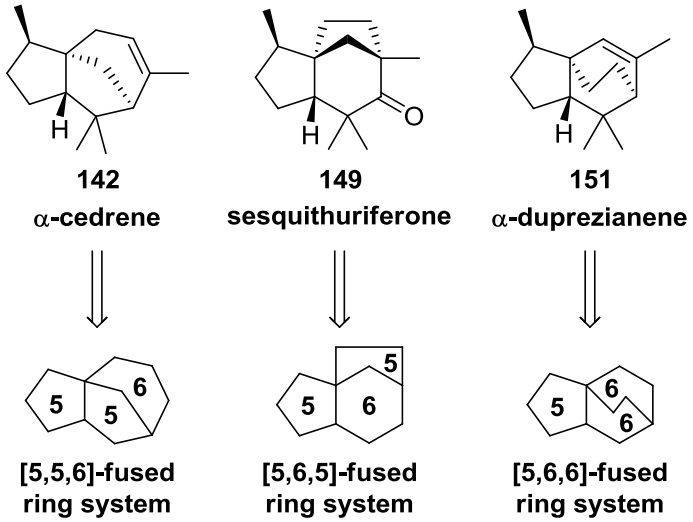


Figure 2.3

Structurally similar to cedrene, all of the isolated products featured a common fused tricyclic core, with some variation in ring sizes. Three of these compounds were of particular interest to our research team and as such are crucial to this programme of work. These compounds are highlighted below wherein it can be seen that α-cedrene **142** possesses a [5,5,6]-fused ring system, sesquithuriferone **149** differs with a [5,6,5]-fused ring system, and α-duprezianene **151** features a [5,6,6]-fused ring system (**Scheme 2.1**). The complexity of these compounds has led to much interest, as, from a synthetic perspective; no common concise synthesis to fused structures of this type is as yet apparent.



Scheme 2.1

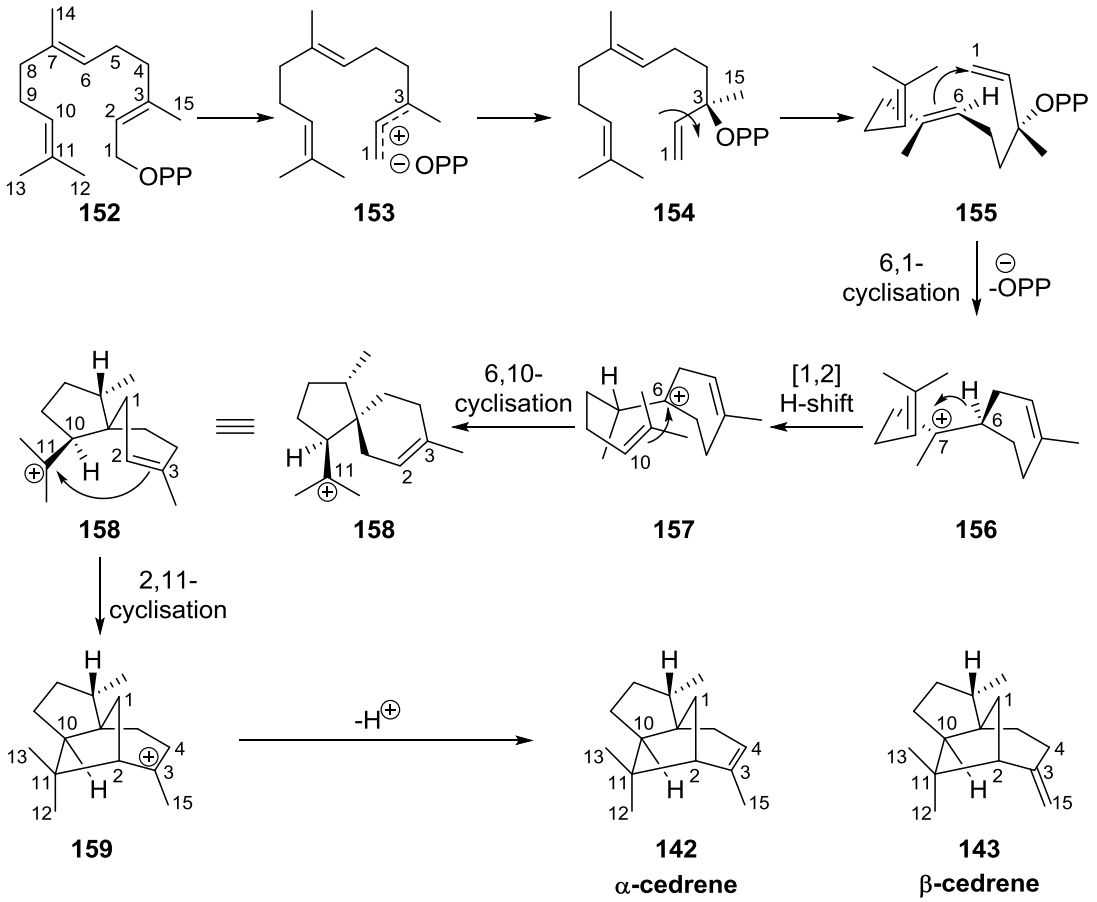
1.2 Biosynthetic pathway

Within nature, the majority of sesquiterpenes are formed through complex rearrangement reactions of carbocations derived from farnesyl pyrophosphate (OPP). These reactions are mediated by a class of enzymes known as sesquiterpene synthases, with a great deal of investigation having been performed to further understand these pathways.[150–152] It has been determined that in general sesquiterpene formation occurs through three major stages:

i) Carbocation generation
ii) Carbocation rearrangement
iii) Carbocation neutralisation by deprotonation of nucleophilic attack

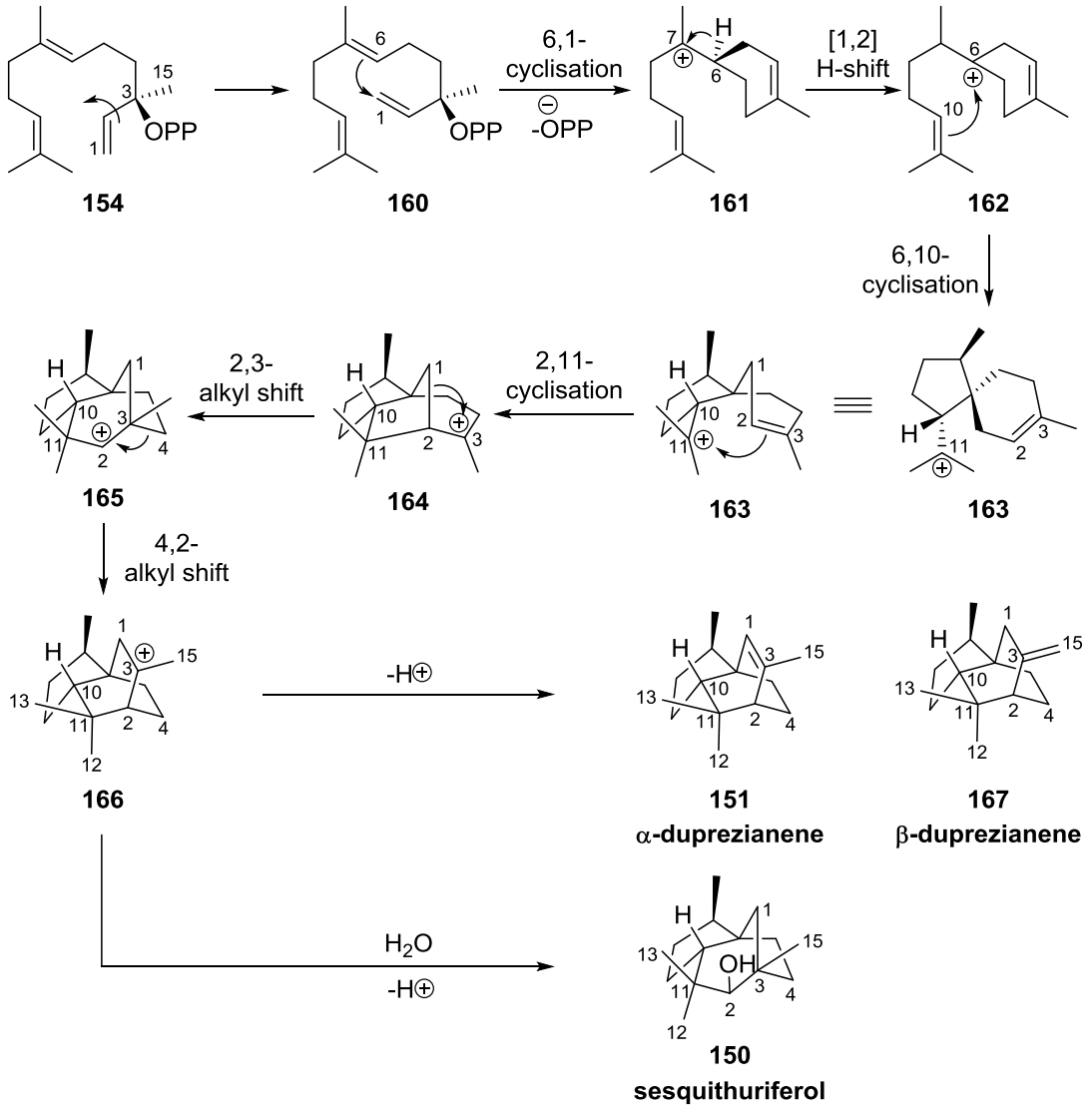
Tantillo and co-workers attempted to use computational methods to provide additional insight into these biosynthetic pathways.[153] To this end, they were able to formally resolve the pathways responsible for the formation of various sesquiterpenes, including some of those isolated by Barrero and co-workers. The elucidated biosynthetic pathway for formation of α-cedrene **142** and β-cedrene **143** is shown below (**Scheme 2.2**). Thus, starting from farnesyl pyrophosphate, **152**, an initial 1,3-pyrophosphate rearrangement occurs, proceeding through carbocation **153**

to generate intermediate **154** and initiate the biosynthetic pathway. Rotation within the molecule can then occur to prepare conformer **155**, which can then accommodate the cyclisation cascade which follows. Firstly, a six-membered ring is formed in **156**, a 1,2-H shift then follows to quench the generated cation, and a subsequent cyclisation affords the five-membered ring, **158**. One final cyclisation provides the [5,5,6]-fused tricyclic core, which can then be deprotonated to yield α-cedrene **142** and β-cedrene **143**.



Scheme 2.2

Further to this, Tantillo and co-workers were able to display just how closely linked the other members of this family of natural products were, with many other compounds accessible from common intermediates and subtle conformational alterations.[153] An example of this is the somewhat common biosynthetic pathway of sesquithuriferol **150**, α-duprezianene **151**, and β-duprezianene **167** (**Scheme 2.3**).



Scheme 2.3

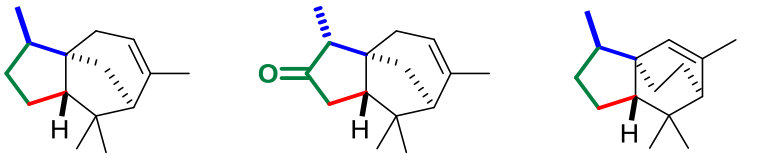
The process again initiates *via* rearrangement of farnesyl pyrophosphate **152** yielding intermediate **154** (**c.f. Scheme 2.2**). In this instance, an alternative rotation generates conformer **160**, with cyclisation following to yield the six-membered ring in **161**. Subsequent steps furnish the five-membered ring in **163**, followed by formation of a [5,5,6]-fused ring system in **164**. At this stage, the present cation allows an alkyl shift to occur generating a [5,6,5]-fused ring system, which is followed by a further alkyl shift to produce the required [5,6,6]-fused tricyclic structure **166**. From this common intermediate, the pathway can be completed by either deprotonation to yield α-duprezianene **151** and β-duprezianene **167** or nucleophilic attack by water, followed by an alkyl shift and deprotonation to yield sesquithuriferol **150**.

2 Previous and proposed work

2.1 Previous work

With such a close biosynthetic link within this family of natural products, it was evident that a general synthetic strategy to access one compound potentially would allow access to other compounds of interest within the family. Within our laboratories, a large amount of synthetic endeavour has been focused on investigations into the syntheses of several of these cedrene related natural products.[104,111,154–157] Indeed, these studies stemmed from the fact that structures such as these provide an interesting application of the PKR. Chiefly, it was envisioned that the challenging carbocyclic cores present within these compounds could be efficiently furnished through the initial generation of a cyclopentenone provided by the PKR.

The focus of this chapter is concerned with attempts towards the total synthesis of the natural product α-duprezianene **151** (**Figure 2.4**). In devising a route toward this target, the previously completed formal synthesis of α-cedrene **142**, and total synthesis of 2-*epi*-α-cedren-3-one **144**, within our laboratory, was examined. In both cases, an intramolecular PKR was employed as the key step to efficiently generate a cyclopentenone, and consequently, the requisite fused tricyclic core.

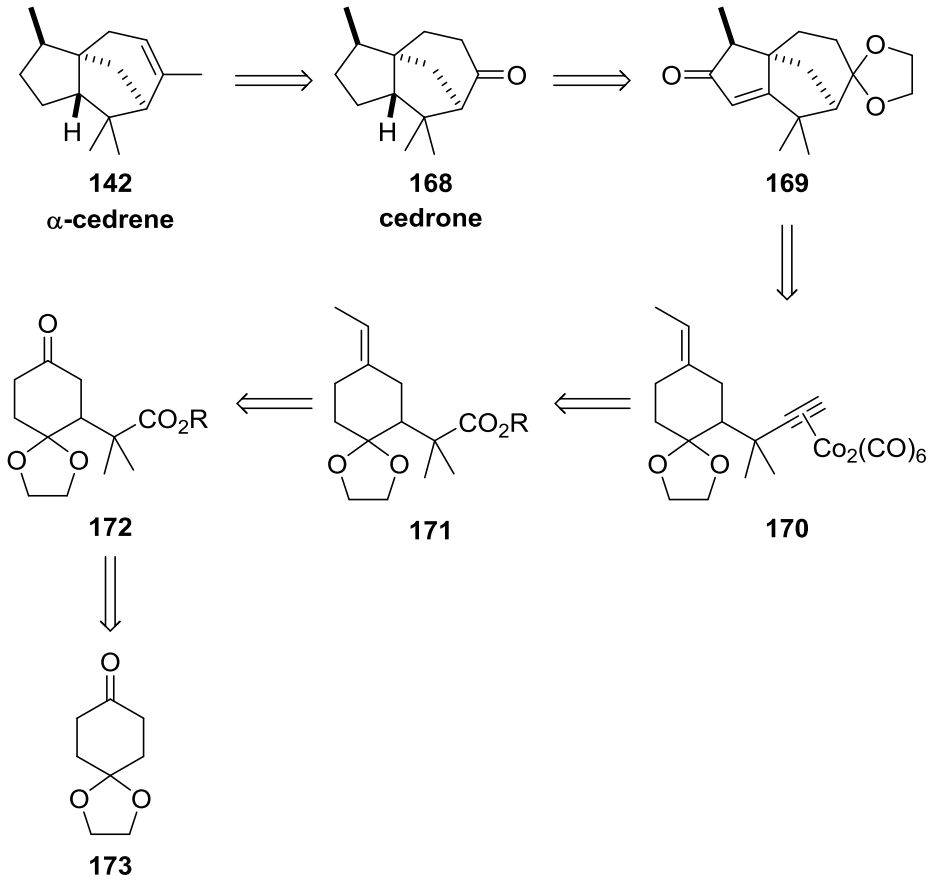


142 α-cedrene | **144** 2-*epi*-α-cedrene-3-one | **151** α-duprezianene

Figure 2.4

2.1.1 Synthesis of α-cedrene

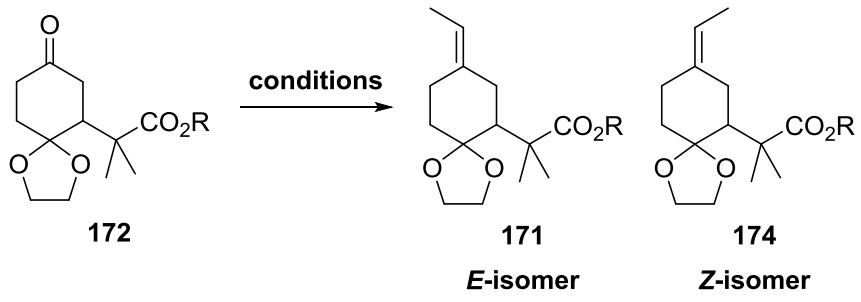
The first reported total synthesis of α-cedrene, **142**, was performed by Stork and co-workers, in 1955, closely following their initial characterisation of the compound.[141,158] Since this time, several other syntheses of cedrene have been reported.[159–165] The complex fused tricyclic core has proven to be a significant challenge, with a variety of approaches having been attempted, including various cycloadditions and radical methods. In 2001, within our laboratory, a formal stereoselective synthesis of α-cedrene **142** was achieved; our retrosynthetic analysis is shown below, highlighting the key transformations involved in this concise synthetic approach. (**Scheme 2.4**).[104,111,154]



Scheme 2.4

To achieve the desired formal synthesis, cedrone **168** was sought as a target. Indeed, in a number of previous reports, α-cedrene **142** was readily accessed from cedrone **168** in two steps.[158,161,164] As such, it was determined that cedrone **168** could be produced, in short order, from the PKR product **169**. Importantly, by incorporating the intramolecular PKR reaction at an advanced stage in the reaction sequence, high levels of complexity could be avoided in the early stages of synthesis, allowing rapid generation of the basic structural scaffold from simple and readily accessible starting materials. In order to yield the requisite PKR product, the alkyne cobalt complex precursor **170** was required, with this intermediate available through a concise series of relatively simple transformations from compound **171**. The olefin moiety of compound **171** could be furnished through a Wittig reaction with the carbonyl unit of compound **172**. It was proposed that generating an olefin with a selective *E*-geometry, in which the vinylic methyl was *trans* in relation to the bridging methylene group, would provide the correct relative orientation of the methyl in PKR product **169**, and, in turn, the final product α-cedrene **142**. Finally, intermediate **172**, featuring the ester side chain, would be produced from the commercially available mono-protected starting material 1,4-cyclohexanedione **173**.

Thus, in a forward synthetic sense, from starting material **173**, intermediate **172** was rapidly furnished, in three steps with relatively little issue. However, when olefination was attempted it was observed that the originally employed conditions produced the undesired *Z*-olefin **174** in excess (1:2 *E*:Z) as an inseparable mixture (**Scheme 2.5 & Table 2.1**).[111]



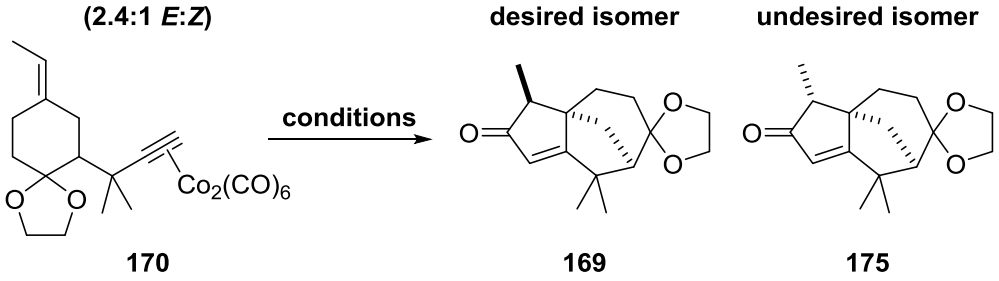
Scheme 2.5

Entry	R Group	Conditions	Yield (%)	171:174
1	Et	$Ph_3P^+EtBr^-$, *n*-BuLi, THF, 0 °C, 2 h	92	1:2
2	Me	$Ph_3P^+EtCl^-$, NaHMDS, THF, r.t., 16 h	75	2.5:1

Table 2.1

On examining ketone **172** it features an inherent lack of steric discrimination resulting in difficulty in engendering selectivity in either orientation. Despite this, through optimisation, significantly improved conditions were developed providing the desired *E*-geometry in excess (2.5:1 *E*:*Z*) (**Scheme 2.5 & Table 2.1**).[104,155]

Following olefination, a series of three relatively trivial transformations could be employed to produce the enyne efficiently. Typical conditions were then utilised to yield the alkyne cobalt complex **170** in near quantitative quantities. A systematic screening of promoters for the subsequent PKR was then performed (**Scheme 2.6 & Table 2.2**). Optimised conditions were as such identified with *n*-BuSMe promotion, providing a 2.4:1 separable diastereomeric mixture of **169** and **175** in an excellent 95% yield and short reaction time (**Table 2.2**, **Entry 3**).[104]

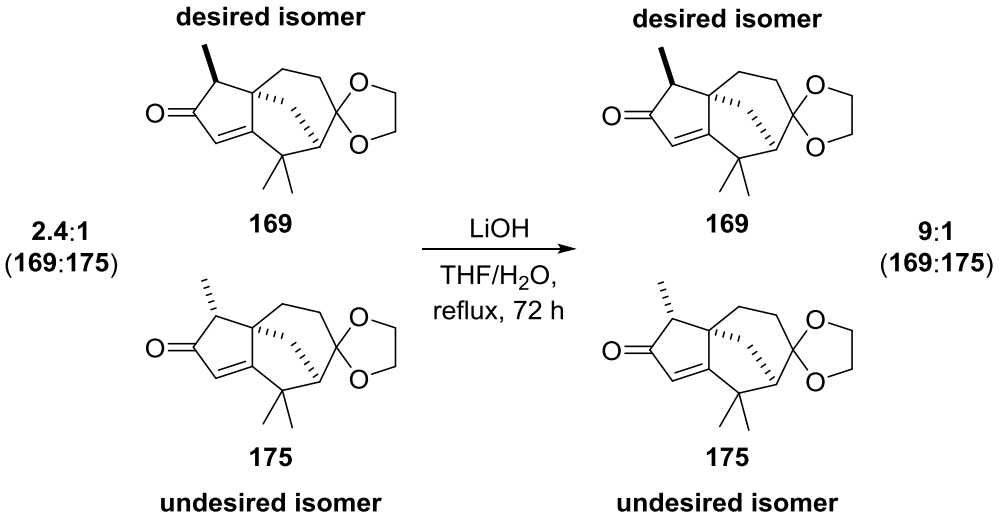


Scheme 2.6

Entry	Conditions	Yield (%)	169:175
1	TMANO·$2H_2O$, acetone, r.t., 16 h	91	2.4:1
2	NMO·H_2O, DCM, r.t., 16 h	84	2.4:1
3	*n*-BuSMe, DCE, reflux, 30 min	95	2.4:1
4	Polymer-supported sulfide, DCE, reflux, 30 min	80	2.4:1

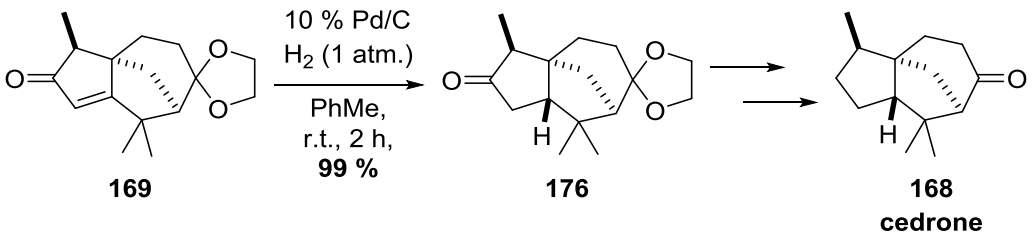
Table 2.2

A subsequent α-methyl epimerisation strategy was developed to provide further access to the desired cyclopentenone epimer **169** (**Scheme 2.7**). Crucially, it was discovered that refluxing the mixture of epimers in a THF/water mixture with lithium hydroxide successfully converted the 2.4:1 ratio of cyclopentenone products to a 9:1 ratio in favour of the desired epimer **169**.[104] This strategy essentially rectified the initial olefin selectivity issues observed.



Scheme 2.7

Following successful generation of the desired cyclopentenone epimer **169**, the synthetic strategy required removal of the enone functionality. As such, an extremely effective, facially selective, hydrogenation was performed to generate compound **176** (**Scheme 2.8**).[104,111] The formal synthesis could then be completed through a relatively trivial four-step process that generated cedrone **168**.

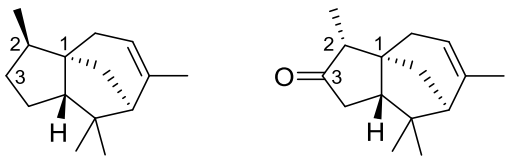


Scheme 2.8

Thus, through development of an efficient synthetic strategy, employing the PKR in its key tricyclic formation step, the formal total synthesis of α-cedrene **142** was accomplished *via* generation of cedrone **168** in 11 % overall yield over 14 steps. This success clearly demonstrated the access which the PKR approach could provide towards the synthesis of this family of complex natural products.

2.1.2 Synthesis of 2-*epi*-α-cedren-3-one

Following the successful formal synthesis of α-cedrene **142** within our laboratory, investigation into alternative related sesquiterpene products was initiated. To this end, the synthesis of 2-*epi*-α-cedren-3-one **144** was attempted (**Figure 2.5**).[156] Upon inspecting the structure of **144**, a general resemblance to α-cedrene, **142**, can be observed. The critical structural differences are a carbonyl group present at C3 in 2-*epi*-α-cedren-3-one **144** and an epimeric methyl group at C2.



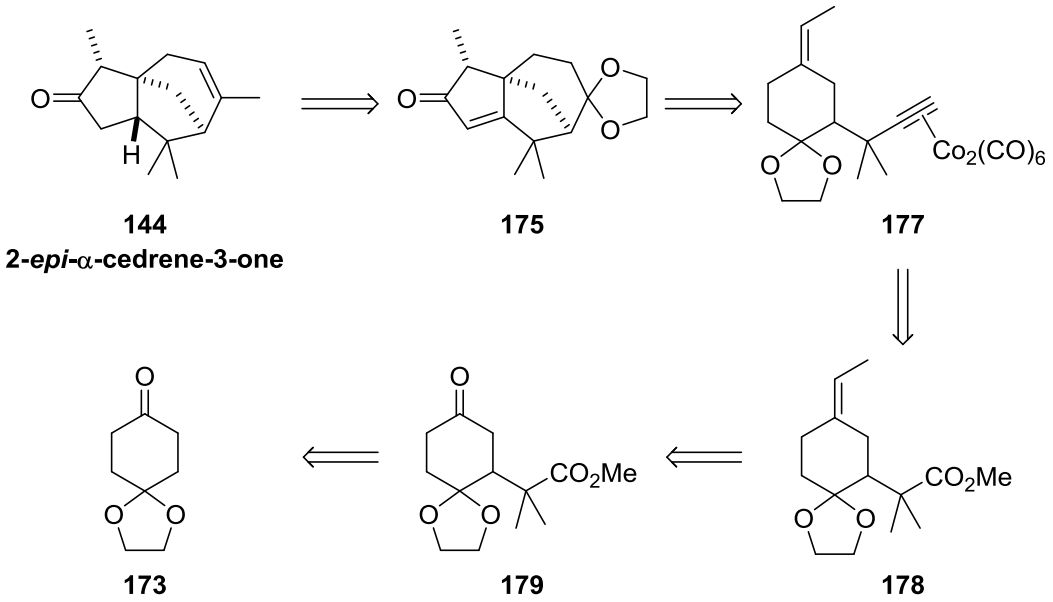
142 α-cedrene

144 2-*epi*-α-cedrene-3-one

Figure 2.5

The overall similarities between 2-*epi*-α-cedren-3-one, **144**, and α-cedrene, **142**, primarily that they both possess a [5,5,6] tricyclic fused carbon core, allowed much of the previously developed synthetic strategy to be employed.[156] Retrosynthetically, it can be observed that 2-*epi*-α-cedren-3-one, **144**, could be generated from a similar PKR product, **175**, previously accessed as an undesired isomer in the α-cedrene, **142** synthesis (**Scheme 2.9**). The alkyne cobalt complex **177**, which would furnish the desired cyclopentenone product, features, in this instance, a *Z*-geometry olefin. Selective Wittig methodologies would be employed on ketone **179**, to access the

desired isomer **178**. Once again, the starting material would be the commercially available mono-protected 1,4-cyclohexanedione **173**.



144
2-*epi*-α-cedrene-3-one

175

177

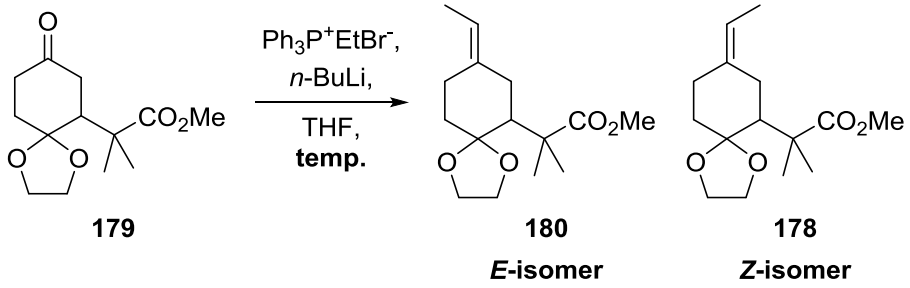
173

179

178

Scheme 2.9

While much of the route was influenced from that of α-cedrene **142**, several improvements were made which greatly increased the efficiency of the overall synthesis. One such advancement was found whilst investigating the selectivity of the olefination reaction. It was discovered that low temperatures enforced high selectivity of the desired *Z*-geometry olefination, whilst still producing excellent overall yields (**Scheme 2.10 & Table 2.3**). It can be noted that when the reaction temperature was reduced from r.t. to –100 °C the selectivity increased significantly (**Table 2.3, Entry 3**). This selectivity could be further enhanced through liquid nitrogen mediated cooling to -196 °C, and slow warming to -90 °C, with an excellent *E*:Z ratio of 1:9.2 resulting (**Table 2.3, Entry 6**). Pleasingly, yields of over 90 % were also achieved in all cases.

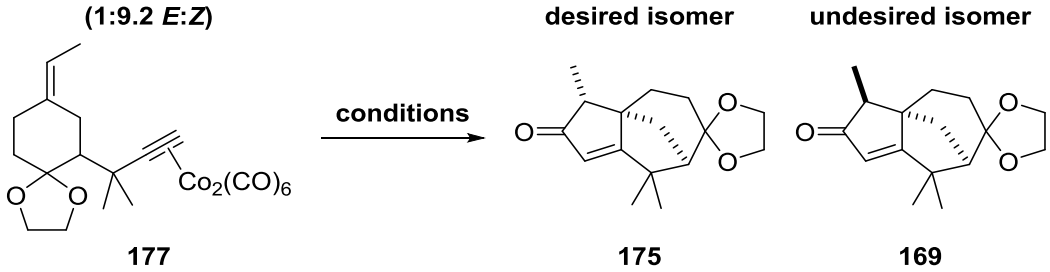


Scheme 2.10

Entry	Temp. (°C)	Yield (%)	180:178
1	r.t.	92	1:2.0
2	-78	99	1:4.0
3	-100	93	1:6.0
4	-196 – r.t	99	1:7.2
5	-196 – (-78)	99	1:8.0
6	-196 – (-90)	95	1:9.2

Table 2.3

With respect to the key PKR step, it was found that the optimum conditions employed in the synthesis of α-cedrene yielded the desired cyclopentenone product **175** in an excellent 83 % yield and a 9.2:1 excess (**Scheme 2.11 & Table 2.4**, **Entry 1**). Following this, the odourless sulfide conditions developed within our laboratory were trialled and found to improve the yield of product formation to 92 % (**Table 2.4**, **Entry 2**).[121] These conditions were of benefit as the sulfides odourless nature was of obvious practical advantage when the reaction was carried out on large scale.

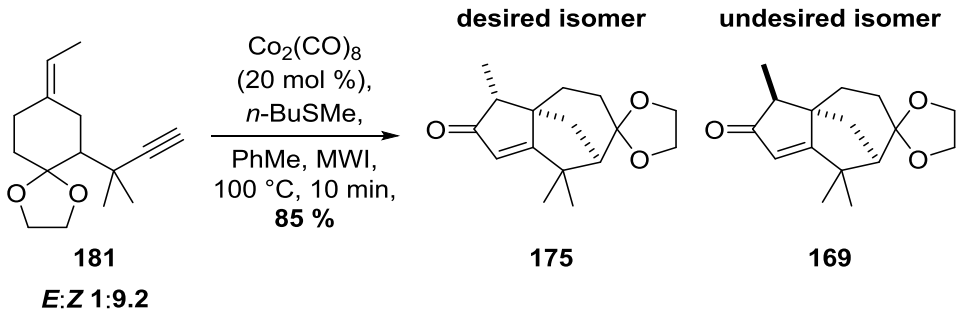


Scheme 2.11

Entry	Conditions	Yield (%)	175:169
1	*n*-BuSMe, DCE, reflux, 30 min	83	9.2:1
2	DodSMe, DCE, reflux, 40 min	92	9.2:1

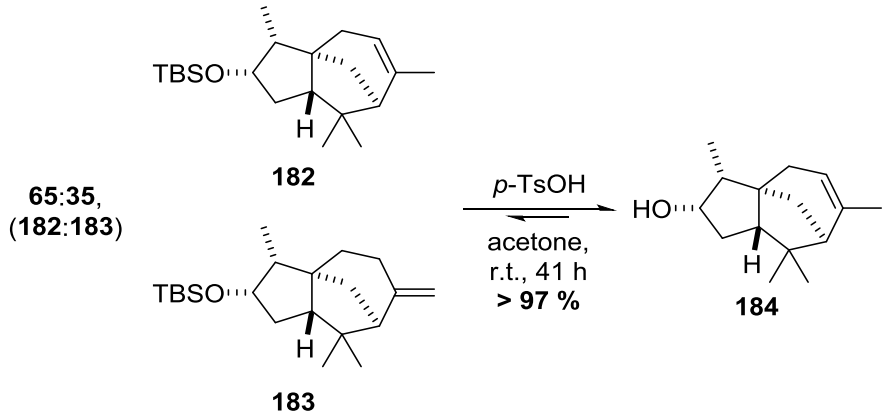
Table 2.4

With the success of the stoichiometric PKR, attention was turned to its catalytic variant. Several reaction conditions were investigated with the optimum found to be a 20 mol% loading of $Co_2(CO)_8$ with *n*-BuSMe as an additive, which upon 10 minutes of MWI, produced an excellent yield of 85 % (**Scheme 2.12**).



Scheme 2.12

Towards the end of the synthesis, an isomeric mixture of *tert*-butyldimethylsilyl (TBS) protected compounds **182** & **183** was produced. It was discovered that stirring these mixed isomers in *p*-toluenesulfonic acid (*p*-TsOH) afforded TBS deprotection with concomitant double bond migration, converting the undesired *exocyclic*-isomer to its *endocyclic* variant (**Scheme 2.13**). It should be noted however that this double bond migration was found to be fairly slow, with up to 41 h required to generate greater than 97 % of the desired compound **184**.



Scheme 2.13

Through a combination of previously reported chemistry and the outstanding developments and advances of efficiency described, the synthesis of 2-*epi*-α-cedren-3-one, **144** was completed in 16 steps with 17 % overall yield.

2.2. Proposed work

2.2.1 Proposed synthesis of α-duprezianene

Originally fully characterised in 1996 by Barrero and co-workers, α-duprezianene **151** is a member of the cedrene family of sesquiterpene natural products (**Figure 2.6**).[148,149] Although isolated from *Juniperus thurifera*, it had also been previously isolated in 1977 from C*upressus dupreziana* by Piovetti and co-workers, with its structure then tentatively assigned by Kirtany and co-workers.[166,167] Inspection of the literature revealed that at there has been no successfully completed total synthesis of α-duprezianene **151**. As such, it was proposed that a synthetic strategy, built upon previously developed chemistry within our laboratory, could be devised to allow for an elegant and robust route to this compound. Thus, it was believed that the synthesis of α-duprezianene **151** could be accomplished through initial generation of an enyne precursor followed by a key PKR, which would, in turn, furnish the target's complex skeletal structure.

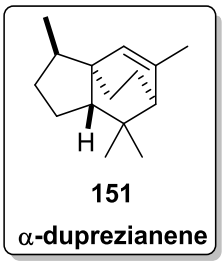


Figure 2.6

On examination of α-duprezianene's structure it becomes clear that while similarities to α-cedrene **142** and 2-*epi*-α-cedren-3-one **144** exist, there is a variance in the ring sizes of the fused tricyclic skeleton (**Figure 2.7**). Both α-cedrene, **142**, and 2-*epi*-α-cedren-3-one, **144**, feature [5,5,6] tricyclic core, whereas α-duprezianene, **151**, features a [5,6,6] tricyclic core. Akin to α-cedrene, α-duprezianene has no functionality at the C3 carbon and its methyl group at C2 is *anti* with respect to the internal ethylene bridging unit. It was clear that a novel synthetic strategy was required in order to achieve the synthesis of α-duprezianene. However, it was hoped that much of the developed chemistry shown in our previous studies could be applied.

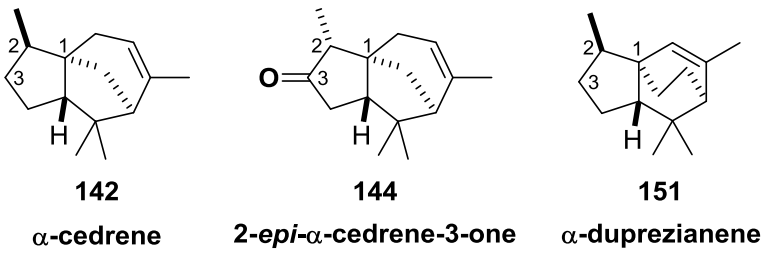
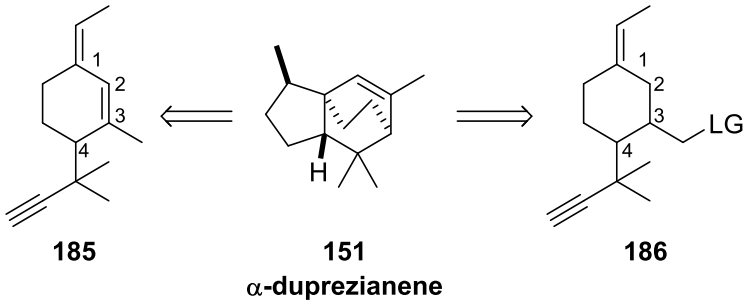


Figure 2.7

In developing the synthesis, the first consideration was the formation of the required [5,6,6]-fused ring skeleton. As had been previously shown, an extremely efficient way to generate this complexity in one step was through use of the PKR. With this in mind, the structure of the requisite PKR precursor was considered (**Scheme 2.14**). To generate the [5,6,6]-fused ring system it was essential that the alkyne side chain originated from C4 of the 6-membered ring rather than the C3 as had previously been

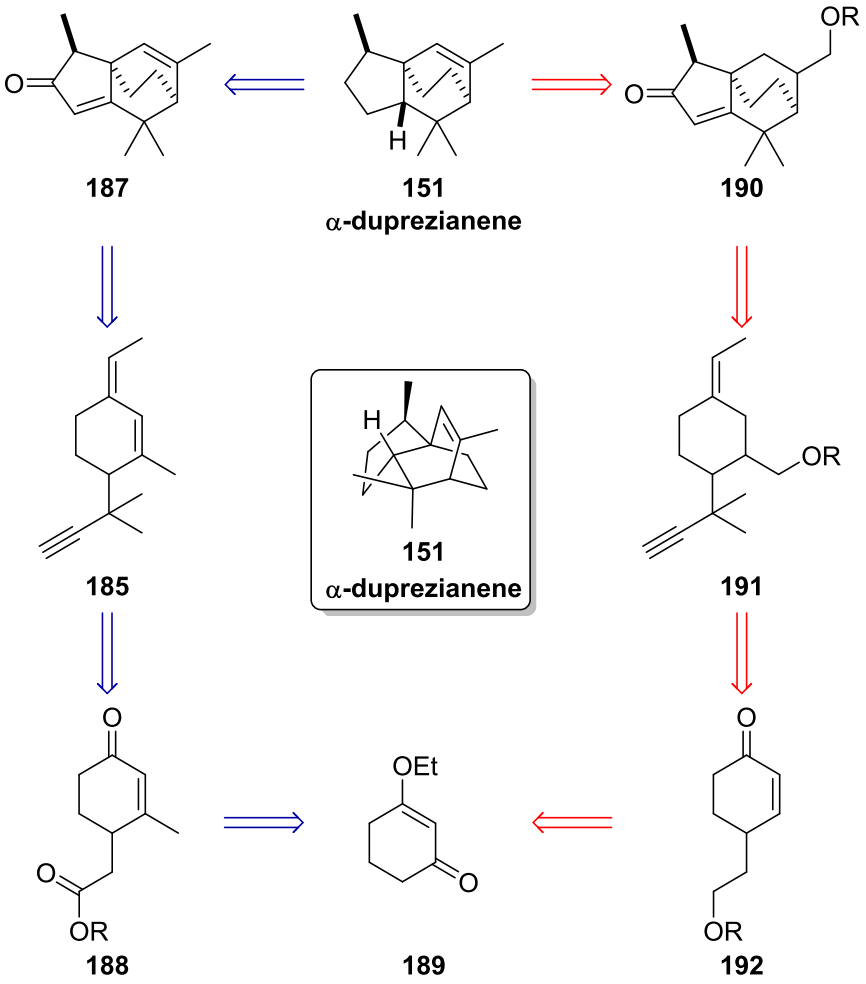
the case. On examination of the literature it was discovered that no such PKR had been performed with substrates of this type. As such, it was considered that the desired novel PKR would pose a significant challenge, although it was hoped that with the wealth of promotional methods available the desired transformation could be achieved. This synthesis would then also act to further extend the potential substrate scope of the intramolecular PKR.



Scheme 2.14

The second consideration in design of the PKR precursor was the formation of the *endocyclic* olefin in the final product; as such two precursors were proposed (**Scheme 2.14**). The first potential precursor, **185**, featured the required *endocyclic* olefin prior to the key PKR. It was thought that while this was a potentially efficient strategy the added diene functionality prior to PKR would serve to further restrict the already extremely challenging cyclisation. The second hypothesised precursor possessed a side chain originating from C3, which featured a leaving group **186**. It was thought that elimination of this group, after the PKR, would provide a mixture of *endocyclic* and *exocyclic* olefin isomers. These mixed isomers could then hopefully be forced to an excess of the *endocyclic* olefin through double bond migration as previously described in the synthesis of 2-*epi*-α-cedren-3-one **144**.[156] Finally, with regards the desired relative stereochemistry, as previously discussed, the vinylic methyl moiety's geometric isomerism would be crucial. In this instance a *Z*-geometry olefin was required to ensure a *syn* relationship was maintained with respect to the bridging ring unit.

With the proposed precursors in mind, a convergent retrosynthetic strategy towards **185** and **186** was developed (**Scheme 2.15**). In the first strategy, the desired natural target, could be produced through transformation of cyclopentenone **187**, with would be yielded from the PKR of diene precursor **185**. Generation of this precursor would be mediated by selective olefination, *gem*-dimethyl insertion and ester elaboration of the enone intermediate **188**. The enone could then in turn be furnished through alkylation and hydrolysis of the commercially available compound **189**.



Scheme 2.15

Alternatively, if pursuing the saturated precursor, the final target **151** could be formed through transformation of cyclopentenone **190** (**Scheme 2.15**). In this instance the requisite olefin in the final product would be generated through

elimination in the late stages of the synthesis. As discussed, it was hoped that this cyclopentenone intermediate **190** would be yielded from the PKR of saturated precursor **191**, which, in turn, would be formed from selective olefination, ether chain elaboration, and *gem*-dimethyl insertion of enone **192**. In this instance, a conjugate addition strategy would be required to install the desired side chain, and, as such an ether rather than ester chain would be employed to aid in chemoselectivity. Orthogonal protection would also have to be assessed at this point. Finally, the enone **192**, could be generated from the same commercially available compound **189**.

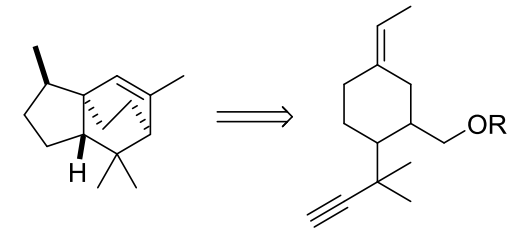
Having proposed potential strategies towards the target for this programme of work, synthetic evaluations could be initiated with the hope that a robust route towards the desired precursors would be developed. This would initially allow for investigation into this novel PKR, which would serve to enhance the scope of the reaction overall. Further to this, with successful cyclisation established, attempts towards completion of the desired natural target would be pursued. The following section details these endeavours.

3 Results and discussion

3.1 Saturated PKR precursor

3.1.1 Synthetic route 1

With two potential strategies towards α-duprezianene **151** determined, which was to be pursued first was considered. The key PKRs, previously employed within our syntheses of sesquiterpene targets, had proved extremely efficient. However, the novelty and extended nature of the proposed PKR suggested a significantly more challenging transformation. As such, it was deliberated that the added planarity and conformational restriction of precursor **185**, imbued by the cyclohexene ring, was thought to further restrict the cyclisation potential. This, in turn, led initial synthetic effort to focus on the perceived more flexible precursor **191** (**Scheme 2.16**).



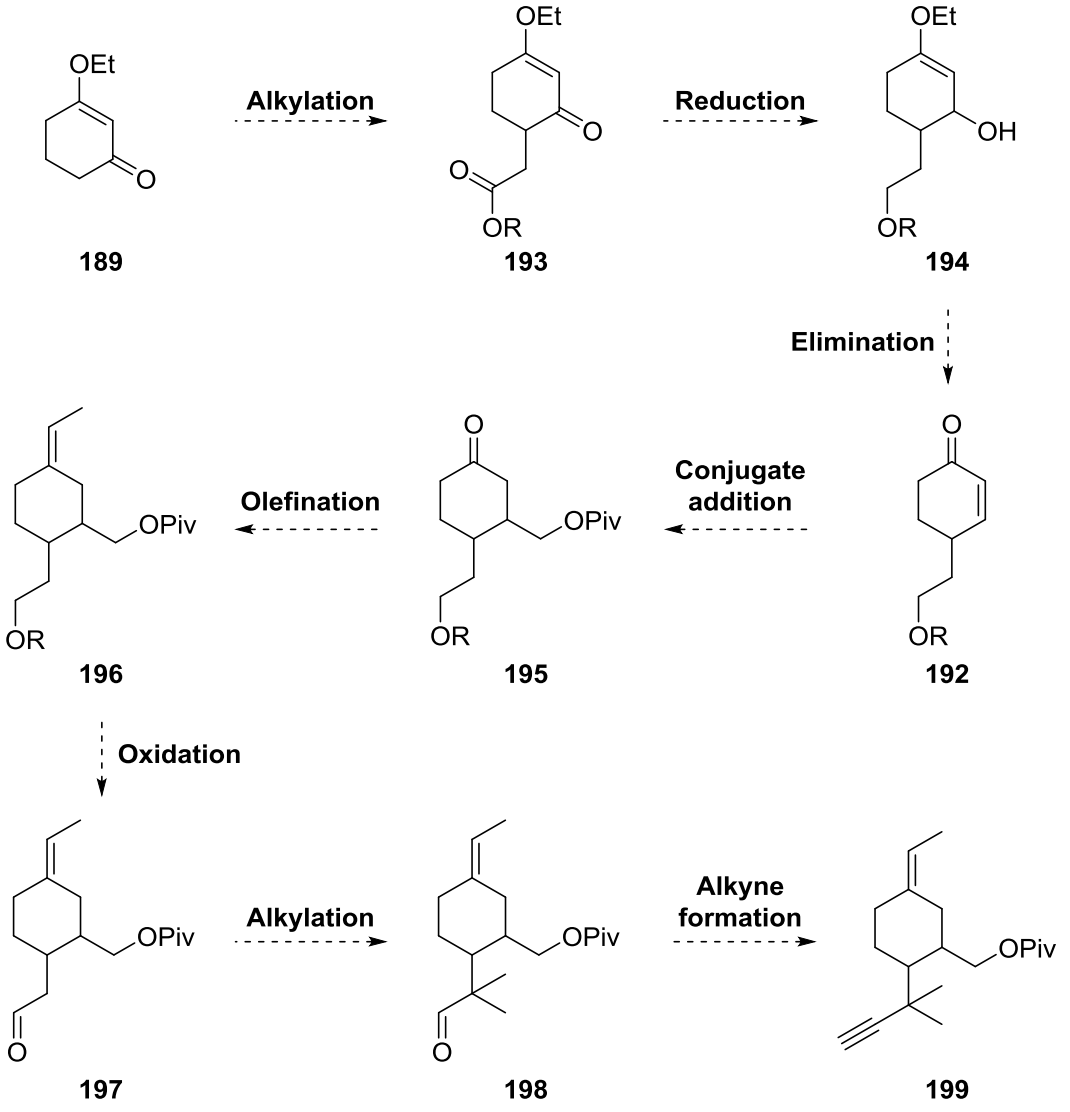
151
α-duprezianene

191

Scheme 2.16

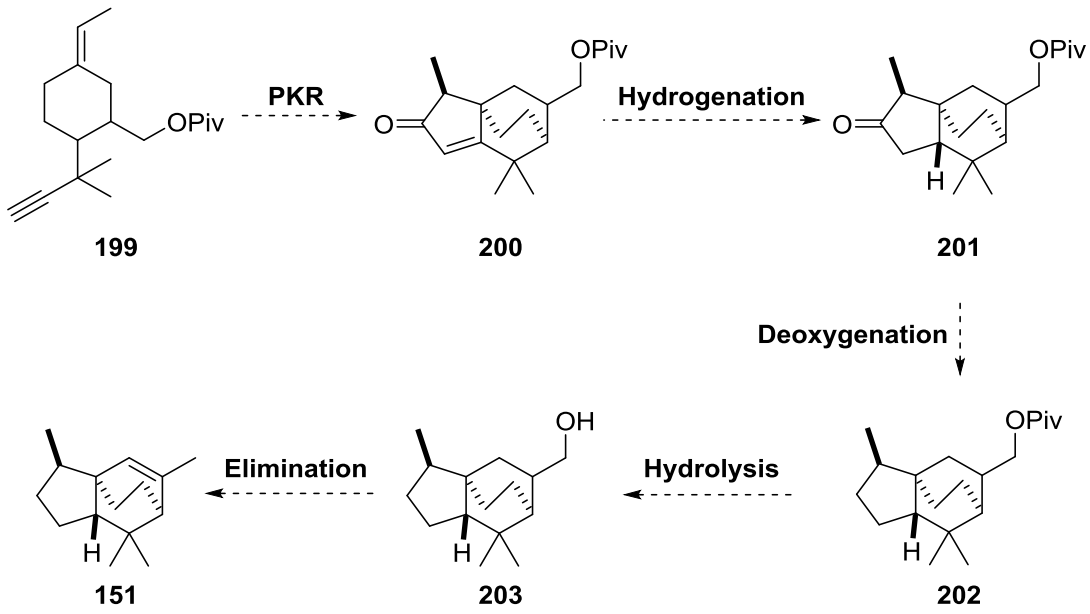
With the initial focus determined, a viable synthetic route towards a suitable saturated PKR precursor was developed (**Scheme 2.17**). Thus, alkylation of commercially available compound, **189**, would provide ester **193**. Global reduction of the ester and ketone moieties would then be performed, yielding intermediate **194**. It was considered, at this point, that protection of the primary alcohol might be required; however, this would be established within the synthesis. A subsequent acid-catalysed hydrolysis of the enol ether would also serve to eliminate the secondary alcohol to afford enone **192**. With this enone in hand, a conjugate addition protocol reported by Knochel and co-workers could then be employed to

install a pivaloyl alkyl chain at C3, furnishing intermediate **195**.[168,169] It was theorised that this pivaloyl group would be stable enough to survive the ensuing synthetic steps while providing functionality allowing for the requisite final elimination. Olefination of the ketone unit could be attempted, with high selectivity of the *Z*-geometry olefin, **196**, desired. Oxidation would follow, with protecting group removal beforehand if required, to produce the aldehyde **197**. This aldehyde, **197**, would then provide the requisite functionality to install the *gem*-dimethyl group present in intermediate **198** through deprotonation and alkylation. Finally, alkynylation of aldehyde **198** could be performed to yield the key enyne precursor **199**.



Scheme 2.17

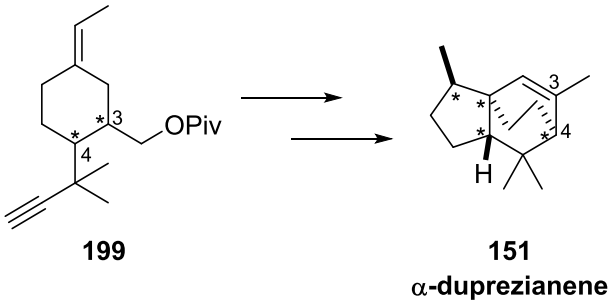
With enyne **199** in hand the key step of the synthesis, the novel PKR, could be trialled under various promotional methodologies (**Scheme 2.18**). Successful PKR would yield the complex [5,6,6]-fused tricycle **200** which can undergo a facially selective hydrogenation to afford intermediate **201**. Following this, deoxygenation of the ketone unit present in the five membered ring is required to yield compound **202**. At this stage, the ester functionality of the previously installed pivaloyl group could be cleaved to yield the primary alcohol **203**; this alcohol can then be further functionalised through mesylation or tosylation with a final base promoted elimination furnishing the required olefin. This is most likely to occur as a mixture of *exo*- and *endocyclic* isomers. However, as previously discussed, it is expected that synthetic methodology discovered within our laboratory should promote olefin migration generating an excess of the final compound α-duprezianene **151**.



Scheme 2.18

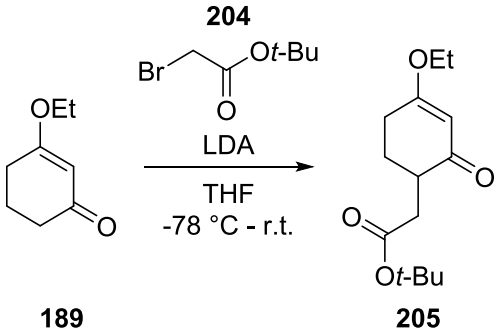
At this stage it should be noted that in the proposed route to the saturated enyne precursor **199**, two uncontrolled chiral centres are generated within the molecule at both C3 and C4. Absolute control of these centres is however not essential for the stereoselective synthesis of α-duprezianene **151**. Following the desired PKR the centre at C4 will be fixed by virtue of the [5,6,6]-fused ring system formed. In the

last stages of the synthesis elimination to generate the requisite olefin wiould remove the chiral centre at C3. As such the key selectivity required is that of a *Z*-geometry olefin prior to the PKR and a facially selective hydrogenation in the later stages.



Scheme 2.19

The synthetic strategy was thus initiated through a kinetic alkylation originally described by Stork and co-workers.[170] Employment of the *tert*-butyl ester **204**, was observed throughout the literature, and, as such, it was decided that the initial alkylation attempts would also employ this reagent (**Scheme 2.20 & Table 2.5**).[171]



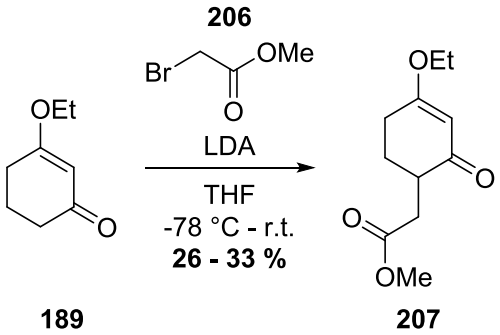
Scheme 2.20

Entry	Scale (mmol)	Eq. LDA	Yield (%)
1	1.43	1.5	61
2	42.80	1.5	93
3	35.67	1.1	99

Table 2.5

The reaction proceeded through preformation of lithium diisopropylamide (LDA) *in situ*, followed by addition of compound **189** to generate the enolate. Ester, **204**, was then added to quench this enolate and yield product **205**. Pleasingly, the first attempt at this reaction was found to afford the desired compound **205** in 61 % yield (**Table 2.5**, **Entry 1**). Furthermore, upon increasing the scale of the reaction an excellent 93 % yield was achieved (**Table 2.5**, **Entry 2**). Interestingly, it was discovered that decreasing the amount of LDA employed further improved the reaction, with yields as high as 99 % attained (**Table 2.5**, **Entry 3**).

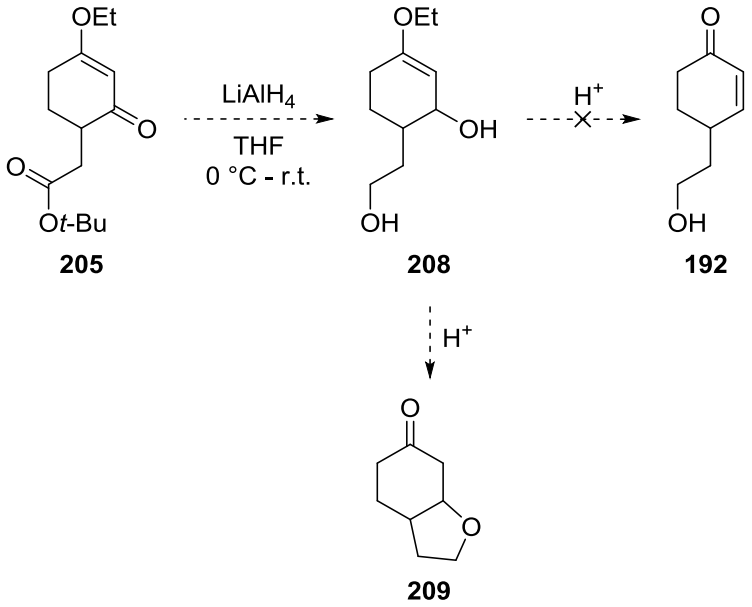
In the interest of atom economy, the methyl ester **206** was also investigated as an alternative reagent (**Scheme 2.21**). Similar conditions to the previously described reaction were employed; disappointingly, it was found that generation of the product **207** was achieved in much poorer yields of 26 – 33 %. It was considered that this decrease in yield this resulted from the methyl ester's potential lability. It was clear from these experiments the bulkier *tert*-butyl ester containing compound **205** provided a favourable starting point for the ensuing synthetic route.



Scheme 2.21

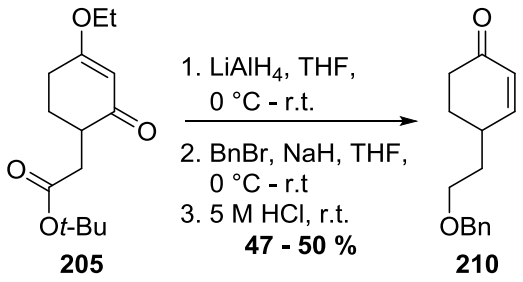
With the initial alkylation performing robustly and multigram quantities of the ester product available, attention turned to production of the enone **192** (**Scheme 2.22**). Originally, it had been proposed that a global reduction would generate diol **208**, and it was then hoped that acid-catalysed hydrolysis of the enol group would afford the enone **192** through elimination of the protonated secondary alcohol. Unfortunately, examination of the literature suggested that whilst diol **208** could be accessed, acid

catalysed hydrolysis would likely result in the formation of the bicycle **209** through spontaneous cyclisation.[172]



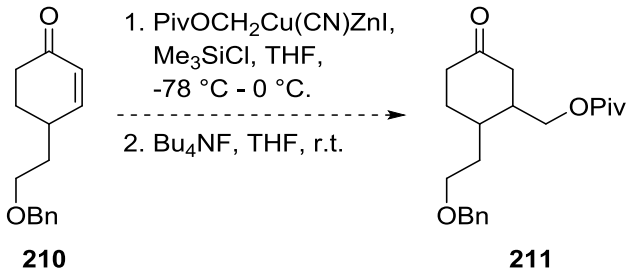
Scheme 2.22

With this knowledge, a new strategy was proposed in which a protecting group would be installed on the primary alcohol following reduction. Examination of the literature surrounding this area provided a procedure in which the ester, **205**, would be transformed into benzyl protected enone, **210**, in three steps with no intermediate isolation (**Scheme 2.23**).[173] The reaction would proceed through a global reduction, with subsequent benzylation of the resulting primary alcohol. Finally, addition of aqueous hydrochloric acid would achieve the required enol hydrolysis and yield the enone **210**. On first attempt the multistep reaction was found to proceed efficiently, yielding enone **210** in 50 % over three steps. Pleasingly, this process proved relatively robust with similar yields observed on scale up of the protocol.



Scheme 2.23

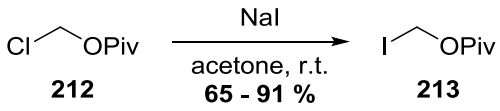
With a route to multigram quantities of enone **210** successfully developed, attention was turned to the conjugate addition process, needed to install the required side chain at C3 (**Scheme 2.24**). As previously discussed, a perceived suitable procedure had previously been reported by Knochel and co-workers on simple enone substrates.[168,169] The proposed reaction however possessed areas of concern; firstly, only moderate yields were observed when the reaction was performed on similar substrates, and, secondly, the reaction required considerably complex and challenging practical conditions. Nevertheless, it was thought that this conjugate addition protocol provided rapid access to an advanced intermediate in an atom economical fashion, and as such, the conditions warranted experimental exploration.



Scheme 2.24

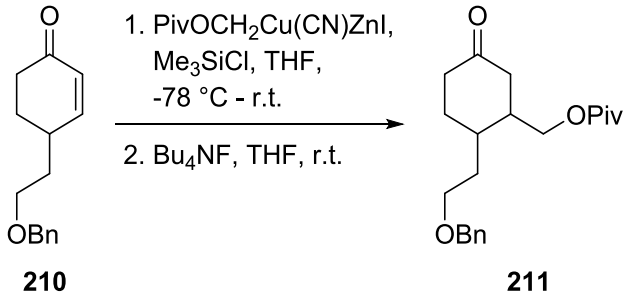
In order to apply these conjugate addition conditions, the pivaloyl containing side chain **213** was first required. It was suggested within the literature that iodinated side chain **213** could be prepared, in multigram quantities, from the commercially available chloromethyl pivalate **212** through classical Finkelstein conditions (**Scheme 2.25**).[168,169] Initial attempts with these conditions resulted in successful

generation of the desired compound **213** in 65 % yield. Pleasingly, with subsequent attempts the yield was found to greatly improve to 91 %.



Scheme 2.25

With reagent **213** in hand the proposed conjugate addition could be attempted (**Scheme 2.26 & Table 2.6**). Thus, the mixed metal reagent was prepared through initial addition of iodomethyl pivalate, **213**, to zinc dust, which had been activated with 1,2-dibromoethane and trimethylsilyl chloride (TMSCl), to form (pivaloyloxy)methyl zinc iodide ($PivOCH_2ZnI$). A solution of this reagent was then added to a solution of $CuCN{\cdot}2LiCl$, formed through mixture of CuCN and LiCl, generating the carbenoid $PivOCH_2Cu(CN)ZnI$. To this reagent was added TMSCl and the desired electrophile. Following this, the generated trimethylsilyl enol ether could be cleaved through addition of tetrabutylammonium fluoride (TBAF).



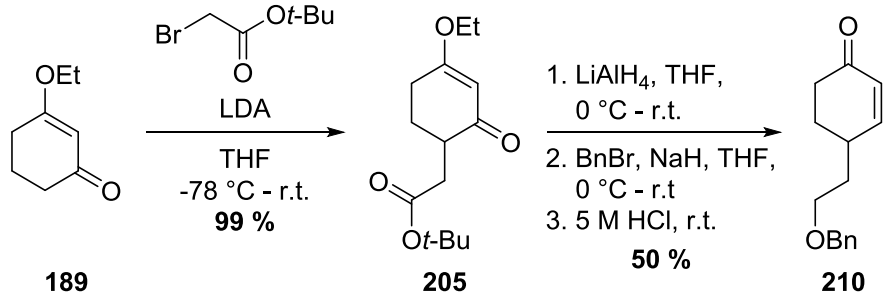
Scheme 2.26

Entry	Scale (mmol)	Eq. 213	Alkyl zinc formation	Yield (%)
1	1.84	1.35	1 h at r.t.	-
2	3.06	2.00	2 h at r.t.	-
3	3.06	2.00	1 h at 10 – 15 °C	-
4	3.06	2.00	2 h at 10 – 15 °C	-

Table 2.6

For the initial attempts, the literature suggested conditions were applied; as such, 1.35 eq. of iodomethyl pivalate was employed while the alkyl zinc reagent's ($PivOCH_2ZnI$) formation was performed over 1 h at r.t. (**Scheme 2.26 & Table 2.6**, **Entry 1**). Disappointingly, the reaction profile was extremely poor with none of the desired product **211** apparent. Starting material **210** appeared present but could not be isolated. Following this, an attempt was made using 2.0 eq. of the conjugate addition reagents; the time allowed for alkyl zinc formation was also increased to 2 h with the belief that more of the requisite mixed metal reagent would be formed (**Table 2.6**, **Entry 2**). Regrettably, this appeared to have no effect as once again no product was yielded. At this point, it was considered that the iodomethyl pivalate **213** may be unstable within the reaction conditions. In an attempt to prevent decomposition, the alkyl zinc formation was carried at the lower temperature of 10 – 15 °C. Unfortunately, this lower temperature formation provided no apparent benefit to the reaction (**Table 2.6**, **Entries 3 & 4**).

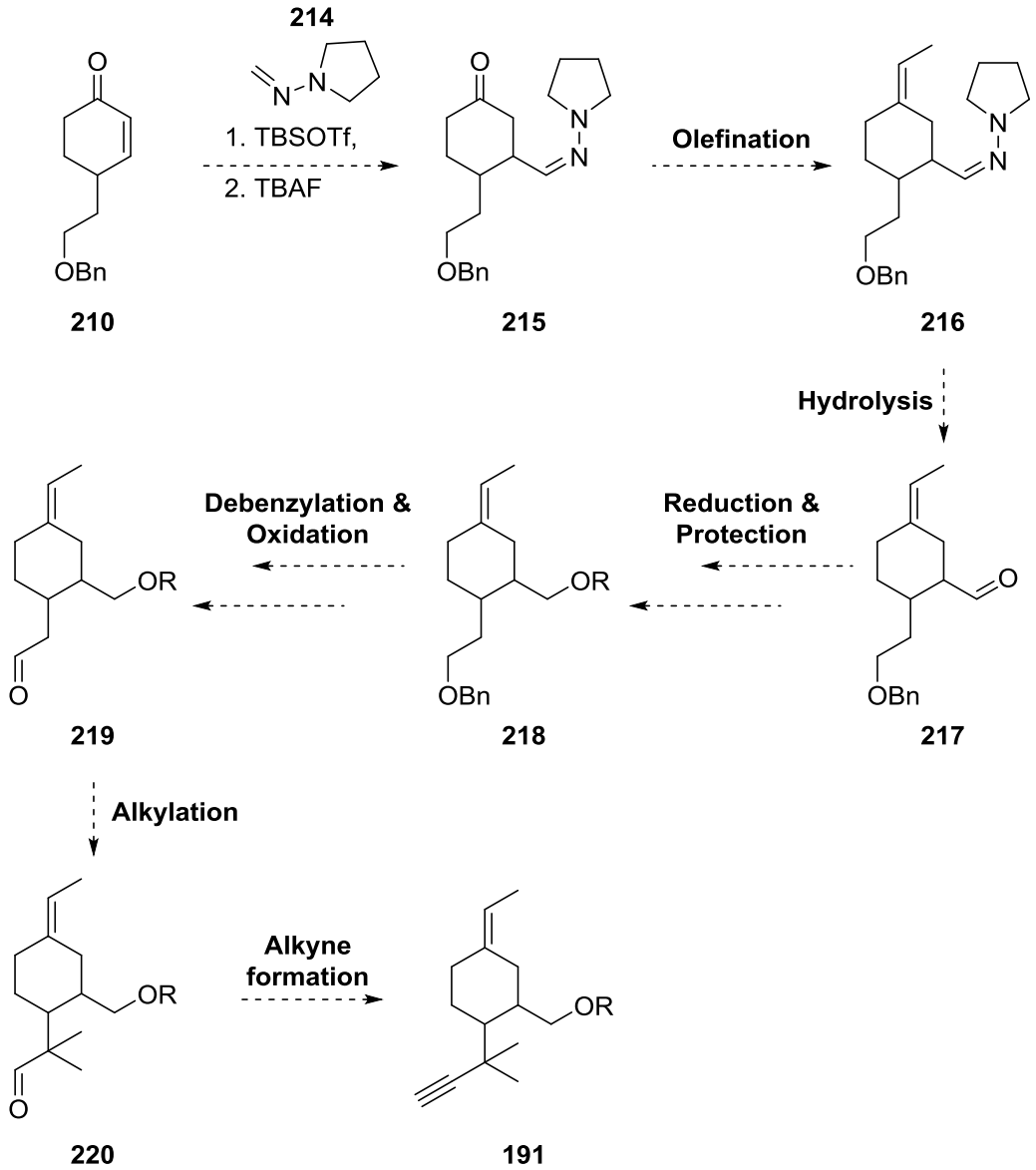
The outcome of this short trial clearly showed that an alternative strategy was required to access a suitable saturated PKR precursor. However, a robust and reliable synthetic sequence to the enone **210** had been established; this compound was acknowledged as an important intermediate, which provided numerous possibilities for further synthetic elaboration (**Scheme 2.27**). With this in mind, alternative synthetic strategies deriving from enone **210** were considered.



Scheme 2.27

3.1.2 Synthetic route 2

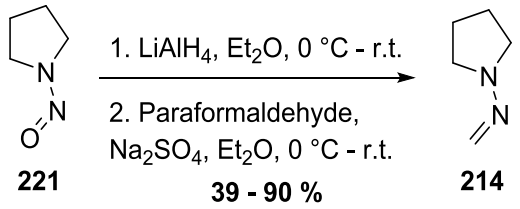
A secondary synthetic strategy towards a saturated PKR precursor was proposed in which the previously developed chemistry to enone **210** could be employed. Once again, it was hoped that a conjugate addition would be used to introduce an appropriate side chain at C3 (**Scheme 2.28**).



Scheme 2.28

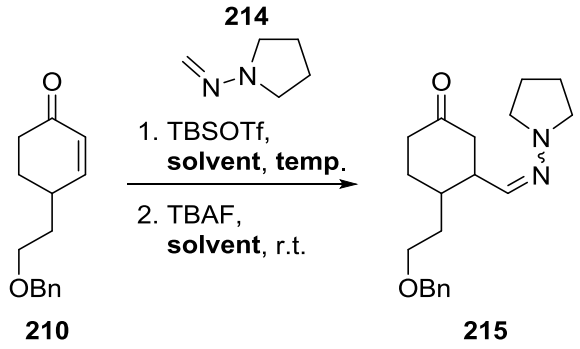
To this end, a report by Lassaletta and co-workers was noted in which a umpolung reagent was employed in a conjugate addition (**Scheme 2.28**).[174] This protocol had previously been employed within our laboratories to efficiently effect such a transformation.[157] It was thought that intermediate **215**, resulting from this conjugate addition, provided a starting point for a more trivial, albeit longer, synthetic route towards the PKR precursor **191**. Thus, following generation of **215**, selective olefination could be attempted to yield intermediate **216**. Subsequent hydrolysis would then generate aldehyde intermediate **217**, which provided a number of routes for further functionalisation. Indeed, it was considered that an effective strategy would involve reduction to the primary alcohol followed by protection to furnish a compound of type **218**. Crucially, to be an effective protecting group it would need to be orthogonal to allow for debenzylation. Oxidation of the afforded alcohol would provide aldehyde **219** which would in turn, allow installation of the *gem*-dimethyl unit present in compound **220**. As before, a final alkyne formation step would be required to provide the necessary PKR precursor **191**.

In order to attempt the proposed conjugate addition, it was necessary to first synthesise the requisite hydrazone **214** (**Scheme 2.29**). Literature conditions provided a one-pot route from the commercially available *N*-nitrosopyrrolidine **221**, in which an initial reduction was carried out followed by condensation with paraformaldehyde to generate the desired hydrazone **214**.[175] Initial attempts at this reaction were found to furnish the final product **214** in a suboptimal 39 % yield. The hydrazone species **214** was considered to be somewhat unstable and challenging to isolate. Pleasingly, however, improvement in handling over subsequent attempts resulted in elevation of the yield to 90 %.



Scheme 2.29

With successful generation of hydrazone **214** in multi-gram quantities, the proposed conjugate addition to afford **215** could be attempted (**Scheme 2.30 & Table 2.7**). In this protocol intial promotion of the electrophile would be mediated by t*ert*-butyldimethylsilyl triflate (TBSOTf) addition. Following this hydrazone **214** would act as a formyl anion equivalent, which would be installed through nucleophilic attack. This would generate the silyl enol ether adduct, however subsequent addition of TBAF would afford the desired product. Initial attempts followed literature conditions, which employed diethyl ether as the solvent with the reaction performed at 0 °C (**Table 2.7**, **Entry 1**).[174] Pleasingly, these conditions furnished the desired product **215** in a moderate 41 % yield. Previous work within our laboratories showed that adopting a lower temperature in THF provided greater efficiency.[157] Thankfully, this was found to be the case with the product **215** furnished in an increased 66 % yield using these modified conditions (**Table 2.7**, **Entry 2**).



Scheme 2.30

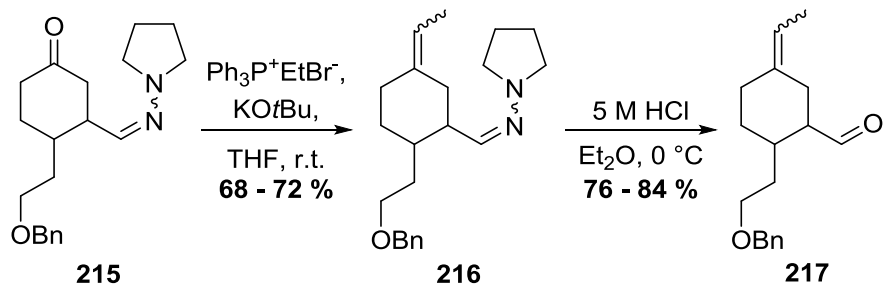
Entry	Scale (mmol)	Solvent	Temp.	Yield (%)
1	0.87	Et_2O	0 °C	41
2	1.48	THF	-78 °C – r.t.	66

Table 2.7

It should be noted that the conjugate addition, although successful, resulted in a complex mixture of stereoisomers. The introduction of an uncontrolled stereocentre at C3, and a further potential mixture of isomers from the hydrazone moiety made characterisation extremely difficult. At this stage an NMR specialist was consulted who attempted to further elucidate the mixture of isomers present. To this end,

several techniques were employed including numerous 2D NMR techniques and the more recently developed Pure Shift NMR methodologies (with this method able to collapse multiplets to single signals allowing better resolution of the spectrum). Unfortunately, the complex nature of the data prevented any further determination. It was, however, hoped that on progressing to the desired PKR the resulting compound data would be simplified. Having said this, the skeletal structure of this compound, and further compounds arising from the substrate, were confirmed *via* characteristic NMR signals, high-resolution mass spectrometry (HRMS), and IR spectroscopy As such the synthetic route was continued without exact knowledge of the isomeric mixture of the produced compounds.

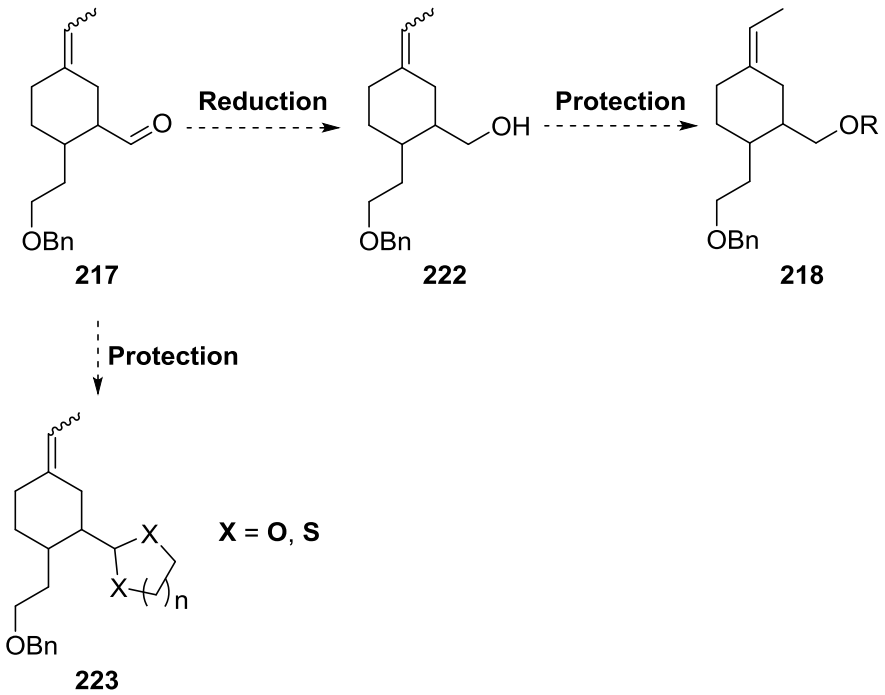
With the conjugate addition successfully applied, a subsequent olefination of the carbonyl moiety was required to progress the synthesis. As previously discussed, to achieve the correct relative stereochemistry of the final product, a *Z*-selective olefination was desired. As a result of the complex mixture of isomers present in compound **215** it was, however, considered that determination of selectivity would be near impossible at this stage. Consequently, with a desire to proceed through the synthesis towards the key novel PKR, and thus test this challenging proposed transformation, generation of selectivity was at this point ignored. As such, olefination of intermediate **215** was attempted using ethyltriphenylphosphonium bromide as the ylide source, under standard Wittig conditions at r.t. Pleasingly, the desired product **216** was afforded in good yield as a complex mixture of isomers. This reaction was found to be extremely robust, with subsequent attempts and increases in scale found to produce similar respectable yields (**Scheme 2.31**).



Scheme 2.31

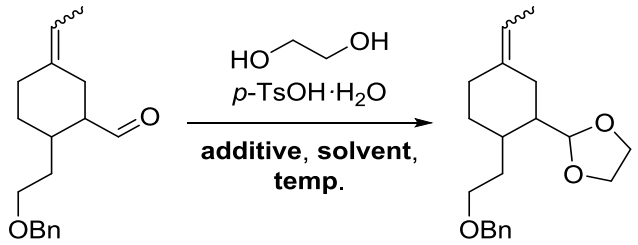
With olefin **216** in hand the hydrazone moiety could be removed to reveal aldehyde **217**; this aldehyde would then provide an efficient point for further functionalisation. The hydrazone unit was rapidly hydrolysed in excellent yield in the presence of 5 M hydrochloric acid (HCl) at 0 °C (**Scheme 2.31**). Unfortunately, despite removal of the hydrazone moiety, the associated NMR complexity remained and prevented further elucidation of the isomeric content.

With access to aldehyde **217**, the proposed synthetic strategy was once again evaluated. The original strategy would follow through reduction of the aldehyde **217** to afford alcohol **222**, subsequent protection would generate a compound of type **218** (**Scheme 2.32**). Alternatively, the aldehyde unit could be directly protected yielding a compound of type **223**. In both cases, an orthogonal protection strategy would be required allowing facile removal of the benzyl moiety in the following steps. It was considered that direct protection of the aldehyde would shorten the route to the enyne precursor, allowing the key novel PKR to be attempted in a rapid fashion. As such, it was decided that initial research would focus on direct protection of aldehyde **217**.



Scheme 2.32

To this end, initial efforts to protect the aldehyde group proceeded through the attempted formation of dioxolane species **224** (**Scheme 2.33 & Table 2.8**). Numerous conditions for a protection of this type were identified within the literature. In the first instance, protection of **217** was attempted through reaction with ethylene glycol and catalytic *p*-TsOH·H_2O in PhMe at 60 °C (**Table 2.8**, **Entry 1**).[176] The potential reversibility of this reaction required that 4 Å molecular sieves (4 Å MS) were added to sequester the generated water. This procedure was found to be somewhat successful, generating protected compound **224** in a moderate 56 % yield as a complex mixture of isomers. In an attempt to improve reaction efficiency, alternative conditions were trialled, in which, protection was performed in PhH at r.t. with trimethylorthoformate as a water abstracting additive (**Table 2.8, Entry 2**).[177] To our delight, these conditions furnished the dioxolane product **224** in an excellent 84 % yield. Finally, triethylorthoformate was used in place of trimethyl orthoformate; unfortunately, no improvement resulted (**Table 2.8**, **Entry 3**).



217 **224**

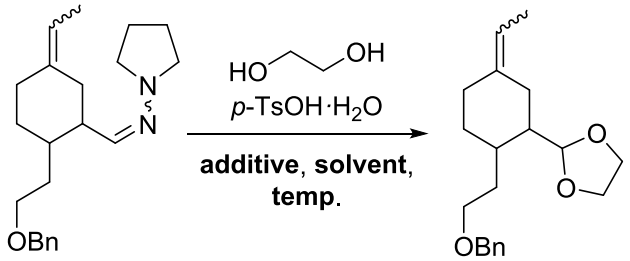
Scheme 2.33

Entry	Additive	Solvent	Temp.	Yield (%)
1	4 Å MS	PhMe	60 °C	56
2	trimethylorthoformate	PhH	r.t.	84
3	triethylorthoformate	PhH	r.t.	75

Table 2.8

Despite the direct aldehyde protection progressing very efficiently, an attempt to further improve the synthetic route was made. It was considered that a one-pot hydrolysis and protection procedure from hydrazone **216** might be possible as the conditions employed all featured catalytic acid. Success in this regard would further

shorten the route towards the key enyne precursor. Studies were initiated through reaction of hydrazone **216** with ethylene glycol and catalytic *p*-TsOH·H_2O in PhMe at 60 °C with added 4 Å MS (**Scheme 2.34 & Table 2.9**, **Entry 1**). Unfortunately, these conditions proved not suitable with the dioxolane **224** failing to be observed within the reaction mixture. The alternative conditions, with trimethylorthoformate as an additive, were attempted with no conversion evident at r.t. or when, the reaction mixture was further heated to reflux (**Table 2.9**, **Entry 2**). At this stage, and with an alternative, albeit more stepwise, procedure already in place, no further endeavours towards this direct protection strategy were made.



216 **224**

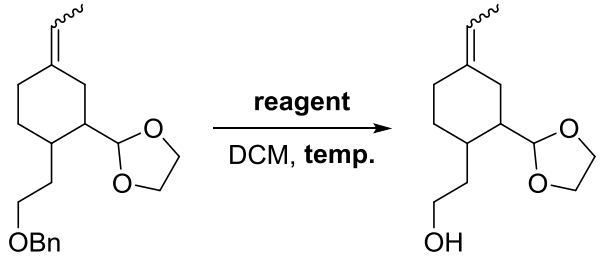
Scheme 2.34

Entry	Additive	Solvent	Temp.	Yield (%)
1	4 Å MS	PhMe	60 °C	-
2	trimethylorthoformate	PhH	r.t. - reflux	-

Table 2.9

With protection of the aldehyde achieved, attention turned to removal of the benzyl unit and subsequent synthetic transformations towards the desired enyne. While numerous methods for benzyl deprotection exist, Lewis acid-based conditions were considered to be the most suitable for the current molecule.[178] It was considered that Lewis acid-based procedures provided the opportunity for particularly mild benzyl cleavage, and, as such would potentially allow survival of the acetal moiety. With this in mind, the literature was examined and conditions which employed the commercially available Lewis acid $BCl_3.SMe_2$ at r.t. were discovered.[179,180] When these conditions were applied to dioxolane **224** the resulting reaction profile was extremely poor with none of the free alcohol **225** detected (**Scheme 2.35 & Table**

2.10, **Entry 1**). It should be noted, however, that despite the poor reaction profile, the benzyl unit appeared to have been cleaved as no aromatic signals were observed in the ^{1}H NMR analysis of the crude reaction mixture. It was theorised that the dioxolane had also been cleaved, or partially cleaved, allowing other transformations to occur. In an attempt to control the reactivity of the system, the reaction temperature was reduced to -78 °C. Unfortunately, once again the reaction profile was similarly poor with no trace of the desired alcohol **225** (**Table 2.10**, **Entry 2**).



224 **225**

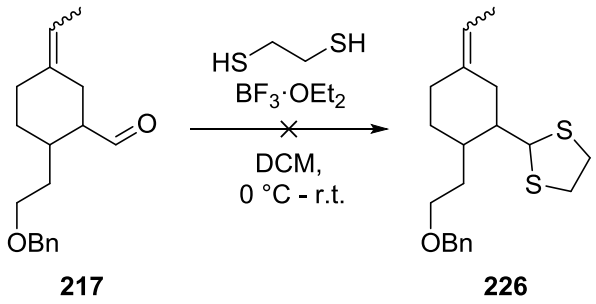
Scheme 2.35

Entry	Scale (mmol)	Reagent	Temp.	Yield (%)
1	0.45	$BCl_3 \cdot SMe_2$	r.t.	-
2	0.32	$BCl_3 \cdot SMe_2$	-78 °C	-
3	0.32	TMSI	r.t.	-
4	0.16	TMSI	-78 °C	-

Table 2.10

In a further attempt to selectively cleave the benzyl unit the milder Lewis acid, trimethylsilyl iodide (TMSI), was employed. The initial reaction was performed at r.t., with rapid conversion of the starting material (SM) observed (**Scheme 2.35 & Table 2.10**, **Entry 3**). Regrettably, the analysis of the mixture of products produced, showed no evidence of the benzyl group, and also lacked the dioxolane functionality present in the desired product **225**. A final attempt was made through reducing the temperature to -78 °C, as before (**Table 2.10, Entry 4**). To our disappointment, this was not successful, with a similar mixture of unknown products observed.

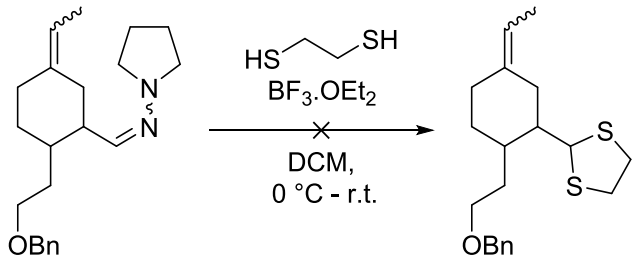
As selective cleavage of the benzyl ether had failed with the current molecule, an alternative aldehyde protecting group was investigated. To this end, it was considered that thioacetal protection might provide a more stable compound, and as such generation of thioacetal **226** was attempted. Examination of the literature provided suitable conditions from aldehyde **217**, proceeding *via* reaction with 1,2-dithioethane promoted by $BF_3 \cdot OEt_2$ in DCM (**Scheme 2.36**).[176] Unfortunately, when attempted, a mixture of products resulted with no trace of thioacetal **226** apparent.



217 **226**

Scheme 2.36

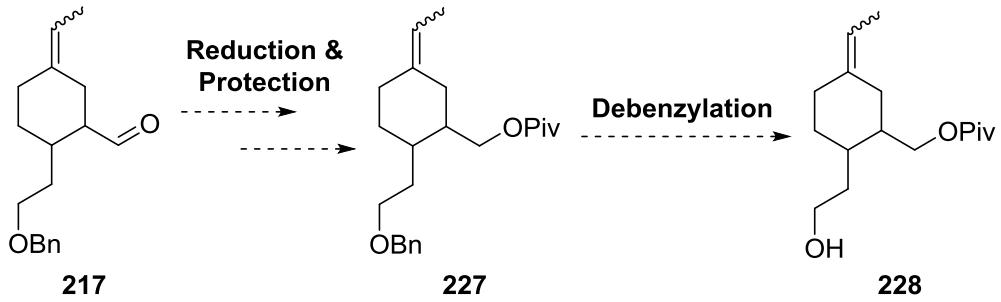
In addition to the above, it had been suggested by Fernández and co-workers that thioacetal protection could be achieved directly from a hydrazone substrate. As such, this was trialled from intermediate **216**, but regrettably this was also found to be unsuccessful (**Scheme 2.37**).



216 **226**

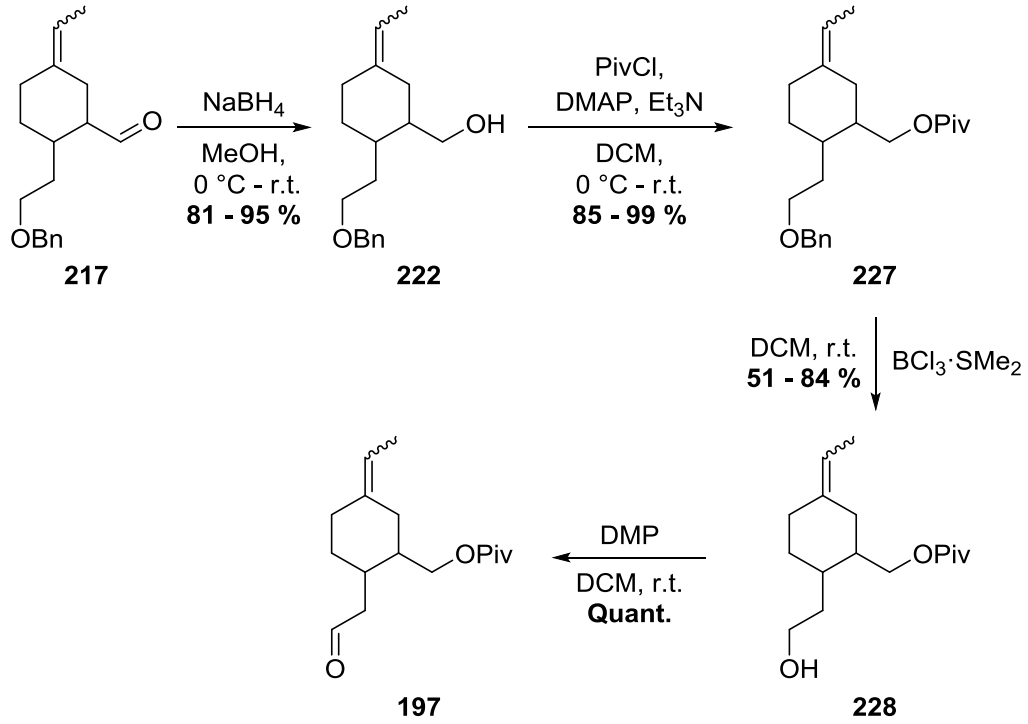
Scheme 2.37

Having found the aldehyde protection route to be unsuitable, it was considered that the originally proposed strategy, featuring aldehyde reduction and subsequent protection, should be examined (**Scheme 2.38**). Lewis acid-based conditions were still desired for the benzyl cleavage so an appropriate orthogonal alcohol protecting group would be required. It was discovered that acetates and bulky silyl units would stand the best chance of survival under these conditions.[179] With this is mind, a pivaloyl unit was considered to be the ideal protecting group as this would ultimately generate the originally desired enyne structure (**c.f. Scheme 2.17**).



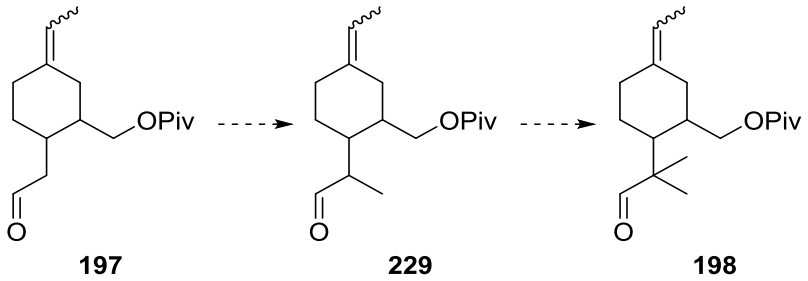
Scheme 2.38

Efforts towards this strategy began with a sodium borohydride-mediated reduction of aldehyde **217** to deliver the alcohol **222** (**Scheme 2.39**). Pleasingly, this proceeded without incident affording compound **222** in excellent yields. Protection of alcohol **222** was then attempted through reaction with pivaloyl chloride, triethylamine and sub-stoichiometric quantities of DMAP. This reaction was found to proceed efficiently constructing the desired pivaloyl protected intermediate **227** in exceptional yields. At this point, benzyl cleavage could once again be attempted, with the previously employed $BCl_3 \cdot SMe_2$ conditions used to initiate investigations. Encouragingly, on the first attempt these conditions furnished the desired free alcohol **228** in a moderate 51 % yield. To our delight, with subsequent attempts, a vast improvement in yield was observed. Finally, with alcohol **228** in hand, a Dess-Martin oxidation, employing Dess–Martin periodinane (DMP), was performed to yield aldehyde **197** quantitatively albeit as a complex mixture of isomers.



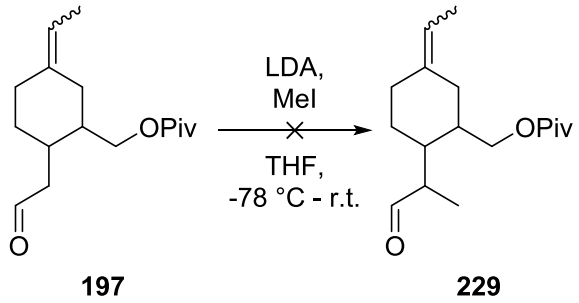
Scheme 2.39

At this stage, with aldehyde **197** in hand, installation of the *gem*-dimethyl was investigated. To achieve this transformation, a double enolate alkylation strategy was devised (**Scheme 2.40**). Previously, within our laboratories, a similar strategy had been employed to successfully install a *gem*-dimethyl unit α- to a ketone moiety.[157] Using this procedure, it was hoped that following the first enolate formation and alkylation, the intermediate mono-methyl species, **229**, could be isolated and subjected to a second alkylation providing *gem*-dimethyl aldehyde **198**.



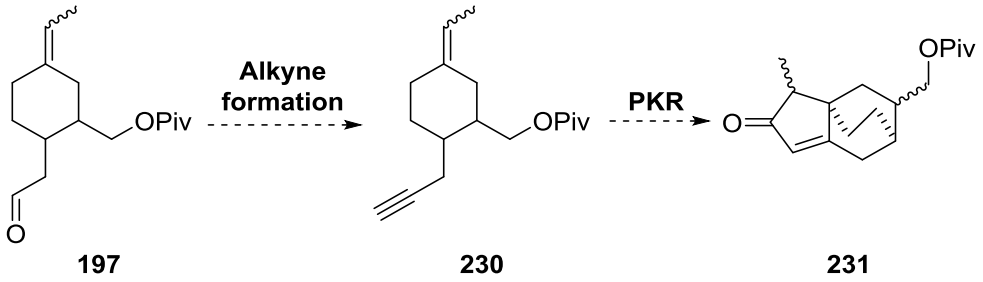
Scheme 2.40

With a synthetic strategy in place, the initial alkylation to provide mono-methyl intermediate, **229**, was trialled following previously employed conditions **(Scheme 2.41**). As such, initial enolate formation was mediated through deprotonation with LDA, this enolate was then quenched through addition of iodomethane. Unfortunately, upon subsequent work-up and isolation no trace of desired product, **229** was detected. Crucially, the characteristic aldehyde signal was not detected in any of the recovered material. The reaction was repeated numerous times, however in no instance was mono-methyl compound **229**, observed. Regrettably, based upon experimental observations, it was speculated that given the known instability of aldehydes, the substrate might be unsuitable to survive such conditions.



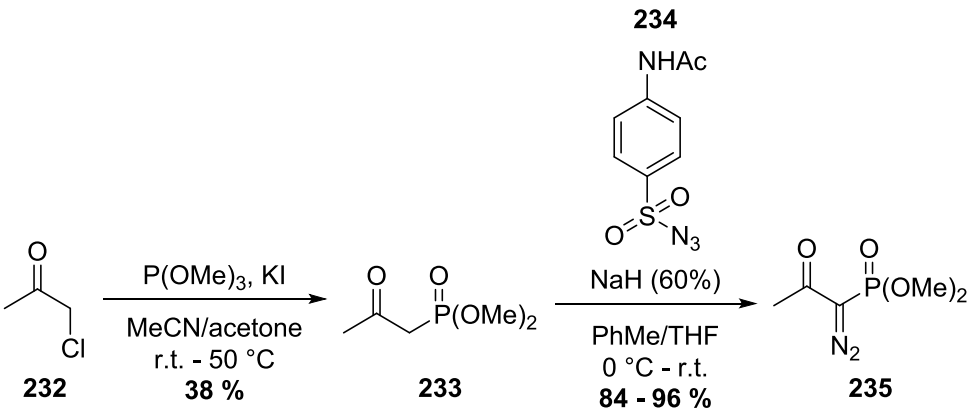
Scheme 2.41

At this stage, with installation of the *gem*-dimethyl unit having proved unsuccessful, it was proposed that before further investigation of this transformation an alternative strategy should be investigated. It seemed that formation of a suitable enyne, even one lacking the target compound's requisite gem-dimethyl moiety, was the best course of action when considering the challenging nature of the proposed PKR. As such alkyne formation could be performed on aldehyde **197** to yield enyne **230**. This would, in turn, allow the novel PKR mediated formation of a [5,6,6]-fused structure, such as **231** to be trialled **(Scheme 2.42**). It was also considered that should the cyclisation proceed successfully to construct tricycle **231**, methods for installation of the *gem*-dimethyl group post PKR might be developed.



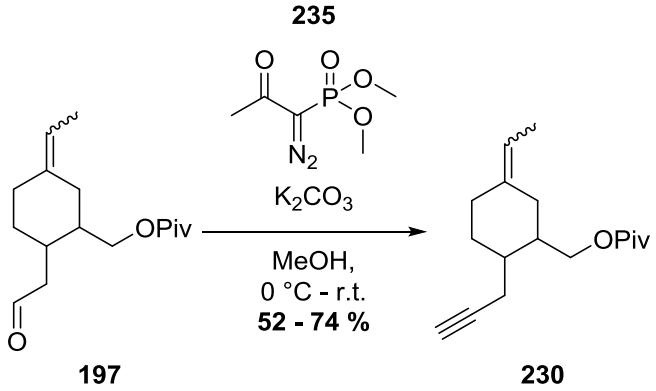
Scheme 2.42

With this new strategy in mind, the initial endeavour was alkyne formation. An alkyne formation method, which has been used previously within our laboratories to great success, is reaction of the appropriate aldehyde with the Ohira-Bestmann reagent **235**.[104,111] Preparation of the Ohira-Bestmann reagent has been extensively detailed in the literature, with numerous improvements to the original procedure described.[181–183] The selected synthetic strategy proceeded through initial generation of alkyl phosphonate **233** *via* a Michaelis-Arbuzov reaction between chloroacetone **232** and trimethyl phosphite **233** (**Scheme 2.43**).[184] It should be noted that, in this case the alkyl phosphonate **233** was afforded in relatively poor yield, however, enough was produced to continue the reagent formation. Subsequent diazo transfer with the commercially available azide **234** generated good quantities of the desired Ohira-Bestmann reagent **235** in excellent yield.



Scheme 2.43

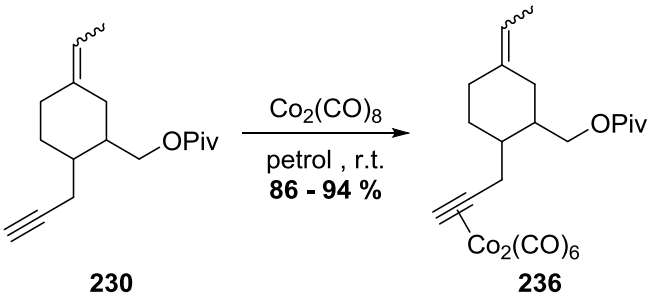
Having produced the requisite alkyne formation reagent, the transformation of aldehyde **197** to enyne **230** was trialled (**Scheme 2.44**). To our delight, the reaction was found to be successful, affording requisite enyne **230** in a moderate 52 % yield, as complex mixture of isomers. Pleasingly, a subsequent attempt at this reaction improved the yield to as high as 74 %. Thus, with a successful strategy developed that allowed the effective generation of a suitable enyne precursor, the novel PKR could be investigated.



Scheme 2.44

3.1.3 Attempts towards the novel PKR

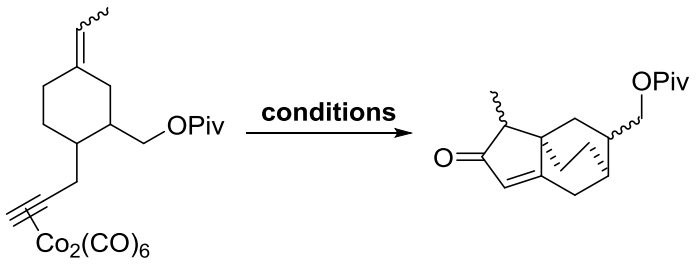
With an appropriate enyne, **230**, in hand, the first step in our study of this novel [5,6,6]-fused ring forming PKR was complexation of the alkyne moiety to generate the required hexacarbonyl dicobalt species (**Scheme 2.45**). This was performed under typical conditions, with stirring of the alkyne and octacarbonyl dicobalt in petrol at r.t., furnishing the requisite complexed species in characteristically high yields and rapid fashion. As with all other compounds resulting from this strategy, the isolated product was present as a complex and undeterminable mixture of inseparable isomers. However, with the key PKR now in sight it was hoped that some simplification of the associated NMR data may be produced. This could then, in turn, be used to inform the stereochemistry present in the proceeding steps of the synthesis.



230 **236**

Scheme 2.45

In attempting our novel PKR, which would require an extremely challenging cyclisation, the immediately considered conditions were those which had previously found particular success within our laboratories. With regards to this, in previous synthetic endeavours, employment of sulfide promotion, in particular DodSMe, had often provided the relevant cyclopentenone products in the highest observed yields.[156,157] As such, the DodSMe-based conditions were selected as the starting point for investigation of this novel PKR. Regrettably, despite the promising nature of previous results with these conditions, on first attempt the reaction mixture was stirred for 3 days with no discernible change in the profile (**Scheme 2.46 & Table 2.11**, **Entry 1**). Following work-up and isolation, only SM, **236**, and decomplexed alkyne, **230**, were detected, with no trace of the sought after [5,6,6]-fused tricyclic product **231**. In a further attempt, the reaction was repeated on increased scale to allow detection of any minor product formation. (**Table 2.11**, **Entry 2**). In this instance, the reaction mixture was allowed to stir at reflux for 9 days, but again there was no obvious change in profile. Similarly, following work-up and isolation, only SM, **236**, and decomplexed alkyne, **230**, were detected.



236 **231**

Scheme 2.46

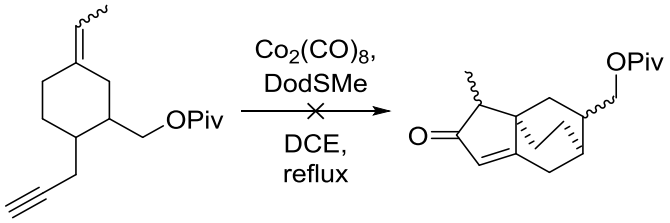
Entry	Scale (mmol)	Conditions	Yield (%)	SM (%)	Alkyne (%)
1	0.18	DodSMe, DCE, reflux	-	21	12
2	0.74	DodSMe, DCE, reflux	-	14	9
3	0.33	NMO·H_2O, DCM, r.t.	-	-	-
4	0.33	NMO·H_2O, DCM, -78 °C – r.t.	-	-	-
5	0.33	TMANO·$2H_2O$, DCM, -78 °C – r.t.	-	-	-

Table 2.11

Since DodSMe did not appear to promote this particular PKR, alternative conditions were examined. Besides sulfides, another well-established class of promoter are amine *N*-oxides (*vide supra*). Indeed, these too had been previously used within our laboratory with great success. To this end, NMO monohydrate and TMANO dihydrate promotion was investigated. Unfortunately, an initial attempt with NMO·H_2O in DCM at r.t. quickly resulted in complete conversion of SM to a complex and unidentifiable mixture of products, none of which resembled desired [5,6,6]-fused tricyclic product **231** (**Table 2.11, Entry 3**). In an attempt to control this reactivity, the reaction was repeated at the lower temperature of –78 °C. Following 4 hours at this temperature, no change in the reaction profile was observed so the mixture was gradually warmed to 0 °C, with no change evident in the profile (**Table 2.11**, **Entry 4**). Consequently, the mixture was allowed to warm gradually to r.t. with continual observation by thin layer chromatography (TLC), however once again a similar mixture of unidentifiable products resulted. Finally, performing the reaction under TMANO·$2H_2O$ promotion again yielded none of the desired product, **231**, (**Table 2.11, Entry 5**).

Within the synthetic sequence of a related natural product attempted within the Kerr group, the best yields for cyclisation were afforded when the precursor alkyne underwent complexation and subsequent cyclisation, promoted by DodSMe, in a one-pot procedure.[157] As a final attempt, with these typically efficient promoters, this one pot protocol was trialled (**Scheme 2.47**). To our disappointment, these

conditions had no effect, yielding none of the desired product, **231**, with only complexed enyne **236** recovered.



230 **231**

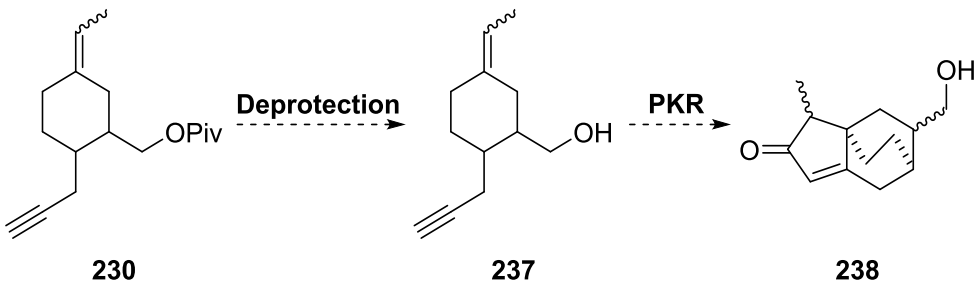
Scheme 2.47

At this point we began to grow concerned that the proposed PKR might not, in fact, be possible from a precursor of this type. While other PKR conditions were available, including non-cobalt procedures, the complete lack of product formation with the largely efficient and most employed promoters suggested a general problem with the substrate, **230**. As such, it was considered that an alternative enyne should be examined. With regards to this, a benefit of the current enyne **230** was the potential for diversification through modulation of the side chain originating at C3. It was thought that this might improve the potential for success with this challenging cyclisation.

3.1.4 Alternative PKR precursor

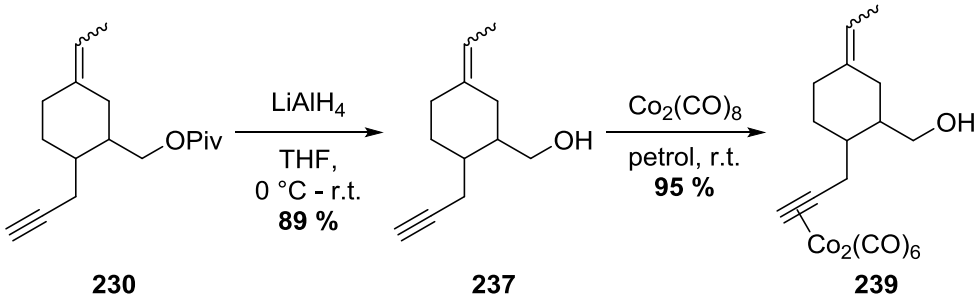
As a starting point for an alternative precursor synthesis it was thought that the pivaloyl moiety was, while extremely stable, particularly bulky. It was considered that for such a challenging cyclisation this added bulk might be causing the observed inhibition. As such it was considered that the pivaloyl functionality on enyne **230** could be cleaved to reveal primary alcohol **237**, following this side-chain transformation could be performed (**Scheme 2.48**). It was also reasoned that free alcohol **237** might itself be a desirable PKR precursor as the compounds steric bulk

would be vastly reduced. In this regard, precedent for PKRs with free alcohols has been set, with numerous examples reported within the literature.[121,185,186]



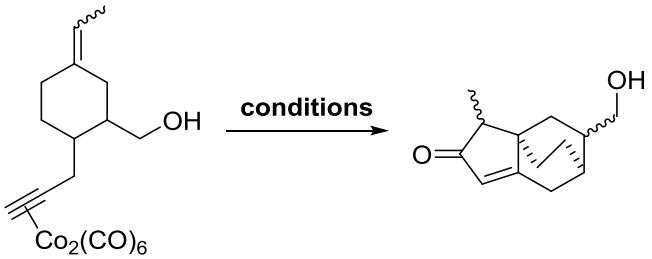
Scheme 2.48

To this end, reduction of pivaloyl featuring enyne, **230**, was attempted with $LiAlH_4$ (**Scheme 2.49**). Pleasingly, this reduction was found to proceed efficiently affording alcohol **237** in high yield. Subsequent complexation, under standard conditions, served to rapidly furnish the alternative PKR precursor **239** in excellent yield.



Scheme 2.49

With a suitable precursor in hand, the subsequent PKR could once again be trialled. Regrettably, when both $NMO{\cdot}H_2O$ and $TMANO{\cdot}2H_2O$ were employed a poor reaction profile resulted, with none of the desired product detected (**Scheme 2.50 & Table 2.12**, **Entries 1 & 2**). Indeed, as with the previous attempts, there was no apparent transformation between –78 °C and 0 °C, with complete conversion to a complex mixture of unknown products observed when the reaction mixture was allowed to warm further.



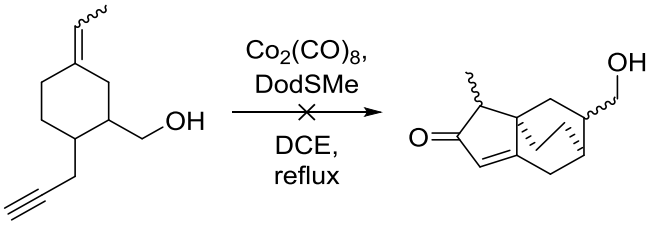
239 **238**

Scheme 2.50

Entry	Scale (mmol)	Conditions	Yield (%)
1	0.19	NMO·H_2O, DCM, -78 °C – r.t.	-
2	0.17	TMANO·$2H_2O$, DCM, -78 °C – r.t.	-

Table 2.12

In a final attempt to stimulate the requisite PKR, the one-pot DodSMe protocol was again attempted. On employing this procedure with free alcohol-featuring enyne, **237**, the reaction mixture was allowed to stir at reflux for six days with continual observation (**Scheme 2.51**). Throughout this time, the appearance of product was not observed. Upon work-up and isolation, only SM and the product of decomplexation were observed, with none of the desired [5,6,6]-fused tricyclic product, **238,** detected.

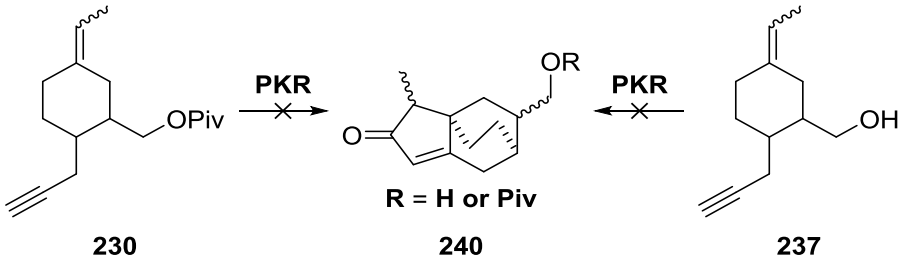


237 **238**

Scheme 2.51

At this stage, it seemed apparent that the proposed novel PKR could not, in fact, be achieved from enyne systems such as **230** or **237** (**Scheme 2.52**). The complete lack of product formation in both of these strategies suggested that substrates of this type featured an inherent lack of reactivity towards the PKR. This was not overly

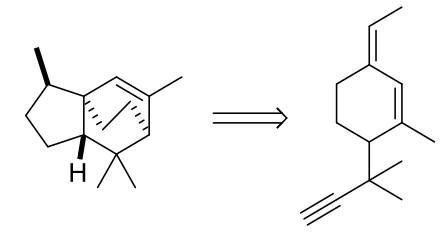
surprising as the proposed cyclisation had always been considered a particularly challenging one. Subsequent computational analysis of these precursors was performed, with the results further reinforcing the difficult in achieving the desired cyclisation from these species (*vide supra*). As such, no further synthetic investigation towards this strategy was performed; attention was instead turned to the alternative diene precursor.



Scheme 2.52

3.2. Diene PKR precursor

With the proposed novel PKR having so far proved elusive, the previously considered diene precursor **185** was re-examined (**Scheme 2.53**). It was hoped that the alternative conformation afforded by this unsaturated species might prove more reactive towards the desired cyclisation. Synthetic routes towards this precursor would also allow for earlier insertion of the requisite *gem*-dimethyl moiety without requiring use of an unstable aldehyde species. Ultimately, it was thought that the synthetic sequence would also be shorter than that of the saturated precursor, as there was no requirement for side chain elaboration. This would allow more rapid formation of a requisite enyne, and in turn, allow investigation of the key PKR. The absence of potential isomeric mixtures, for a greater number of steps within the sequence, would also greatly simplify spectroscopic analysis.



151 **185**

α-duprezianene

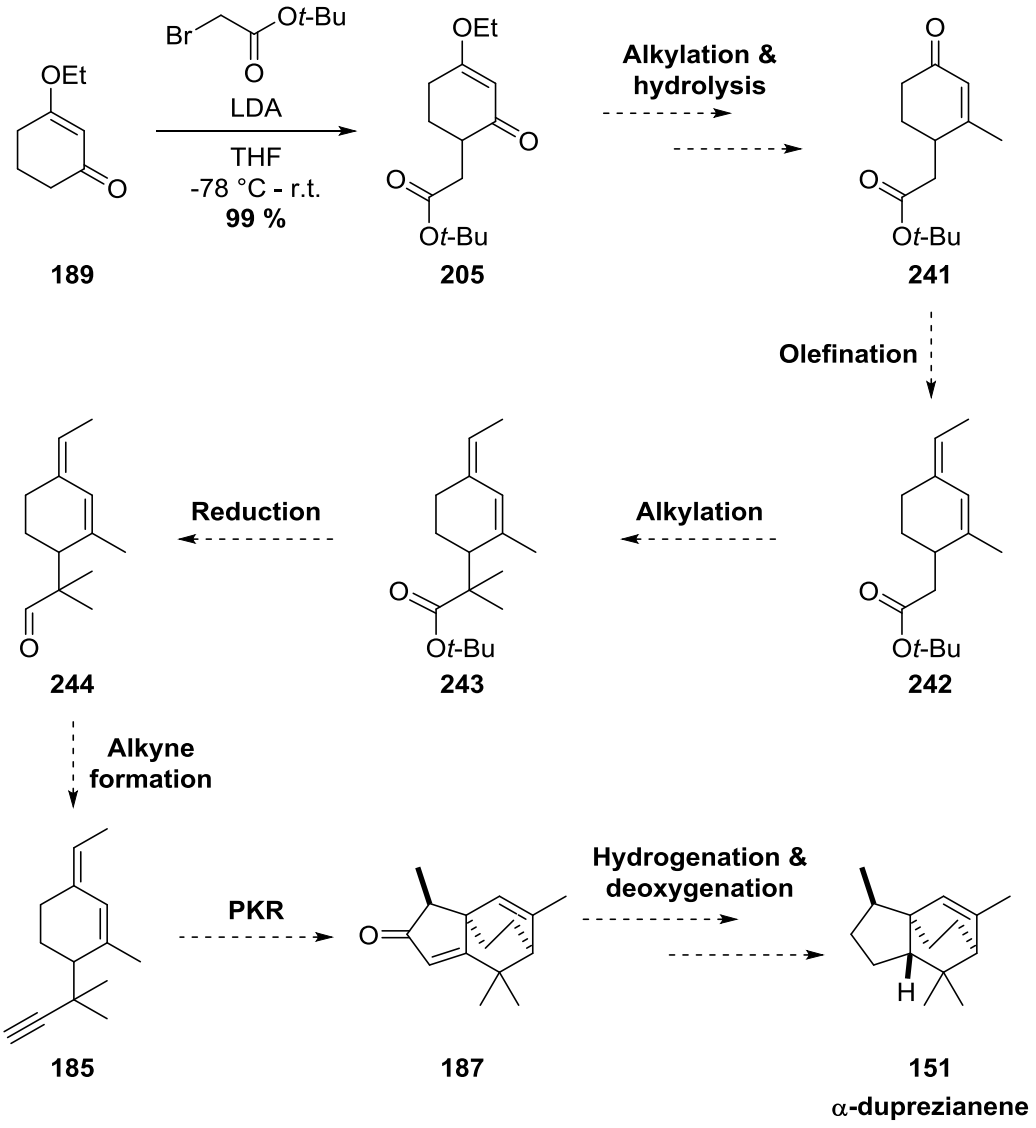
Scheme 2.53

Despite these clear benefits, a number of potential problems were also identified within the proposed synthetic strategy. Firstly, while precursor **185** did not feature any additional uncontrolled chiral centres, it was thought that selective generation of a *Z*-olefin would be challenging due to the lack of steric discrimination within the molecule. As before, this selectivity would influence the final compound's stereochemistry, and as such investigation of this step would be crucial. Secondly, conjugated dienes are known to perform sluggishly and generate alternative non-PKR products, so concerns were raised regarding inhibition of reactivity.[5] However, with regards to this, recent experimental endeavours towards the PKR of such unactivated diene substrates has suggested that alternative metals, such as rhodium, can further promote the reaction.[21] With these potential problems under consideration, investigation into an efficient synthetic strategy for the synthesis of diene PKR precursor **185** commenced.

3.2.1 Synthetic route 1

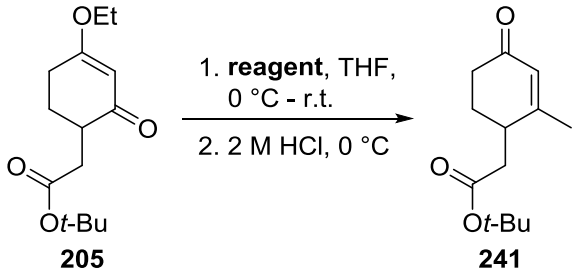
The initially proposed synthetic strategy towards diene PKR precursor **185** was informed by the convergent retrosynthetic analysis previously discussed (**c.f. Scheme 2.15**). As such, the first step would employ the previously developed alkylation protocol to efficiently generate ester **205** from the commercially available compound **189** (**Scheme 2.54**). With intermediate **205** in hand the newly proposed strategy could thus be investigated. To this end, from previously prepared ester **205**, alkylation and subsequent acid mediated hydrolysis would yield enone **241**. At this

stage, selective olefination would be attempted furnishing the requisite diene moiety **242**. The ester functionality could then be used to install the requisite *gem*-dimethyl group, affording **243**. Finally, reduction to aldehyde **244** followed by alkyne formation would generate the desired diene PKR precursor, **185**. Investigation into the novel PKR could at this point be attempted to afford [5,6,6]-fused tricyclic compound **187**. A facially selective hydrogenation would then be sought, with subsequent deoxygenation required to yield the target molecule α-duprezianene **151**.



Scheme 2.54

With a synthetic strategy towards diene precursor **185** devised, experimental efforts were initiated. As anticipated, the previously optimised alkylation was found to yield ester intermediate **205** efficiently. At this stage, literature conditions suggested that a two-step procedure could be performed to afford enone **241**.[187] Alkylation of ester **205** was initially attempted with 1.2 equivalents of MeMgCl solution (**Scheme 2.55 & Table 2.13**, **Entry 1**). Regrettably, following work-up the desired product, **240**, was not detected, with only a mixture of unknown products afforded. The reaction was then attempted with the more reactive MeMgBr, however, a similar reaction profile was observed (**Table 2.13**, **Entry 2**). Concerned that the initial alkylation was performing poorly reactions employing 2 and 3 equivalents of Grignard reagent were attempted. Unfortunately, a similar mixture of products resulted (**Table 2.13**, **Entries 3 & 4**).



Scheme 2.55

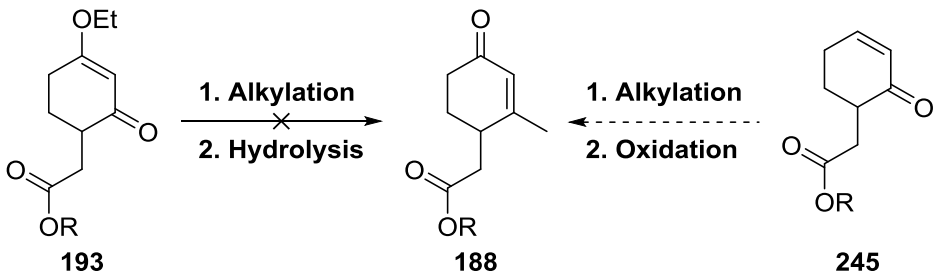
Entry	Scale (mmol)	Reagent	Yield (%)
1	1.18	1.2 eq. MeMgCl	-
2	1.18	1.2 eq. MeMgBr	-
3	1.18	2.0 eq. MeMgBr	-
4	1.18	3.0 eq. MeMgBr	-
5	0.79	1.6 eq. MeLi·LiBr	-
6	0.79	2.0 eq. MeLi·LiBr	-
7	0.98	2.6 eq. MeLi·LiBr	-

Table 2.13

At this stage, it was hypothesised that the ester functionality was interfering with the desired reaction. Deprotonation of the adjacent position was possible and could lead to several side reactions. In order to improve reactivity and selectivity an alternative alkylating reagent, MeLi·LiBr, was employed in place of the typical Grignard reagents. To our disappointment, when 1.6 eq. of this reagent was utilised no further improvement to the reaction profile was observed (**Table 2.13**, **Entry 5**). This process was further investigated, with increased quantities of the MeLi·LiBr complex solution, however, this too failed to yield the desired enone **241** (**Table 2.13**, **Entries 6 & 7**). Having attempted optimisation of the reaction over a number of protocols with no success observed, it was clear that this synthetic sequence would not provide a viable route towards generation of diene PKR precursor, **185**.

3.2.2 Synthetic route 2

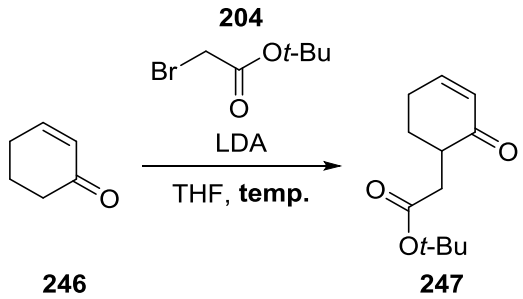
Since it had become apparent that transformation of an ester, such as **193**, to enone **188** was not viable, an alternative route was proposed (**Scheme 2.56**). In this case, an alternative enone, **245**, would first be alkylated to insert the requisite methyl group and generate a tertiary alcohol. With this alcohol in place an oxidative rearrangement could then be attempted to furnish the desired β-substituted enone, **188**. It was also hoped that this procedure could be carried out without full isolation of the tertiary alcohol, increasing efficiency and further reducing the simplicity of analysis within this synthetic strategy.



193 188 245

Scheme 2.56

With this oxidative rearrangement strategy in mind, generation of an enone intermediate of type **245** was sought. Thus, it was considered that alkylation of cyclohexenone, **246**, would first be required, with the hope that our previously optimised alkylation conditions could be employed with this alternative substrate (**Scheme 2.57 & Table 2.14**). To this end, the alkylation of cyclohexenone **246** was attempted using the previously employed protocol. However, the desired product **247** failed to form (**Table 2.14**, **Entry 1**). In an attempt to address this problem, an examination of the literature was performed and a set of alternative conditions were identified.[188] With these new conditions, in which slightly more LDA was employed along with 2 eq. of the requisite electrophile, *t*-butyl bromoacetate **204**, enone intermediate **247** was accessed, albeit in 17 % yield (**Table 2.14**, **Entry 2**). A final attempt was made in which the reaction mixture was quenched at -78 °C, instead of allowing the mixture to warm to r.t., as had been done previously (**Table 2.14**, **Entry 3**). To our delight, this alteration proved successful, with the desired product **247** furnished in a significantly higher yield. This result certainly appeared to suggest that in the case of this particular alkylation control of reaction temperature was, in fact, crucial to the efficiency of the protocol.



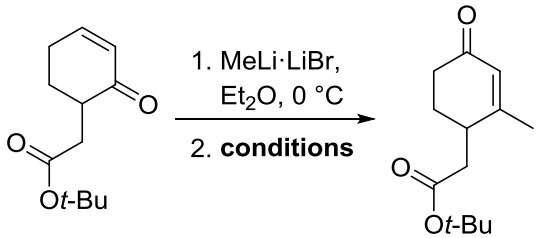
246 **247**

Scheme 2.57

Entry	Eq. LDA	Eq. 204	Temp.	Yield (%)
1	1.1	1.25	-78 °C – r.t.	-
2	1.2	2.00	-78 °C – r.t.	17
3	1.2	2.00	-78 °C	74

Table 2.14

With intermediate **247** in hand, the proposed two step β-substituted enone formation could be investigated. With respect to this, it was noted that throughout the literature chromium oxidants were typically employed to effect such a rearrangement. It was thus decided that first attempts should utilise the readily available oxidant pyridinium chlorochromate (PCC). To this end, the initial attempt was carried out with 1.1 eq. of MeLi·LiBr added to the enone **247** in diethyl ether at 0 °C (**Scheme 2.58** & **Table 2.15**, **Entry 1**). The alkylation was monitored by TLC, with apparent consumption of the SM and formation of a new spot after 2 h. The mixture was worked up and re-dissolved in DCM, then cooled to 0 °C. At this point 1.2 eq. of PCC was added and the mixture was allowed to warm gradually to r.t. Regrettably, on workup and isolation the desired product was not observed, however 13 % of SM was recovered. In an attempt to achieve full conversion, more MeLi·LiBr was added in the first step (**Table 2.15**, **Entry 2**). Unfortunately, once again, enone **241** failed to form, with only a lesser amount of SM recovered. A further attempt was made with the alternative chromium oxidant pyridinium dichromate (PDC), in this case however, neither the desired product **241** nor remaining SM were found (**Table 2.15**, **Entry 3**).



247 **241**

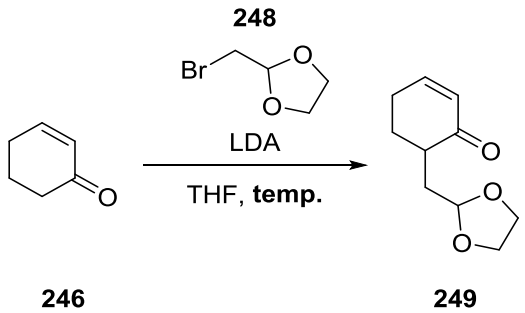
Scheme 2.58

Entry	Scale (mmol)	Eq. MeLi·LiBr	Oxidation	Yield (%)	SM (%)
1	2.38	1.1	1.2 eq. PCC, DCM, 0 °C – r.t.	-	13
2	2.38	1.6	1.2 eq. PCC, DCM, 0 °C – r.t.	-	9
3	1.19	1.1	1.2 eq. PDC, DCM, 0 °C – r.t.	-	-
4	0.57	1.1	2.0 eq. IBX, DMSO, 55 °C	-	23
5	0.66	1.6	3.0 eq. IBX, DMSO, 55 °C	-	-

Table 2.15

Examination of the literature provided an alternative system for the desired oxidative rearrangement in the form of 2-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO).[189] The initial attempt with these new conditions followed a similar protocol to the chromium oxidant studies, with added heating in the oxidative rearrangement step. Disappointingly, once again the desired product, **241**, failed to form with only 23 % of SM recovered (**Table 2.15**, **Entry 4**). A final attempt was made with an increase in the quantities of both MeLi·LiBr and IBX, however, this again failed to yield the desired β-substituted enone (**Table 2.15**, **Entry 5**).

With no apparent success in this strategy it was considered that the ester moiety might be inhibiting this two-step procedure by reacting with the MeLi·LiBr. In an attempt to negate the possible issues, dioxolane containing enone, **249**, was sought as a possible alternative substrate for this oxidative rearrangement procedure (**Scheme 2.59 & Table 2.16**). It was hoped that employment of the previously developed alkylation procedure with 2-bromomethyl-1,3-dioxolane, **248**, as the requisite electrophile, would efficiently provide enone **249**. To this end, the initial reaction was held at –78 °C for 6 hours with no observable change in profile (**Table 2.16, Entry 1**). Following workup and isolation, the desired product was not detected and 67 % of SM was recovered. A second and final attempt was made, whereby the reaction mixture was allowed to warm to 0 °C (**Table 2.16, Entry 2**). Unfortunately, this also failed to improve the reaction, with none of enone **249** afforded and only SM recovered. It appeared that access to enone, **249**, would require significant optimisation time, and, as such, no further investigation was attempted at this point.

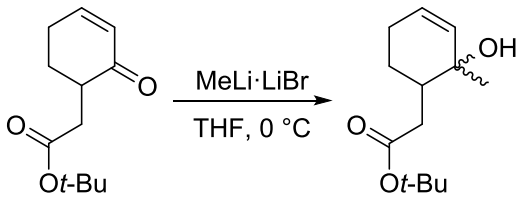


Scheme 2.59

Entry	Temp.	Yield (%)	SM (%)
1	-78 °C	-	67
2	-78 – 0 °C	-	42

Table 2.16

In a final effort to understand the failings of this proposed two-step protocol, the initial MeLi·LiBr alkylation was performed with the intention of isolating the tertiary alcohol. It was considered that if this step proceeded smoothly, further optimisation of the subsequent oxidative rearrangement could be conducted. On attempting this addition, the SM **247** was found to fully convert to a product which resembled the tertiary alcohol, **250** (**Scheme 2.60**). Upon ^{1}H spectroscopic analysis, the isolated product was found to possess many of the characteristic signals of the desired product, however additional signals were also observed. When a sample of this material was sent for HRMS the major signal found was one which appeared to relate to a product of dehydration, such as a diene. It was hypothesised that this dehydration might, in fact, be promoted by the subsequent oxidative rearrangement conditions. It appeared, as such, that this synthetic strategy had inherent problems with the reactivity of the intermediate tertiary alcohol species. As no solution to this problem was forthcoming, investigation into this sequence was halted and an alternative strategy was devised.

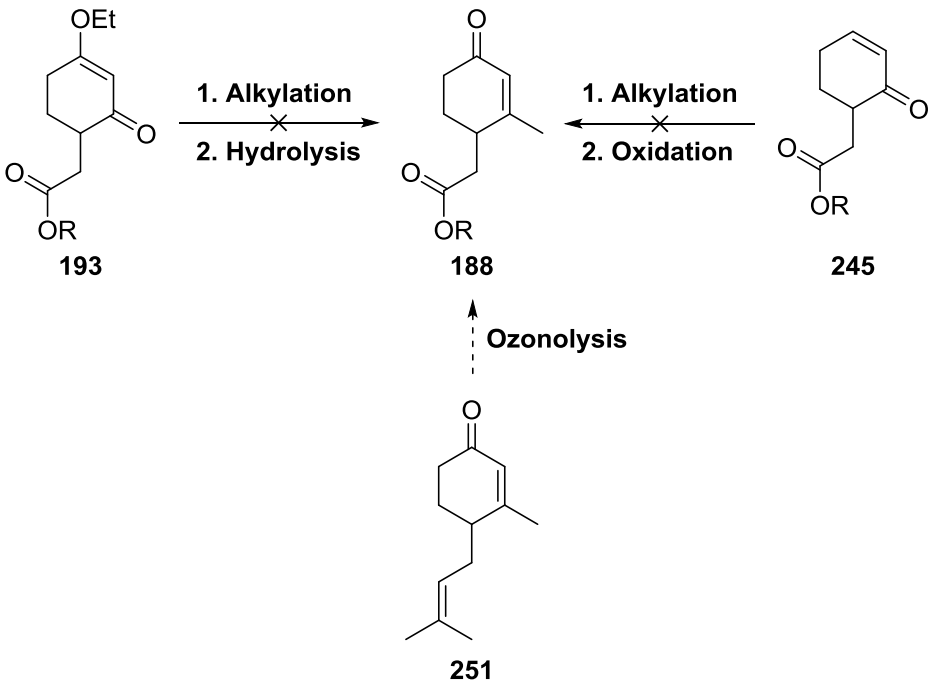


247 **250**

Scheme 2.60

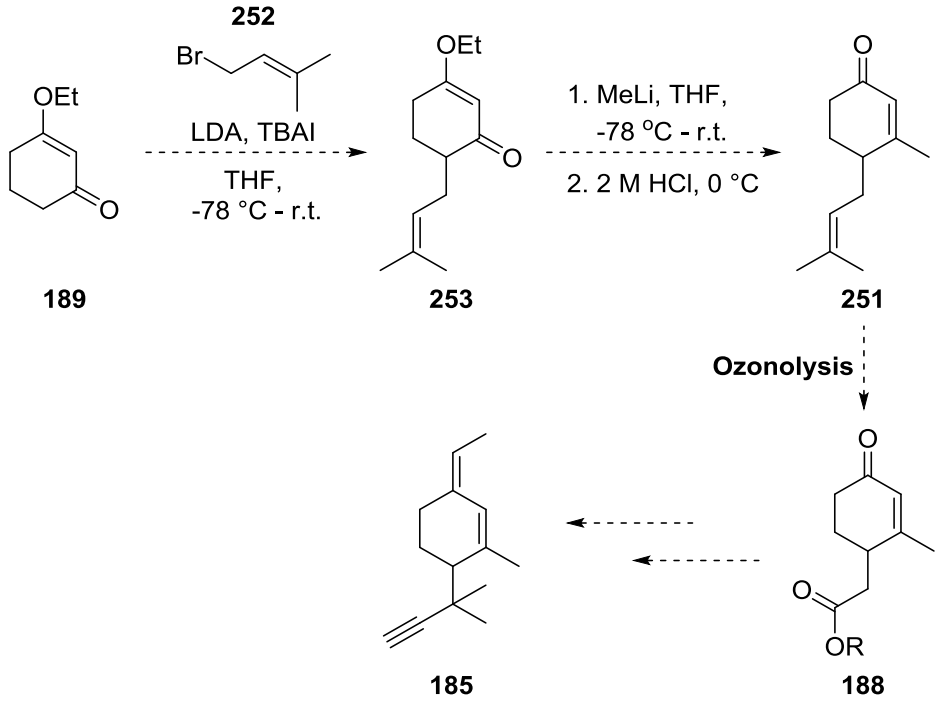
3.2.3 Synthetic route 3

At this point, we still considered the β-substituted enone **188** a key intermediate in the potential synthetic sequence towards diene PKR precursor, **185**. Regrettably, the two previously proposed methods for generation of this enone had failed and as such could not be considered a viable means towards the compound. On examination of these strategies, it was noted that each substrate featured an ester moiety. It was considered that in both cases this ester functionality was impeding the requisite nucleophilic attack at the ring carbonyl. In an effort to address this inherent problem the literature was once again consulted in effort to discover a suitable substrate which could be manipulated towards the desired ester moiety. To this end, it was observed that esters were generated in multiple reports through controlled ozonolysis of prenyl olefin units.[190–193] With this in mind, a final synthetic strategy towards β-substituted enone **188** was proposed, in which prenylated intermediate **251** could be converted to the desired ester through an ozonolysis protocol (**Scheme 2.61**).



Scheme 2.61

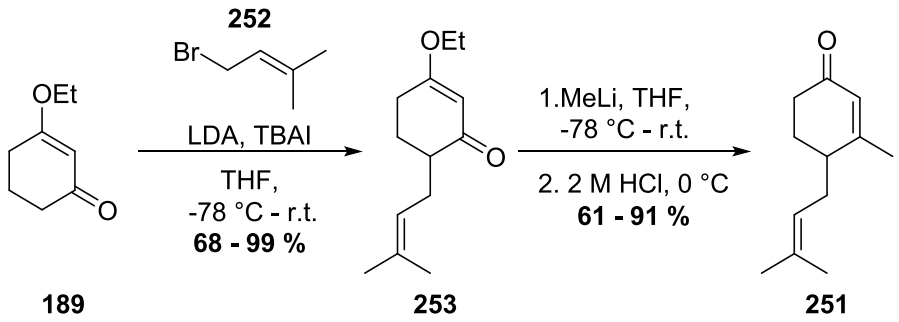
In order to generate the requisite intermediate **251**, a literature procedure would be employed beginning with an alkylation of the previously employed compound **189** to yield prenyl featuring intermediate **253** (**Scheme 2.62**).[194] With access to intermediate **253**, a similar two-step protocol to that previously discussed could be attempted; nucleophilic attack of MeLi followed by hydrolysis. Chiefly, it was hoped that the absence of an ester moiety would allow this procedure to generate the requisite β-substituted enone, **251**, without an issue. At this stage, investigation into a selective ozonolysis, one which reacted only at the prenyl olefin and not the β-substituted enone, would be performed to yield a suitable ester intermediate, such as **188**. This intermediate **188**, could then, through further previously discussed manipulations, be converted to the desired diene PKR precursor, **185**.



Scheme 2.62

Synthetic endeavours in relation to this newly proposed strategy were initiated with an alkylation reaction to generate intermediate **253** (**Scheme 2.63**). Indeed, the reaction was successful, yielding 68 % of the desired compound, with subsequent attempts furnishing intermediate **253** in a maximum of 99 % yield. The subsequent

two-step process proceeded efficiently, generating β-substituted enone **251** in a respectable 61 % yield. Continued attempts raised this yield significantly to a maximum of 91 %. The success of this reaction appears to confirm that in the previously attempted routes the ester moiety was inhibiting the two-step nucleophilic addition/elimination process.

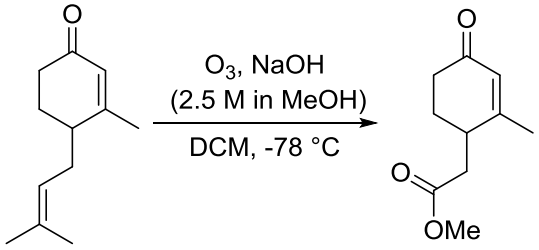


Scheme 2.63

Having generated a reliable and robust route to β-substituted enone **251**, the novel selective ozonolysis could now be evaluated. Examination of the literature suggested a reaction pathway, in which, the aldehyde and carbonyl oxide fragments derived from the primary ozonide would react with methoxide and methanol to generate a hemiacetal and hydroperoxide respectively. These species would then convert to the corresponding methyl ester.[190] This could be achieved by carrying out the ozonolysis in a mixture of DCM and 2.5 M NaOH in methanol.

To this end, the first attempt at the generation of the key ester intermediate employed 5 eq. of 2.5 M NaOH in methanol, with the substrate was subjected to a stream of bubbled ozone for 1 h (**Scheme 2.64 & Table 2.17**, **Entry 1**). Under these conditions, the elusive β-substituted enone **254** was successfully formed in a moderate, but serviceable, 37 % yield. Optimisation of the reaction was thus attempted with the required reaction time the first variable to be investigated. As such, and due to the fact that no SM was recovered after 1 h, a 30 min reaction was attempted, however, this appeared detrimental with a reduced yield of product

afforded and SM now obtained (**Table 2.17**, **Entry 2**). Attempting the reaction for 45 min also provided a poorer reaction profile to the original conditions, showing that, to a limited degree, a longer reaction time was preferable (**Table 2.17**, **Entry 3**). Next, the amount of NaOH was altered, with 10 eq. of 2.5 M NaOH in methanol employed in a 1 h reaction (**Table 2.17**, **Entry 4**). While the yield was observed to marginally rise to 40 %, it appeared that there was no significant benefit gained from this from this increase in NaOH equivalents.



251 **254**

Scheme 2.64

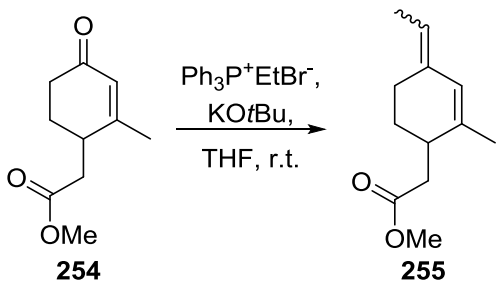
Entry	Scale (mmol)	Eq. NaOH	Time	Yield (%)	SM (%)
1	1.12	5	1 h	37	-
2	1.12	5	30 min	14	39
3	1.12	5	45 min	32	-
4	1.12	10	1 h	40	-
5	3.37	5	2 h	53	-
6	5.61	5	2 h	49	-
7	8.42	5	3 h	55	-
8	11.22	5	4 h	61	-
9	11.22	5	5 h	64	-
10	11.22	5	7 h	50	-

Table 2.17

The reaction scale was then increased, alongside a further increase in reaction time (**Table 2.17**, **Entry 5**). These conditions proved effective providing the highest yield observed so far. On continuing this increase in both scale and reaction time, a general trend of increasing yield was observed, with a maximum of 64 % afforded

from a multigram reaction performed over 5 h (**Table 2.17**, **Entry 9**). Unfortunately, on further increase in time to 7 h the yield decreased to 50 % (**Table 2.17**, **Entry 10**). Considering the complexity and selectivity of this novel reaction, a yield of 64 % on moderate scale was thought to be exceptional. This provided an adequate amount of material for progression, and as such no further optimisation was attempted.

With β-substituted enone **254** in hand, investigation into the subsequent synthetic steps was pursued. The next step in the sequence required selective generation of a *Z*-olefin. In the first instance, room temperature Wittig conditions were explored, with 2 eq. of the relevant ylide employed as a starting point (**Scheme 2.65 & Table 2.18**, **Entry 1**). Disappointingly, through this methodology the olefin, **255**, was yielded in only 20 %. Spectroscopic analysis showed that this reaction had succeeded in being fairly selective, however, this was towards the non-desired *E*-olefin, which was afforded in a 10/1 ratio. This observed selectivity was seen as an issue as reversal of this level of selectivity would not be trivial. Having said this, it was, hoped that this stereochemistry could be reversed through further epimerisation, post-PKR, albeit extending the synthetic route overall. A more pressing issue was the extremely poor yield of the reaction. In an attempt to combat this problem, the quantity of ylide utilised was increased to 3.5 eq., but this unfortunately failed to provide any improvement (**Table 2.18**, **Entry 2**). To our disappointment, an additional increase in ylide equivalents appeared to hinder the reaction further (**Table 10**, **Entry 3**). It was thought the ester moiety present in the β-substituted enone, substrate **254**, might once again be inhibiting the reaction.



254 **255**

Scheme 2.65

Entry	Scale (mmol)	Eq. $Ph_3P^+EtBr^-$	Yield (%)	*E*/*Z*
1	0.52	2.0	20	10/1
2	0.52	3.5	20	10/1
3	0.44	4.0	12	10/1

Table 2.18

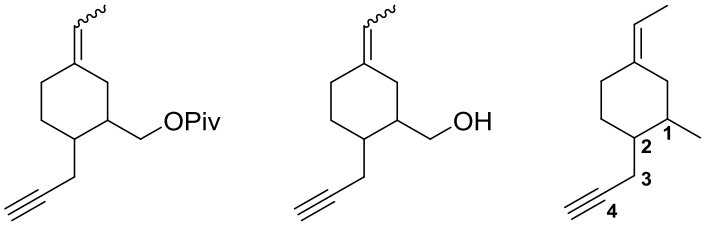
At this point, before any further synthetic investigation was attempted, the opportunity arose to perform some computational studies on the proposed novel PKR. It was hoped that this would provide further insight to this challenging cyclisation before moving forward.

3.3 Computational studies on the novel PKR

In order to further investigate the viability of the PKR computational studies were proposed. Due to the complex nature of the PKR a suitable model system was sought to provide information about the reaction. To this end, it was considered that examination of the conformation and related energy of the proposed enyne substrates would provide some insight. By determining the energy required to achieve an ideal overlap of both the alkyne and alkene functionalities, which would be required within the PKR, the feasibility of achieving the required transformation could be anticipated. It should be noted that this would not be a perfect evaluation as the cobalt complex could not be modelled; this would require a large amount of computation cost and power. Nonetheless, this study was thought essential in order to provide further understanding into this novel transformation.

Investigations were initiated by considering the saturated enyne precursors; it was hoped that a rational for the apparent failure of enynes **230** and **237** within the PKR would be afforded (**Figure 2.8**). To simplify our computational endeavours, model structure **256** was proposed and DFT calculation were performed at the M06L/6-31G(d) level of theory. The study was performed by identifying an optimised

structure, then measuring the difference in potential energy (ΔE) on rotation around the dihedral angle of carbons C1 through C4. Further to this, at each rotation the distance between alkene and alkyne (r (Å)) and angle between alkene and alkyne (β (°)) were also measured. With respect this angle, β (°), it is important to note that a value of β = 0 ° would indicate that the alkene and alkyne are perfectly aligned. Conversely, a value of β = 90 ° shows that the alkene and alkyne are perpendicular to each other.



230 **237** **256**

Figure 2.8

The initial study on enyne **256** was performed on the *anti*-diastereomer, as can be seen below (**Figure 2.9**). The first area explored was the potential energy surface associated with the rotation of the alkyne over the cyclohexane ring. At first inspection it can be seen that the energy required to promote the alkynes rotation is relatively small. Structure **A** corresponds to the conformation, in which the alkene and alkyne are best aligned, thus would represent one of the best candidates for a successful cyclisation. Structure **B** sits at the maximum energy level, but clearly shows that no severe steric interactions arise within the system. In fact, it is the steric repulsion between an equatorial hydrogen and one of the hydrogen atoms in the alkynes methylene unit which accounts for this energy maxima. Importantly, the distance between alkene and alkyne is always larger than 3.0 Å, suggesting that further conformation changes would be required in order to favour any possible cyclisation.

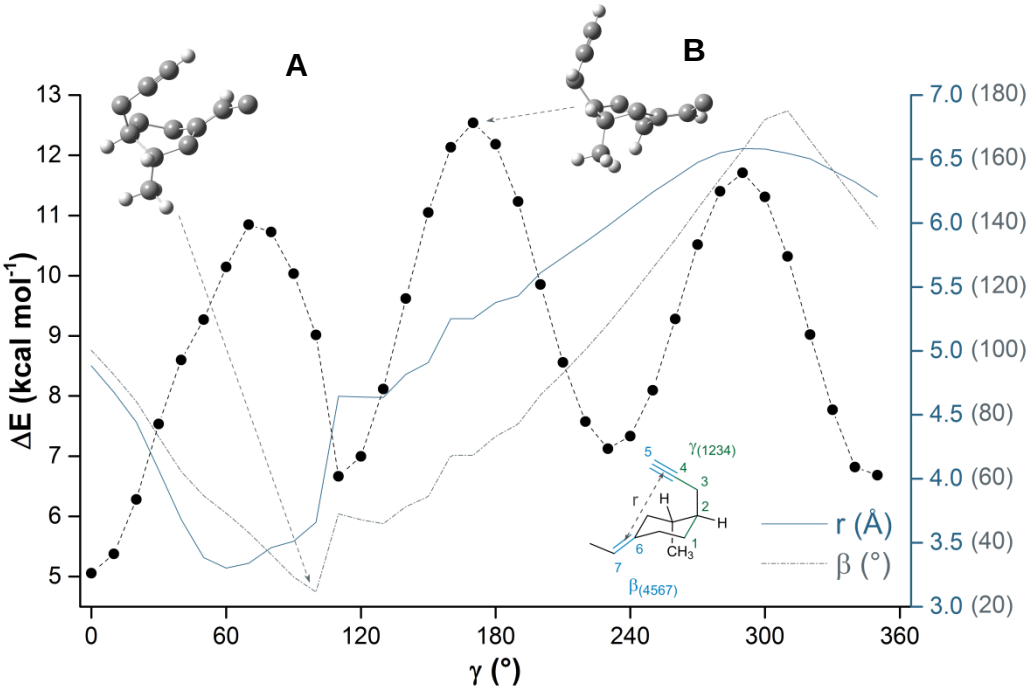


Figure 2.9

Among the possible conformational changes in the system capable of minimise the distance between the alkene and alkyne, the bending of the cyclohexane ring was analysed (**Figure 2.10**). In this case the energy profile associated with the transition from a chair-like conformation to a boat-like conformation is shown. From this study, it can be noted that only small conformation changes are tolerated within the system. A rapid and pronounced increase in energy is observed for dihedral angels higher than 60 °. Interestingly, a good proximity between the alkene and alkyne is never attained, with distances higher than 3.4 Å found for all conformations. When severe ring bending is promoted within the system (γ > 60 °), secondary conformation changes are found to result. These changes serve to further increase the distance between alkene and alkyne, hindering the possibility of cyclisation.

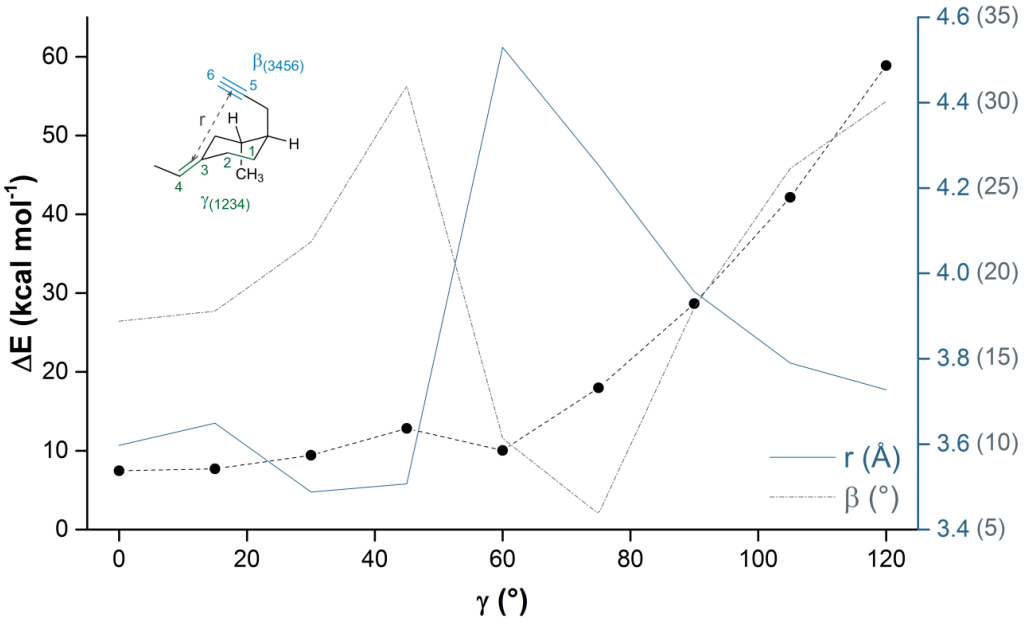


Figure 2.10

An alkyne rotational study was also performed on the *syn*-diastereomer of model system **256**, as is shown below (**Figure 2.11**). In this analysis, it was found that the *syn*-diastereomer presented a very similar profile to that observed for the *anti*-diastereomer (**c**.**f**. **Figure 2.9**). Thus, while no significant energy barrier for the alkyne rotation was found, the distance between the alkene and alkyne was found to be quite large, with all conformations being > 3.0 Å apart. In this case structure **C** sits at the maximum energy level, with a steric clash between equatorial methyl and hydrogen atoms of the methylene unit of the alkyne accounting for this. Interestingly, structure **D**, which is found at the local minimum, also presents the shortest distance between alkene and alkyne, suggesting the most promising conformation for potential cyclisation.

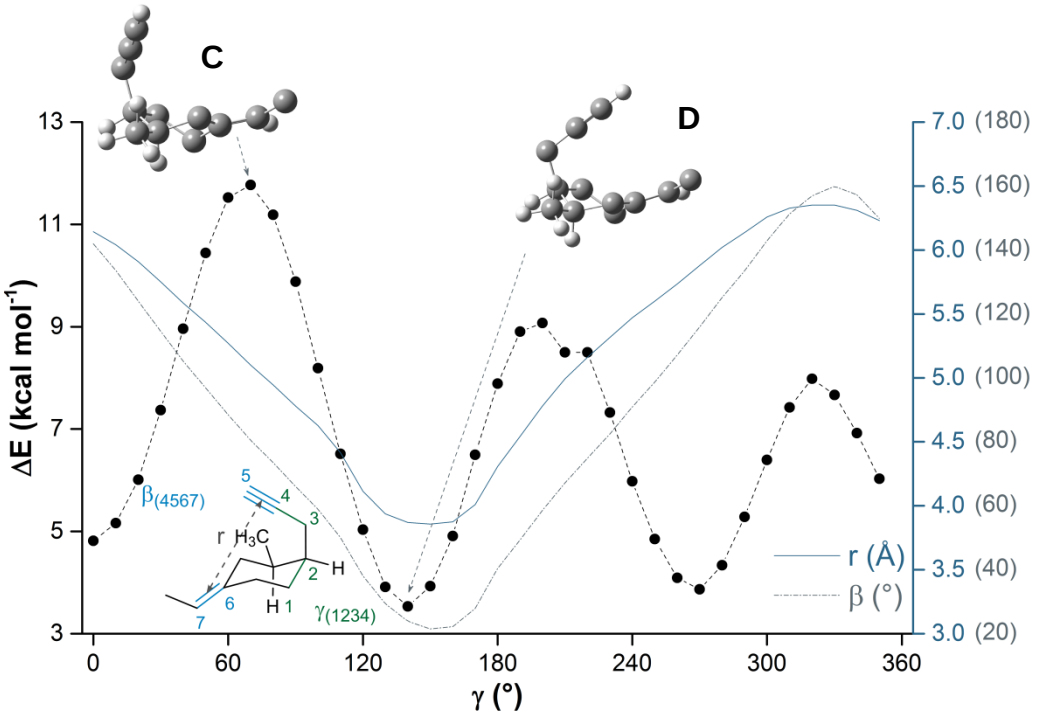


Figure 2.11

Taking structure **D** as a starting point, the energy profile associated with the transition of the cyclohexane ring from a chair-like conformation to a boat-like conformation was analysed. (**Figure 2.12**). Once again the energy required to bend the cyclohexane ring was found to be prohibitively high. In this system, the energy required to promote the bending of the 6-membered ring increases sharply with the degree of distortion, a scenario similar to the observed previously with the *anti*-diastereomer (**c.f. Figure 2.10**). On considering this data, with that previously discussed, it is possible to infer that conformational changes in the cyclohexane ring, which favour proximal interactions between the alkyne and the alkene, possess prohibitively high energy barriers, preventing these systems from engaging in the proposed PKR. This analysis correlates well with our experimental observations in which no cyclisation was observed.

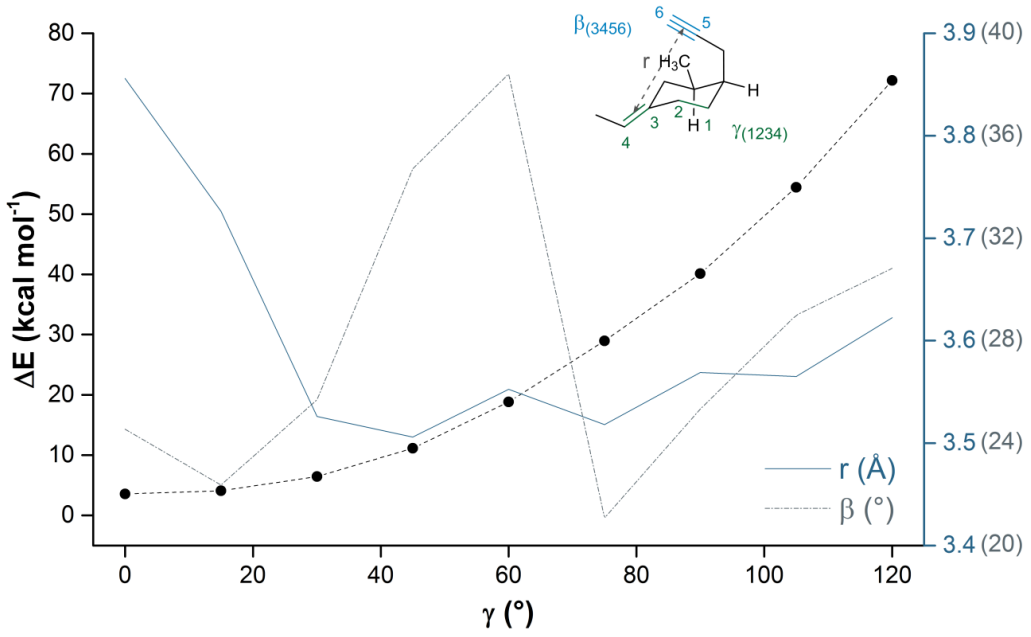


Figure 2.12

We next investigated the proposed diene PKR precursor through the same computational system. In order to better compare to the saturated precursors, we performed this study without the presence of a *gem*-dimethyl unit. Once again, the first area explored was the potential energy surface associated with the rotation of the alkyne unit over the cyclohexane ring (**Figure 2.13**). As we had seen with the saturated precursors, the barrier for the rotation of the alkyne around the cyclohexene ring was reasonably small, indicating that the rotation process is feasible. Structure **E** was found to exist as the maximum potential energy surface, this was once again determined to be the result of steric class between a ring hydrogen and a hydrogen on the methylene unit of the alkyne chain. Conversely, structure **F** was found to exist at a local minimum, with a good overlap of the alkene and alkyne. Despite this overlap, the distance between these groups was once again thought to be rather large.

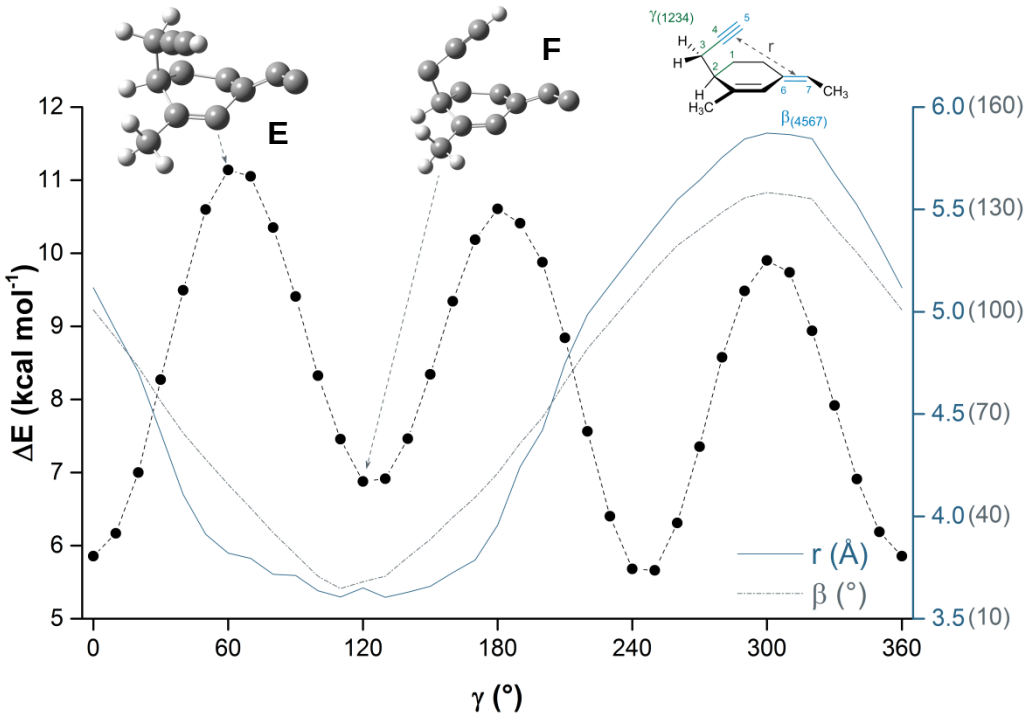


Figure 2.13

Similar to the saturated species, the perceived best conformation, structure **F** was studied while attempting to minimise the distance between alkene and alkyne units. To this end, the energy profile for transition from a half-chair like conformation to a twist-boat like conformation was examined (**Figure 2.14**). On attempting this, it was noted that there was a significant energy penalty observed for this interconversion. It was found that, for example, it was necessary to overcome a 20 kcal mol^{-1} barrier in order to bring the alkene and alkyne close to each other in distances lower than 4 Å. Unfortunately, this strongly suggested that cyclisation from this template was rather unlikely.

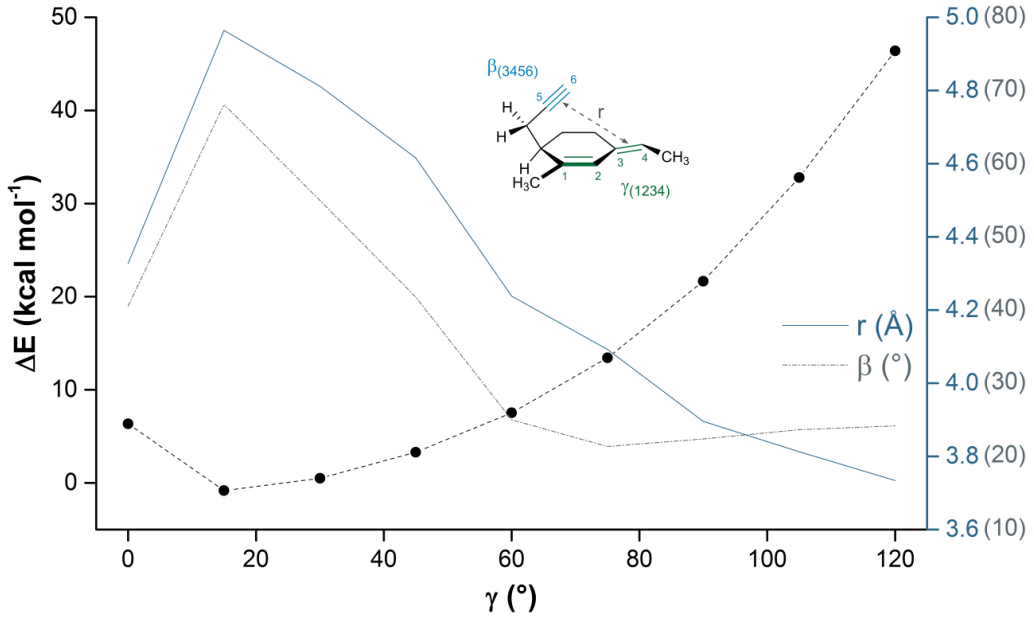


Figure 2.14

Finally, having discovered that the diene precursor was apparently unsuitable for the proposed PKR without the presence of a gem-dimethyl unit, we added this group and performed similar analyses. It was considered that the presence of this unit might reduce the observed distance between alkene and alkyne functionalities without the requirement to overcome large energy barriers. Thus, the energy profile for transition from a half-chair like conformation to a twist-boat like conformation was examined (**Figure 2.15**). From this analysis we can see that this structure possesses a better energy profile for small distortion angles, although the alkene and alkyne are still too distant from each other to promote the cyclisation. Also, beyond γ = 80 the backbone of the cyclohexene passes through an eclipsed conformation and forces the alkene to bend away from the alkyne. From this point and beyond, the potential energy surface indicates a steep increase in energy, and good candidates for the cyclisation are only found in regions of extreme distortions of the ring. This information strongly suggests that this substrate, if successfully accessed would be unlikely to perform the requisite novel PKR.

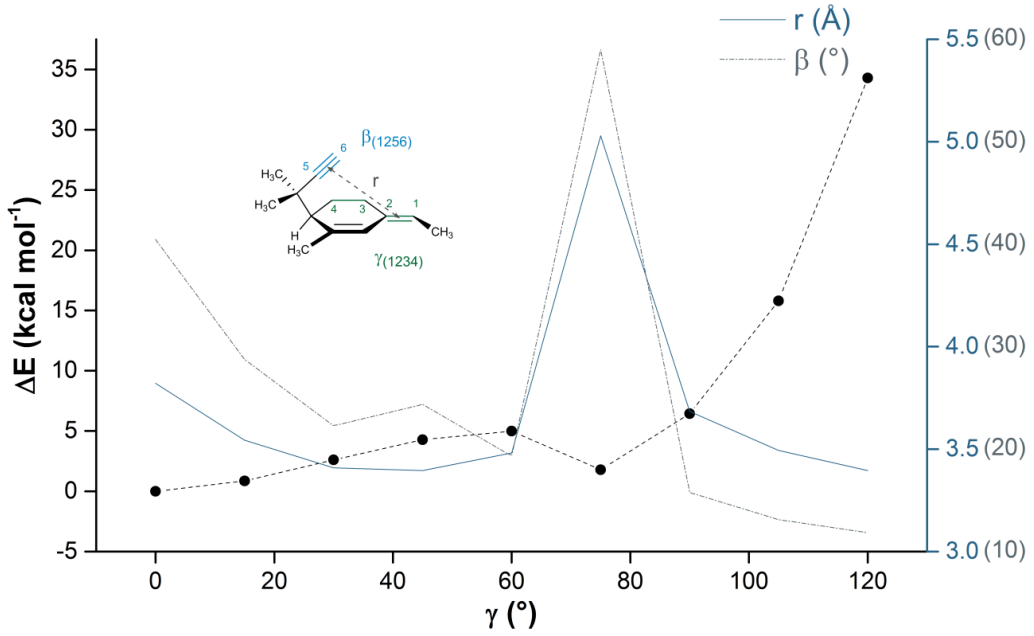
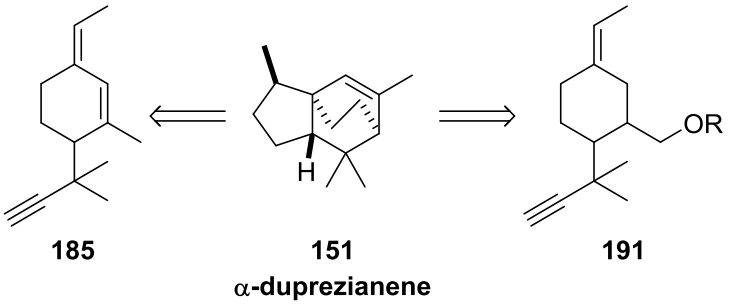


Figure 2.15

As these studies do not include the cobalt complex we cannot be certain about the requisite energy cost to achieve the transition state, which would initiate the PKR. However, it is suggested that the conformational restriction of the molecules, prior to complexation, is not favourable for the proposed cyclisation. These results coupled with our experimental observations suggested strongly that an alternative strategy towards the target molecule, and associated [5,6,6]-fused sesquiterpene natural products, was required.

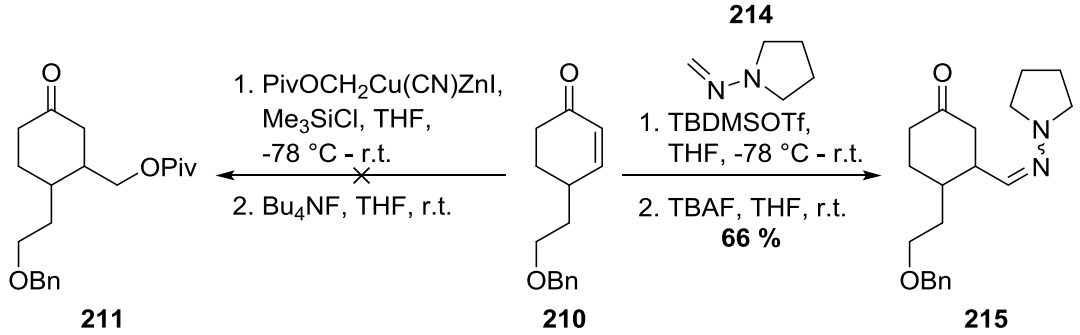
4 Summary

In summary, towards formation of [5,6,6]-fused natural target, α-duprezianene **151**, a series of synthetic strategies were proposed and investigated (**Scheme 2.66**). To this end, two potential precursors for the key PKR were proposed and evaluated.



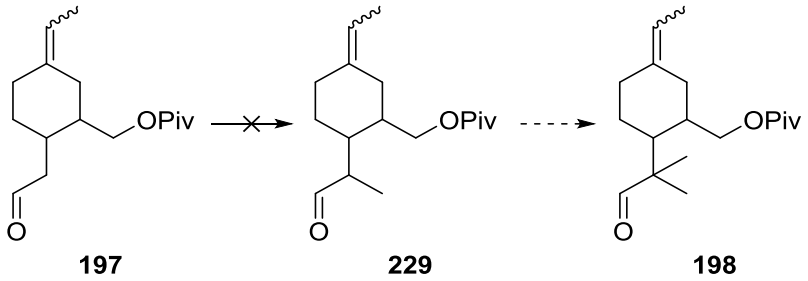
Scheme 2.66

The first precursor to be examined was the saturated enyne **191**. With regards to this, the originally proposed route allowed robust access to enone **210**; however, the planned mixed-metal mediated conjugate addition conditions were found to be ineffective (**Scheme 2.67**). Access to enone **210**, however, allowed for strategic diversification. Thus, a secondary route was developed that involved utilisation of a hydrazone conjugate addition methodology to afford the masked aldehyde functionality present in intermediate **215**.



Scheme 2.67

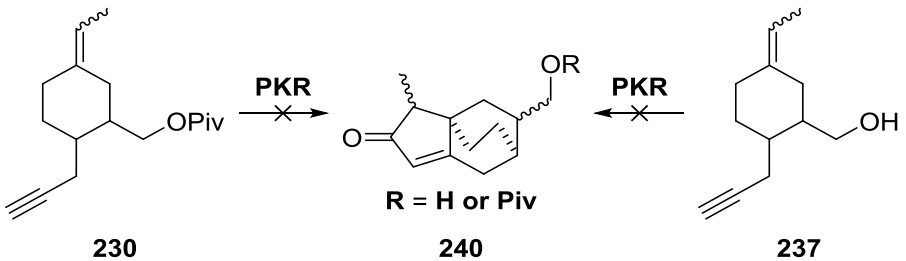
With intermediate **215** in hand, albeit as an unknown mixture of diastereomers, a subsequent series of high-yielding and efficient steps then led to aldehyde **197** (**Scheme 2.68**). At this stage, installation of the requisite *gem*-dimethyl moiety was attempted through a double enolate alkylation strategy. Unfortunately, this proved unsuccessful, with the mono-substituted intermediate **229** found to be inaccessible through these conditions.



197 **229** **198**

Scheme 2.68

In order to test the novel PKR, and with the hope that installation of the *gem*-dimethyl moiety could be performed post-PKR, the enyne **230** was generated effectively from aldehyde **197** (**Scheme 2.69**). Unfortunately, use of the commonly employed, and previously successful, promoters failed to yield the tricyclic PKR product **240**. The free alcohol featuring precursor **237** was also furnished in the hope this alternative enyne would prove a successful cyclisation substrate. Regrettably, under various standard promotion conditions this too failed to yield the desired cyclopentenone product **240**.

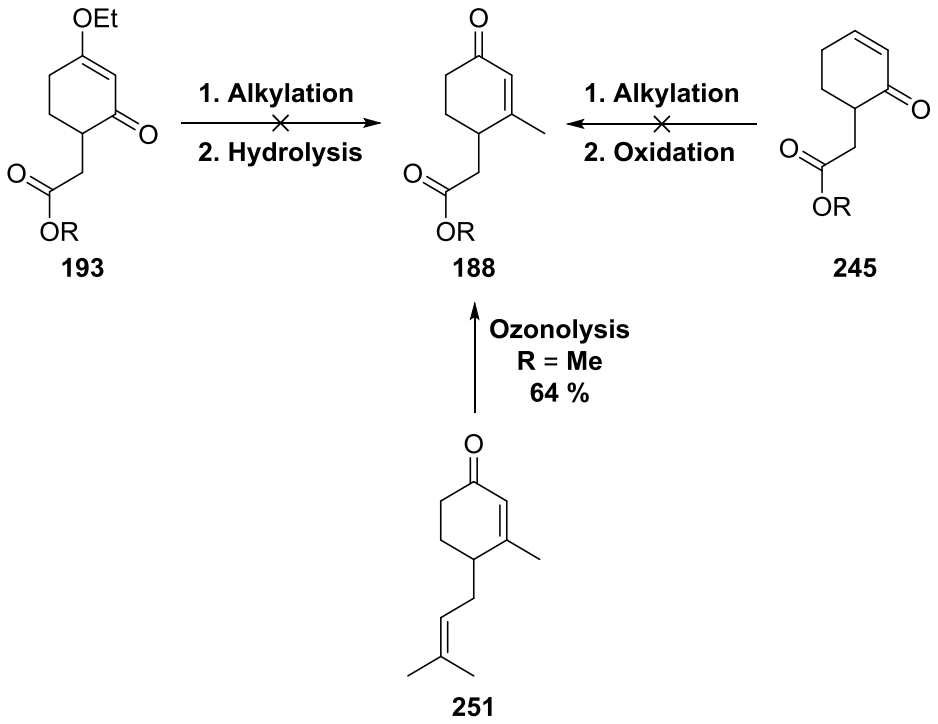


230 **240** **237**

Scheme 2.69

At this point, with the failure of this saturated class of precursors, the alternative diene precursor was evaluated. The proposed synthetic sequence toward diene **185** allowed insertion of the *gem*-dimethyl functionality at an earlier and more stable stage, while the overall route was shorter due to the presence of the internal olefin prior to cyclisation (**c.f. Scheme 2.66**).

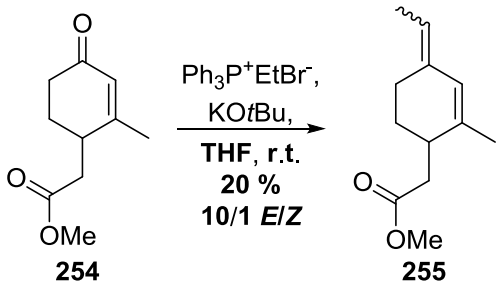
The original proposed route to this precursor employed a literature precedented two-step procedure from intermediate **193** which, it was hoped, would provide rapid and reliable access to key β-substituted enone intermediates of type **188** (**Scheme 2.70**). Unfortunately, this strategy was found to be unsuccessful. An alternative sequence was proposed in which nucleophilic attack of enone **245**, to yield a tertiary alcohol, would be followed by an oxidative rearrangement to yield the β-substituted enone **188**. Once again, despite extensive investigation, the proposed procedure proved unsuccessful and as such the suggested route could not be progressed.



Scheme 2.70

In a final attempt at generation of the desired β-substituted enone intermediate, alternative starting substrates, without ester moieties, were examined. To this end, a synthetic sequence was proposed in which a key ozonolysis reaction would convert prenyl olefin **251** to an ester moiety (**Scheme 2.70**). To our delight, it was discovered this this protocol was effective in generating the crucial ester intermediate of type **188**, in good yields and multigram scales.

With ester **254** in hand, a subsequent olefination was attempted using Wittig conditions (**Scheme 2.71**). Initial reactions proceeded in poor yields, possibly due to interaction with the ester moiety, and, regrettably, appeared to generate the diene **255** with high levels of *E*-selectivity. It was considered that continuation of the strategy with the observed selectivity would lead to a majority of the undesired diastereomer. Either alteration of this selectivity would be required or epimerisation post-PKR would have to be attempted.

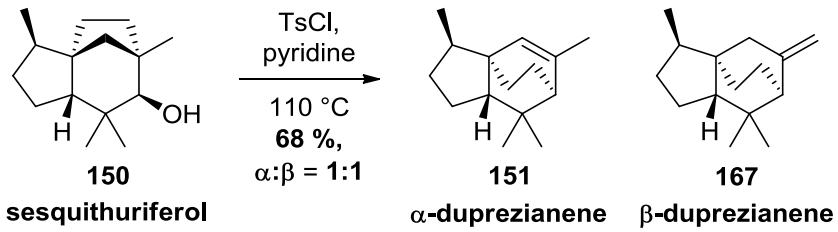


Scheme 2.71

At this point, computational studies on the generated saturated enyne precursors and the proposed diene precursor were conducted to validate the feasibility of our key metal-mediated cyclisation reaction. These studies served to further confirm what was becoming clear through experimental effort. Indeed, it appeared that formation of the [5,6,6]-fused tricyclic structures was not possible from precursors of this type. To this end, no further synthetic endeavour was expended on generation of the natural target through these methods, with an alternative strategy thus considered.

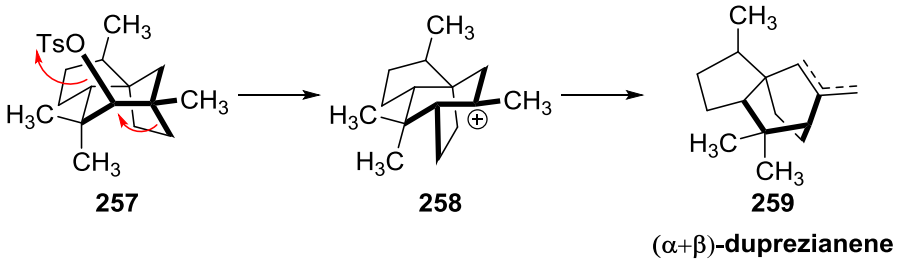
5 Future work

Within the literature, it was noted that the only instance in which enantiomerically pure α-duprezianene **151** had been synthesised was from the related natural product sesquithuriferol **150** (**Scheme 2.72**). Barrero and co-workers were able to convert sesquithuriferol **150** through reaction with tosyl chloride and pyridine at forcing temperatures, successfully yielding a 1:1 mixture of α-duprezianene **151** and β-duprezianene **167**.[148,149] This transformation was performed on small scale from isolated sesquithuriferol **150** allowing further confirmation of the structural and stereochemical assignment of these elusive natural products.



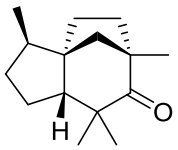
Scheme 2.72

The transformation was proposed to occur in a biomimetic manner (**Scheme 2.73**). As such, following initial tosylation to yield intermediate **257**, a [1,2]-alkyl shift would occur to produce cationic intermediate **258**, which would then be quenched to afford the observed mixture of α- and β-duprezianene **259**.



Scheme 2.73

With knowledge of this biomimetic transformation, an alternative strategy towards the desired natural product α-duprezianene **151** was considered. Previously, within our group the related natural product sesquithuriferone **149** was investigated but a complete synthesis was not elucidated (**Figure 2.16**). As such, it was proposed that a synthetic strategy towards this natural product could be developed which would, in turn, allow access to sesquithuriferol **150** and thus, through the described transformation, α-duprezianene **151** and β-duprezianene **167**. In this way, a key PKR would provide a route towards multiple natural products of the cedrene related sesquiterpene family, this would essential fulfil the original goal of the project albeit in an alternative fashion. Crucially, from our experience in the field, the key PKR in this strategy will present as a far more viable transformation. Full details are discussed in the following chapter.



149
sesquithuriferone

Figure 2.16

6. Experimental

6.1 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 argon atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[195]

- Dry DCM, Et_2O, THF, and PhMe were obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system. All other solvents were used as purchased unless required dry, wherein distillation under argon over calcium hydride was performed prior to use.
- TBAF was obtained as a 1.0 M solution in THF.
- $BCl_3.SMe_2$ was obtained as a 2.0 M solution in DCM.
- *n*-BuLi and MeLi were obtained as solutions in hexanes or Et_2O, respectively, and standardised using salicylaldehyde phenylhydrazone.[196]
- MeMgCl and MeMgBr were obtained as solutions in THF and Et_2O, respectively and standardised using salicylaldehyde phenylhydrazone.[196]
- Petroleum ether refers to petroleum ether in the boiling point (b.p.) range 40-60 °C unless otherwise stated.

Instrumentation and data

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV_{254}. Plates were 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 Shimadzu IRAffinity-1 machine.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 101 MHz, respectively. Coupling constants are reported in Hz and refer to $^{3}J_{\text{H-H}}$ interactions, unless otherwise stated.

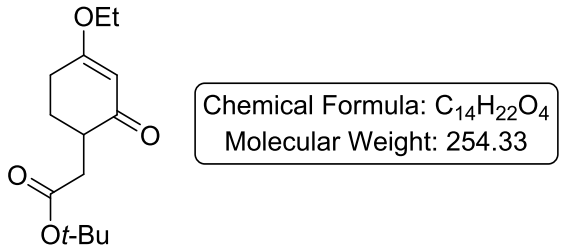
High resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap XL instrument at the EPSRC Mass Spectrometry facility at the University of Wales, Swansea.

All calculations were performed by Renan Zorzatto at the University of Strathclyde, Glasgow.

DFT calculations were performed with the Gaussian09 quantum chemistry package.[197] Geometry optimisations and frequency calculations were performed using the hybrid meta-GGA exchange correlation functional of Thular and Zhao - M06L with the associated 6-31G(d) basis set.[198,199] Dihedral angle scans were obtained through sequential constrained optimisations, process in which the angle of interest was increased in small steps and a new optimum structure was obtained at each stage. Distances between the alkyne and alkene moieties of relevant molecules were obtained by computing the length of the vector connecting the centre point of these bonds. Associated angles were directly obtained from the scalar product of relevant bond vectors. The output files used to derive the data presented in **Figures 2.5 – 2.15** are presented in electronic Appendix A.

6.2 Experimental procedures and compound analyses

Preparation of *tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, 205.[200]



General procedure A

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added di*iso*propylamine (DIPA) (a) and THF (b). The solution was then cooled to 0 °C and slow addition of *n*-BuLi (c) was performed. The resulting solution was stirred at 0 °C for 15 min then cooled to -78 °C. A mixture of compound (d) in THF (e) was then introduced through dropwise addition, with the resulting mixture stirred at -78 °C for a further 1 h. Finally, *tert*-butyl 2-bromoacetate **204** (f) was slowly added and the reaction mixture was allowed to warm gradually to r.t. over an allocated time (g). The reaction was quenched through addition of a saturated aqueous NH_4Cl solution (50 mL) and extraction was subsequently performed with Et_2O (50 mL × 3). The combined organics were washed with water (50 mL × 2) and brine (50 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give product (h).

Scheme 2.20, Table 2.5

The following experiments were performed using **General procedure A**. Results are reported as: (a) volume of DIPA, (b) volume of THF, (c) volume of *n*-BuLi, (d) volume of 3-ethoxycyclohex-2-enone **189**, (e) volume of THF, (f) volume of tert-

butyl 2-bromoacetate **204**, (g) time, and (h) yield of *tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **205** as a white solid.

Entry 1: (a) 0.32 mL, 2.28 mmol, (b) 1.5 mL, (c) 0.86 mL, 2.14 mmol, 2.5 M in hexanes, (d) 0.20 mL, 1.43 mmol, (e) 0.5 mL, (f) 0.26 mL, 1.78 mmol, (g) 16 h, and (h) 221 mg, 61 % yield.

Entry 2: (a) 6.25 mL, 85.60 mmol, (b) 24 mL, (c) 10.28 mL, 25.70 mmol, 2.5 M in hexanes, (d) 6.23 mL, 42.80 mmol, (e) 8 mL, (f) 7.90 mL, 53.52 mmol, (g) 20 h, and (h) 10.12 g, 93 % yield.

Entry 3: (a) 3.13 mL, 42.80 mmol, (b) 20 mL, (c) 18.69 mL, 39.24 mmol, 2.1 M in hexanes, (d) 5.19 mL, 35.67 mmol, (e) 7 mL, (f) 6.58 mL, 44.56 mmol, (g) 18 h, and (h) 9.00 g, 99 % yield.

Melting point: 67 - 69 °C

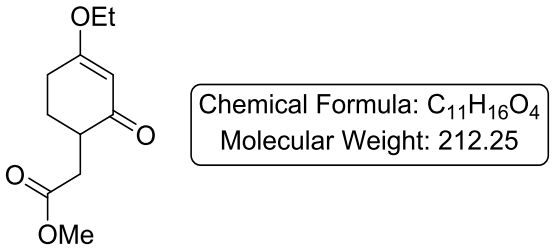
FTIR (**cm^{-1}**): 2976, 2932, 2913, 1726, 1643, 1602.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.29 (d, 1H, ^{4}J = 1.6 Hz, vinylic C<u>H</u>), 3.91-3.79 (m, 2H, OC<u>H</u>$_2$CH$_3$), 2.79 (dd, 1H, ^{2}J = 16.0 Hz, J = 5.0 Hz, alkyl C<u>H</u>), 2.67-2.59 (m, 1H, alkyl C<u>H</u>), 2.55-2.46 (m, 1H, alkyl C<u>H</u>), 2.34 (ddd, 1H, ^{2}J = 17.6 Hz, J = 5.0, 3.1 Hz, alkyl C<u>H</u>), 2.15 **(**dd, 1H, ^{2}J = 16.2 Hz, J = 7.6 Hz, alkyl C<u>H</u>), 2.08-2.02 (m, 1H, alkyl C<u>H</u>), 1.73 (ddd, 1H, ^{2}J = 25.0 Hz, J = 12.5, 5.0 Hz, alkyl C<u>H</u>), 1.41 (s, 9H, alkyl C<u>H</u>$_3$), 1.31 ppm (t, 3H, J = 7.0 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 198.2, 176.0, 171.1, 101.1, 79.4, 63.3, 41.5, 35.0, 28.0, 27.2, 26.1, 13.2 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{14}H_{23}O_4$ (M^+ + H): 255.1591. Found: 255.1592.

Preparation of methyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **207**.



Scheme 2.21

The following experiments were performed using **General procedure A**. Results are reported as: (a) volume of DIPA, (b) volume of THF, (c) volume of *n*-BuLi, (d) volume of 3-ethoxycyclohex-2-enone **189**, (e) volume of THF, (f) volume of methyl 2-bromoacetate **206**, (g) time, and (h) yield of methyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **207** as a pale yellow oil.

Run 1: (a) 1.59 mL, 11.41 mmol, (b) 4 mL, (c) 5.10 mL, 10.70 mmol, 2.1 M in hexanes, (d) 1.04 mL, 7.13 mmol, (e) 1.5 mL, (f) 0.84 mL, 8.91 mmol, (g) 20 h, and (h) 400 mg, 26 % yield.

Run 2: (a) 1.20 mL, 8.56 mmol, (b) 4 mL, (c) 3.70 mL, 7.84 mmol, 2.1 M in hexanes, (d) 1.04 mL, 7.13 mmol, (e) 1.5 mL, (f) 1.35 mL, 14.26 mmol, (g) 29 h, and (h) 497 mg, 33 % yield.

FTIR (**cm^{-1}**): 2984, 2947, 1732, 1653, 1602.

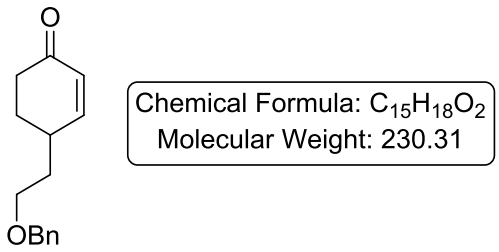
^{1}H NMR (**400 MHz, CDCl$_3$**): 5.34 (d, 1H, ^{4}J = 1.6 Hz, vinylic C<u>H</u>), 3.94-3.85 (m, 2H, OC<u>H</u>$_2$CH$_3$), 3.69 (s, 3H, OC<u>H</u>$_3$), 2.93 (dd, 1H, ^{2}J = 16.5 Hz, J = 5.3 Hz, alkyl C<u>H</u>), 2.76-2.68 (m, 1H, alkyl C<u>H</u>), 2.61-2.52 (m, 1H, alkyl C<u>H</u>), 2.39 (ddd, 1H, ^{2}J = 17.6 Hz, J = 4.8, 2.9 Hz, alkyl C<u>H</u>), 2.28 (dd, 1H, ^{2}J = 16.4 Hz, J = 7.8 Hz, alkyl

CH), 2.13-2.06 (m, 1H, alkyl CH), 1.78 (ddd, 1H, ^{2}J = 25.1 Hz, J = 12.6, 5.3 Hz, alkyl CH), 1.35 ppm (t, 3H, J = 7.1 Hz, OCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): 199.0, 177.3, 173.4, 102.1, 64.5, 51.8, 42.4, 34.7, 29.2, 27.3, 14.3 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{11}H_{17}O_4$ (M^+ + H): 213.1121. Found: 213.1123.

Preparation of 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210**.



General procedure B

To a flame dried, round bottom flask fitted with a reflux condenser, magnetic stirrer bar, and an argon inlet was added $LiAlH_4$ (a) and THF (b). The solution was then cooled to 0 °C and a mixture of *tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **205** (c) in THF (d) was introduced through dropwise addition. The resulting suspension was stirred at 0 °C for 1 h then allowed to warm to r.t. and stirred for a further 2 h. The mixture was cooled to 0 °C and quenched through slow addition of a saturated aqueous Na_2SO_4 solution. The mixture was then allowed to warm to r.t. and stirred for the allotted time (e). The mixture was filtered and the residue was thoroughly washed with Et_2O. The filtrate was then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product, which, without purification, was dissolved in THF (f) and slowly added to a suspension of NaH (g) in THF (h) at 0 °C under nitrogen. The mixture was stirred at 0 °C for 30 min then allowed to warm to r.t. and stirred for a further 30 min, before cooling back to 0 °C, followed by the slow addition of benzyl bromide (i). The mixture was then allowed to warm to r.t. and stirred for the allotted time (j), after which it was acidified

through addition of 5 M HCl (k) and stirred for a subsequent duration (l). Following this, the reaction mixture was extracted with Et_2O (50 mL x 3), the combined organics were then washed with saturated aqueous $NaHCO_3$ solution (50 mL), water (50 mL × 2), and brine (50 mL), before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210** (m).

Scheme 2.23

The following experiments were performed using **General procedure B**. Results are reported as: (a) amount of $LiAlH_4$, (b) volume of THF, (c) amount of *tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **205**, (d) volume of THF, (e) time, (f) volume of THF, (g) amount of NaH, (h) volume of THF, (i) volume of benzyl bromide, (j) time, (k) volume of 5 M HCl, (l) time, and (m) yield of 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210** as a colourless oil.

Run 1: (a) 197 mg, 5.17 mmol, (b) 5 mL, (c) 597 mg, 2.35 mmol, (d) 5 mL, (e) 16 h, (f) 5 mL, (g) 85 mg, 3.55 mmol, (h) 5 mL, (i) 0.57 mL, 4.82 mmol, (j) 20 h, (k) 5 mL, (l) 4 h, and (m) 271 mg, 50 % yield.

Run 2: (a) 1.26 g, 33.18 mmol, (b) 32 mL, (c) 3.83 g, 15.08 mmol, (d) 32 mL, (e) 20 h, (f) 32 mL, (g) 543 mg, 22.62 mmol, (h) 32 mL, (i) 3.68 mL, 30.91 mmol, (j) 11 h, (k) 15 mL, (l) 2 h, and (m) 1.63 g, 47 % yield.

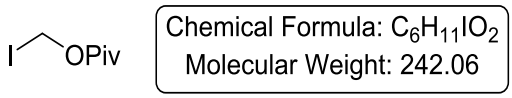
FTIR (**cm^{-1}**): 3086, 3062, 2926, 2860, 1674, 1495, 1452, 1090.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.38-7.28 (m, 5H, ArH), 6.88 (ddd, 1H, J = 10.2 Hz, 2.8, ^4J = 1.4 Hz, vinylic CH), 5.98 (ddd, 1H, J = 10.2 Hz, ^4J = 2.4, 0.8 Hz, vinylic CH), 4.53 (s, 2H, OCH_2Ph), 3.62-3.56 (m, 2H, $BnOCH_2$), 2.70-2.61 (m, 1H, alkyl CH), 2.52-2.46 (m, 1H, alkyl CH), 2.40-2.32 (m, 1H, alkyl CH), 2.15-2.07 (m, 1H, alkyl CH), 1.90-1.81 (m, 1H, alkyl CH), 1.75-1.65 ppm (m, 2H, alkyl CH).

^{13}C NMR (**101 MHz, $CDCl_3$**): 198.9, 154.0, 137.2, 128.1, 127.6, 126.8, 126.7, 72.2, 66.5, 35.9, 33.5, 32.3, 27.7 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{15}H_{19}O_2$ (M^+ + H): 231.1380. Found: 231.1375.

Preparation of iodomethyl pivalate, **213**.[169]



General procedure C

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added NaI (a) in acetone (b). To this suspension was added a mixture of chloromethyl pivalate, **212** (c) and acetone (d). The reaction mixture was then allowed to stir at r.t. for the allotted time (e). The reaction mixture was diluted with Et_2O (50 mL) and filtered, and the filtrate was concentrated to yield a brown oil. This brown residue was dissolved in Et_2O (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (30 mL × 2), the organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* fractional distillation (b.p. ca. 60 °C/ 1 mbar) to give iodomethyl pivalate **213** (f).

Scheme 2.25

The following experiments were performed using **General procedure C**. Results are reported as: (a) amount of NaI, (b) volume of acetone, (c) volume of chloromethyl pivalate, **212**, (d) volume of acetone, (e) time, and (f) yield of iodomethyl pivalate, **213** as a colourless oil.

Run 1: (a) 4.48 g, 29.88 mmol, (b) 7 mL, (c) 1.91 mL, 13.28 mmol, (d) 6 mL, (e) 19 h, and, (f) 2.09 g, 65 % yield.

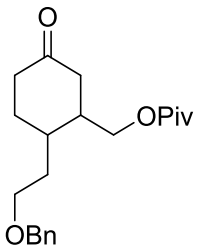
Run 2: (a) 11.20 g, 74.70 mmol, (b) 17 mL, (c) 4.78 mL, 33.20 mmol, (d) 14 mL, (e) 16 h, and, (f) 7.31 g, 91 % yield.

FTIR (**cm^{-1}**): 2974, 2936, 2874, 1751, 1479, 1092, 1034.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.92 (s, 2H, alkyl C$\underline{H}_2$), 1.18 ppm (s, 9H, alkyl C$\underline{H}_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 175.4, 38.0, 30.5, 25.7 ppm.

Attempted preparation of (2-(2-(benzyloxy)ethyl)-5-oxocyclohexyl)methyl pivalate, **211**.



Chemical Formula: $C_{21}H_{30}O_4$
Molecular Weight: 346.47

General procedure D

To a flame dried, round bottom flask fitted with a thermometer, a magnetic stirrer bar, and an argon inlet was added zinc dust (a) in THF (b), which was then activated with 1,2-dibromoethane (c) and TMSCl (d). The reaction mixture was then equilibrated to temperature (e). To this was added a mixture of iodomethyl pivalate **213**, (f) in THF (g) and the reaction mixture was then allowed to stir for the allotted time (h). This solution was cooled to -20 °C and transferred *via* cannula to a second flame dried, round bottom flask fitted with a thermometer, a magnetic stirrer bar, and an argon inlet containing a solution of CuCN (i), LiCl (j) and THF (k) stirring at -20 °C. Following addition, the reaction mixture was allowed to warm to 0 °C and stirred for 5 mins. The mixture was then cooled to -78 °C and TMSCl (l) was added followed by a solution of 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210** (m) in THF (n). The reaction mixture was then allowed to warm gradually to r.t. over the allotted time (o) while stirring. The reaction mixture was poured into a conical flask

containing a magnetic stirrer, saturated aqueous NH_4Cl solution (100 mL) and 1 M NaOH (25 mL), which had been cooled to 0 °C. The mixture was allowed to stir at 0 °C for 30 mins, then allowed to warm to r.t., and stirred for a further 30 mins. The mixture was subsequently extracted with Et_2O (30 mL × 3), the organics were combined before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was then dissolved in THF (p), TBAF (q) was added, and the reaction mixture was then allowed to stir at r.t. for 1 h. The reaction mixture was once again extracted with Et_2O (30 mL × 2), the combined organics were then washed with saturated aqueous $NaHCO_3$ solution (20 mL), water (10 mL × 2), and brine (20 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Unfortunately, the desired product, (2-(2-(benzyloxy)ethyl)-5-oxocyclohexyl)methyl pivalate, **211**, was not detected.

Scheme 2.26, **Table 2.6**

The following experiments were performed using **General procedure D**. Results are reported as: (a) amount of zinc, (b) volume of THF, (c) volume of 1,2-dibromoethane, (d) volume of TMSCl, (e) temperature, (f) amount of iodomethyl pivalate **213**, (g) volume of THF, (h) time, (i) amount of CuCN, (j) amount of LiCl, (k) volume of THF, (l) volume of TMSCl, (m) amount of 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210**, (n) volume of THF, (o) time, (p) volume of THF, and (q) volume of TBAF.

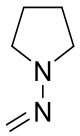
Entry 1: (a) 324 mg, 4.96 mmol, (b) 0.5 mL, (c) 0.01 mL, 0.12 mmol, (d) 0.01 mL, 0.01 mmol, (e), r.t. (f) 600 mg, 2.48 mmol, (g) 1.5 mL, (h) 1 h, (i) 222 mg, 2.48 mmol, (j) 210 mg, 4.96 mmol, (k) 1.5 mL, (l) 0.35 mL, 2.73 mmol, (m) 424 mg, 1.84 mmol, (n) 1.5 mL, (o) 16 h, (p) 5 mL, and (q) 2.73 mL, 2.73 mmol.

Entry 2: (a) 803 mg, 12.24 mmol, (b) 1.5 mL, (c) 0.03 mL, 0.35 mmol, (d) 0.03 mL, 0.25 mmol, (e), r.t. (f) 1.48 mg, 6.12 mmol, (g) 3.5 mL, (h) 2 h, (i) 548 mg, 6.12 mmol, (j) 519 mg, 12.24 mmol, (k) 4 mL, (l) 0.85 mL, 6.73 mmol, (m) 705 mg, 3.06 mmol, (n) 4 mL, (o) 18 h, (p) 10 mL, and (q) 6.73 mL, 6.73 mmol.

Entry 3: (a) 803 mg, 12.24 mmol, (b) 1.5 mL, (c) 0.03 mL, 0.35 mmol, (d) 0.03 mL, 0.25 mmol, (e) 10 – 15 °C, (f) 1.48 mg, 6.12 mmol, (g) 3.5 mL, (h) 1 h, (i) 548 mg, 6.12 mmol, (j) 519 mg, 12.24 mmol, (k) 4 mL, (l) 0.85 mg, 6.73 mmol, (m) 705 mg, 3.06 mmol, (n) 4 mL, (o) 16 h, (p) 10 mL, and (q) 6.73 mL, 6.73 mmol.

Entry 4: (a) 803 mg, 12.24 mmol, (b) 1.5 mL, (c) 0.03 mL, 0.35 mmol, (d) 0.03 mL, 0.25 mmol, (e) 10 – 15 °C, (f) 1.48 mg, 6.12 mmol, (g) 3.5 mL, (h) 2 h, (i) 548 mg, 6.12 mmol, (j) 519 mg, 12.24 mmol, (k) 4 mL, (l) 0.86 mL, 6.73 mmol, (m) 705 mg, 3.06 mmol, (n) 4 mL, (o) 18 h, (p) 10 mL, and (q) 6.73 mL, 6.73 mmol.

Preparation of *N*-(pyrrolidin-1-yl)methanimine, **214**.[175]



Chemical Formula: $C_5H_{10}N_2$
Molecular Weight: 98.15

General procedure E

To a flame dried, round bottom flask fitted with a reflux condenser, magnetic stirrer, bar and an argon inlet was added $LiAlH_4$ (a) and Et_2O (b). The solution was then cooled to 0 °C and a mixture of 1-nitrosopyrrolidine **221** (c) in Et_2O (d) was introduced through dropwise addition. The resulting suspension was stirred at 0 °C for 1 h then allowed to warm to r.t. and stirred for a further 3 h. The reaction mixture was cooled to 0 °C and quenched through slow addition of saturated aqueous Na_2SO_4 solution. The reaction mixture was then allowed to warm to r.t. and stirred for the allotted time (e). To the reaction mixture was added Et_2O (f), the mixture was then cooled to 0 °C and paraformaldehyde (g) was added. The mixture was then allowed to warm to r.t. and stirred for a further time period (h) before the mixture was filtered and the residue was thoroughly washed with Et_2O. The filtrate was then dried over Na_2SO_4, filtered, and carefully concentrated *in vacuo* to give the crude product. The

crude material was purified *via* fractional distillation (b.p. ca. 88 °C/ 189 mbar) to give *N*-(pyrrolidin-1-yl)methanimine, **214** (i).

Scheme 2.29

The following experiments were performed using **General procedure E**. Results are reported as: (a) amount of $LiAlH_4$, (b) volume of Et_2O, (c) amount of 1-nitrosopyrrolidine **221**, (d) volume of Et_2O, (e) time, (f) volume of Et_2O, (g) amount of paraformaldehyde, (h) time, and (i) yield of *N*-(pyrrolidin-1-yl)methanimine, **214** as a colourless oil.

Run 1: (a) 2.88 g, 75.90 mmol, (b) 100 mL, (c) 3.00 g, 29.96 mmol, (d) 20 mL, (e) 16 h, (f) 30 mL, (g) 1.17 g, 38.95 mmol, (h) 39 h, and (i) 1.14 g, 39 % yield.

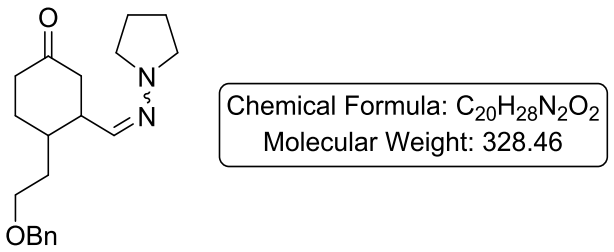
Run 2: (a) 8.41 g, 221.64 mmol, (b) 360 mL, (c) 11.09 g, 110.82 mmol, (d) 84 mL, (e) 20 h, (f) 112 mL, (g) 4.33 g, 144.07 mmol, (h) 72 h, and (i) 9.78 g, 90 % yield.

FTIR (**cm^{-1}**): 2967, 2832, 1564.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.03 (d, 1H, ^{2}J = 12.0 Hz, vinylic N=C<u>H</u>), 5.96 (d, 1H, ^{2}J = 12.0 Hz, N=C<u>H</u>), 3.19-3.16 (m, 4H, alkyl C<u>H</u>), 1.90-1.86 ppm (m, 4H, alkyl C<u>H</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 121.3, 50.5, 23.4 ppm.

Preparation of 4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one, **215**.



Scheme 2.30, Table 2.7, Entry 1

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210** (200 mg, 0.87 mmol) in Et_2O (4 mL) and the solution was cooled to 0 °C. To this solution was added TBSOTf (0.25 mL, 1.09 mmol) through dropwise addition and the reaction mixture was then stirred at 0 °C for 30 min. A mixture of *N*-(pyrrolidin-1-yl)methanimine, **214** (171 mg, 1.74 mmol) in Et_2O (2 mL) was then added to the reaction mixture dropwise and the resulting solution was stirred for 2 h**.** The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude material was dissolved in Et_2O (4 mL) and TBAF (1.09 mL, 1.09 mmol) was added. The reaction mixture was then allowed to stir at r.t. for 30 mins. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL x 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 90 % Et_2O in petroleum ether) to give 4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one, **215** (116 mg, 41 % yield) as a pale yellow oil.

Scheme 2.30, Table 2.7, Entry 2

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 4-(2-(benzyloxy)ethyl)cyclohex-2-en-1-one, **210** (340 mg, 1.48 mmol) in THF (10 mL) and the solution was cooled to -78 °C. To this solution was added TBSOTf (0.62 mL, 2.71 mmol) dropwise and the reaction mixture was then stirred at -78 °C for 30 mins. A mixture of *N*-(pyrrolidin-1-yl)methanimine, **214** (426 mg, 4.34 mmol) in THF (5 mL) was then added to the reaction mixture dropwise and the resulting solution was then allowed to warm gradually to r.t. while stirring over 19 h. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo.* The crude material was dissolved in THF (10 mL) and TBAF (2.71 mL, 2.71 mmol) was added. The reaction mixture was then allowed to stir at r.t. for 30 mins. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 90 % Et_2O in petroleum ether) to give 4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one, **215** (321 mg, 66 % yield) as a pale yellow oil.

4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one, **215**, was isolated as a complex and inseparable mixture of isomers.

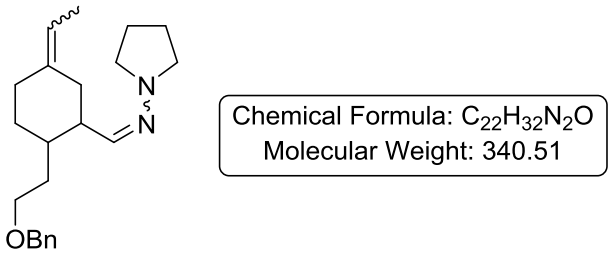
FTIR (**cm^{-1}**): 3083, 3060, 2966, 2872, 1708, 1454, 1335, 1093.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.36-7.26 (m, 5H, Ar<u>H</u>), 6.40 & 6.36 (d, 1H in total, *J* = 6.1 Hz, N=C<u>H</u>, ratio 3:2), 4.54-4.46 (m, 2H, PhC<u>H</u>$_2$O), 3.59-3.53 (m, 2H, BnOC<u>H</u>$_2$), 3.11-3.06 (m, 4H, NC<u>H</u>), 2.49 (d, 1H, *J* = 5.2 Hz, alkyl C<u>H</u>), 2.45-2.28 (m, 3H, alkyl C<u>H</u>), 2.24-1.97 (m, 2H, alkyl C<u>H</u>), 1.89-1.83 (m, 5H, alkyl C<u>H</u>), 1.81-1.58 (m, 2H, alkyl C<u>H</u>), 1.50-1.38 ppm (m, 1H, alkyl C<u>H</u>).

^{13}C NMR (101 MHz, $CDCl_3$): 138.6, 138.0, 134.6 128.5, 127.8, 73.2, 73.1, 68.4, 68.1, 51.6, 51.4, 47.3, 45.5, 44.9, 43.4, 40.6, 40.1, 36.8, 35.6, 33.1, 31.8, 30.5, 28.1, 23.2, 23.1 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{20}H_{29}N_2O_2$ (M^+ + H): 329.2224. Found: 329.2226.

Preparation of 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216**.



General procedure F

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added ethyltriphenylphosphonium bromide (a) and THF (b). To this suspension was added KO*t*Bu (c). The reaction mixture was allowed to stir at r.t. for 30 mins before a mixture of 4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one**, 215** (d) in THF (e) was added. The reaction mixture was then stirred for the allotted time (f). After this time, the reaction mixture was diluted with saturated aqueous NH_4Cl solution (30 mL) and subsequent extraction was performed with Et_2O (30 mL × 3). The combined organics were then washed with water (25 mL × 2), and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216** (g).

Scheme 2.31

The following experiments were performed using **General procedure F**. Results are reported as: (a) amount of ethyltriphenylphosphonium bromide, (b) volume of THF, (c) amount of KO*t*Bu, (d) amount of 4-(2-(benzyloxy)ethyl)-3-((pyrrolidin-1-ylimino)methyl)cyclohexan-1-one, **215**, (e) volume of THF, (f) time, and (g) yield of 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216** as a colourless oil.

Run 1: (a) 2.47 g, 6.64 mmol, (b) 11 mL, (c) 745 mg, 6.64 mmol, (d) 544 mg, 1.66 mmol, (e) 11 mL, (f) 17 h, and (g) 406 mg, 72 % yield.

Run 2: (a) 11.09 g, 29.88 mmol, (b) 50 mL, (c) 3.35 g, 29.88 mmol, (d) 2.45 g, 7.47 mmol, (e) 50 mL, (f) 4 h, and (g) 1.72 g, 68 % yield.

1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216**, was isolated as a complex and inseparable mixture of isomers.

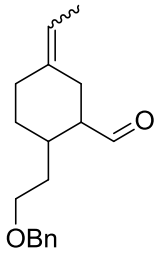
FTIR (**cm^{-1}**): 3086, 3062, 2922, 2857, 1593, 1452, 1338, 1099.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.37-7.29 (m, 5H, ArH), 6.56, 6.45 & 6.41 (d, 1H in total, J = 6.1 Hz, N=CH, ratio 0.7:0.15:0.15), 5.32-5.14 (m, 1H, vinylic CH), 4.56-4.47 (m, 2H, PhCH_2O), 3.58-3.53 (m, 2H, BnOCH_2), 3.14-3.06 (m, 4H, NCH), 2.67-2.18 (m, 3H, alkyl CH), 2.15-2.00 (m, 1H, alkyl CH), 1.96-1.78 (m, 6H, alkyl CH), 1.76-1.48 (m, 6H, alkyl CH), 1.42-1.29 ppm (m, 1H, alkyl CH).

^{13}C NMR (**101 MHz, $CDCl_3$**): 142.6, 140.2, 139.8, 138.9, 138.8, 137.7, 136.8, 136.3, 128.4, 127.7, 127.6, 117.44, 117.40, 116.5, 116.4, 72.99, 72.95, 72.92, 68.50, 69.47, 68.44, 51.98, 51.86, 51.71, 51.68, 48.8, 47.9, 43.3, 43.0, 41.9, 40.9, 38.0, 37.2, 36.9, 36.0, 35.9, 34.0, 33.2, 33.0, 32.8, 32.5, 32.0, 30.6, 29.4, 27.3, 26.9, 23.0, 13.0, 12.9 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{22}H_{33}N_2O$ (M^+ + H): 341.2587. Found: 341.2591.

Preparation of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, 217.



Chemical Formula: $C_{18}H_{24}O_2$
Molecular Weight: 272.39

General procedure G

To a round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216** (a) in Et_2O (b). This solution was cooled to 0 °C, 5 M HCl (c) was added, and the reaction mixture was then stirred for the allotted time (d). Extraction of the reaction mixture was performed with Et_2O (30 mL × 3) and the combined organics were then washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL), before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217** (e).

Scheme 2.31

The following experiments were performed using **General procedure G**. Results are reported as: (a) amount of 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216**, (b) volume of Et_2O, (c) volume of 5M HCl, (d) time, and, (e) yield of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217** as a colourless oil.

Run 1: (a) 100 mg, 0.29 mmol, (b) 4 mL, (c) 1 mL, (d) 30 min, and, (e) 66 mg, 84 % yield.

Run 2: (a) 1.94 g, 5.91 mmol, (b) 20 mL, (c) 7 mL, (d) 1 h, and, (e) 1.22 g, 76 % yield.

2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217**, was isolated as a complex and inseparable mixture of isomers.

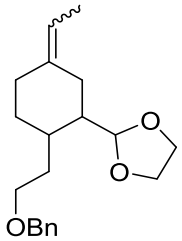
FTIR (**cm^{-1}**): 3063, 3030, 2918, 2857, 1721, 1445, 1098.

^{1}H NMR (**400 MHz, $CDCl_3$**): 9.73, 9.62 & 9.58 (d, 1H in total, *J* = 3.0 Hz, C<u>H</u>O, ratio 0.7:0.15:0.15), 7.37-7.27 (m, 5H, Ar<u>H</u>), 5.31-5.21 (m, 1H, vinylic C<u>H</u>), 4.52-4.49 (m, 2H, PhC<u>H$_2$</u>O), 3.55-3.51 (m, 2H, BnOC<u>H$_2$</u>), 2.68-2.41 (m, 2H, alkyl C<u>H</u>), 2.33-1.95 (m, 4H, alkyl C<u>H</u>), 1.93-1.62 (m, 3H, alkyl C<u>H</u>), 1.58 (br d, 3H, *J* = 6.2 Hz, alkyl CH_3) 1.55-1.47 ppm (m, 1H, alkyl C<u>H</u>).

^{13}C NMR (101 MHz, $CDCl_3$): 205.8, 205.7, 204.9, 204.8, 138.61, 138.56, 128.5, 127.8, 127.7, 118.5, 118.3, 117.92, 117.89, 73.1, 73.0, 68.18, 68.16, 67.83, 67.81, 56.7, 55.8, 52.4, 52.2, 35.6, 35.5, 35.01, 34.96, 34.79, 34.77, 34.0, 33.9, 32.1, 31.7, 31.5, 31.1, 30.8, 29.7, 27.0, 26.5, 26.0, 12.90, 12.86 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{18}H_{28}O_2N$ ($M^+ + NH_4$): 290.2115. Found: 290.2117.

Preparation of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224**.



Chemical Formula: $C_{20}H_{28}O_3$
Molecular Weight: 316.44

General procedure H

To a flame dried, round bottom flask fitted with a condenser, a magnetic stirrer bar, and an argon inlet was added 4Å MS (a), the starting substrate (b), ethylene glycol (c), *p*-TsOH·H_2O (d), and PhMe (e). The reaction mixture was then heated to 60 °C and allowed to stir for (f). The reaction mixture was then extracted with Et_2O (30 mL × 3) and the combined organics were washed with water (25 mL × 2), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224** (g).

General procedure I

To a flame dried, round bottom flask fitted with a condenser, a magnetic stirrer bar, and an argon inlet was added the 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217** (a), ethylene glycol (b), additive (c), *p*-TsOH·H_2O (d), and PhH (e). The reaction mixture was then allowed to stir at r.t. for the allocated time (f). After this, the reaction mixture was extracted with Et_2O (30 mL × 3) and the combined organics were washed with water (25 mL × 2), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224** (g).

Scheme 2.33, **Table 2.8**, **Entry 1**

The following experiment was performed using **General procedure H**. Results are reported as: (a) amount of 4Å MS, (b) amount of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217**, (c) volume of ethylene glycol, (d) amount of *p*-TsOH·H_2O (e) volume of PhMe, (f) time, and (g) yield of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane**, 224** as a colourless oil.

Entry 1: (a) 30 mg, (b) 100 mg, 0.37 mmol, (c) 0.03 mL, 0.44 mmol, (d) 8 mg, 0.04 mmol, (e) 3 mL, (f) 17 h, and (g) 66 mg, 56 % yield.

Scheme 2.33, **Table 2.8**, **Entries 2 & 3**

The following experiments were performed using **General procedure I**. Results are reported as: (a) amount of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217**, (b) volume of ethylene glycol, (c) additive employed and volume used, (d) amount of *p*-TsOH·H2O, (e) volume of PhH, (f) time, and, (g) yield of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane**, 224** as a colourless oil.

Entry 2: (a) 100 mg, 0.37 mmol, (b) 0.08 mL, 1.48 mmol, (c) trimethylorthoformate, 0.06 mL, 0.56 mmol, (d) 63 mg, 0.33 mmol, (e) 2 mL, (f) 18 h, and, (g) 98 mg, 84 % yield.

Entry 3: (a) 100 mg, 0.37 mmol, (b) 0.09 mL, 0.37 mmol, (c) triethylorthoformate, 0.09 mL, 0.56 mmol, (d) 63 mg, 0.33 mmol, (e) 2 mL, (f) 16 h, and, (g) 88 mg, 75 % yield.

Scheme 2.34, **Table 2.9**, **Entry 1**

The following experiment was performed using **General procedure H**. Results are reported as: (a) amount of 4Å MS, (b) amount of 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216**, (c) volume of ethylene glycol, (d) amount of *p*-TsOH·H_2O (e) volume of PhMe, (f) time, and (g) yield of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane**, 224**.

Entry 1: (a) 30 mg, (b) 100 mg, 0.29 mmol, (c) 0.03 mL, 0.35 mmol, (d) 6 mg, 0.03 mmol, (e) 3 mL, (f) 48 h, and, (g) 0 mg, 0 % yield.

Scheme 2.34, **Table 2.9**, **Entry 2**

To a flame dried, round bottom flask fitted with a condenser, a magnetic stirrer bar, and an argon inlet was added 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-*N*-(pyrrolidin-1-yl)methanimine, **216** (100 mg, 0.29 mmol), ethylene glycol (0.08 mL,

1.48 mmol), trimethyl orthoformate (0.06 mL, 0.56 mmol), *p*-TsOH·H_2O (63 mg, 0.33 mmol) and PhH (2 mL). The reaction mixture was then allowed to stir at r.t. for 16 h. The desired product was not observed at this time, and as such the reaction mixture was heated to reflux and allowed to stir for a further 6 h. After this time, the reaction mixture was extracted with Et_2O (30 mL × 3) and the combined organics were washed with water (25 mL × 2), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Regrettably, the desired product 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224** was not observed.

2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224**, was isolated as a complex and inseparable mixture of isomers.

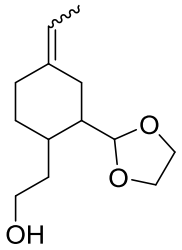
FTIR (**cm^{-1}**): 3076, 3059, 2916, 2874, 1452, 1099.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.35-7.27 (m, 5H, ArH), 5.22-5.17 (m, 1H, vinylic CH), 4.96, 4.95, 4.75 & 4.74 (d, 1H in total, *J* = 5.5 Hz, OCHO, ratio 2:2:3:3), 4.55-4.46 (m, 2H, PhCH_2O), 3.96-3.79 (m, 4H, OCH), 3.57-3.49 (m, 2H, BnOCH_2), 2.61-2.27 (m, 1H, alkyl CH), 2.24-1.93 (m, 4H, alkyl CH), 1.91-1.71 (m, 3H, alkyl CH), 1.61-1.50 ppm (m, 5H, alkyl CH).

^{13}C NMR (**101 MHz, $CDCl_3$**): 138.80, 138.75, 138.13, 137.97, 137.5, 137.4, 128.5, 127.8, 127.6, 116.8, 116.4, 105.55, 105.48, 104.77, 104.75, 73.0, 69.3, 69.2, 68.6, 65.1, 65.0, 64.9, 64.8, 64.6, 45.9, 45.3, 45.1, 44.2, 35.3, 35.20, 35.18, 34.5, 34.3, 33.5, 33.02, 32.96, 32.85, 32.78, 32.4, 31.5, 30.4, 29.5, 28.6, 27.9, 26.6, 26.3, 25.6, 23.8, 12.89, 12.85, 12.82 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{20}H_{29}O_3$ (M^+ + H): 317.2111. Found: 317.2114.

Attempted preparation of 2-(2-(1,3-dioxolan-2-yl)-4-ethylidenecyclohexyl)ethan-1-ol, **225**.



Chemical Formula: $C_{13}H_{22}O_3$
Molecular Weight: 226.32

General procedure J

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane**, 224** (a) and DCM (b). This solution was held at the allocated temperature (c) and the Lewis acid reagent (d) was added dropwise. The reaction mixture was then allowed to stir for the allotted time (e). The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Regrettably, the desired product 2-(2-(1,3-dioxolan-2-yl)-4-ethylidenecyclohexyl)ethan-1-ol, **225** was not formed.

Scheme 2.35, **Table 2.10**, **Entries 1 & 2**

The following experiments were performed using **General procedure J**. Results are reported as: (a) amount of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dioxolane, **224**, (b) volume of DCM, (c) temperature, (d) Lewis acid reagent employed and volume used, and (e) time.

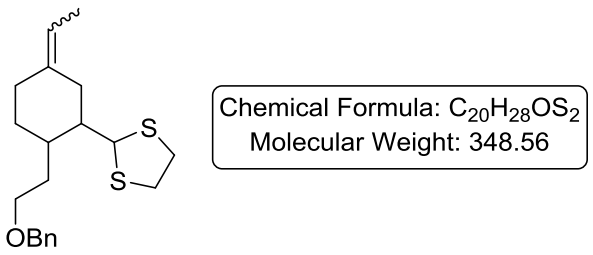
Entry 1: (a) 142 mg, 0.45 mmol, (b) 1.5 mL, (c) r.t., (d) $BCl_3{\cdot}SMe_2$, 0.45 mL, 0.90 mmol, and (e) 4 h.

Entry 2: (a) 100 mg, 0.32 mmol, (b) 1 mL, (c) -78 °C, (d) $BCl_3 \cdot SMe_2$, 0.45 mL, 0.90 mmol, and (e) 4 h.

Entry 3: (a) 100 mg, 0.32 mmol, (b) 3.5 mL, (c) r.t., (d) TMSI, 0.06 mL, 0.42 mmol, and (e) 6 h.

Entry 4: (a) 50 mg, 0.16 mmol, (b) 2 mL, (c) -78 °C, (d) TMSI, 0.03 mL, 0.21 mmol, and (e) 2 h.

Attempted preparation of 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dithiolane, **226**.



General procedure K

To a flame dried, round bottom flask fitted with a condenser, a magnetic stirrer bar, and an argon inlet was added the starting substrate (a) in DCM (b) and the solution was then cooled to 0 °C. To the reaction mixture was added 1,2-ethanedithiol (c) and $BF_3 \cdot OEt_2$ (d), and the mixture was then allowed to warm to r.t. and stirred for the allotted time (e). After this time, the reaction mixture was extracted with Et_2O (30 ml × 3) and washed with 1 M NaOH (25 ml). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Regrettably, the desired product 2-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-1,3-dithiolane **226** was not observed.

Scheme 2.36

The following experiments were performed using **General procedure K**. Results are reported as: (a) amount of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217**, (b) volume of DCM, (c) volume of 1,2-ethanedithiol, (d) volume of $BF_3.OEt_2$, and (e) time.

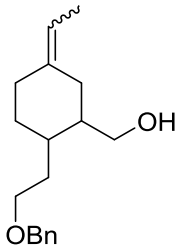
Run 1: (a) 200 mg, 0.73 mmol, (b) 4 mL, (c) 0.09 mL, 1.10 mmol, (d) 0.14 mL, 1.10 mmol, and (e) 16 h.

Scheme 2.37

The following experiments were performed using **General procedure K**. Results are reported as: (a) amount of 1-(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)-N-(pyrrolidin-1-yl)methanimine, **216**, (b) volume of DCM, (c) volume of 1,2-ethanedithiol, (d) volume of $BF_3 \cdot OEt_2$, and (e) time.

Run 1: (a) 150 mg, 0.55 mmol, (b) 3 mL, (c) 0.07 mL, 0.83 mmol, (d) 0.10 mL, 0.83 mmol, and (e) 19 h.

Preparation of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222**.



Chemical Formula: $C_{18}H_{26}O_2$
Molecular Weight: 274.40

General procedure L

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217** (a) in MeOH (b). The solution was cooled to 0 °C and $NaBH_4$ (c) was added. The reaction mixture was then allowed to warm to r.t. and stirred for a further period of time (d). The reaction was quenched through addition of saturated aqueous $NaHCO_3$ solution (20 ml) and extraction was subsequently performed with Et_2O (30 ml × 3). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222** (e).

Scheme 2.39

The following experiments were performed using **General procedure L**. Results are reported as: (a) amount of 2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexane-1-carbaldehyde, **217**, (b) volume of MeOH, (c) amount of $NaBH_4$, (d) time, and (e) yield of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222** as a pale yellow oil.

Run 1: (a) 386 mg, 1.42 mmol, (b) 8 mL, (c) 81 mg, 2.13 mmol, (d) 4 h, and (e) 316 mg, 81 % yield.

Run 2: (a) 100 mg, 0.37 mmol, (b) 2 mL, (c) 21 mg, 0.56 mmol, (d) 16 h, and (e) 97 mg, 95 % yield.

(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222**, was isolated as a complex and inseparable mixture of isomers.

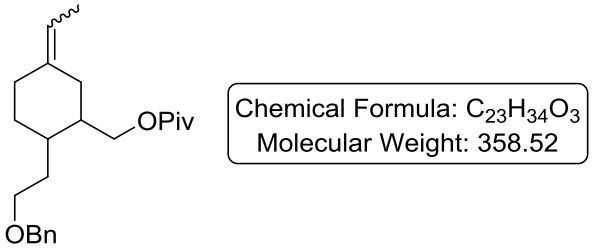
FTIR (**cm^{-1}**): 3401, 3063, 3030, 2918, 2859, 1452, 1362**,** 1096.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.37-7.26 (m, 5H, ArH), 5.27-5.15 (m, 1H, vinylic CH), 4.55-4.47 (m, 2H, $PhCH_2O$), 3.73-3.50 (m, 4H, $BnOCH_2$ + CH_2OH), 2.58-2.24 (m, 1H, alkyl CH), 2.21-2.08 (m, 1H, alkyl CH), 2.06-1.67 (m, 6H, alkyl CH) 1.60-1.46 (m, 4H, alkyl CH), 1.45-1.32 ppm (m, 1H, alkyl CH).

^{13}C NMR (**101 MHz, $CDCl_3$**): 138.8, 138.7, 138.4, 137.4, 137.3, 128.6, 127.91, 127.87, 117.3, 117.2, 116.1, 116.0, 73.3, 69.4, 68.9, 66.1, 65.5, 65.4, 62.8, 45.9, 45.1, 42.8, 42.4, 39.2, 37.4, 35.9, 35.58, 35.54, 35.1, 34.8, 34.7, 33.4, 33.1, 32.4, 31.0, 30.6, 30.5, 30.3, 30.1, 28.8, 27.1, 25.7, 15.5, 12.85, 12.82 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{18}H_{27}O_2$ (M^+ + H): 275.2006. Found: 275.2008.

Preparation of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methyl pivalate, **227**.



General procedure M

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222** (a) in DCM (b). The solution was cooled to 0 °C and DMAP (c), Et_3N (d), and pivaloyl chloride (e) were added. The reaction mixture was allowed to warm to r.t. and stirred for a period of time (f). The reaction mixture was diluted with water (20 ml) and extracted with Et_2O (30 ml × 3). The combined organics were then washed with brine (40 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methyl pivalate, **227** (g).

Scheme 2.39

The following experiment was performed using **General procedure M**. Results are reported as: (a) amount of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222**, (b) volume of DCM, (c) amount of DMAP, (d) volume of Et_3N, (e) volume of pivaloyl chloride, (f) time, and (g) yield of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methanol, **222** as a pale yellow oil.

Run 1: (a) 95 mg, 0.36 mmol, (b) 10 mL, (c) 20 mg, 0.16 mmol, (d) 0.1 mL, 0.72 mmol, (e) 0.07 mL, 0.58 mmol, (f) 23 h, and (g) 110 mg, 85 % yield.

Run 2: (a) 892 mg, 3.02 mmol, (b) 30 mL, (c) 221 mg, 1.81 mmol, (d) 1.05 mL, 7.55 mmol, (e) 0.60 mL, 4.83 mmol, (f) 16 h, and (g) 1.07 g, 99 % yield.

(2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methyl pivalate, **227**, was isolated as a complex and inseparable mixture of isomers.

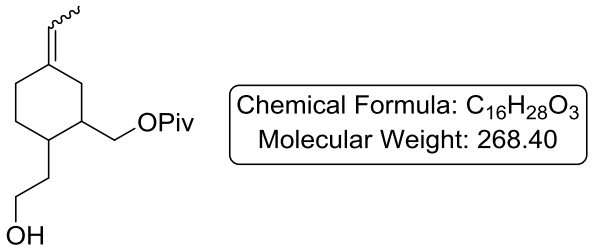
FTIR (**cm^{-1}**): 3063, 3030, 2970, 2927, 2860, 1726, 1479, 1454, 1283, 1155, 1101.

^{1}H NMR (**400 MHz, $CDCl_3$**): 7.34-7.27 (m, 5H, ArH), 5.31-5.10 (m, 1H, vinylic CH), 4.52-4.46 (m, 2H, $PhCH_2O$), 4.16-3.82 (m, 2H, $PivOCH_2$), 3.57-3.48 (m, 2H, $BnOCH_2$), 2.58-2.40, (m, 1H, alkyl CH), 2.27-2.11 (m, 1H, alkyl CH), 2.09-1.76 (m, 4H, alkyl CH), 1.73-1.46 (m, 7H, alkyl CH), 1.22-1.18 ppm (m, 9H, alkyl CH_3).

^{13}C NMR (**101 MHz, $CDCl_3$**): 178.8, 178.72, 178.67, 178.63, 138.7, 137.9, 136.1, 136.0, 128.5, 127.75, 127.69, 127.65, 127.62, 118.3, 118.0, 116.54, 116.48, 73.0, 68.6, 68.5, 68.4, 66.9, 66.8, 63.8, 63.6, 42.7, 42.0, 39.1, 39.0, 38.90, 38.87, 38.5, 38.2, 35.81, 35.76, 35.53, 35.48, 35.36, 32.92, 32.87, 32.3, 32.0, 31.6, 31.4, 30.3, 30.2, 29.5, 29.1, 27.4, 27.2, 26.8, 26.7, 26.4, 12.89, 12.85, 12.82, 12.76 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{23}H_{35}O_3$ (M^+ + H): 359.2581. Found: 359.2584.

Preparation of (5-ethylidene-2-(2-hydroxyethyl)cyclohexyl)methyl pivalate, **228**.



General procedure N

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methyl pivalate, **227** (a) in DCM (b). To this solution was added $BCl_3 \cdot SMe_2$ (c) dropwise and the reaction mixture was then allowed to stir at r.t. for the allotted time (d). The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 ml) and extracted with Et_2O (25 ml × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (5-ethylidene-2-(2-hydroxyethyl)cyclohexyl)methyl pivalate, **228** (e).

Scheme 2.39

The following experiments were performed using **General procedure N**. Results are reported as: (a) amount of (2-(2-(benzyloxy)ethyl)-5-ethylidenecyclohexyl)methyl pivalate, **227** (b) volume of DCM, (c) volume of $BCl_3 \cdot SMe_2$, (d) time, and (e) yield of (5-ethylidene-2-(2-hydroxyethyl)cyclohexyl)methyl pivalate, **228** as a pale yellow oil.

Run 1: (a) 120 mg, 0.33 mmol, (b) 1 mL, (c) 0.33 mL, 0.66 mmol, (d) 4 h, and (e) 45 mg, 51 % yield.

Run 2: (a) 300 mg, 0.84 mmol, (b) 3 mL, (c) 0.84 mL, 1.68 mmol, (d) 2 h, and (e) 189 mg, 84 % yield.

(5-ethylidene-2-(2-hydroxyethyl)cyclohexyl)methyl pivalate, **228**, was isolated as a complex and inseparable mixture of isomers.

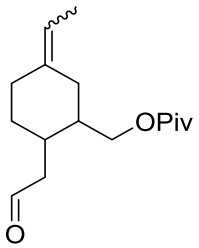
FTIR (**cm^{-1}**): 3445, 2926, 2872, 1728, 1285, 1157, 1055, 1034.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.32-5.12 (m, 1H, vinylic C<u>H</u>), 4.15-3.82 (m, 2H, OC<u>H</u>), 3.78-3.63 (m, 2H, OC<u>H</u>), 2.60-2.41 (m, 1H, alkyl C<u>H</u>), 2.28-2.12 (m, 1H, alkyl C<u>H</u>), 2.11-2.01 (m, 1H, alkyl C<u>H</u>), 1.96-1.74 (m, 3H, alkyl C<u>H</u>), 1.66-1.44 (m, 7H, alkyl C<u>H</u>), 1.21-1.19 ppm (m, 9H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 178.81, 178.76, 178.73, 137.82, 137.80, 118.3, 118.1, 116.6, 116.5, 66.9, 66.8, 63.9, 63.7, 61.3, 61.2, 60.89, 60.87, 42.9, 42.1, 39.2, 39.1, 38.94, 38.90, 38.7, 38.2, 36.2, 36.1, 35.6, 35.5, 35.4, 35.2, 35.1, 34.6, 32.5, 31.6, 30.4, 30.3, 29.5, 29.2, 27.4, 26.8, 26.4, 12.84, 12.79, 12.76, 12.7 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{16}H_{29}O_3$ (M^+ + H): 269.2111. Found: 269.2113.

Preparation of (5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197**.



Chemical Formula: $C_{16}H_{26}O_3$
Molecular Weight: 266.38

Scheme 78

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(2-hydroxyethyl)cyclohexyl)methyl pivalate, **228**

(100 mg, 0.37 mmol) in DCM (4 ml). To this solution, was added DMP (174 mg, 0.41 mmol) and the reaction mixture was allowed to stir for 1 h at r.t. The reaction mixture was quenched with a 1:1 mixture of 10 % aqueous $Na_2S_2O_3$ solution (10 ml) and saturated aqueous $NaHCO_3$ solution (10 ml). Subsequent extraction was performed with Et_2O (30 ml × 3) and the combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197** (99 mg, Quant. yield) as a pale yellow oil.

(5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197**, isolated as a complex and inseparable mixture of isomers.

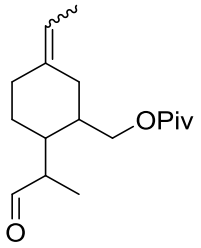
FTIR (**cm^{-1}**): 2959, 2920, 2872, 1742, 1479, 1283, 1150, 1034.

^{1}H NMR (**400 MHz, $CDCl_3$**): 9.78-9.75 (m, 1H, C<u>H</u>O), 5.31-5.13 (m, 1H, vinylic C<u>H</u>), 4.09-3.85 (m, 2H, PivOC<u>H</u>), 2.73-2.28 (m, 3H, alkyl C<u>H</u>), 2.27-1.91 (m, 4H, alkyl C<u>H</u>), 1.86-1.67 (m, 1H, alkyl C<u>H</u>), 1.62-1.30 (m, 5H, alkyl C<u>H</u>), 1.21-1.18 ppm (m, 9H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**100 MHz, $CDCl_3$**): 202.1, 201.9, 201.8, 201.7, 178.7, 178.6, 137.0, 135.2, 135.1, 118.8, 118.5, 117.2, 117.1, 66.6, 66.5, 66.1, 66.0, 64.0, 63.7, 48.0, 47.9, 46.2, 45.8, 42.7, 41.9, 39.3, 39.1, 39.0, 38.90, 38.88, 38.8, 37.9, 35.4, 34.9, 33.9, 33.8, 33.5, 33.4, 33.0, 32.7, 32.6, 31.8, 31.1, 30.5, 30.4, 29.3, 27.3, 25.9, 24.3, 24.2, 23.5, 12.9, 12.83, 12.78 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{16}H_{27}O_3$ (M^+ + H): 267.1955. Found: 267.1957.

Attempted preparation of (5-ethylidene-2-(1-oxopropan-2-yl)cyclohexyl)methyl pivalate, **229**.

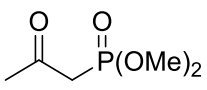


Chemical Formula: $C_{17}H_{28}O_3$
Molecular Weight: 280.41

Scheme 2.41

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (0.09 mL, 0.61 mmol) and THF (6 mL). The solution was then cooled to 0 °C and slow addition of *n*-BuLi (0.28 mL, 0.58 mmol, 2.0 M in hexanes) was performed. The resulting solution was stirred at 0 °C for 15 min then cooled to -78 °C. A mixture of (5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197** (100 mg, 0.38 mmol) in THF (2 mL) was added slowly before allowing the solution to warm to r.t. and stirring for a further 1 h. The mixture was then cooled to -78 °C and MeI (0.04 mL, 0.61 mmol) was added dropwise. Upon complete addition, the mixture was allowed to warm to r.t., where it was stirred for 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Regrettably, the desired product was not detected.

Preparation of dimethyl (2-oxopropyl)phosphonate, **233**.[184]



Chemical Formula: $C_5H_{11}O_4P$
Molecular Weight: 166.11

Scheme 2.43

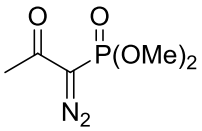
To a flame dried, round bottom flask fitted with a reflux condenser, magnetic stirrer bar, and an argon inlet was added chloroacetone **232** (12.90 mL, 162.02 mmol) and trimethyl phosphite (20.10 g, 162.02 mmol) in a mixture of MeCN (45 mL) and acetone (39 mL). To this mixture was slowly added KI (26.90 g, 162.02 mmol) and the reaction mixture was then stirred at r.t. for 6 h. Following this, the reaction mixture was heated to 50 °C and stirred for a further 4 h. The mixture was then filtered through a pad of celite, which was washed thoroughly with Et_2O. The organics were then concentrated *in vacuo* and the crude material was purified *via* fractional distillation (b.p. ca. 84 °C/1 mbar) to give dimethyl (2-oxopropyl)phosphonate, **233** (10.24 g, 38 % yield) as a colourless oil.

FTIR (**cm^{-1}**): 2958, 2855, 1712, 1360, 1251, 1060.

^{1}H NMR (**400 MHz, $CDCl_3$**): 3.76 (d, 6H, $J_{P\text{-}H}$ = 11.2 Hz, OC$\underline{H}_3$), 3.07 (d, 2H, $^{2}J_{P\text{-}H}$ = 22.8 Hz, alkyl C$\underline{H}_2$), 2.29 ppm (s, 3H, alkyl C$\underline{H}_3$)**.**

^{13}C NMR (**101 MHz, $CDCl_3$**): 199.7 (d, $^{2}J_{C\text{-}P}$ = 6.0 Hz), 53.1 (d, $^{2}J_{C\text{-}P}$ = 6.7 Hz), 42.3 (d, $^{1}J_{C\text{-}P}$ = 128.0 Hz), 31.5 ppm.

Preparation of dimethyl (1-diazo-2-oxopropyl)phosphonate, **235**.[201]



Chemical Formula: $C_5H_9N_2O_4P$
Molecular Weight: 192.11

General procedure O

To a flame dried, round bottom flask fitted with a reflux condenser, magnetic stirrer bar, and an argon inlet was added dimethyl (2-oxopropyl)phosphonate, **233** (a) in PhMe (b). The reaction mixture was cooled to 0 °C and sodium hydride (60 % dispersion in mineral oil) (c) was added in portions. The reaction mixture was then stirred for 1 h. After this time, a mixture of 4-acetamidobenzenesulfonyl azide **234**

(d) in THF (e) was then added to the reaction mixture through dropwise addition. The mixture was allowed to warm to r.t. and stirred for a further time period (f). The reaction mixture was diluted with petroleum ether (40 mL), and then filtered through a pad of celite, which was washed thoroughly with Et_2O. The organics were then concentrated *in vacuo* and the crude material was purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give dimethyl (1-diazo-2-oxopropyl)phosphonate, **235** (g).

Scheme 2.43

The following experiments were performed using **General procedure O**. Results are reported as: (a) amount of dimethyl (2-oxopropyl)phosphonate, **233** (b) volume of PhMe, (c) amount of sodium hydride (60 % dispersion in mineral oil), (d) amount of 4-acetamidobenzenesulfonyl azide **234**, (e) volume of THF, (f) time, and (g) yield of dimethyl (1-diazo-2-oxopropyl)phosphonate, **235** as a yellow oil.

Run 1: (a) 2.80 g, 16.86 mmol, (b) 70 mL, (c) 742 mg, 18.55 mmol, (d) 4.57 g, 18.55 mmol, (e) 18 mL, (f) 20 h, and (g) 2.72 g, 84 % yield.

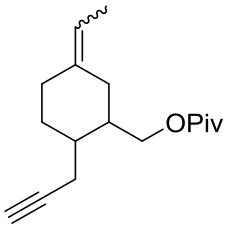
Run 2: (a) 2.00 g, 12.04 mmol, (b) 50 mL, (c) 530 mg, 13.24 mmol, (d) 3.26 g, 13.24 mmol, (e) 14 mL, (f) 16 h, and (g) 2.22 g, 96 % yield.

FTIR (cm^{-1}): 2959, 2855, 2118, 1655, 1364, 1265, 1242, 1179, 1165, 1013.

^{1}H NMR (**400 MHz, $CDCl_3$**): 3.82 (d, 6H, $J_{P\text{-}H}$ = 11.8 Hz, OC$\underline{H}_3$), 2.24 ppm (s, 3H, alkyl C$\underline{H}_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 189.9 (d, $^2J_{C\text{-}P}$ = 13.2 Hz), 124.3 (d, $^1J_{C\text{-}P}$ = 950.3 Hz), 53.6 (d, $^2J_{C\text{-}P}$ = 5.9 Hz), 27.2 ppm.

Preparation of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230**.



Chemical Formula: $C_{17}H_{26}O_2$
Molecular Weight: 262.39

General procedure P

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197** (a) in MeOH (b) and the resulting solution was cooled to 0 °C. To this was added K_2CO_3 (c) followed by a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate, **235** (d) in MeOH (e) through dropwise addition. The reaction mixture was then warmed to r.t. and allowed to stir for a period of time (f). The reaction mixture was quenched with water (20 mL) and subsequent extraction was performed with Et_2O (30 mL × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230** (g).

Scheme 2.44

The following experiments were performed using **General procedure P**. Results are reported as: (a) amount of (5-ethylidene-2-(2-oxoethyl)cyclohexyl)methyl pivalate, **197**, (b) volume of MeOH, (c) amount of K_2CO_3, (d) amount of dimethyl (1-diazo-2-oxopropyl)phosphonate, **235**, (e) volume of MeOH, (f) time, and (g) yield of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230** as a pale yellow oil.

Run 1: (a) 549 mg, 2.06 mmol, (b) 17 mL, (c) 854 mg, 6.18 mmol, (d) 989 mg, 5.15 mmol, (e) 17 mL, (f) 20 h, and (g) 279 mg, 52 % yield.

Run 2: (a) 67 mg, 0.25 mmol, (b) 2 mL, (c) 104 mg, 0.75 mmol, (d) 121 mg, 0.63 mmol, (e) 2 mL, (f) 17 h, and (g) 49 mg, 74 % yield.

(5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230**, was isolated as a complex and inseparable mixture of isomers.

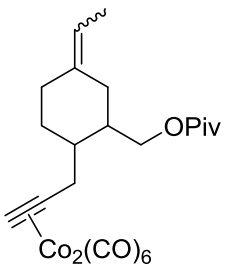
FTIR (**cm^{-1}**): 3296, 2970, 2920, 2872, 2361, 2342, 1727, 1459, 1283, 1159.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.31-5.12 (m, 1H, vinylic C<u>H</u>), 4.09-3.86 (m, 2H, PivOC<u>H</u>), 2.62-2.10 (m, 5H, alkyl C<u>H</u>), 2.09-1.75 (m, 4H, alkyl CH), 1.72-1.53 (m, 4H, alkyl C<u>H</u>), 1.48-1.32 (m, 1H, alkyl C<u>H</u>), 1.22-1.18 ppm (m, 9H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 178.7, 178.63, 178.58, 137.6, 135.6, 135.4, 118.6, 118.3, 116.9, 116.8, 83.3, 83.2, 82.3, 70.03, 70.02, 69.51, 69.46, 66.7, 66.6, 63.8, 63.5, 41.6, 40.8, 39.2, 39.0, 38.9, 38.8, 38.7, 38.43, 38.39, 38.1, 38.0, 35.6, 35.1, 32.7, 31.8, 30.4, 30.2, 29.8, 29.4, 28.7, 27.3, 27.0, 26.1, 22.7, 21.6, 21.3, 12.90, 12.85, 12.79 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{17}H_{27}O_2$ (M^+ + H): 263.2006. Found: 263.2006.

Preparation of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236**.



Chemical Formula: $C_{23}H_{26}Co_2O_8$
Molecular Weight: 548.32

General procedure Q

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230** (a) in petroleum ether (30-40 b.p.) (b). To the resulting solution was added Co_2CO_8 (c) and the reaction mixture was stirred at r.t. for the allocated time (d). The reaction mixture was then concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 15 % Et_2O in petroleum ether) to give (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236** (e).

Scheme 2.45

The following experiments were performed using **General procedure Q**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230**, (b) volume of petroleum ether (30-40 b.p.), (c) amount of Co_2CO_8, (d) time, and (e) yield of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236** as a brown oil.

Run 1: (a) 100 mg, 0.38 mmol, (b) 8 mL, (c) 137 mg, 0.40 mmol, (d) 5 h, and (e) 179 mg, 86 % yield.

Run 2: (a) 100 mg, 0.38 mmol, (b) 8 mL, (c) 137 mg, 0.40 mmol, (d) 3 h, an, (e) 196 mg, 94 % yield.

(5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236**, was isolated as a complex and inseparable mixture of isomers.

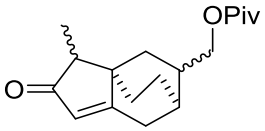
FTIR (**cm^{-1}**): 2972, 2932, 2874, 2361, 2342, 2091, 2046, 2006, 1728, 1458, 1283, 1153.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.09-6.06 (m, 1H, complexed alkyne C<u>H</u>), 5.36-5.15 (m, 1H, vinylic C<u>H</u>), 4.19-3.88 (m, 2H, PivOC<u>H</u>), 3.33-2.47 (m, 3H, alkyl C<u>H</u>), 2.29-2.12 (m, 2H, alkyl C<u>H</u>), 2.08-1.79 (m, 3H, alkyl C<u>H</u>), 1.78-1.50 (m, 4H, alkyl CH), 1.47-1.37 (m, 1H, alkyl C<u>H</u>), 1.28-1.17 ppm (m, 9H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 200.0, 178.72, 178.69, 137.0, 135.1, 135.0, 119.1, 118.9, 117.3, 117.2, 74.5, 74.32, 74.28, 66.6, 66.5, 63,4, 63.1, 42.7, 41.8, 41.5, 40.93, 40.86, 39.0, 38.9, 38.7, 38.5, 38.20, 38.16, 37.9, 35.4, 34.7, 32.1, 31.2, 29.9, 29.8, 29.5, 28.6, 27.4, 26.4, 26.2, 12.95, 12.91, 12.83 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{23}H_{30}Co_2O_8N$ ($M^+ + NH_4$): 566.0630. Found: 566.0625.

Attempted preparation of ((3*a*,6)-3-methyl-2-oxo-2,3,4,5,6,7-hexahydro-3*a*,6-ethanoinden-5-yl)methyl pivalate, **231**.



Chemical Formula: $C_{18}H_{26}O_3$
Molecular Weight: 290.40

General procedure R

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, argon inlet and a condenser was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236** (a) in DCE (b). To the resulting solution was added DodSMe (c) and the mixture was then heated to reflux and stirred for the allotted time (d). The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) however only SM, **236** (e) and decomplexed alkyne **230** (f) were returned. The desired product, **231**, was not formed.

General procedure S

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236** (a) in DCM (b). The resulting solution was stirred held at allocated temperature (c) and amine *N*-oxide (d) was added, followed by further stirring for (e). The reaction was monitored and the temperature was varied as required. The reaction mixture was filtered through celite and concentrated *in vacuo*. Unfortunately, the desired product, **231**, failed to form.

Scheme 2.46, Table 2.11, Entries 1 & 2

The following experiments were performed using **General procedure R**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236**, (b) volume of DCE, (c) volume of DodSMe, (d) time, (e) yield of SM, **236**, and (f) yield of decomplexed alkyne **230**.

Entry 1: (a) 100 mg, 0.18 mmol, (b) 4 mL, (c) 0.24 mL, 0.90 mmol, (d) 72 hours, (e) 21 mg, 21 % yield, and (f) 6 mg, 12 % yield.

Entry 2: (a) 403 mg, 0.74 mmol, (b) 17 mL, (c) 0.91 mL, 3.74 mmol, (d) 216 h, (e) 56 mg, 14 % yield, and (e) 17 mg, 9 % yield.

Scheme 2.46, Table 2.11, Entries 3, & 4

The following experiments were performed using **General procedure S**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236**, (b) volume of DCM, (c) temperature, (d) amount of NMO.H_2O, and (e) time.

Entry 3: (a) 180 mg, 0.33 mmol, (b) 5 mL, (c) r.t., (d) 303 mg, 2.24 mmol, and, (e) 2 h.

Entry 4: (a) 180 mg, 0.33 mmol, (b) 5 mL, (c) -78 °C for 4 h, allowed to warm to 0 °C and stirred for 3 h, then allowed to warm to r.t. (d) 303 mg, 2.24 mmol, and (e) 1 h.

Scheme 2.46, Table 2.11, Entry 5

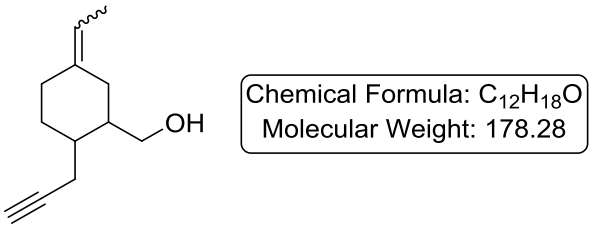
The following experiment was performed using **General procedure S**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate dicobalthexacarbonyl complex, **236**, (b) volume of DCM, (c) temperature, (d) amount of TMANO.$2H_2O$, and (e) time.

Entry 5: (a) 180 mg, 0.33 mmol, (b) 5 mL, (c) -78 °C for 4 h, allowed to warm to 0 °C and stirred for 3 h, then allowed to warm to r.t. (d) 249 mg, 2.24 mmol, and (e) 1 h.

Scheme 2.47

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, an argon inlet and a condenser was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230** (50 mg, 0.19 mmol) in DCE (5 mL). To the resulting solution was added Co_2CO_8 (68 mg, 0.20 mmol) and the mixture was stirred at r.t. for 3 h. DodSMe (206 mg, 0.95 mmol) was added and the mixture was then heated to reflux and stirred for 120 h. The reaction mixture was then filtered through celite and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) however only complexed alkyne, **236**, (26 mg, 25 % yield) was returned, and the desired product, **231**, was not formed.

Preparation of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol, **237**.



Scheme 2.49

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, an argon inlet and a condenser, was added $LiAlH_4$ (19 mg, 0.49 mmol) and THF (1 mL), this suspension was then cooled to 0 °C. To this was added a mixture of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methyl pivalate, **230**, (108 mg, 0.41 mmol) and THF (1 mL). The mixture was stirred at 0 °C for 1 h, then allowed to warm to r.t. and stirred for a further 2 h. The mixture was cooled to 0 °C and quenched through slow addition of saturated aqueous Na_2SO_4 solution. The mixture was filtered and the residue was thoroughly washed with Et_2O. The filtrate was then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 70 % Et_2O in petroleum ether) to give (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol, **237**, (65 mg, 89 % yield) as a colourless oil.

(5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol, **237**, isolated as a complex and inseparable mixture of isomers.

FTIR (**cm^{-1}**): 3356, 3302, 2918, 2862, 2363, 2339, 1445, 1026.

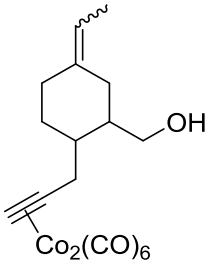
^{1}H NMR (**400 MHz, $CDCl_3$**): 5.27-5.15 (m, 1H, vinylic C<u>H</u>), 3.66-3.44 (m, 2H, C<u>H</u>OH), 2.60-2.31 (m, 1H, alkyl C<u>H</u>), 2.29-2.08 (m, 3H, alkyl C<u>H</u>), 2.07-1.80 (m, 5H, alkyl C<u>H</u>), 1.78-1.53 (m, 4H, alkyl C<u>H</u>), 1.50-1.39 ppm (m, 1H, alkyl C<u>H</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 138.13, 138.06, 136.6, 136.5, 117.8, 117.7, 116.43, 116.35, 83.8, 82.0, 69.8, 69.4, 65.3, 65.2, 62.35, 62.28, 44.6, 43.8, 41.8, 41.4, 38.9,

37.9, 37.7, 37.54, 37.50, 35.7, 34.7, 33.0, 32.0, 30.4, 30.2, 29.4, 28.8, 27.0, 25.7, 22.79, 22.77, 20.9, 20.7, 12.8 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{12}H_{19}O$ (M^+ + H): 179.1430. Found: 179.1426.

Preparation of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex, **239**.



Chemical Formula: $C_{18}H_{18}Co_2O_7$
Molecular Weight: 464.20

Scheme 2.49

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol, **237**, (70 mg, 0.39 mmol) in petroleum ether (10 mL). To the resulting solution was added Co_2CO_8 (140 mg, 0.41 mmol) and the reaction mixture was stirred at r.t. for 3 h. The reaction mixture was concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 20 % Et_2O in petroleum ether) to give (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex, **239**, (172 mg, 95 % yield) as a brown oil.

(5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex, **239**, isolated as a complex and inseparable mixture of isomers.

FTIR (**cm^{-1}**): 3325, 2920, 2862, 2361, 2332, 2089, 2045, 1994, 1445, 1030.

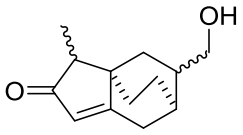
^{1}H NMR (**400 MHz, $CDCl_3$**): 6.07-6.03 (m, 1H, complexed alkyne C<u>H</u>), 5.32-5.20 (m, 1H, vinylic H), 3.74-3.57 (m, 2H, C<u>H</u>OH), 3.30-2.48 (m, 3H, alkyl C<u>H</u>), 2.34-

1.79 (m, 5H, alkyl C<u>H</u>), 1.70-1.50 (m, 4H, alkyl C<u>H</u>), 1.49-1.39 ppm (m, 1H, alkyl C<u>H</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 200.1, 137.6, 137.5, 136.4, 136.3, 118.3, 118.2, 116.9, 116.8, 95.5, 95.4, 74.31, 74.26, 65.5, 65.4, 62.20, 62. 15, 45.1, 44.3, 42.0, 41.7, 41.5, 41.3, 40.7, 40.6, 38.8, 38.4, 38.0, 37.6, 37.4, 35.2, 34.9, 32.4, 31.4, 30.3, 29.7, 29.33, 29.27, 26.3, 12.9, 12.8 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{18}H_{19}Co_2O_7$ (M^+ + H): 464.9789. Found: 464.9781.

Attempted preparation of (3*a*,6)-5-(hydroxymethyl)-3-methyl-4,5,6,7-tetrahydro-3*a*,6-ethanoinden-2(3*H*)-one, **238**.



Chemical Formula: $C_{13}H_{18}O_2$
Molecular Weight: 206.29

General procedure T

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex **239** (a) in DCM (b). The resulting solution was stirred at held at allocated temperature (c) and amine *N*-oxide (d) was added, followed by further stirring for (e), The reaction was monitored and the temperature was varied as required. The reaction mixture was filtered through celite and concentrated *in vacuo*. The desired product, **238**, was not formed.

Scheme 2.50, **Table 2.12**, **Entry 1**

The following experiment was performed using **General procedure T**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex, **239**, (b) volume of DCM, (c) temperature, (d) amount of $NMO{\cdot}H_2O$, and (e) time.

Entry 1: (a) 90 mg, 0.19 mmol, (b) 6 mL, (c) -78 °C for 5 h, allowed to warm to 0 °C and stirred for 2 h, then allowed to warm to r.t., (d) 180 mg, 1.33 mmol, and (e) 2 h.

Scheme 2.50, **Table 2.12**, **Entry 2**

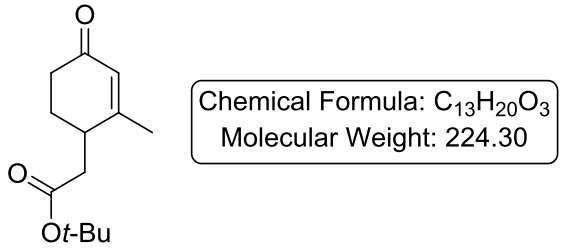
The following experiment was performed using **General procedure T**. Results are reported as: (a) amount of (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol dicobalthexacarbonyl complex, **239**, (b) volume of DCM, (c) temperature, (d) amount of TMANO·$2H_2O$, and (e) time.

Entry 2: (a) 80 mg, 0.17 mmol, (b) 6 mL, (c) -78 °C for 6 h, allowed to warm to 0 °C and stirred for 2 h, then allowed to warm to r.t., (d) 132 mg, 1.19 mmol, and (e) 1 h.

Scheme 2.51

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, an argon inlet and a condenser was added (5-ethylidene-2-(prop-2-yn-1-yl)cyclohexyl)methanol, **237**, (50 mg, 0.29 mmol) in DCE (7 mL). To the resulting solution was added Co_2CO_8 (100 mg, 0.29 mmol) and the mixture was stirred at r.t. for 3 h. DodSMe (0.25 mL, 0.95 mmol) was added and the mixture was then heated to reflux and stirred for 144 h. The reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) however only SM, **236**, (7 mg 14 % yield) and complexed alkyne **239** (16 mg, 12 % yield) were returned, and the desired product, **238**, was not formed.

Attempted preparation of *tert*-butyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **241**.



General procedure U

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added *tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **205** (a) and THF (b). Slow addition of the organometallic reagent (c) was then performed at 0 °C. The solution was then stirred for 1 h, before warming to r.t. and stirring for a further (d). The mixture was cooled to 0 °C and 2 M HCl (e) was added with stirring for a further period of time (f). The mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Unfortunately, the desired product, *tert*-butyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **241** had failed to form.

Scheme 2.55, **Table 2.13**

The following experiment was performed using **General procedure U**. Results are reported as: (a) amount of (*tert*-butyl 2-(4-ethoxy-2-oxocyclohex-3-en-1-yl)acetate, **205**, (b) volume of THF, (c) organometallic reagent employed and volume used, (d) time, (e) volume of 2 M HCl, and, (f) time.

Entry 1: (a) 300 mg, 1.18 mmol, (b) 4 mL, (c) MeMgCl (3.0 M in THF), 0.47 mL, 1.42 mmol, (d) 2 h, (e) 1 mL, and, (f) 3 h.

Entry 2: (a) 300 mg, 1.18 mmol, (b) 4 mL, (c) MeMgBr (3.0 M in Et_2O), 0.47 mL, 1.42 mmol, (d) 2 h, (e) 1 mL, and, (f) 2 h.

Entry 3: (a) 300 mg, 1.18 mmol, (b) 4 mL, (c) MeMgBr (3.0 M in Et_2O), 0.79 mL, 2.36 mmol, (d) 3 h, (e) 1 mL, and, (f) 2 h.

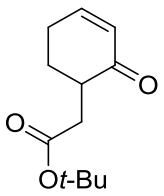
Entry 4: (a) 300 mg, 1.18 mmol, (b) 4 mL, (c) MeMgBr (3.0 M in Et_2O), 1.18 mL, 3.54 mmol, (d) 3 h, (e) 1 mL, and, (f) 1 h.

Entry 5: (a) 200 mg, 0.79 mmol, (b) 2 mL, (c) MeLi·LiBr (1.5 M in Et_2O), 0.84 mL, 1.26 mmol, (d) 3 h, (e) 0.6 mL, (f) 3 h.

Entry 6: (a) 200 mg, 0.79 mmol, (b) 2 mL, (c) MeLi·LiBr (1.5 M in Et_2O), 1.05 mL, 1.58 mmol, (d) 4 h, (e) 0.6 mL, (f) 3 h.

Entry 7: (a) 250 mg, 0.98 mmol, (b) 2 mL, (c) MeLi·LiBr (1.5 M in Et_2O), 1.70 mL, 2.55 mmol, (d) 1 h, (e) 0.6 mL, (f) 2 h.

Preparation of *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247**.



Chemical Formula: $C_{12}H_{18}O_3$
Molecular Weight: 210.27

General procedure V

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (a) and THF (b). The solution was then cooled to 0 °C and slow addition of *n*-BuLi (c) was performed. The resulting solution was stirred at 0 °C for 15 min then cooled to -78 °C. A mixture of 2-cyclohexen-1-one **246** (d) in THF (e) was introduced *via* dropwise addition, with the resulting mixture stirred at -78 °C for a further 1 h. Finally, *tert*-butyl 2-bromoacetate, **204** (f) was slowly added and the reaction mixture was allowed to stir for the allocated time (g) at the specified temperature (h). The reaction was quenched through addition of saturated aqueous NH_4Cl solution (50 mL) and extraction was subsequently performed with Et_2O (50 mL × 3). The combined organics were washed with water (50 mL × 2) and brine (50 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247**, (i).

Scheme 2.57, **Table 2.14**

The following experiments were performed using **General procedure V**. Results are reported as: (a) volume of DIPA, (b) volume of THF, (c) volume of *n*-BuLi, (d) volume of 2-cyclohexen-1-one **246**, (e) volume of THF, (f) volume of *tert*-butyl 2-bromoacetate, **204**, (g) time, (h) temperature, and, (i) yield of *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247** as a colourless oil.

Entry 1: (a) 0.87 mL, 6.24 mmol, (b) 2 mL, (c) 2.93 mL, 5.72 mmol, 1.95 M, (d) 0.50 mL, 5.20 mmol, (e) 2 mL, (f) 0.96 mL, 6.50 mmol, (g) 16 h, and, (h) r.t., and (i) 0 mg, 0 % yield.

Entry 2: (a) 0.95 mL, 6.76 mmol, (b) 8 mL, (c) 3.2 mL, 6.24 mmol, 1.95 M, (d) 0.50 mL, 5.20 mmol, (e) 7 mL, (f) 1.54 mL, 10.40 mmol, (g) 17 h, (h) r.t., and (i) 190 mg, 17 % yield.

Entry 3: (a) 0.95 mL, 6.76 mmol, (b) 8 mL, (c) 3.2 mL, 6.24 mmol, 1.95 M, (d) 0.50 mL, 5.20 mmol, (e) 7 mL, (f) 1.54 mL, 10.40 mmol, (g) 2 h, (h) -78 °C, and (i) 812 mg, 74 % yield.

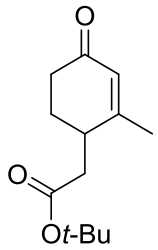
FTIR (**cm^{-1}**): 2976, 2932, 2872, 1724, 1678, 1368, 1146, 1126.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.96-6.91 (m, 1H, vinylic C<u>H</u>), 6.00 (ddd, 1H, ^{3}J = 10.1 Hz, 2.9, ^{4}J = 1.2 Hz, vinylic C<u>H</u>), 2.83-2.75 (m, 2H, alkyl C<u>H</u>), 2.50-2.33 (m, 2H, alkyl C<u>H</u>), 2.21-2.14 (m, 1H, alkyl C<u>H</u>), 2.14-2.07 (m, 1H, alkyl C<u>H</u>), 1.84-1.74 (m, 1H, alkyl C<u>H</u>), 1.44 ppm (s, 9H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 198.8, 170.9, 148.9, 128.5, 79.6, 42.9, 34.9, 27.7, 27.2, 25.0 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{12}H_{19}O_3$ (M^+ + H): 211.1329. Found: 211.1326.

Attempted preparation of *tert*-butyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **241**.



Chemical Formula: $C_{13}H_{20}O_3$
Molecular Weight: 224.30

General procedure W

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247** (a) and Et_2O (b). Slow addition of MeLi·LiBr complex (c) was then performed at 0 °C and the mixture was stirred for 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude material was then dissolved in a solution of DCM (d) which was cooled to 0 °C. To this mixture was added compound (e), the mixture was then allowed to warm to r.t. and stirred for a further (f). The mixture was diluted with Et_2O (30 mL) and celite was added, the mixture was then filtered and the residue was thoroughly washed with Et_2O. The filtrate was concentrated *in vacuo* and the crude material purified *via* column chromatography (petroleum ether to 80 % Et_2O in petroleum ether). A complex mixture of unknown products was obtained along with SM, **247**, the desired product *tert*-butyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **241**, had failed to form.

General procedure X

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247** (a) and Et_2O (b). Slow addition of MeLi·LiBr complex (c) was then performed at 0 °C and the mixture was stirred for 2 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then dissolved in DMSO (d), IBX was added and the mixture was heated to 55 °C. The mixture was stirred at this temperature for (e), following cooling to r.t. water (20 mL) was added and the mixture was extracted with Et_2O (25 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 80 % Et_2O in petroleum ether). A complex mixture of unknown products was obtained along with SM, **247**, (f) the desired product *tert*-butyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **241**, was not formed.

Scheme 2.58, Table 2.15, Entries 1, & 2

The following experiments were performed using **General procedure W**. Results are reported as: (a) amount of *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247**, (b) volume of Et_2O, (c) volume of MeLi·LiBr complex, (d) volume of DCM, (e) oxidant employed and amount used, (f) time, and (g) amount of recovered SM, **247**.

Entry 1: (a) 500 mg, 2.38 mmol, (b) 30 mL, (c) 1.75 mL, 2.62 mmol, 1.5 M in Et_2O, (d) 50 mL (e) PCC, 617 mg, 2.86 mmol, (f) 6 h, and (g) 65 mg, 13 % recovered SM.

Entry 2: (a) 500 mg, 2.38 mmol, (b) 30 mL, (c) 2.54 mL, 3.81 mmol, 1.5 M in Et_2O, (d) 50 mL (e) PCC, 617 mg, 2.86 mmol, (f) 16 h, and (g) 45 mg, 9 % recovered SM.

Entry 3: (a) 250 mg, 1.19 mmol, (b) 15 mL, (c) 0.87 mL, 1.31 mmol, 1.5 M in Et_2O, (d) 24 mL (e) PDC, 538 mg, 1.43 mmol, (f) 6 h, and (g) 0 mg, 0 % recovered SM.

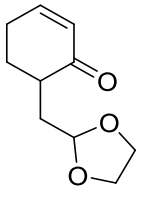
Scheme 2.58, Table 2.15, Entries 4 & 5

The following experiments were performed using **General procedure X**. Results are reported as: (a) amount of *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247**, (b) volume of Et_2O, (c) volume of MeLi·LiBr complex, (d) volume of DMSO, (e) amount of IBX, (f) time, and (g) amount of recovered SM, **247**.

Entry 4: (a) 120 mg, 0.57 mmol, (b) 7 mL, (c) 0.42 mL, 0.63 mmol, 1.5 M in Et_2O, (d) 3 mL (e) 319 mg, 1.14 mmol, (f) 16 h, and, (g) 28 mg, 23 % recovered SM.

Entry 5: (a) 140 mg, 0.66 mmol, (b) 8 mL, (c) 0.71 mL, 1.06 mmol, 1.5 M in Et_2O, (d) 3 mL (e) 554 mg, 1.98 mmol, (f) 6 h, and, (g) 0 mg, 0 % recovered SM.

Attempted preparation of 6-((1,3-dioxolan-2-yl)methyl)cyclohex-2-en-1-one, **249**.



Chemical Formula: $C_{10}H_{14}O_3$
Molecular Weight: 182.22

General procedure Y

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (a) and THF (b). The solution was then cooled to 0 °C and slow addition of *n*-BuLi (c) was performed. The resulting solution was stirred at 0 °C for 15 min then cooled to -78 °C. A mixture of 2-cyclohexen-1-one **246** (d) in THF (e) was introduced through dropwise addition, with the resulting mixture stirred at -78 °C for a further 1 h. Finally, 2-bromomethyl-1,3-dioxolane **248** (f) was slowly added and the reaction mixture was allowed to stir for allotted time (g) at the specified temperature (h). The reaction was quenched through addition of saturated aqueous NH_4Cl solution (50 mL) and extraction was subsequently performed with Et_2O (50 mL × 3). The combined organics were washed with water (50 mL × 2) and brine (50 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) however the desired product 6-((1,3-dioxolan-2-yl)methyl)cyclohex-2-en-1-one, **249**, was not obtained, with only SM, **246**, (i) recovered.

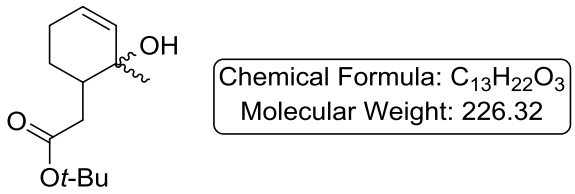
Scheme 2.59, **Table 2.16**

The following experiments were performed using **General procedure Y**. Results are reported as: (a) volume of DIPA, (b) volume of THF, (c) volume of *n*-BuLi, (d) volume of 2-cyclohexen-1-one **246**, (e) volume of THF, (f) volume of 2-bromomethyl-1,3-dioxolane **248**, (g) time, (h) temperature, and (i) amount of recovered SM, **246**.

Entry 1: (a) 0.95 mL, 6.76 mmol, (b) 8 mL, (c) 3.2 mL, 6.24 mmol, 1.95 M, (d) 0.50 mL, 5.20 mmol, (e) 7 mL, (f) 1.08 mL, 10.40 mmol, (g) 3 h, (h) -78 °C, and (i) 335 mg, 67 % recovered SM.

Entry 2: (a) 0.95 mL, 6.76 mmol, (b) 8 mL, (c) 3.2 mL, 6.24 mmol, 1.95 M, (d) 0.50 mL, 5.20 mmol, (e) 7 mL, (f) 1.08 mL, 10.40 mmol, (g) 7 h, (h) 0 °C, and (i) 210 mg, 42 % recovered SM.

Attempted preparation of *tert*-butyl 2-(2-hydroxy-2-methylcyclohex-3-en-1-yl)acetate, 250.



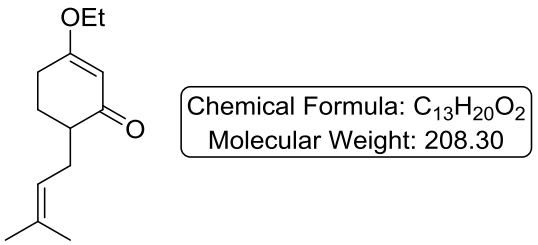
Scheme 2.60

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added *tert*-butyl 2-(2-oxocyclohex-3-en-1-yl)acetate, **247** (200 mg, 0.95 mmol) and Et_2O (9 mL). Slow addition of MeLi.LiBr complex (124 mg, 1.14 mmol) was then performed at 0 °C and the mixture was stirred for 3 h. The mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with Et_2O (25 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether). A compound with characteristic signals of the desired product *tert*-butyl 2-(2-hydroxy-2-methylcyclohex-3-en-1-yl)acetate, **250**, was isolated, however, it appeared that this material was decomposing. HRMS suggested that the product of dehydration was also present. No further characterisation was attempted.

Diagnostic peaks for 250

^{1}H NMR (400 MHz, $CDCl_3$): 5.65-5.61 (m, 1H, predicted vinylic C<u>H</u>), 5.57-5.53 (m, 1H, predicted vinylic C<u>H</u>), 1.42 (s, 9H, predicted alkyl C<u>H</u>$_3$), 1.12 ppm (s, 3H, predicted alkyl C<u>H</u>$_3$).

Preparation of 3-ethoxy-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **253**.[194]



General procedure Z

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (a) and THF (b). The solution was then cooled to 0 °C and slow addition of *n*-BuLi (c) was performed. The resulting solution was stirred at 0 °C for 15 mins then cooled to -78 °C. A mixture of 3-ethoxycyclohex-2-enone **189** (d) in THF (e) was introduced *via* dropwise addition, with the resulting mixture stirred at -78 °C for a further 1 h. Following this, TBAI (f) was added and the solution was stirred for 10 mins. Finally, 3,3-dimethylallyl bromide **252** (g) was slowly added and the reaction mixture was allowed to warm to r.t. and stirred for the allocated time (h). The reaction was quenched through addition of saturated aqueous NH_4Cl solution (50 mL) and extraction was subsequently performed with Et_2O (50 mL × 3). The combined organics were washed with saturated aqueous $NaHCO_3$ solution (30 mL), and brine (50 mL) before being dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to yield 3-ethoxy-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **253**, (i).

Scheme 2.63

The following experiments were performed using **General procedure Z**. Results are reported as: (a) volume of DIPA, (b) volume of THF, (c) volume of *n*-BuLi, (d) volume of 3-ethoxycyclohex-2-enone **189**, (e) volume of THF, (f) amount of TBAI, (g) volume of 3,3-dimethylallyl bromide **252**, (h) time, and (i) yield of 3-ethoxy-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **253** as a colourless oil.

Run 1: (a) 0.65 mL, 4.64 mmol, (b) 8 mL, (c) 2.04 mL, 4.28 mmol, 2.1 M, (d) 0.52 mL, 3.57 mmol, (e) 4 mL, (f) 790 mg, 2.14 mmol, (g) 0.50 mL, 4.29 mmol, (h) 18 h, and (i) 504 mg, 68 % yield.

Run 2: (a) 10.18 mL, 72.67 mmol, (b) 120 mL, (c) 31.94 mL, 67.08 mmol, 2.1 M, (d) 8.14 mL, 55.90 mmol, (e) 60 mL, (f) 12.39 g, 33.54 mmol, (g) 7.75 mL, 67.08 mmol, (h) 16 h, and (i) 11.55 g, 99 % yield.

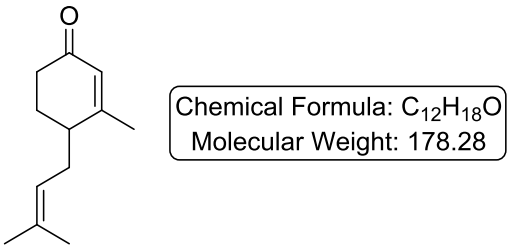
FTIR (**cm^{-1}**): 2980, 2932, 2866, 1653, 1605, 1377, 1186.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.30 (s, 1H, vinylic C<u>H</u>), 5.11-5.06 (m, 1H, vinylic C<u>H</u>), 3.90-3.83 (m, 2H, OC<u>H</u>$_2$CH$_3$), 2.54-2.47 (m, 1H, alkyl C<u>H</u>), 2.40-2.36 (m, 2H, alkyl C<u>H</u>), 2.21-2.14 (m, 1H, alkyl C<u>H</u>), 2.11-2.05 (m, 1H, alkyl C<u>H</u>), 2.04-1.98 (m, 1H, alkyl C<u>H</u>), 1.71-1.63 (m, 4H, alkyl C<u>H</u>), 1.59 (s, 3H, alkyl C<u>H</u>$_3$), 1.33 ppm (t, 3H, *J* = 7.3 Hz, OCH$_2$C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 200.2, 176.0, 132.4, 121.1, 101.4, 63.2, 44.7, 27.3, 27.1, 25.0, 24.9, 16.9, 13.2 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{13}H_{21}O_2$ (M^+ + H): 209.1536. Found: 209.1533.

Preparation of 3-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **251**.[202]



General procedure A'

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 3-ethoxy-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **253** (a) and THF (b). Slow addition of MeLi (c) was then performed at -78 °C and the mixture was stirred for 2 h before warming to r.t. and stirring for a further time period (d). The solution was then cooled to 0 °C and 2 M HCl (e) was added with stirring for a further time period (f). To the mixture was added 3 M NaOH solution (10 ml), the organics were then extracted with Et_2O (25 mL × 3). The combined organics washed with saturated aqueous $NaHCO_3$ solution and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 3-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **251**, (g).

Scheme 2.63

The following experiments were performed using **General procedure A'**. Results are reported as: (a) amount of 3-ethoxy-6-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **253**, (b) volume of THF, (c) volume of MeLi, (d) time, (e) volume of 2 M HCl, (f) time, and, (g) yield of 3-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **251** as a colourless oil.

Run 1: (a) 504 mg, 2.42 mmol, (b) 4 mL, (c) 2.00 mL, 3.20 mmol, 1.6 M (d) 2 h, (e) 2.5 mL, (f) 1 h, and, (g) 263 mg, 61 % yield.

Run 2: (a) 12.29 g, 59.02 mmol, (b) 84 mL, (c) 48.00 mL, 76.80 mmol, 1.6 M (d) 3 h, (e) 30 mL, (f) 2 h, and, (g) 9.60 g, 91 % yield.

FTIR (**cm^{-1}**): 2967, 2914, 2864, 1668, 1624, 1439, 1248.

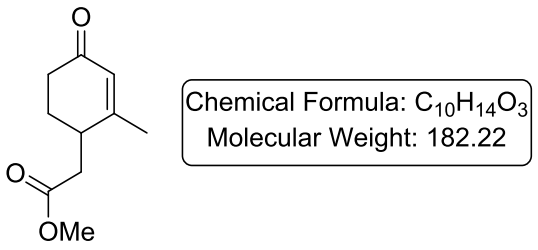
^{1}H NMR (**400 MHz, $CDCl_3$**): 5.77 (s, 1H, vinylic C<u>H</u>), 5.07-5.03 (m, 1H, vinylic C<u>H</u>), 2.40-2.32 (m, 1H, alkyl C<u>H</u>), 2.28-2.17 (m, 3H, alkyl C<u>H</u>), 2.14-2.06 (m, 1H,

alkyl C<u>H</u>), 1.99-1.93 (m, 1H, alkyl C<u>H</u>), 1.91 (s, 3H, alkyl C<u>H</u>$_3$), 1.84-1.76 (m, 1H, alkyl C<u>H</u>), 1.66 (s, 3H, alkyl C<u>H</u>$_3$), 1.56 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): 199.4, 165.6, 133.8, 126.9, 121.8, 40.0, 34.0, 29.7, 26.5, 25.8, 23.0, 17.8 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{12}H_{19}O$ (M^+ + H): 179.1430. Found: 179.1428.

Preparation of methyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **254**.



General procedure B'

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 3-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-one, **251** (a) 2.5 M methanolic NaOH (b), and DCM (c). This solution was cooled to -78 °C and ozone was bubbled through the reaction solution for a set period of time (d). The reaction mixture was then diluted with Et_2O (10 mL) and water (10 mL) and allowed to warm to r.t., before being extracted with Et_2O (25 mL × 3). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 80 % Et_2O in petroleum ether) to give methyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **254** (e), and recovered SM, **251** (f).

Scheme 2.64, **Table 2.17**

The following experiments were performed using **General procedure B'**. Results are reported as: (a) amount of 3-methyl-4-(3-methylbut-2-en-1-yl)cyclohex-2-en-1-

one, **251**, (b) volume of 2.5 M methanolic NaOH, (c) volume of DCM, (d) time, (e) yield of desired product, methyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **254** as a pale yellow oil, and (f) amount of recovered SM, **251**.

Entry 1: (a) 200 mg, 1.12 mmol, (b) 2.24 mL, 5.60 mmol (c) 9 mL, (d) 1 h, (e) 75 mg, 37 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 2: (a) 200 mg, 1.12 mmol, (b) 2.24 mL, 5.60 mmol, (c) 9 mL, (d) 30 min, (e) 25 mg, 14 % yield, and (f) 78 mg, 39 % recovered SM.

Entry 3: (a) 200 mg, 1.12 mmol, (b) 2.24 mL, 5.60 mmol, (c) 9 mL, (d) 45 min, (e) 66 mg, 32 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 4: (a) 200 mg, 1.12 mmol, (b) 4.48 mL, 11.2 mmol, (c) 9 mL, (d) 1 h, (e) 82 mg, 40 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 5: (a) 600 mg, 3.37 mmol, (b) 6.74 mL, 16.85 mmol, (c) 28 mL, (d) 2 h, (e) 324 mg, 53 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 6: (a) 1 g, 5.61 mmol, (b) 11.22 mL, 28.05 mmol, (c) 46 mL, (d) 2 h, (e) 504 mg, 49 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 7: (a) 1.5 g, 8.42 mmol, (b) 16.84 mL, 42.10 mmol, (c) 70 mL, (d) 3 h, (e) 850 mg, 55 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 8: (a) 2 g, 11.22 mmol, (b) 22.44 mL, 56.10 mmol, (c) 94 mL, (d) 4 h, (e) 1.25 g, 61 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 9: (a) 2 g, 11.22 mmol, (b) 22.44 mL, 56.10 mmol, (c) 94 mL, (d) 5 h, (e) 1.32 g, 64 % yield, and (f) 0 mg, 0 % recovered SM.

Entry 10: (a) 2 g, 11.22 mmol, (b) 22.44 mL, 56.10 mmol, (c) 94 mL, (d) 7 h, (e) 1.03 g, 50 % yield, and (f) 0 mg, 0 % recovered SM

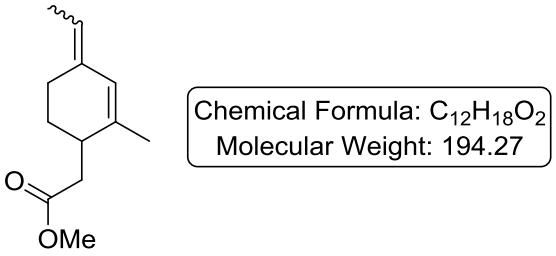
FTIR (**cm^{-1}**): 2951, 2913, 2874, 1734, 1697, 1625, 1435, 1250, 1194, 1175.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.79 (s, 1H, vinylic C<u>H</u>), 3.65 (s, 3H, OC<u>H</u>$_3$), 2.76-2.72 (m, 1H, alkyl C<u>H</u>), 2.58-2.52 (m, 1H, alkyl C<u>H</u>), 2.42-2.31 (m, 2H, alkyl C<u>H</u>), 2.29-2.21 (m, 1H, alkyl C<u>H</u>), 2.09-2.01 (m, 1H, alkyl C<u>H</u>), 1.89 (s, 3H, alkyl C<u>H</u>$_3$), 1.86-1.77 ppm (m, 1H, alkyl C<u>H</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 198.7, 172.3, 163.0, 127.7, 51.9, 36.3, 35.9, 34.0, 27.4, 22.6 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{10}H_{15}O_3$ (M^+ + H): 183.1016. Found: 183.1011.

Preparation of methyl 2-(4-ethylidene-2-methylcyclohex-2-en-1-yl)acetate, **255**.



General procedure C'

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added ethyltriphenylphosphonium bromide (a) and THF (b). To this suspension was added KO*t*Bu (c). The reaction mixture was allowed to stir at r.t. for 30 mins before a solution of methyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate,

254 (d) in THF (e) was added. The mixture was then stirred for a further period of time (f). The reaction mixture was diluted with saturated aqueous NH_4Cl solution (30 mL) and extraction was performed with Et_2O (30 mL × 3). The combined organics were washed with water (25 mL × 2) and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 10 % Et_2O in petroleum ether) to give methyl 2-(4-ethylidene-2-methylcyclohex-2-en-1-yl)acetate, **255**, (f) with specified *E*/*Z* selectivity (g).

Scheme 2.65, **Table 2.18**

The following experiments were performed using **General procedure C'**. Results are reported as: (a) amount of ethyltriphenylphosphonium bromide, (b) volume of THF, (c) amount of KO*t*Bu, (d) amount of methyl 2-(2-methyl-4-oxocyclohex-2-en-1-yl)acetate, **254**, (e) volume of THF, (f) yield of product, methyl 2-(4-ethylidene-2-methylcyclohex-2-en-1-yl)acetate, **255** as a colourless oil, and (g) *E*/*Z* selectivity of product, **255**.

Entry 1: (a) 386 mg, 1.04 mmol, (b) 1 mL, (c) 117 mg, 1.04 mmol, (d) 94 mg, 0.52 mmol, (e) 1 mL, (f) 20 mg, 20 % yield, and (g) 10/1.

Entry 2: (a) 676 mg, 1.82 mmol, (b) 1 mL, (c) 204 mg, 1.82 mmol, (d) 94 mg, 0.52 mmol, (e) 1 mL, (f) 20 mg, 20 % yield, and (g) 10/1.

Entry 3: (a) 653 mg, 1.76 mmol, (b) 1 mL, (c) 197 mg, 1.76 mmol, (d) 80 mg, 0.44 mmol, (e) 1 mL, (f) 10 mg, 12 % yield, and (g) 10/1.

Methyl 2-(4-ethylidene-2-methylcyclohex-2-en-1-yl)acetate, **255**, isolated as a 10/1 mixture of *E*/*Z* isomers.

FTIR (**cm^{-1}**): 2928, 2857, 1736, 1435, 1279, 1161, 1140.

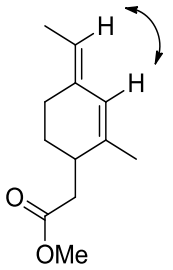
^{1}H NMR (**400 MHz, $CDCl_3$**,): 6.19 & 5.80 (s, 1H in total, vinylic CH ratio 1:10), 5.22 & 5.15 (q, 1H in total, *J* = 6.9 Hz, vinylic C<u>H</u>, ratio 10:1), 3.67 & 3.64 (s, 3H in total, OC<u>H</u>$_3$, ratio 10:1), 2.58-2.47 (m, 2H, alkyl C<u>H</u>), 2.33-2.17 (m, 3H, alkyl C<u>H</u>), 1.73-1.56 ppm (m, 8H, alkyl C<u>H</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 172.6, 134.7, 134.3, 127.1, 119.0, 50.1, 36.0, 35.1, 26.2, 20.9, 19.8, 12.1 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{12}H_{19}O_2$ (M^+ + H): 195.1380. Found: 195.1377.

See appendix for the NOESY spectrum of compound **255**. The major product features a key NOE correlation between the two olefinic protons, confirming the major *E*-configuration

Key NOE correlation



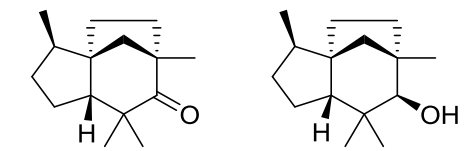
Chapter 3

The formal total synthesis of sesquithuriferone & related sesquiterpenes

1 Introduction

1.1 Sesquithuriferone

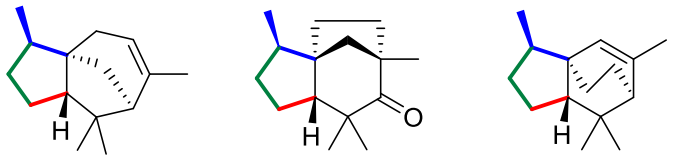
Tricyclic sesquiterpene sesquithuriferone **149** was first isolated from *Eremorphila georgei* by Ghisalberti and co-workers in 1976 (**Figure 3.1**).[203] The research team were able to elucidate the structure of this interesting compound, along with several related natural products. Further to this, Barrero and co-workers found sesquithuriferone **149** along with the first isolation of sesquithuriferol **150** on examination of *Juniperus thurifera*. Indeed, structural elucidation of sesquithuriferol **150** was, in fact, accomplished through chemical correlation with sesquithuriferone **149**.[148,149] A similar biosynthetic pathway to that previously described in the introductory section to the previous chapter is responsible for generation of these products in nature. At present, little is known of the biological role of sesquithuriferone **150**, though recent biological screening has identified potential cytotoxicity.[204]



149 **sesquithuriferone** **150** **sesquithuriferol**

Figure 3.1

On examining the structure of sesquithuriferone **149** it can be seen to contain four chiral centres, three of which are contiguous (**Figure 3.2**). It is also composed of a fused [5,6,5]-ring system, containing only one major functional group: a ketone present in the six-membered ring. When comparing this structure to the previously discussed α-cedrene **142**, and α-duprezianene **151**, obvious differences in both atomic composition and ring size can be noted. However, again a 5-memebered ring is present which lends itself to potential synthesis *via* initial generation of a cyclopentenone through PKR.



142 α-cedrene **149** sesquithuriferone **151** α-duprezianene

Figure 3.2

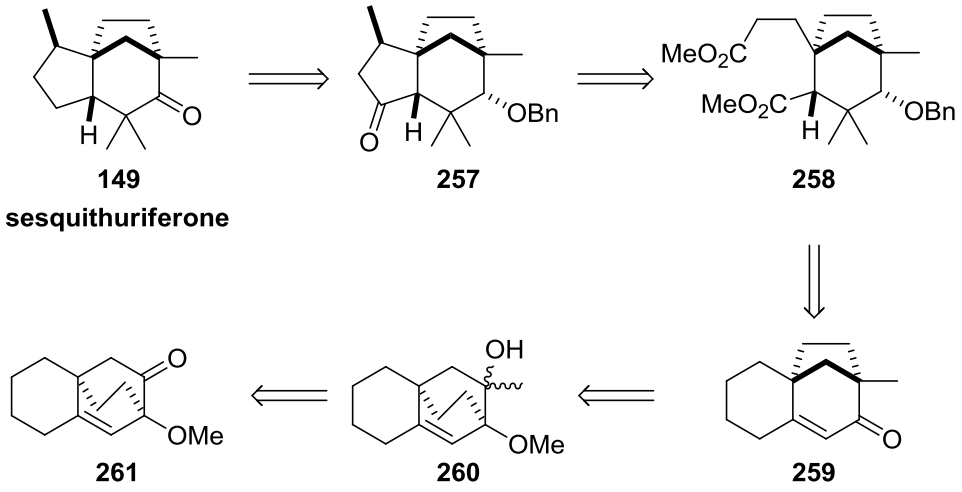
Thus, the focus of this chapter is concerned with attempts towards the total synthesis of the natural product sesquithuriferone **149**. It was hoped that synthesis of this key natural product would allow access to a variety of related elusive targets such as sesquithuriferol **150** and α-duprezianene **151** through key intramolecular PKR methodology.

2 Previous and proposed work

2.1 Previous work

2.1.1 Previous syntheses of sesquithuriferone

To date, sesquithuriferone **149** has been has been successfully synthesised on two occasions, the first of which was reported by Subba Rao and co-workers in 1994.[205] Within this synthesis, it was envisioned that sesquithuriferone **149** could be formed from cyclopentenone **257**, with this tricyclic core, in turn, generated through cyclisation of di-ester **258** (**Scheme 3.1**). This di-ester would be afforded through a series of several steps concluding with fragmentation of the 6-membered ring present in intermediate **259**. Key to this overall strategy was the construction of the [6,6,5]-fused tricyclic species **259** from known [6,6,6]-fused ketone **261**.[206] This was proposed to occur through a Lewis acid-promoted rearrangement of alcohol **260** to afford ketone **259**.

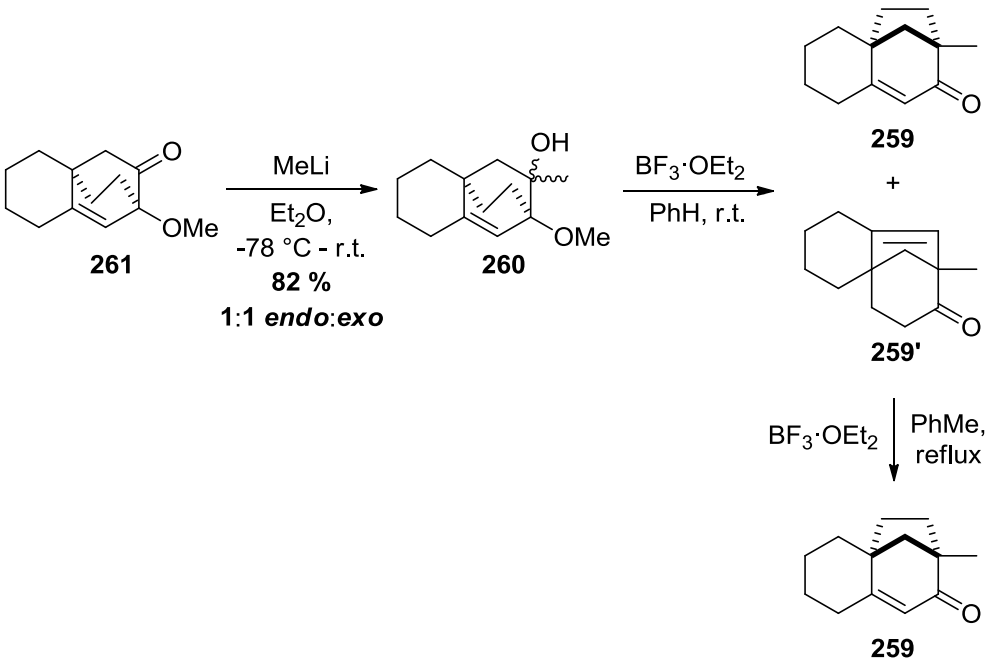


149 **sesquithuriferone** **257** **258** **259** **260** **261**

Scheme 3.1

With this proposal in place, the first step, formation of alcohol **260**, was investigated. As such MeLi was added to ketone **261**, resulting in a 1:1 (*endo*:*exo*) mixture of the alcohol **260** (**Scheme 3.2**). This lack of facial selectivity was not concerning as the subsequent Lewis acid-promoted rearrangement would involve formation of tertiary

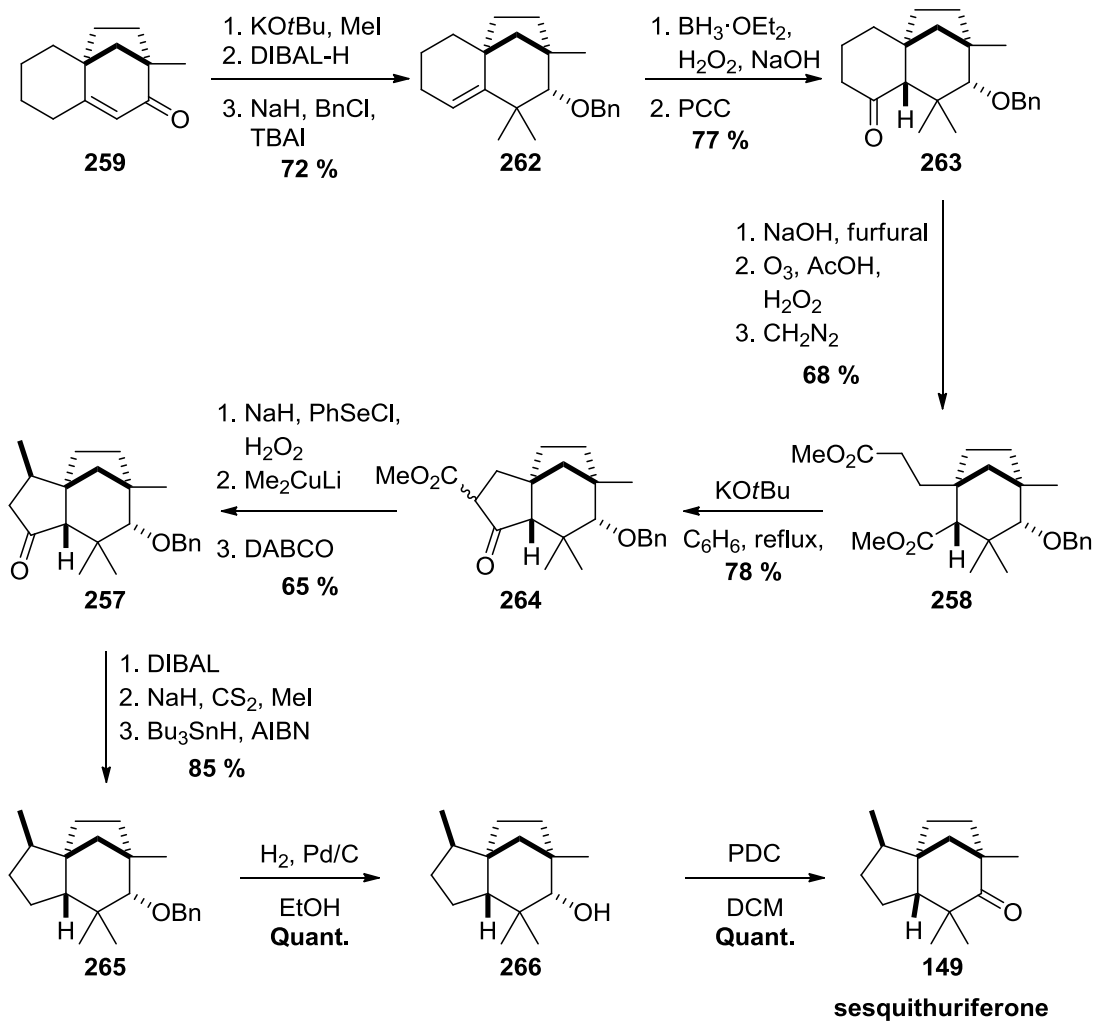
carbocation at this chiral centre. Regrettably, treatment of this mixture of diastereomers with $BF_3{\cdot}OEt_2$ was found to promote both the expected migration of the bridging ethylene forming desired product **259**, and an unforeseen migration of the vinyl moiety to produce **259'**. This unexpected result was further studied through separation of the *exo*- and *endo*-isomers of **260**; these were then individually treated with Lewis acid. Through these experiments it was revealed that the *exo*-isomer predominantly formed the unexpected product **259'**, while the *endo*-isomer largely produced the desired ketone **259**, however, in both cases mixtures of products remained. This result suggested that the rearrangement was, in fact, much more concerted than had previously been envisioned, with the alkyl migration largely dictated by the nature of the starting isomer. Pleasingly, a comprehensive screening of reaction conditions revealed that refluxing the mixture with Lewis acid in PhMe promoted a second rearrangement of compound **259'** yielding the desired ketone **259** almost exclusively.



Scheme 3.2

With ketone **259** in hand, the sequence was thus progressed through initial dialkylation of the enone moiety to install the requisite *gem*-dimethyl (**Scheme 3.3**). The ketone was then reduced and benzyl protection of the free alcohol was

performed to yield intermediate **262**. Hydroboration followed by oxidation was employed to afford the ketone **263** as a single diastereomer. To achieve the necessary ring fragmentation, an initial condensation with furfural was performed; ozonolysis was then carried out to afford a diacid, which then underwent esterification to generate **258**.

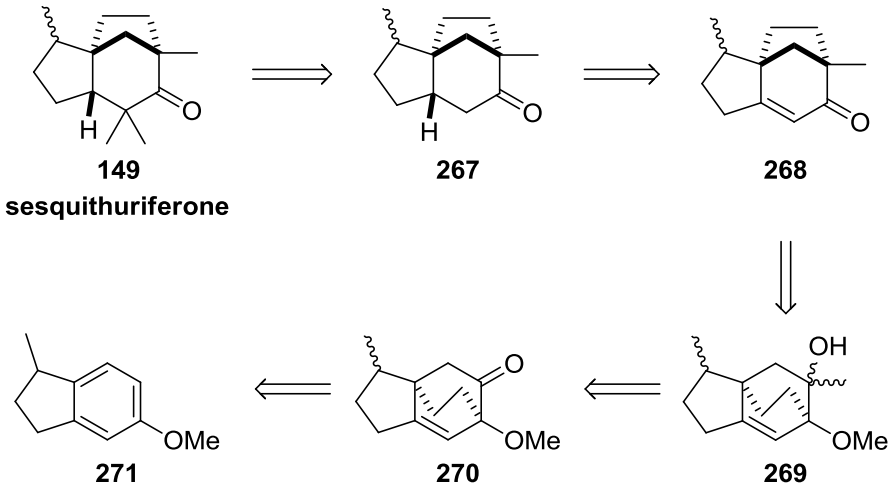


Scheme 3.3

Diester **258** acted as an adequate substrate for Dieckmann condensation yielding β-ketoester **264**, which now featured the requisite 5-membered ring (**Scheme 3.3**). This step was followed by enone formation using selenium methodologies, with the enone allowing selective addition of the required methyl unit using the corresponding cuprate, affording intermediate **257**. Reduction was then performed, followed by a Barton-McCombie deoxygenation procedure to generate advanced intermediate **265**.

At this stage hydrogenation was employed to effectively cleave the benzyl protecting group and, in turn, generate compound **266**, an interesting sesquiterpene in its own right. The stereoselective synthesis of sesquithuriferone **149** was thus completed through oxidation of this secondary alcohol.

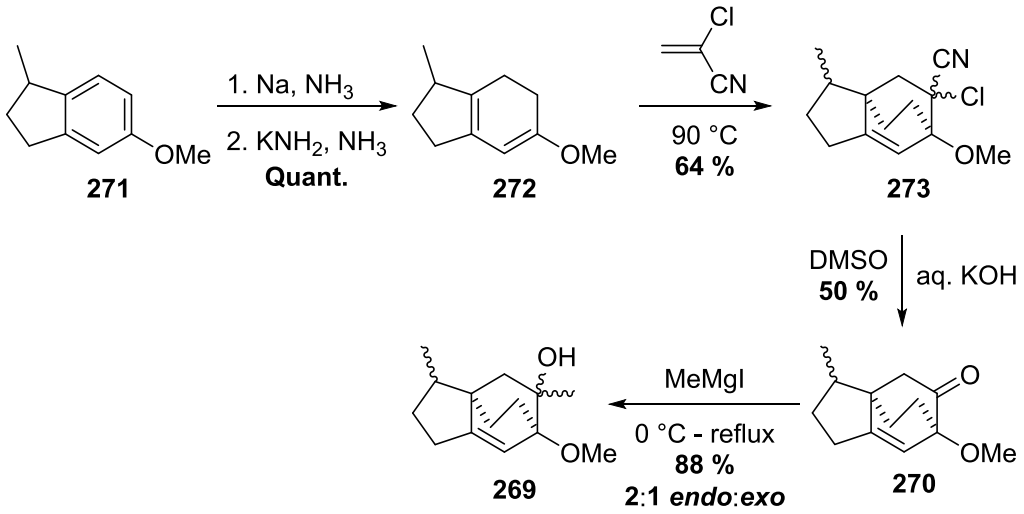
Following this impressive piece of work, in 1995, Subba Rao and co-workers revised the synthesis of sesquithuriferone **149**.[207] In this approach, it was proposed that the corresponding Lewis acid-mediated rearrangement would again be employed; however, the requisite 5-membered ring would already be installed at this point. Thus sesquithuriferone **149** would be generated from ketone **267**, which would, in turn, be produced from the enone intermediate **268** (**Scheme 3.4**). At this stage, the enone intermediate **268** would be derived through Lewis acid-promoted rearrangement of tertiary alcohol intermediate **269**. This key intermediate would be afforded through alkylation of ketone **270**, ultimately arising from the known starting material **271**.[208] It was recognised that a limitation of this of this synthetic route would be the formation of sesquithuriferone **149** as a mixture of epimers. This strategy however would certainly provide a concise route to the target, and it was then hoped that the route could be attempted with an enantioenriched starting material to avoid this problem.



Scheme 3.4

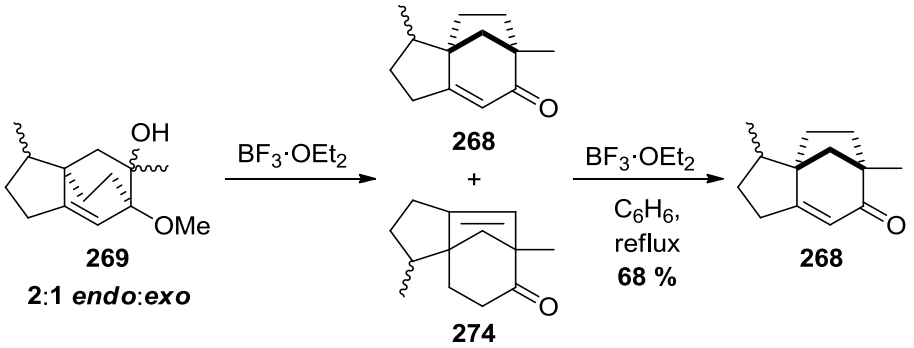
Accordingly, **271** was partially reduced *via* Birch protocols and the intermediate was then exposed to basic conditions to afford conjugated diene **272** (**Scheme 3.5**). A Diels-

Alder reaction was then performed with high levels of regioselectivity to furnish the [5,6,6]-fused tricyclic intermediate **273** as a mixture of diastereomers. This intermediate was then readily hydrolysed to ketone **270**, with the desired tertiary alcohol then furnished through Grignard addition producing **269** in a 2:1 mixture (*endo*:*exo*).



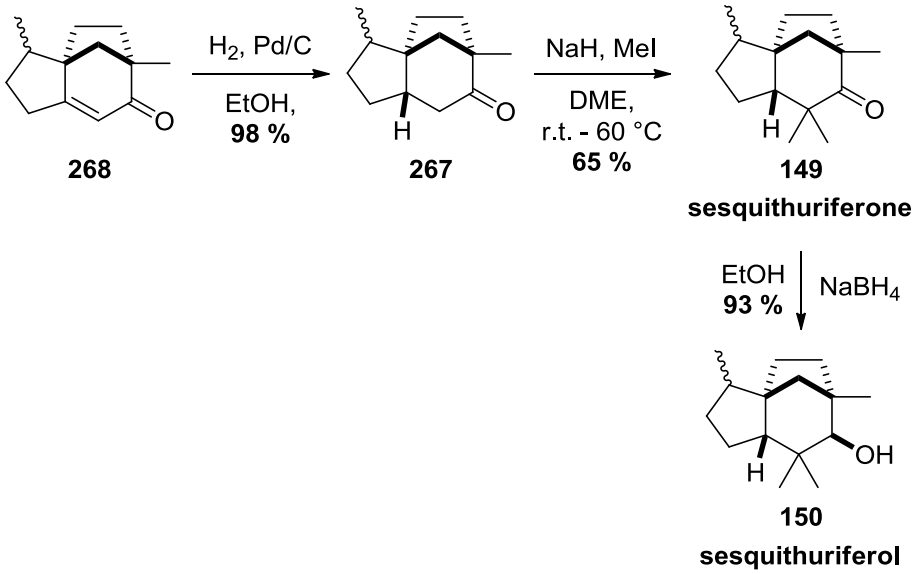
Scheme 3.5

At this stage, the key Lewis acid-based rearrangement could be attempted. As before, the *endo* isomer was found to readily transform into the desired enone **268**, with the *exo* isomer forming the familiar intermediate **274** (**Scheme 3.6**). Pleasingly, once again, refluxing this mixture was found to yield the desired enone **268** near exclusively.



Scheme 3.6

From this point onwards the conciseness of the synthesis becomes evident, with the vast majority of the required functionality already in place. Thus, catalytic hydrogenation of enone **268** was performed to furnish ketone **267**, with the desired facial selectivity observed (**Scheme 3.7**). Indeed, it was proposed by the authors that hydrogenation from the opposite face of the molecule was not favoured due to the steric repulsion of the ethylene bringing unit. Finally, double alkylation to install the requisite *gem*-dimethyl was performed through stirring of ketone **267** in a suspension of NaH and MeI affording the target molecule sesquithuriferone **149** as a mixture of isomers with respect to the methyl unit on the 5-membered ring. In addition to this achievement, a subsequent reduction of the ketone was performed and found to proceed selectively affording the related sesquiterpene, sesquithuriferol **150**, as a mixture of isomers.

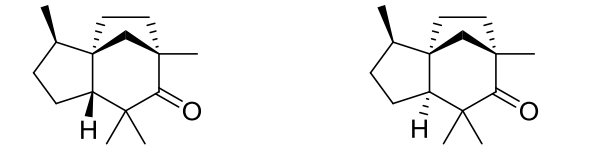


Scheme 3.7

2.1.2 Synthesis of 5-*epi*-sesquithuriferone

At this present time, Subba Rao and co-workers are the only group to have reported a stereoselective synthesis of sesquithuriferone **149**. However, in 2004, Goeke and co-workers attempted to access sesquithuriferone **149** in an asymmetric manner (**Figure**

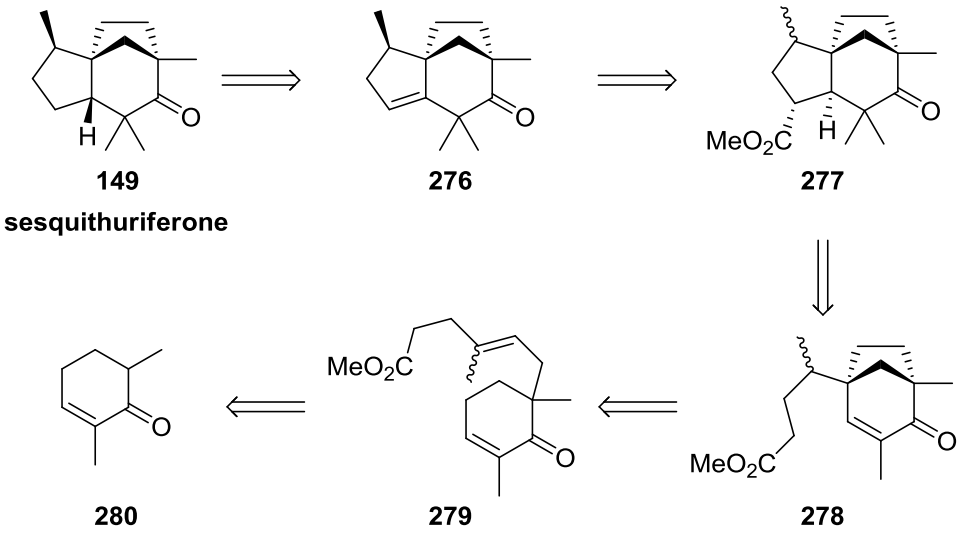
3.3).[209] Unfortunately, it was found that sesquithuriferone **149** could not be accessed through their proposed route. To their credit, however, they did report the successfully formation of the closely related product 5-*epi*-sesquithuriferone **275**.



149 **275**
sesquithuriferone **5-*epi*-sesquithuriferone**

Figure 3.3

In their synthetic approach, focused towards formation of sesquithuriferone **149**, it was hoped that the final target would be delivered through facially selective hydrogenation of intermediate **276** (**Scheme 3.8**). Intermediate **276** would be generated through oxidative decarboxylation of keto ester species **277**. This [5,6,5]-fused species was to be formed by intramolecular ester-enolate addition to the enone unit in **278**, with this expected to proceed *via* the least sterically encumbered face. This key intermediate would be furnished through an aluminium mediated rearrangement of **279**, which, in turn, would arise through alkylation of enone **280**.

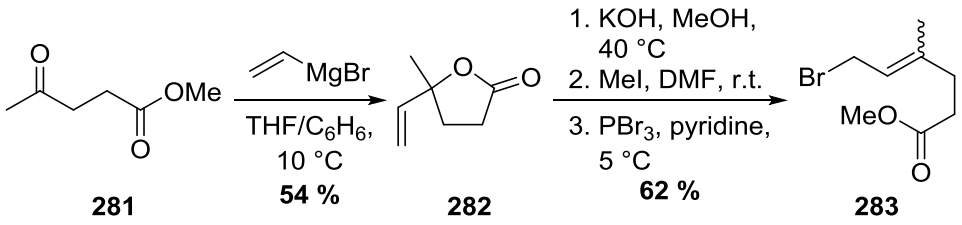


149 **276** **277**
sesquithuriferone

280 **279** **278**

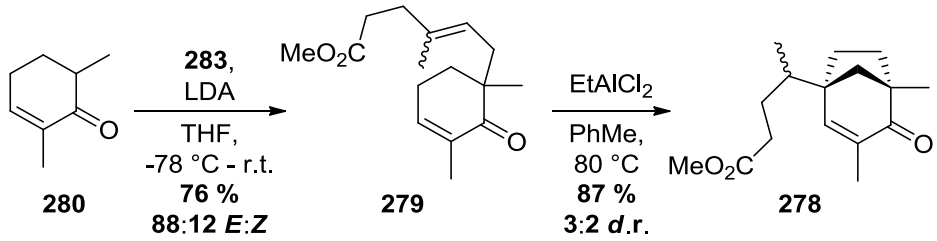
Scheme 3.8

Before the synthetic strategy could begin synthesis of the relevant side chain was required. As such, a three step protocol from starting from the commercially available ketoester **281** was employed (**Scheme 3.9**). The sequence began with a nucleophilic attack by vinyl Grignard reagent to form a tertiary alcohol, which cyclised *in situ* to afford **282**. This intermediate was then hydrolysed and esterified to form the open chain ester, which finally was brominated to afford side chain **283**.



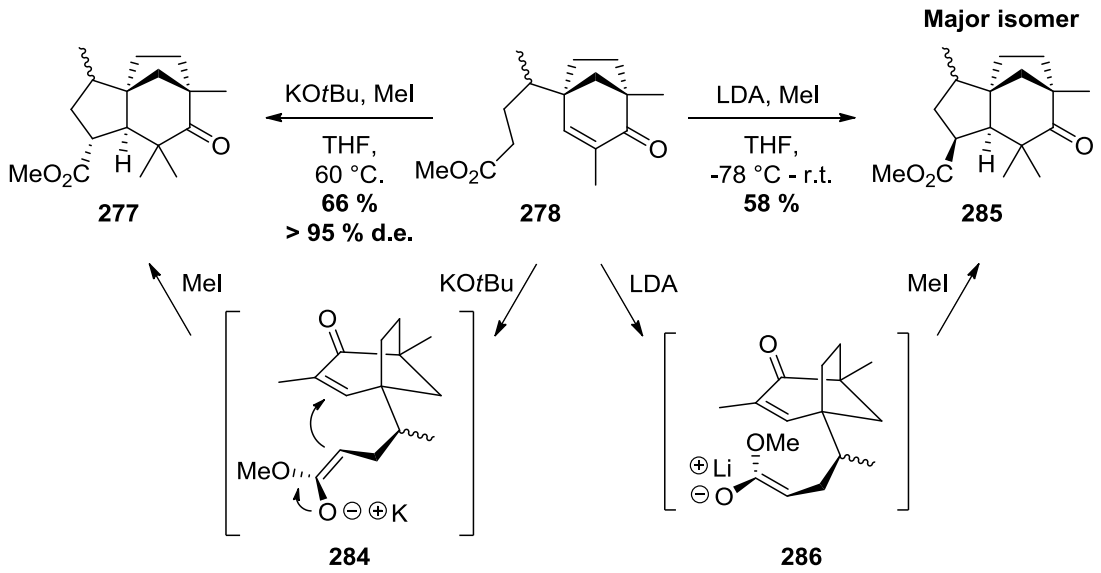
Scheme 3.9

With side chain **283** in hand, alkylation of enone **280** was attempted and found to yield the desired intermediate **279** efficiently (**Scheme 3.10**). At this stage, the proposed cyclisation to form the bicycle **278** could be attempted. Intramolecular cyclisations of this type had previously been explored and developed by the Goeke group, with the hope that similar conditions could be employed here.[210] This cyclisation is non-trivial mechanistically, however detailed discussion of its pathway was provided in the accompanying publication. The authors were pleased to reveal that the exposure of intermediate **279** to $EtAlCl_2$ at 80 °C efficiently facilitated the formation of **278** as a 3:2 mixture of diastereomers.



Scheme 3.10

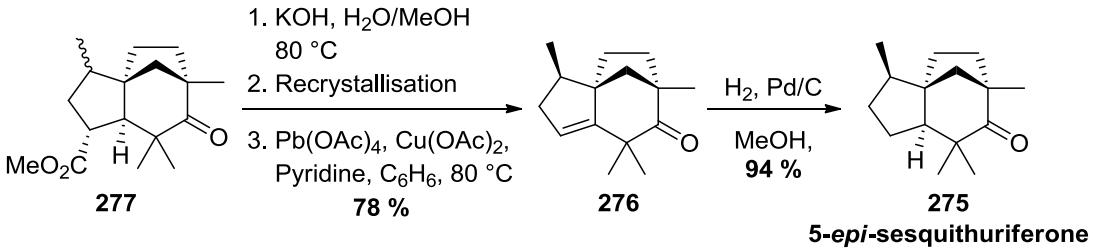
Towards synthesis of the [5,6,5]-fused tricyclic core, initial attempts to facilitate the base-mediated cyclisation were found to be somewhat problematic. It was discovered that on treatment with LDA, a complex mixture of diastereomers was isolated, with the major isomer present being compound **285** (**Scheme 3.11**). This compound was observed to feature an *anti*-relationship between the ester and bridgehead hydrogen. This was proposed by the authors to occur as the result of an initial *Z*-configured ester-enolate formation **286**, which would approach the enone in an s-*cis* conformation. Conversely, enolate formation using KO*t*Bu resulted in a higher level of control, with a preferential *syn* relationship obtained as the major component **277**. The authors proposed that this resulted from formation of an *E*-configured ester-enolate **284** could approach from an s-*trans* conformation, thus adding from the *exo* face and generating the desired isomer in excess.



Scheme 3.11

With the correct isomer **277** in hand, the synthesis was progressed by first hydrolysing the ester moiety to the free acid (**Scheme 3.12**). Following this, fractional crystallisation was performed, providing a purity of 98 % *d.e.* of this free acid, which was then subjected to a oxidative decarboxylation reaction affording advanced intermediate **276** in good yield. The final step in their sequence towards

sesquithuriferone **149** was to be a steric controlled facially selective hydrogenation. Regrettably on attempting this only the epimer, 5-*epi*-sesquithuriferone **275**, was obtained. A number of other hydrogenation methods were subsequently attempted, with no change in selectivity observed.

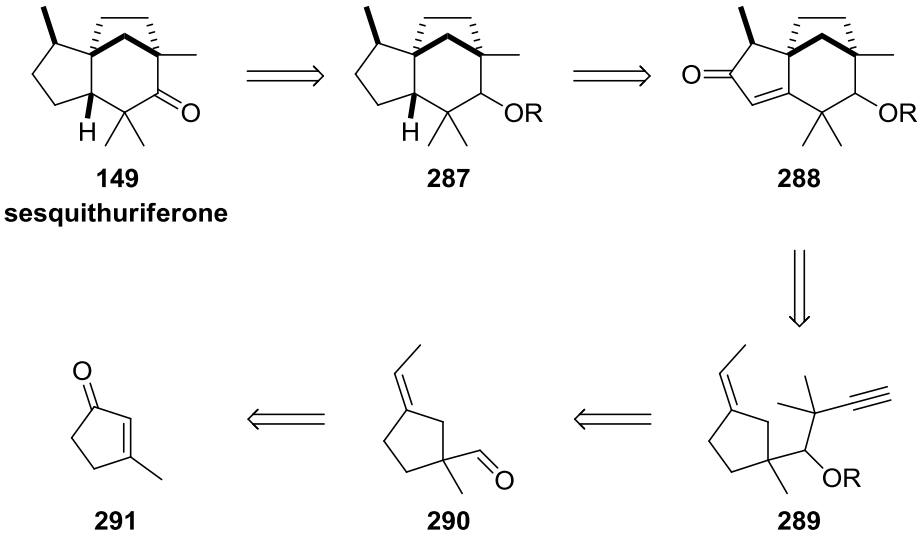


Scheme 3.12

To date, no other attempts to synthesise sesquithuriferone **149** and sesquithuriferol **150** have been reported within the literature. The examples presented serve to highlight the challenges involved in the synthesis of small, complex, sesquiterpenes. These impressive syntheses, while providing access to the skeletal structure of sesquithuriferone **149**, feature a few significant drawbacks. The syntheses are somewhat specific with a need for formation of initially complex substrates with limited functional handles, which are then converted into the desired structures through rearrangement. A more general synthesis, providing access to this class of sesquiterpenes, would be extremely desirable. It was considered that a PKR strategy could provide a rapid and efficient formation of the [5,6,5]-fused tricyclic core, generating much of the required structural complexity in one step. From our experience in the field, this PKR could also be affected from a relatively simple substrate which would hopefully be trivial to prepare. With these challenge in mind we attempted to access this target and the related family of sesquiterpene products *via* a novel PKR methodology.

2.1.3 Attempted synthesis of sesquithuriferone *via* the PKR

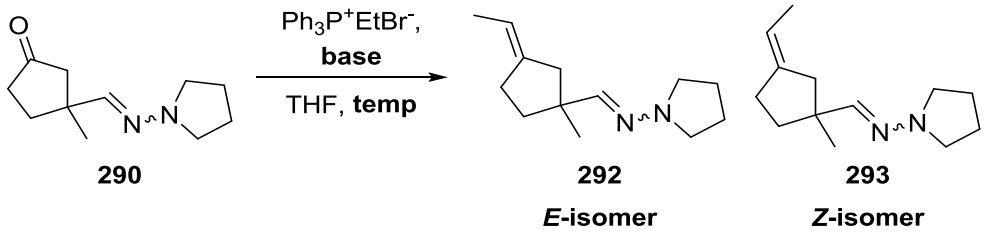
Following our previous successful strategies towards α-cedrene **142** and 2-*epi*-α-cedren-3-one **144**, we turned our attention to sesquithuriferone **149**. It was once again considered that complexity could be introduced at an advanced stage through use of a key intramolecular PKR. Indeed, it was envisioned that sesquithuriferone **149** could be constructed from the advanced intermediate **287**, wherein a protected alcohol would tolerate the required transformation to this point and provide the functionality for the final ketone formation (**Scheme 3.13**).[157] This intermediate would be formed from the [5,6,5]-fused enone species **288** which would, in turn, be readily accessed from an intramolecular PKR of enyne of type **289**. Preparation of this key enyne would be mediated through addition of an alkynyl side chain to aldehyde **290**. Finally, this aldehyde **290**, would be afforded through conjugate addition of commercially available enone **291**, with subsequent *Z*-selective olefination.



Scheme 3.13

With a potential strategy in place, synthetic efforts towards sesquithuriferone **149** were initiated within the Kerr research team. As such, a successful conjugate addition was employed to form ketone **290**. At this point attention turned to

generation of the key *Z*-selective olefin. During these investigations, a temperature study involving the olefination of **290**, demonstrated that a significant level of selectivity could be achieved through the implementation of a low temperature protocol (**Scheme 3.14 & Table 3.1**). Unfortunately, it was found that as the selectivity was greatly improved, poor levels of conversion resulted. On discovering this, the unselective olefination, conducted with KO*t*Bu at r.t., was employed with the aim of incorporating the required selectivity at a later stage within the synthesis, through an epimerisation strategy (**Table 3.1**, **Entry 1**).



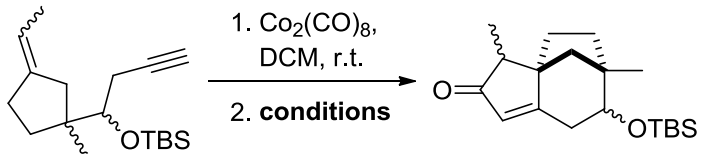
Scheme 3.14

Entry	Base	Temp	Yield (%)	292:293
1	KO*t*Bu	r.t.	94	1:1
2	KO*t*Bu	0 °C	54	2:5
3	*n*-BuLi	-30 °C	42	1:4
4	*n*-BuLi	-78 °C	32	1:7

Table 3.1

Following formation of the olefin, several routes were investigated to install an appropriate alkynyl side chain, such as is present in intermediate **289**. To this end, it was discovered that the proposed PKR was particularly challenging with many of the synthesised potential substrates failing to cyclise. To circumvent this issue, a systematic study of the enynes structural framework was performed. Following this screening, it was discovered the *gem*-dimethyl group appeared to be the major structural characteristic preventing efficient cyclisation. While it had been hoped that this feature would engender a restricted rotation effect, improving the reaction, it was considered that the added steric bulk may be causing interference. The PKR was also found not to progress without protection of the alcohol. With this knowledge,

pleasingly, enyne **294** was identified as a suitable PKR precursor, with the associated cyclisation found to proceed, albeit in moderate yields, under a variety of promotional methods (**Scheme 3.15 & Table 3.2**).



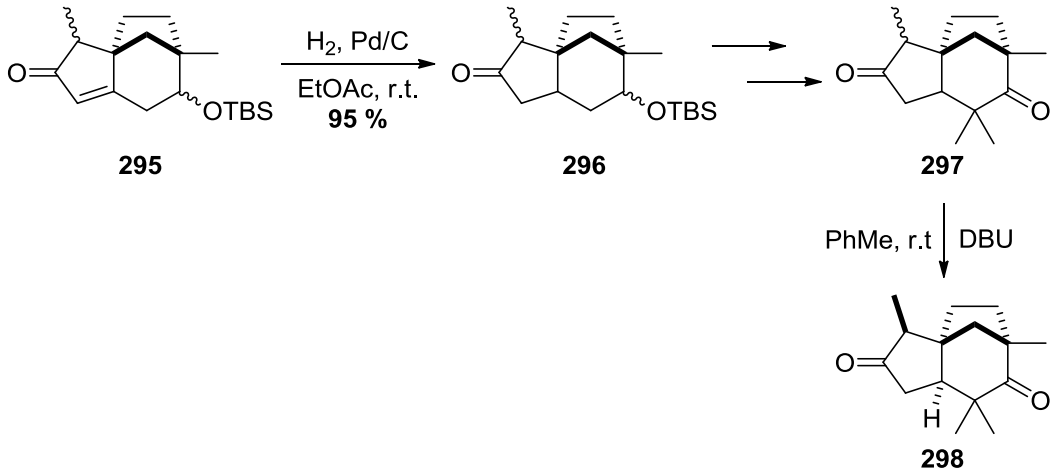
294 **295**

Scheme 3.15

Entry	Conditions	Yield (%)
1	DodSMe, DCM, reflux, 12 h	58
2	TMANO·$2H_2O$, DCM, r.t. 8 h	49
3	TMANO·$2H_2O$, DCM, 0 °C, 8 h	48

Table 3.2

With [5,6,5]-fused intermediate **295** in hand a hydrogenation was performed to remove the enone functionality (**Scheme 3.16**). It was hoped that this hydrogenation would proceed with facial selectivity, encouraged by the ethyl backbone of the fused system. However, due to the complex mixture of diastereomers present, determination of this selectivity was not possible; as such the synthesis was progressed to advanced intermediate **297**. An epimerisation procedure was then performed, on this mixture of isomers, to yield compound **298** as a single diastereomer. This procedure allowed formation of correct relative orientation of the methyl unit on the five-membered ring, despite the unselective olefination previously employed. Regrettably, further analysis at this stage also revealed that the bridgehead hydrogen had been embedded in the opposite orientation to that required in sesquithuriferone **149**. With a challenging final chemoselective deoxygenation required, and the possibility of only accessing the undesired epimer of the target compound, the current route was at this point halted, with the need for re-evaluation evident.

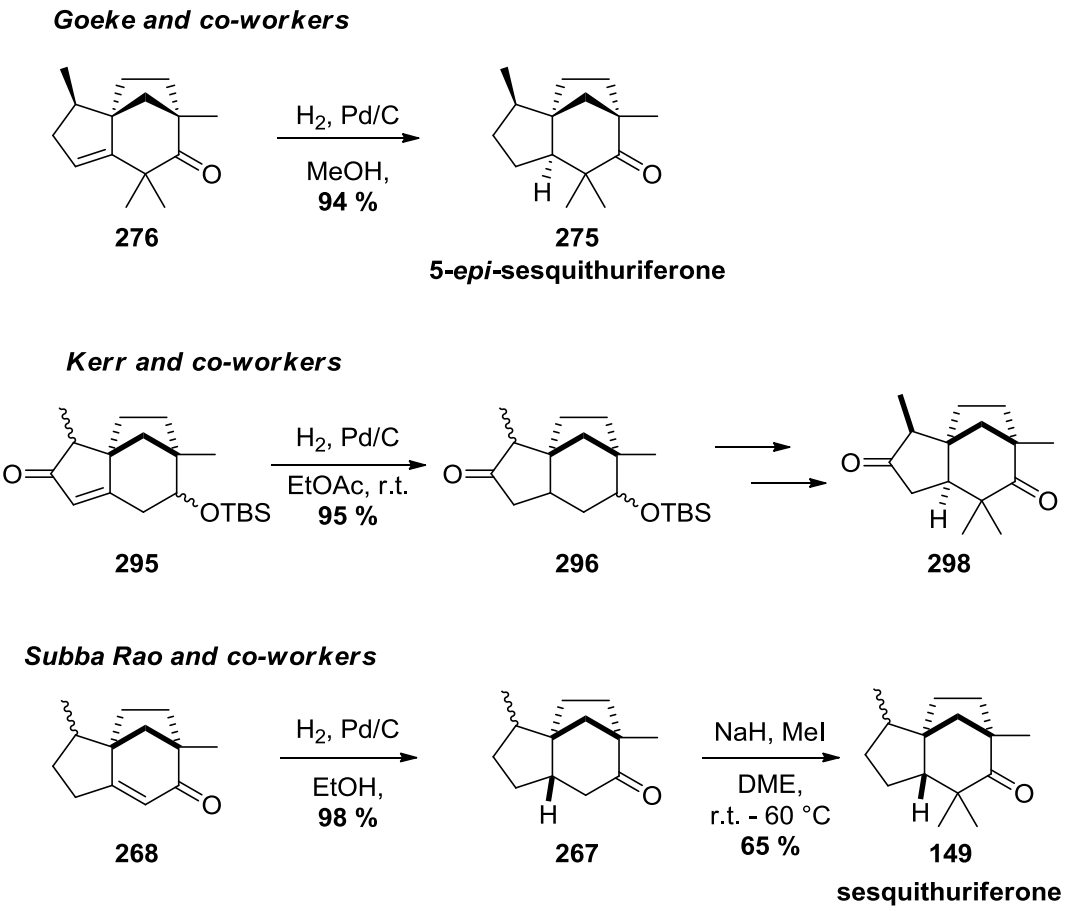


Scheme 3.16

2.2 Proposed work

2.2.1 Proposed synthesis of sesquithuriferone

In proposing a potential synthesis of sesquithuriferone and related products, we first closely examined the previously discussed routes towards this natural target. From work within our own laboratories it was clear that the [5,6,5]-fused tricyclic skeleton could, in fact, be formed efficiently through the PKR. This was encouraging when considering the difficulties encountered during the previously attempted synthesis of α-duprezianene using this methodology. However, a clear problem with these syntheses was installation of the bridgehead hydrogen in the correct orientation. Thus we reflected on the observations made in these previous syntheses (**Scheme 3.17**).

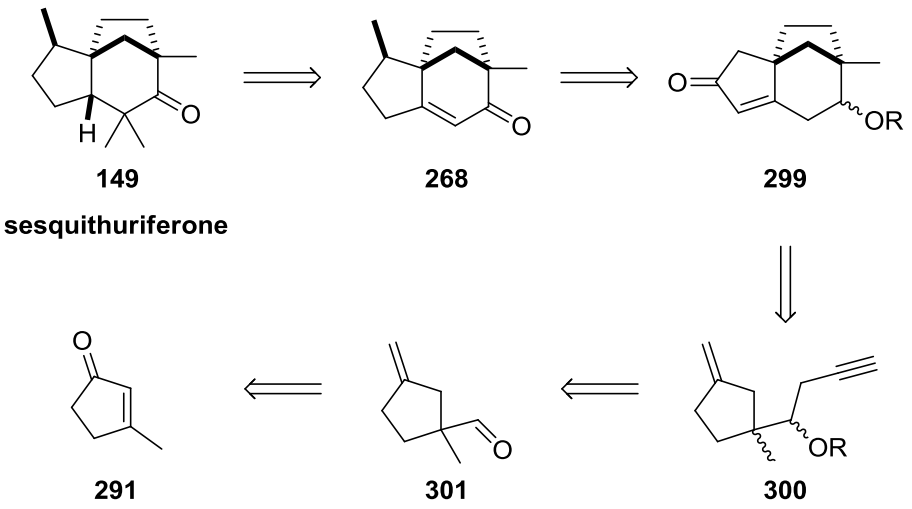


Scheme 3.17

To this end, it appeared that the desired facial selectivity could not be effected through hydrogenation of an olefin in the 5-membered ring (**Scheme 3.17**). However, when the olefin was embedded in the 6-membered ring **268**, the hydrogenation was found to proceed efficiently with formation of the desired *syn*-relationship to the methylene bridge present in the 6-membered ring, as reported by Subba Rao and co-workers. This suggested to us that formation of an intermediate such as **267** would be crucial to formation of the desired natural target in a stereoselective manner.

With this in mind, an appropriate retrosynthesis was proposed, wherein sesquithuriferone **149** would be afforded through hydrogenation and alkylation of enone **268**, as had previously been shown (**Scheme 3.18**). Crucially, as an epimerisation process post-PKR has been shown to produce the correct relative

orientation of the methyl unit, it was considered that installation of this this methyl could be attempted at a later stage, and highlighted enone **299** as our new PKR product. Additionally, the terminal olefin in enyne **300**, was expected to be far more reactive in the key PKR to produce cyclopentenone **299**, when compared the previously employed internal variant. Indeed, characterisation would also be simplified through reduction in the number of isomers possible at this stage. Enyne **300** would be furnished through addition of an alkynyl side chain to aldehyde **301**. Finally, this aldehyde intermediate **301** would originate from conjugate addition and subsequent olefination of the previously employed commercially available enone **291**.



149 **268** **299**

sesquithuriferone

291 **301** **300**

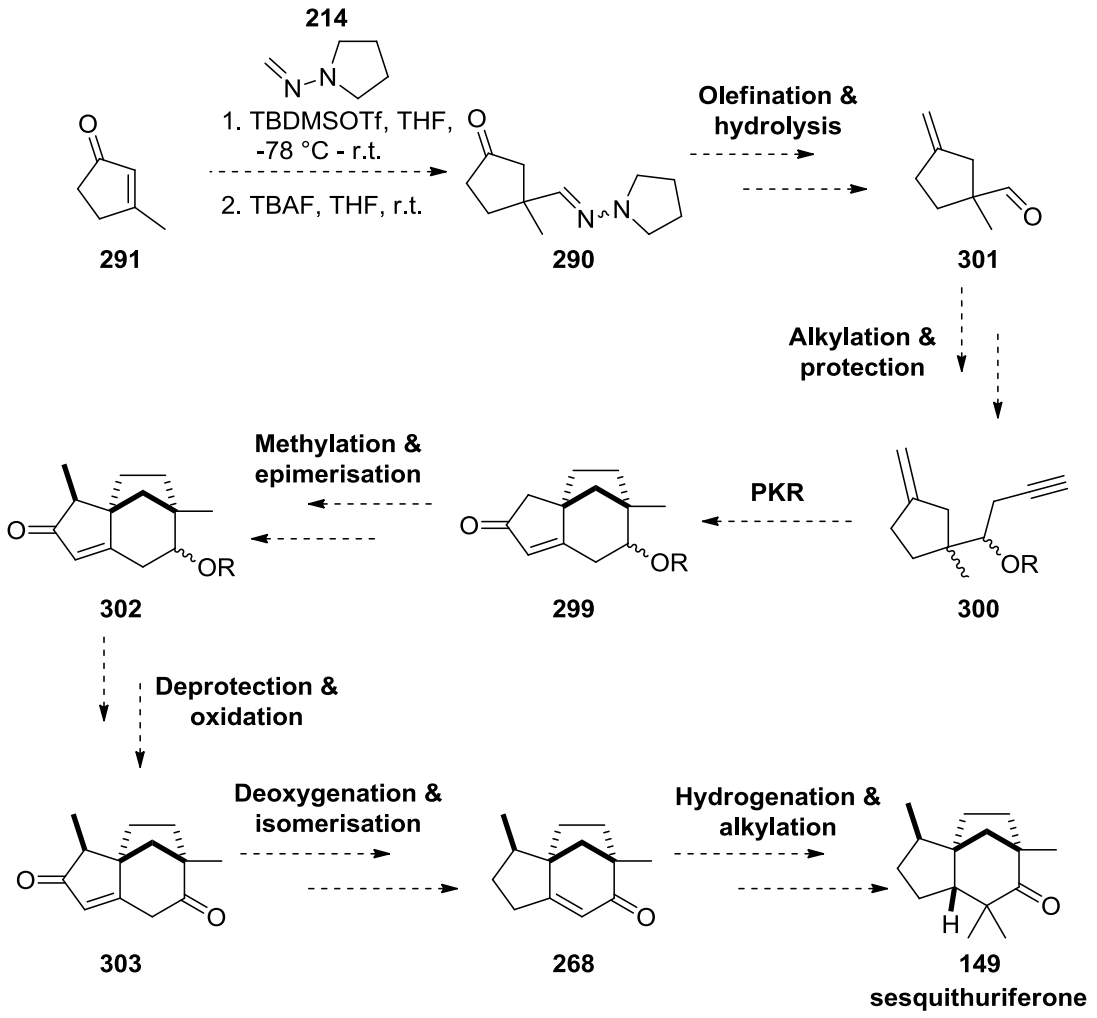
Scheme 3.18

Having proposed a potential strategy towards the target for this programme of work, synthetic evaluations could be initiated with the hope that a robust route towards the key intermediate **268** would be developed. Based on previously reported syntheses, formation of this intermediate would, in turn, act as a formal total synthesis of sesquithuriferone, sesquithuriferol, and α- and β-duprezianene. The following section details these endeavours.

3 Results and discussion

3.1 Synthetic route 1

With a suitable strategy towards sesquithuriferone **149**, and other related natural products in place, a viable and efficient synthetic route was investigated (**Scheme 3.19**). The synthesis would be initiated by utilisation of the previously employed conjugate addition methodology, generating intermediate **290**. Following this, olefination and hydrolysis would afford the aldehyde **301**, which could then be alkylated and protected to generate the alternative enyne **300**, at this stage, as a mixture of isomers.

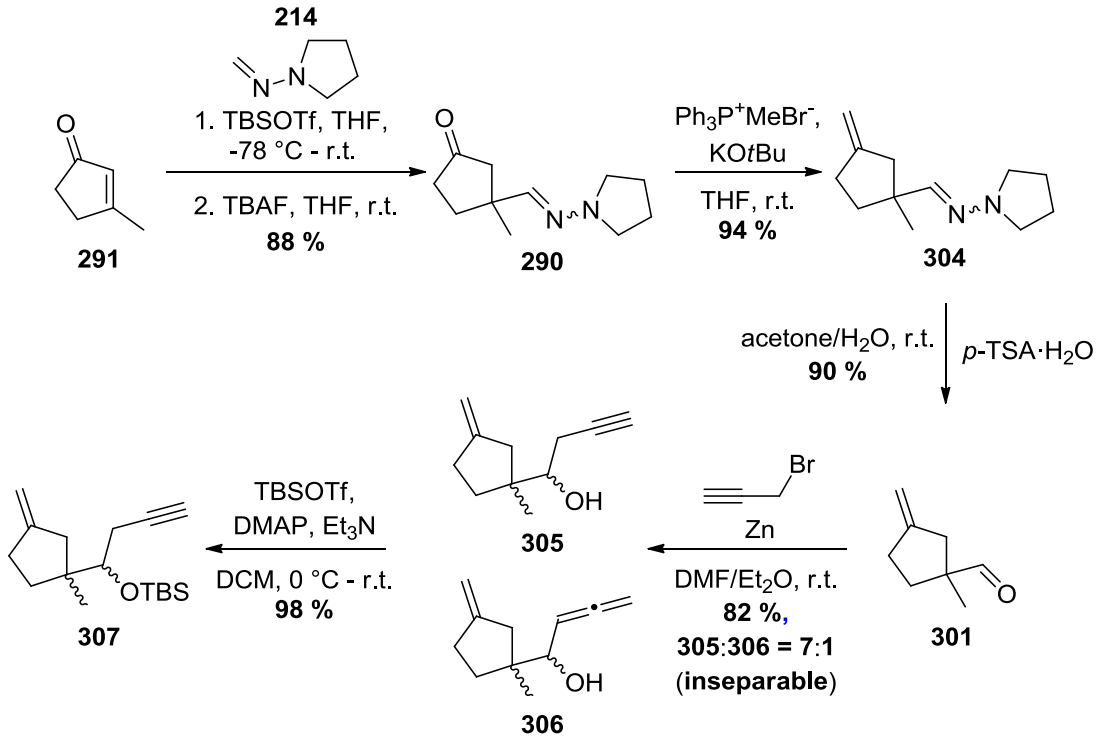


Scheme 3.19

With enyne **300** in hand, investigation of the PKR could be performed (**Scheme 3.19**). In the previously attempted synthesis of sesquithuriferone this step had proved somewhat inefficient. However, it was hoped that the use of a terminal olefin within this substrate, rather than the previous ethylidene unit, would improve this performance of the key cyclisation. The enone functionality within PKR product **299** would, at this stage, allow for kinetic enolate formation and alkylation, installing the requisite methyl unit on the 5-membered ring. Investigation into epimerisation would then be performed, with previous results suggesting epimerisation would favour the desired relative stereochemistry, yielding intermediate **302**. Deprotection and oxidation would then be attempted, to form the ketone present in intermediate **303**. Selective deoxygenation of the enone moiety would then be sought, with subsequent isomerisation attempted to yield the 6-memebered enone **268**. Reaching this stage would constitute a formal total synthesis of sesquithuriferone **149**, which could thus be completed, as previously reported, through facially selective hydrogenation and alkylation to install the *gem*-dimethyl unit.[207]

Investigations into the proposed sequence were thus initiated through conjugate addition; with requisite hydrazone **214**, formed in the same manner as previously discussed (**c.f. Scheme 2.29**). This conjugate addition was found to procede efficiently, affording intermediate **290** in excellent yields on multigram scales (**Scheme 3.20**). Formation of the terminal olefin **304** was then accomplished without incident, using Wittig conditions, with subsequent acid-catalysed hydrolysis performed to generate aldehyde **301**. At this point, installation of the alkynyl sidechain was required. To this end, a Barbier-type reaction was employed, in which the relevant organozinc reagent was prepared from propargyl bromide, before addition of aldehyde **301**. The transformation was found to proceed in high yield, but unfortunately a mixture of products was found to result. Both the desired alkynyl product **305** and the corresponding allenic product **306** were afforded, with no possibility for separation, owing to their similar polarities. Despite this, it was noted that the desired alkyne product, **305**, had been formed in an extremely selective manner, with a 7:1 ratio of alkyne to allene present within the mixture. With the transformation performing reasonably efficiently, it was decided that the mixture would be taken on through the synthesis, with a view to separation at a later stage.

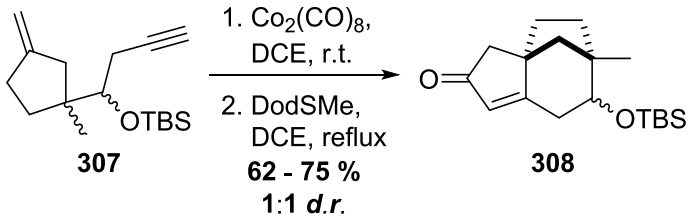
While much of the skeletal framework required to attempt the key PKR had been constructed, a final protection of the molecule's secondary alcohol was needed to ensure an efficient cyclisation. It was decided that a TBS group would be employed, as this had proved to be suitably robust in the previous cyclisation attempt. To our delight, on protection of the secondary alcohol in this manner, it was found that the physical properties of the molecule had been suitably altered to allow for separation of the allenic by-product and isolation of the desired enyne **307**.



Scheme 3.20

Having accessed enyne **307** the key PKR cyclisation could be attempted. To this end, the previously employed DodSMe promotional conditions were decided upon as the first point of investigation. In addition to this, a two-step procedure would be attempted, with initial formation of the cobalt-complexed alkyne used without further purification. To our delight, on attempting this cyclisation under these, conditions the desired [5,6,5]-fused tricyclic structure **308** was efficiently furnished in 62 % yield (**Scheme 3.21**). Additionally, further attempts were found to improve the process, delivering the desired PKR product in as high as 75 % yield. This outcome

is a marked improvement compared to the 58 % yield achieved when an ethylidene unit was employed in the molecule, clearly showing that the terminal olefin system is more favourable (**c.f. Scheme 3.15 & Table 3.2**).



Scheme 3.21

It was noted that the [5,6,5]-system was delivered as a 1:1 mixture of diastereomers, stemming from the uncontrolled stereogenic centre bearing the OTBS moiety. It was thought separation of these diastereomers would provide a simplification in characterisation and would thus provide greater insight in the challenging steps to come. As such, separation of these diastereomers was attempted *via* column chromatography. Unfortunately, however, complete separation was not found to be viable through these methods. Despite this, during separation attempts, when one isomer was isolated in excess, crystallisation was observed. These crystals were examined and found to be suitable for X-ray diffraction. As such, a crystal structure of single diastereomer **309** was successfully produced (**Figure 3.4**). This crystal structure elegantly displays the complexity which has been efficiently produced though a single PKR. Visualisation of this skeletal structure further highlights the benefits of this PKR strategy when compared to those previously discussed.

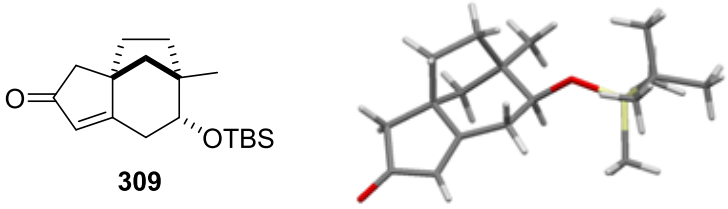
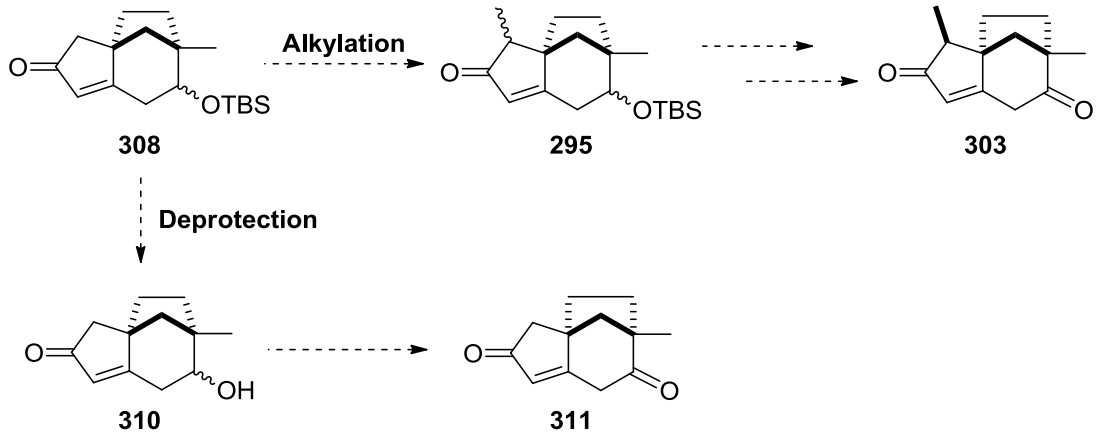


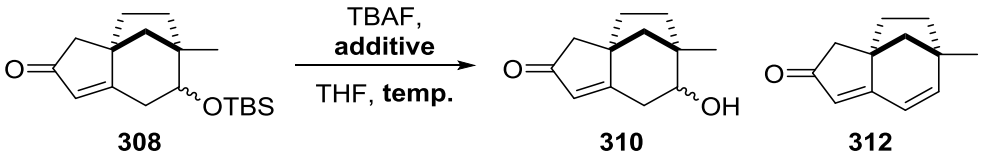
Figure 3.4

As separation of the mixture of diasteromers proved challenging it was decided that the 1:1 mixture of compound **308** would be carried through the subsequent steps. The sterogenic centre would ultimately be removed in the later stages of the synthesis so further attempts at separation seemed unnecessary at this point. However, with the crystal structure, provided through these separation attempts, further validating the strategy, the subsequent synthetic steps were once again considered. The next transformation would be alkylation to install the requisite methyl unit α to the carbonyl moiety, thus generating intermediate **295** (**Scheme 3.22**). This alkylation was, however, expected to proceed without facial selectivity, and as such, in the steps to follow, an epimerisation strategy would be necessary to afford the desired stereochemistry. Crucially, following this, cleavage of the TBS unit and oxidation of the revealed secondary alcohol would be required to furnish advanced intermediate **303**. As the steps to come were an unknown to us, in the first instance it was decided that this deprotection, to yield secondary alcohol **310**, and oxidation, to dicarbonyl species **311**, would be attempted prior to the alkylation. This would allow us to assess the key steps with simpler characterisation data than that which would be produced following alkylation. Once a strategy had been decided upon, alkylation and epimerisation would again become the focus following the PKR.



Scheme 3.22

To begin our investigations into this deprotection and oxidation sequence, typical TBAF cleavage conditions were applied (**Scheme 3.23 & Table 3.3**, **Entry 1**). The reaction progress was followed by TLC analysis, with the SM **308** observed to quickly convert to a new spot. To our surprise, on isolation of the product the expected secondary alcohol **310** was not observed, and instead what we surmised to be the product of elimination, compound **312** was obtained in **79** % yield. It was considered that TBAF might be too harsh for this particular species, and so, in an effort to control the reaction the temperature was lowered (**Table 3.3**, **Entry 2**). Unfortunately, this alteration did not serve to change the result, with 68 % of the elimination product **312** produced, and once again no trace of alcohol **310** was observed.



Scheme 3.23

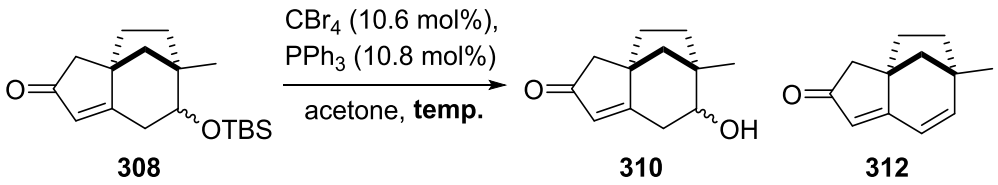
Entry	Additive	Temp.	310 Yield (%)	312 Yield (%)	SM (%)
1	-	r.t	-	**79**	-
2	-	0 °C	-	**68**	-
3	AcOH	r.t.	-	-	**Quant.**
4	AcOH	reflux	-	**28**	**49**
5	NH_4F	r.t.	-	**47**	-

Table 3.3

In an attempt to afford the desired alcohol, a number of reports were found which discussed additives to the TBAF protocol, removing the inherent basicity which could favour alternative transformations. One such described additive was acetic acid (AcOH), which was stirred with TBAF before the addition of substrate.[211] On applying this protocol at r.t., the elimination was successfully halted, but no other transformation was observed, with quantitative return of the SM **308** (**Table 3.3**, **Entry 3**). Under more forcing conditions, with the reaction heated to reflux, slow

conversion was observed after several hours. (**Table 3.3**, **Entry 4**). Disappointingly, this again only appeared to be formation of the eliminated product **312**, thus on isolation after 7 h, a mixture of SM **308** and eliminated product **312** was afforded. A final attempt was made with the alternative additive NH_4F, but unfortunately this too failed to produce the desired alcohol **310** (**Table 3.3**, **Entry 5**).[212]

To effect the desired depotection, alternative conditions were sought. Within our research group, a suitably neutral protocol for the deprotection of silyl groups, acetals and ketals had been previously developed, employing sub-stoichiometric quantities of CBr_4 and PPh_3.[213] We were keen to see if these conditions would prove successful in the challenging deprotection faced. Thus, the reaction was performed as descirbed, at r.t. Regrettably, however the product of elimination **312** was once again found to form (**Scheme 3.24**, **Table 3.4**, **Entry 1**). A second attempt was made at a lower temperature, but unfortunately, in this instance no conversion was observed (**Table 3.4**, **Entry 2**).



Scheme 3.24

Entry	Temp.	310 Yield (%)	312 Yield (%)	SM (%)
1	r.t	**-**	**95**	-
2	0 °C	**-**	**-**	**98**

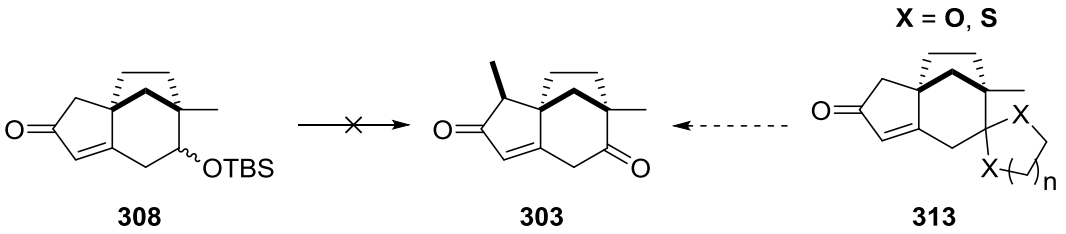
Table 3.4

At this stage, it seemed evident that an alternative protection strategy was required to allow continuation of our proposed synthetic sequence. Despite this, the successful and high yielding PKR proved encouraging in our goal of completion of the synthesis of sesquithuriferone and the subsequent related natural products. With this

key cyclisation proceeding efficiently it was decided that the current route would be re-examined, with a variety of synthetic improvements possible.

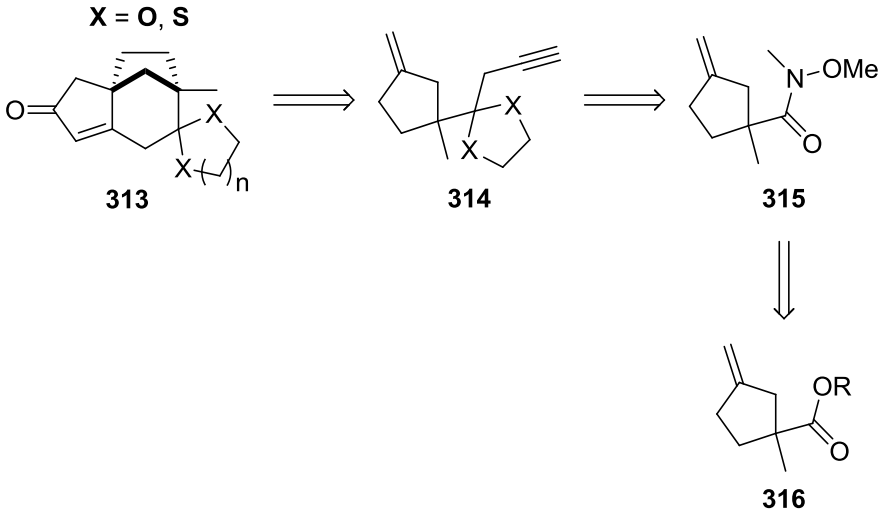
3.2 Synthetic route 2

With the deprotection of TBS protected alcohol **308** proving particularly challenging, it was clear that alternative tactics was required to access key dicarbonyl intermediate **303** (**Scheme 3.25**). Towards this end, an alternative precursor was considered. It was thought that a protected ketone, of type **313**, would serve to provide a much more tractable route towards **311**. This route would also prove shorter overall, as additional oxidation steps would not be required following the PKR.



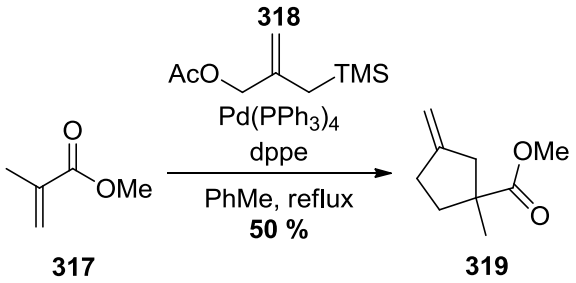
Scheme 3.25

Having set an intermediate of type **313** as an immediate synthetic goal, a retrosynthetic analysis was performed in order to develop a method towards its formation. To this end, it was considered that the desired intermediate **313** could potentially be produced through the novel PKR of an enyne of type **314** (**Scheme 3.26**). Our significant success with the PKR of related enyne **307** provided us with hope that successful formation of the [5,6,5]-fused tricyclic structure could be achieved. To provide access to an enyne of this type, an intermediate Weinreb amide **315** was proposed. This would be a suitable electrophile for the requisite nucleophilic attack to install the alkynyl side chain. Subsequent ketone protection could then be performed. Finally, the Weinreb amide **315** could be furnished through fairly trivial transformations from ester **316**.



Scheme 3.26

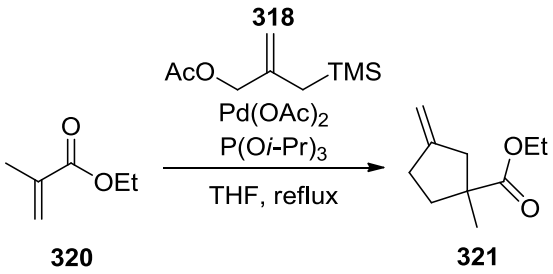
With this new strategy in place consideration was given to generation of ester **316**. It was thought that our previous strategy could be employed up to formation of aldehyde **301** (**c.f. Scheme 3.20**). This aldehyde could then be further converted to an ester of type **316**. This process would, however, require several steps, further extending the overall synthesis. This was deemed a somewhat inelegant strategy; however, on inspection of the literature, a potential single step formation of the desired ester featuring compound **316** was discovered. In 1983, Trost and co-workers reported a palladium-mediated cycloaddition which appeared well suited to our needs.[214,215] In these publications they showed that α,β-unsaturated ketones, -esters, -nitriles, -sulfones and -lactones could all serve as suitable substrates within this system, with yields found to be moderate across the substrate range (**Scheme 3.27**). Key to their process was use of commercially available 2-((trimethylsilyl)methyl)allyl acetate, **318**, which served as a stable source of tri-methylenemethane.



Scheme 3.27

In addition to Trost's initial work, examples of this protocol's use as a key step in other synthetic programmes was found.[216] This provided good rational for utilisation of this methodology as a first step within our synthetic sequence, and, as such, an investigation into the validity of this reaction was initiated. Our first attempt towards formation of ester **321** employed the conditions proposed within the literature (**Scheme 3.28 & Table 3.5**, **Entry 1**). We were encouraged to see that some of the desired product, **321**, had been formed through these conditions; however, the yield was extremely low. The reaction was repeated with a longer time at reflux, and this served to improve the product yield but only to 26 % (**Table 3.5**, **Entry 2**). On examining the reaction profile, it appeared that intermediates related to 2-((trimethylsilyl)methyl)allyl acetate were present within the mixture, but these could not however be successfully isolated. As it appeared that quantities of compound **318** had failed to convert within the mixture it was decided that the amount of ethyl methacrylate **320** would be increased in an attempt to optimise the reaction and allow its use within our strategy. Thus, reactions were performed with 2 eq. and 3 eq. of ethyl methacrylate **320**, with, in each case, an increase in yield observed (**Table 3.5**, **Entries 2 & 3**). Of note, is that the yield on employing 3 eq. was comparable with that described by Trost and co-workers on a very similar substrate (**c.f. Scheme 3.27**). At this point, the amount of ethyl methacrylate **320** was increased to 3.25 eq., which was found to be the apparent optimum (**Table 3.5**, **Entries 5**, **6 & 7**). To our delight, yields in these cases were found to be as high as 83 % with the reaction able to be successfully performed on multigram scales. This yield shows a significant improvement on that reported by Trost and co-workers, with the only apparent drawback being an increased amount of the cheap and readily available SM

employed. Further increases in equivalents of ethyl methacrylate **320** were found to hinder the reaction, with a drop-off in yield observed (**Table 3.5**, **Entries 7 & 8**).

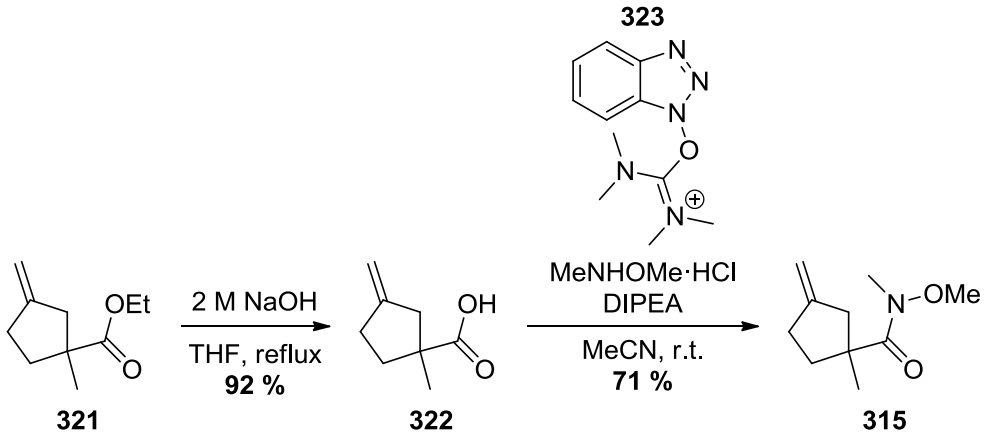


Scheme 3.28

Entry	Scale (mmol)	Eq. 320	Time (h)	Yield (%)
1	2.68	1.00	2	**12**
2	2.68	1.00	15	**26**
3	1.07	2.00	20	**31**
4	5.37	3.00	17	**52**
5	16.10	3.25	18	**70**
6	21.47	3.25	20	**72**
7	53.67	3.25	18	**83**
8	16.10	3.50	16	**66**
9	5.37	4.00	17	**62**

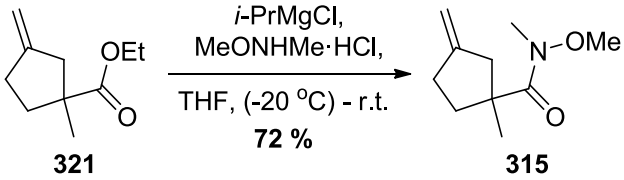
Table 3.5

With a robust and efficient protocol developed to afford ester **321**, synthetic investigations towards Weinreb amide **315** could be initiated. In the first instance, it was decided that this formation would be mediated through amide coupling, as such the ester was hydrolysed to the corresponding acid **322** (**Scheme 3.29**). This hydrolysis was found to require rather forcing conditions, with a need for the ester to be heated to reflux in the presence of base. Despite this, the hydrolysis was found to proceed in excellent yields under these conditions. Following formation of the acid, an amide coupling was performed using compound **23** as a coupling agent. This coupling was found to proceed without incident, affording the desired Weinreb amide **315** in good yield.



Scheme 3.29

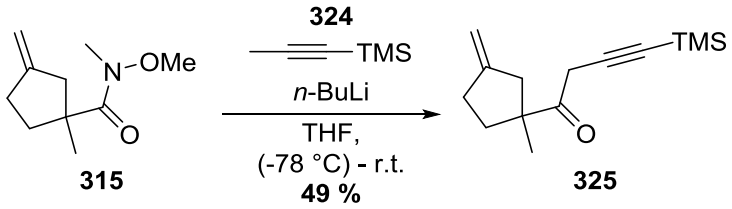
Following our successful, yet stepwise, formation of the Weinreb amide **315**, the literature was examined in the hope that the route could once again be shortened. To this end, conditions were discovered which proposed formation of the Weinreb amide **315** directly from the ester **321** (**Scheme 3.30**).[217] We were somewhat dubious, of the potential for this one step protocol as ester **321** possessed a sterically encumbered environment. Pleasingly, however, on employing these *i*-PrMgCl-mediated conditions the desired Weinreb amide **315** was found to form in yields comparable to those produced through the alternative amide coupling step (**c.f. Scheme 3.29**).



Scheme 3.30

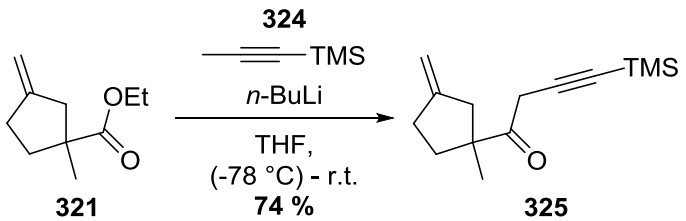
Having successfully developed a concise sequence to Weinreb amide **315**, installation of the requisite alkynyl side chain could be explored. With regard to this, the literature was consulted to find a suitable method for such a reaction. During this examination, an example showing addition of lithiated (trimethylsilyl)propyne to a ketone moiety was found, though unfortunately no such protocol with Weinreb

amides was discovered.[218] The use of this alykne unit was, however, intriguing, as it was considered that its terminal protection would prevent formation of any allene isomer. With this in mind, formation of alkynyl compound **325** was attempted from Weinreb amide **315** using (trimethylsilyl)propyne and *n*-BuLi (**Scheme 3.31**). To our delight, our initially considered conditions were found to be successful, generating the desired compound **325**. However, following multiple attempts, the maximum yield was found to be only 49 %. Depite the moderate yield afforded in these reactions, we were, however, pleased with the success of this novel process.



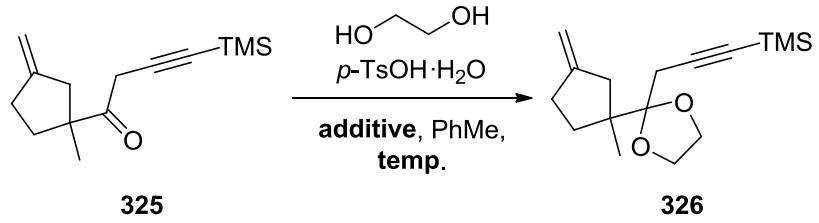
Scheme 3.31

Following the conversion of the Weinreb amide **315**, and with a thought to route elegance, we were curious to see if this alkynylation protocol was applicable to the early ester compound **321**. To our delight, use of these conditions not only proved successful with ester **321** as a substrate, they were also found to be much more efficient, providing protected enyne intermediate **325** in up to 74 % yield (**Scheme 3.32**). It was considered that this improvement might result from the diference in steric encomberance between the weinreb amide **315** and the ester **321**.



Scheme 3.32

The sequence so far had proved extremely successful, surpassing our initial strategic plans. With the advanced enyne intermediate **325** afforded in only two synthetic steps, protection of the ketone moiety was required before deprotection of the alkyne and attempts towards the novel PKR. Towards this goal, typical dioxolane formation conditions were employed (**Scheme 3.33 & Table 3.6**). On attempting this formation at reflux, with 4 Å MS as an additive, no product was detected (**Table 3.6**, **Entry 1**). These conditions also proved destructive, with none of the starting material returned from the reaction. Regrettably, attempting dioxolane formation with trimethylorthoformate as an additive provided a similar result, with none of the protected product **326** afforded (**Table 3.6**, **Entry 2**).



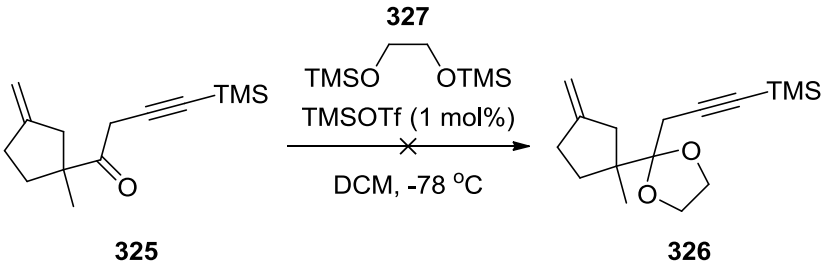
325 **326**

Scheme 3.33

Entry	Additive	Temp.	Yield (%)
1	4 Å MS	reflux	-
2	trimethylorthoformate	r.t.	-

Table 3.6

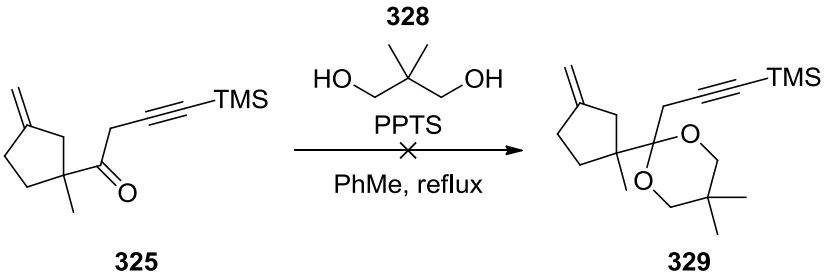
In an effort to provide suitable conditions for protection of enyne **325**, the literature was consulted. From this search, an interesting alternative methodology for dioxolane protection was identified. In this report, the intended protection was mediated by 1,2-bis(trimethylsiloxy)ethane, **327** with TMSOTf as catalyst (**Scheme 3.34**).[219] Crucially, this procedure employed milder conditions and was performed at -78 °C. With the previous reactions converting the SM **325** to unknown products, it was hoped that this lower-temperature protocol might provide more controlled reactivity. Unfortunately, on employing these conditions, the desired product **326** once again was not formed. It was also noted that, even at these lower temperatures, conversion of the SM **325** to a mixture of unknown products had occurred.



325 **326**

Scheme 3.34

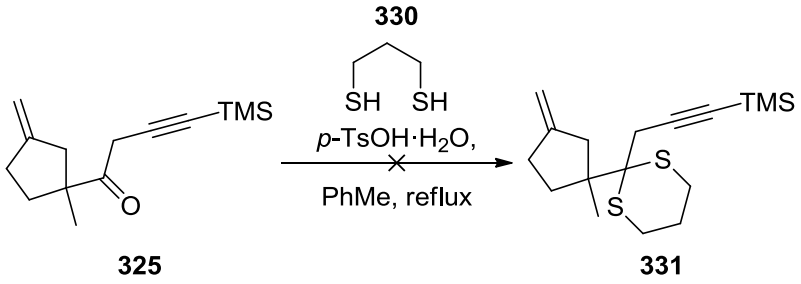
As a final attempt at acetal protection, the alternative 6-membered acetal was investigated. To this end, a protocol was followed which employed 2,2-Dimethyl-1,3-propanediol, **328** with pyridinium *p*-toluenesulfonate (PPTS). Once again however, the methodology called for rather forcing conditions with heating to reflux required (**Scheme 3.35**).[220] Disappointingly, these alternative conditions also proved fruitless; with the SM **325** again converted to unknown materials without any of the desired product **326** observed in the final mixture.



325 **329**

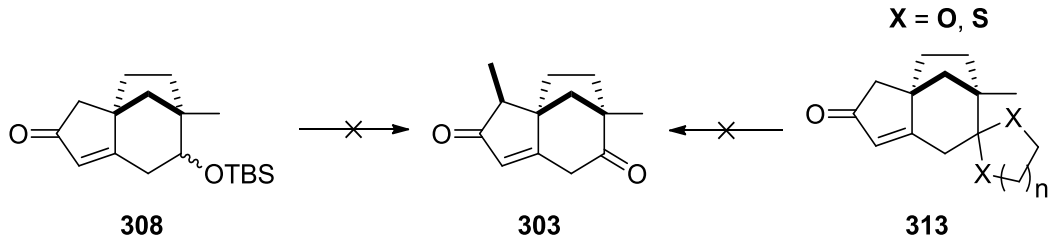
Scheme 3.35

With enyne **325** resistant to acetal protection, the alternative thioacetal was considered. It was thought that this protection strategy would certainly prove stable in the subsequent reactions, however it would most likely prove more challenging to remove following the PKR. Despite this, it was decided that thioacetal protection would be attempted, and as such, the enyne **325** was reacted with 1,3-propanedithiol **330** and *p*-TsOH·H_2O at reflux (**Scheme 3.36**). Regrettably, in a similar manner to the attempted acetal protection, these conditions failed to yield the desired protected enyne **331**.



Scheme 3.36

At this point, it appeared clear that our current strategy would not provide access to key dicarbonyl intermediate **303** (**Scheme 3.37**). In spite of the significant achievements developed within this short synthetic route, enyne **325** had failed to survive all attempts at protection of its ketone; as such, a compound of type **313** could not be accessed. It was considered that enyne **325** was an extremely reactive species, this would account for its conversion to unknown materials during protection attempts. To this end it was noted that no compounds similar to **325**, had been recorded within the literature, potentially confirming the lability of this unit.

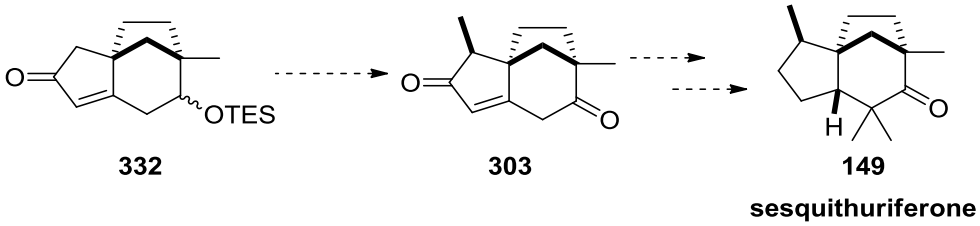


Scheme 3.37

Despite the apparent failure of this synthetic route, it was hoped that the early developments, in particular the rapid formation of ester **321**, would be of use in an alternative strategy towards sesquithuriferone and the related sesquiterpene natural products.

3.3 Synthetic route 3

In considering an alternative tactical approach towards the target molecule, the originally proposed synthesis was re-evaluated (**c.f. Scheme 3.19**). On attempting this strategy, initial success was realised with the only issue being the problematic deprotection of the TBS protected alcohol. Our attempts to circumvent this through ketone protection had, unfortunately failed. We now considered alternative, and more labile, alcohol protection. To this end, the triethylsilyl (TES) protected compound, **332**, was considered a suitable intermediate (**Scheme 3.38**). It was thought that the TES unit would be suitably robust to survive the key PKR, but would prove much more amenable to cleavage when required. As such, following PKR, alkylation could be performed, with subsequent deprotection. On generation of the secondary alcohol, oxidation would be trialled to deliver the key dicarbonyl intermediate **303**. From this point, the steps described previously would be employed to access sesquithuriferone **149**, whose subsequent transformation would then afford the related sesquiterpene natural products.

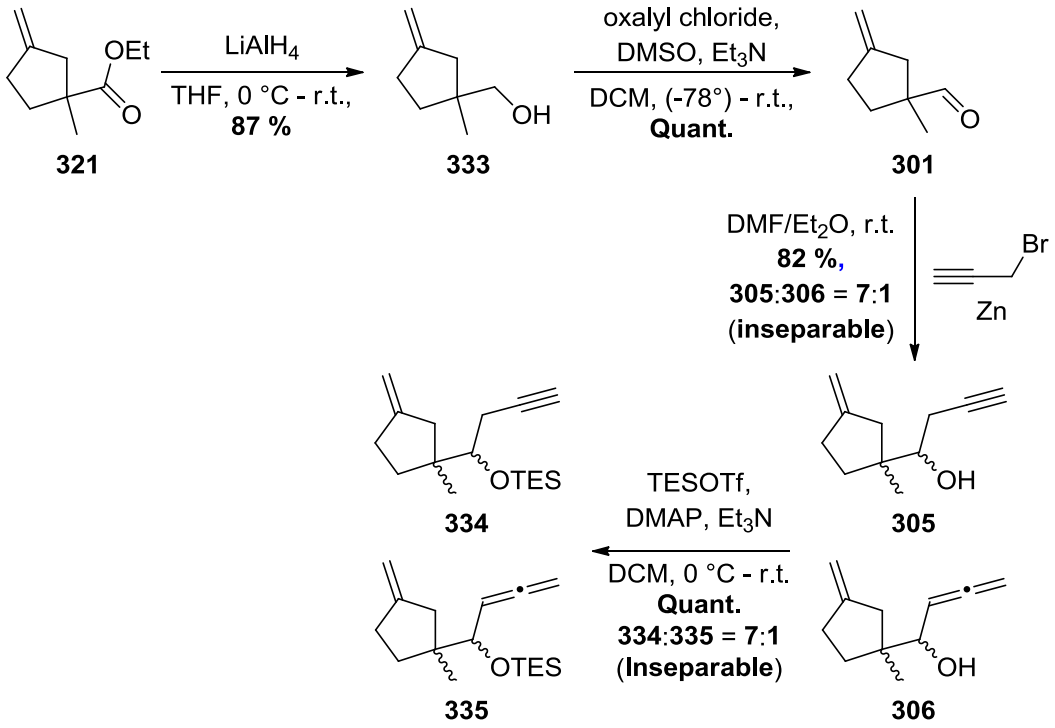


332 **303** **149**
sesquithuriferone

Scheme 3.38

In attempts to reach the TES protected intermediate, the synthesis was expedited through use of the previously developed palladium-mediated cycloaddition (**c.f. Scheme 3.28**). Thus, multigram quantities of the ester intermediate **321** were quickly afforded, and this ester was then reduced efficiently to afford primary alcohol intermediate **333** (**Scheme 3.39**). Oxidation of this alcohol was then performed using Swern conditions. This oxidation was found to be extremely successful, generating the previously accessed aldehyde **301** in quantititative yield.

From this point it was decided that similar chemistry to that previously employed would be used to install the requisite alkynyl side chain (c.f. **Scheme 3.20**). As such, the Barbier conditions were once again employed to afford alkyne **305** and allene **306** as an inseparable mixture of compounds, in a 7:1 ratio. This mixture was not a concern as it was believed that on protection, the mixture would once again beome separable. Unfortunately, on attempting TES protection of the secondary alcohol, despite the reaction proceeding in quantitative yields, the products, **334** & **335**, remained completely inseparable. While this was not ideal, it was considered that this mixture would not greatly affect the synthetic strategy. It was believed that on attempting the PKR on this mixture of enyne, **334**, and allene, **335**, only the enyne would convert. Additionally, the added polarity embued by the generated cyclopentenone would likely make sepration from the extremely lipophilic allene relatively trivial.

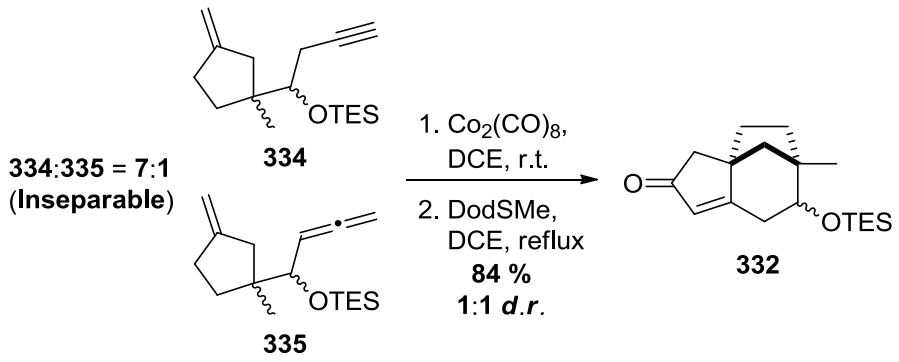


321 **333** **301** **334** **305** **335** **306**

Scheme 3.39

At this point, the key PKR was once again ready to be attempted. It was hoped that this substrate would prove as successful as that previously employed, as no major change to the susbtrate's skeletal structure had been made (**c.f. Scheme 3.21**). With

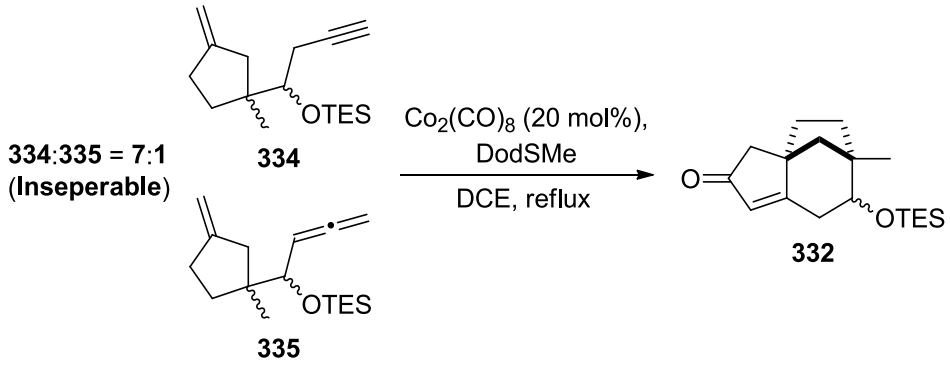
this in mind, the DodSMe promotional conditions were once again employed (**Scheme 3.40**). To our delight, the reaction was found to proceed generating the desired [5,6,5]-fused tricyclic product **332** as a 1:1 mixture of diastereomers, in an even greater yield than that previously observed.



Scheme 3.40

With the success of our stoichiometric PKR protocol, we decided, at this stage, to attempt a catalytic variant which had previously been developed within our laboratories.[156] To this end, conversion of the mixture of alkyne **334** and allene **335** was attempted in one pot with 20 mol% of $Co_2(CO)_8$ (**Scheme 3.41 & Table 3.7**). In the first instance, the originally proposed amount of DodSMe was added to the reaction mixture (**Table 3.7**, **Entry 1**). Pleasingly, the desired product **332** was found to form through these catalytic conditions, however the yield was found to be somewhat low, with only 46 % of product produced. As was the case with the stoichiometric variant a 1:1 mixture of diastereomers was observed. In an attempt to improve the reaction yield, the amount of DodSMe was increased to 3.5 eq. This matched that suggested as optimal in the original publication describing this promotional method (**Table 3.7**, **Entry 2**).[121] This increase was found to provide some benefit, with a yield of 59 % achieved. Finally, the quantity of DodSMe was increased to that which was employed within the stoichiometric variant (**Table 3.7**, **Entry 3**). Once again, this alteration provided a small increased in overall yield, with 65 % of [5,6,5]-fused product **332** afforded. This short study had proved extremely successful, showing that the conditions previously developed within our laboratories could be employed within our attempted total synthesis strategy. This

catalytic approach provides a benefit, in both reducing the amount of transition metal employed in the synthesis and shortening the route overall.

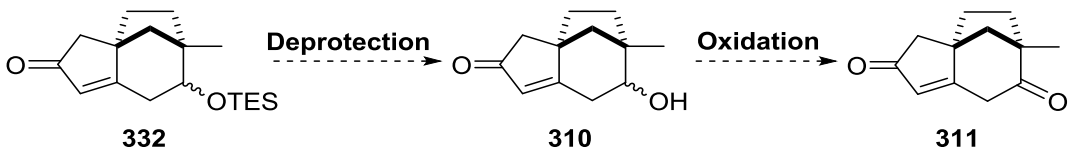


Scheme 3.41

Entry	Eq. DodSMe	Yield (%)	*d.r.*
1	1.2	**46**	**1:1**
2	3.5	**59**	**1:1**
3	4.5	**65**	**1:1**

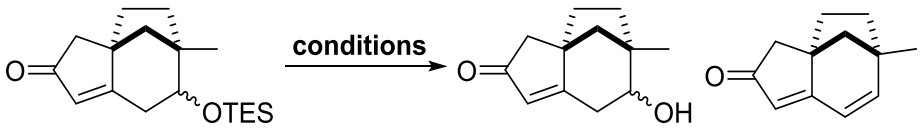
Table 3.7

With a robust and catalytic route towards 5,6,5-fused product **332** in place, it was decided that deprotection would be attempted before alkylation (**Scheme 3.42**). As discussed, it was hoped that the more labile TES functionality would cleave successfully under milder conditions without occurrence of the previously observed elimination. On successful generation of secondary alcohol **310**, oxidation to the dicarbonyl intermediate **311** would be trialled before returning to attempt the required alkylation.



Scheme 3.42

It was considered that while the TES functionality would likely be easier to cleave, mild conditions for its removal would still be preferable. To this end a mild protocol was identified within the literature which employed a sub-stoichiometric quantity of acetyl chloride (AcCl) and MeOH to generate HCl *in situ* (**Scheme 3.43 & Table 3.8**, **Entry 1**).[221] Disappointingly, on applying this method, only the eliminated product, **312**, was afforded. At this point, the conditions previously employed in attempts to deprotect the TBS species were re-evaluated (c.f. **Scheme 3.23 & Table 3.3**). As such, 0.2 M HCl was added to the TES protected compound **332**. Pleasingly the deprotection was found to proceed efficiently, affording the desired secondary alcohol **310** in 74 % yield (**Table 3.8**, **Entry 2**). Interestingly a 2:3 *d.r.* of the free alcohol was generated. Since the SM **332** was present as a 1:1 mixture of diastereomers this suggested that one of the diastereomers was being cleaved preferentially. Finally, on employing TBAF with AcOH, a slight increase in yield to 76 % was observed, and again a 2:3 *d.r.* was found to result (**Table 3.8**, **Entry 3**).



332 **310** **312**

Scheme 3.43

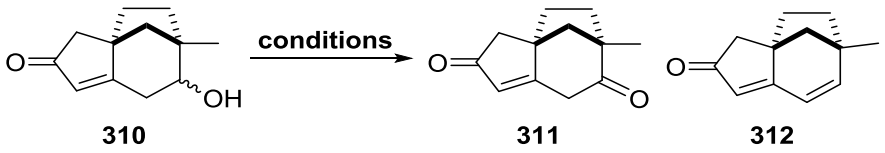
Entry	Conditions	310 Yield (%)	310 *d.r.*	312 Yield (%)
1	AcCl, MeOH, r.t.	**-**	**-**	**64**
2	0.2 M HCl, THF, 0 °C – r.t.	**74**	**2:3**	**-**
3	TBAF, AcOH, THF, 0 °C – r.t.	**76**	**2:3**	**-**

Table 3.8

With the elusive secondary alcohol **310** finally in hand, oxidation to the key dicarbonyl intermediate **311** could be trialled. In the first instance, a Swern oxidation was attempted. Regrettably, however, this was found to only afford the eliminated product **312** (**Scheme 3.44 & Table 3.9**, **Entry 1**). It was now clear that elimination was still a possible pitfall at this stage, despite the previous successful deprotection.

As such the literature was scanned in an attmept to find mild methods which might prove suitable for this oxidation. One such protocol was a $NaHCO_3$ buffered Dess-Martin oxidation which had been employed, with great success, within a similarly challenging total synthesis campaign (**Table 3.9**, **Entry 2**).[222] Disapointingly, applying this method only resulted in complete conversion of the SM **310** into a complex mixture of materials from which no further insight could be gained.

Alternative oxidations were thus considered, with in the first instance a tetrapropylammonium perruthenate (TPAP) oxidation identified and attempted.[223] Once again, however, the protocol was found unsuitable, with a mixture of unknown materials afforded (**Table 3.9**, **Entry 3**). A single electron oxidation protocol was attempted, with in this case catalytic (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and (diacetoxyiodo)benzene (BAIB) as reagents (**Table 3.9**, **Entry 4**).[224] Unfortunately this change in conditions provided no improvement to the previous attempts. Chromium-mediated oxidations were now considered, with the slightly less acidic PDC employed in the first attempt, followed by use of PCC with NaOAc as a buffering agent (**Table 3.9**, **Entry 5 & 6**).[225] Disappointingly, neither of these conditions were found to be successful, with a similar reaction profile to that previously observed. In a final attempt at formation of the desired dicarbonyl compound, **311**, an Oppenauer-type oxidation was identified within the literature and applied to the secondary alcohol **310** (**Table 3.9**, **Entry 7**).[226] No improvement was found from these conditions, with only the eliminated product successfully isolated from the mixture of materials produced.



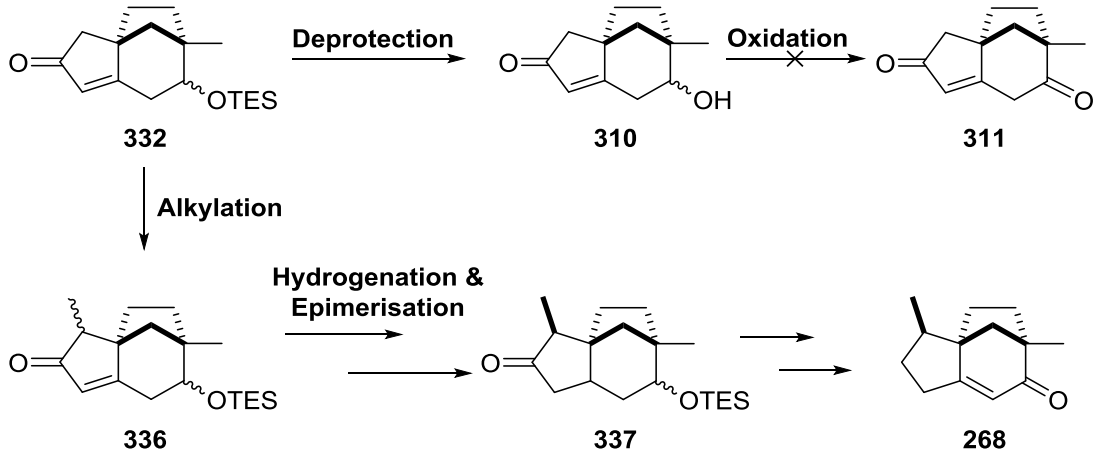
310 **311** **312**

Scheme 3.44

Entry	Conditions	311 Yield (%)	312 Yield (%)
1	oxalyl chloride, DMSO, Et_3N, DCM, (-78 °C) – r.t.	-	**23**
2	DMP, $NaHCO_3$, DCM, r.t.	-	-
3	TPAP, NMO, 4 Å MS, THF, 0 °C – r.t.	-	-
4	TEMPO, BAIB, DCM, r.t.	-	-
5	PDC, DCM, 4 Å MS, r.t.	-	-
6	PCC, NaOAc, DCM, 4 Å MS, r.t.	-	-
7	$(PPh_3)_3RuCl_2$, K_2CO_3, acetone, reflux	-	**25**

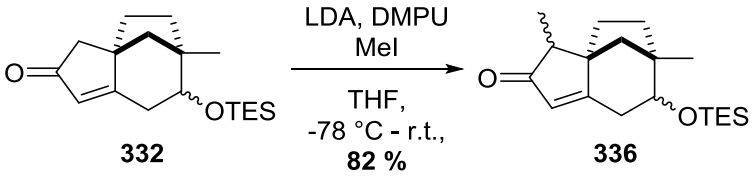
Table 3.9

At this stage, despite the successful generation of secondary alcohol **310**, it was clear that the dicarbonyl intermediate **311** could not be reached through this strategy (**Scheme 3.45**). With this in mind, an alternative, and somewhat more stepwise route was considered, which would make use of the complex and advanced intermediates already generated. As such, it was decided that alkylation of PKR product **332** would be performed to afford intermediate **336**. Rather than attempting epimerisation at this stage, hydrogenation would first be performed to remove the unsaturation present within the molecule. From previous studies towards sesquithuriferone, it was inferred that this would proceed with the undesired facial selectivity (**c**.**f**. **Scheme 3.17**). Epimerisation would then be attempted on this unsaturated species in an attempt to fix the methyl unit in the correct orientation, as in compound **337**. It was hoped that in subsequent transformation, from this advanced intermediate, deoxygenation could be performed, followed by formation of the 6-membered enone, allowing for a formal total synthesis of sesquithuriferone **149**.



Scheme 3.45

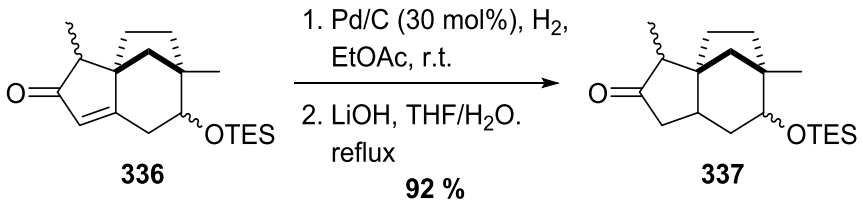
The first step in this new strategy required alkylation of the [5,6,5]-fused tricyclic compound **332**. To this end, a protocol was developed in which an initial kinetic deprotonation was performed, with the resulting enolate quenched by MeI (**Scheme 3.46**). This protocol was found to proceed in excellent yield, affording the desired intermediate **336** in up to 82 % yield. Characterisation of the produced compounds was, however, found to be extremely challenging with the product isolated as a complex mixture of stereoisomers. Further investigation into the isomeric mixture of this compound was performed at a later stage, however for the time being the synthesis was continued without absolute knowledge of the stereochemical nature of this mixture.



Scheme 3.46

Having successfully formed the alkylated intermediate **336**, removal of the alkene in enone **336** was next sought. As such, enone **336** was stirred with Pd/C under an atmosphere of hydrogen (**Scheme 3.47**). This process was found to rapidly afford

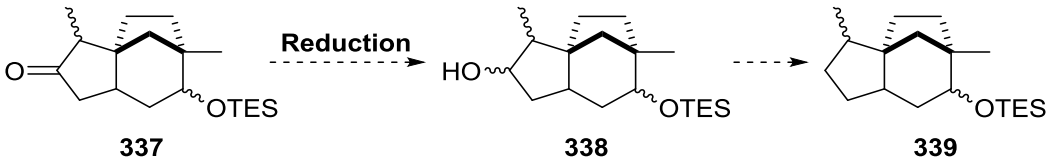
the desired ketone **337**, with the product of this reaction then subjected to attempted epimerisation through stirring with LiOH at reflux over 3 days. These conditions had previously been employed with great success within our previous synthesis of α-cedrene (**c.f. Scheme 2.7**).[104] As we were unable to determine the isomeric content of these compounds the synthesis was continued. It was considered that on formation of the enone **268**, only one uncontrolled stereocentre would remain. This would in turn inform the success of this epimerisation protocol. Further investigation into the isomeric nature of these compounds was, however, performed at a later stage (*vide infra*).



336 **337**

Scheme 3.47

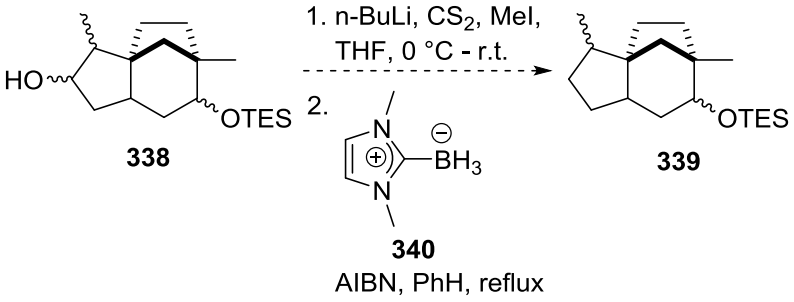
We now considered how best to remove the ketone moiety present within the compound. In previous syntheses within our laboroatories, the Barton-McCombie protocol had been used efficiently to provide such a deoxygenation.[111,154] In order to proceed using this methodology, reduction of the ketone would first be required to afford secondary alcohol **338** (**Scheme 3.48**). The Barton-McCombie reaction would then be performed, with initial formation of the xanthate ester, to afford the desired deoxygenated product **339**.



337 **338** **339**

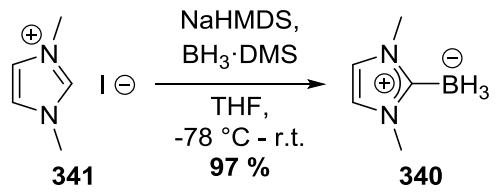
Scheme 3.48

Before inititating this sequence, an interesting alternative to the original Barton-McCombie protocol was brought to our attention. In this reported procedure, following xanthate ester formation, rather than using tributyltin hydride to perform the final deoxygenation, *N*-heterocyclic carbene (NHC) borane **340** was instead employed (**Scheme 3.49**).[227,228] A mechanism involving the formation N-heterocyclic carbene boryl radicals was proposed by the authors.[227] This low molecular weight reagent **340** was extremely attractive, as it appeared relatively simple to synthesise, would be easier to handle than tributyltin hydride, and did not possess the same toxicity profile.



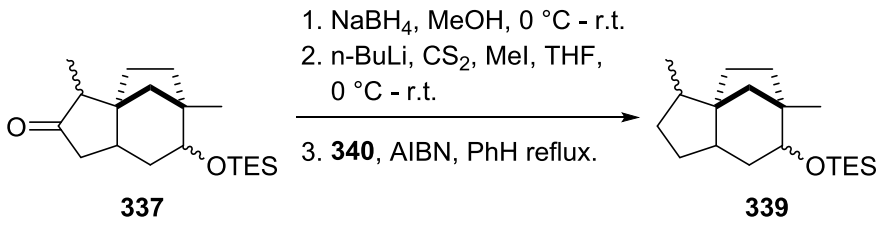
Scheme 3.49

With this protocol decided upon, synthesis of NHC borane **340** was attempted (**Scheme 3.50**). Thus, deprotonation of commercially available imidazolium salt **341** was performed with NaHMDS, followed by addition of BH_3·DMS. This process proved extremely efficient, with the desired compound **340** formed in 97 % yield. With the requisite NHC borane in hand, the deoxygenation could thus be investigated.



Scheme 3.50

The deoxygenation protocol was initiated through reduction of ketone **337** to its related secondary alcohol (**Scheme 3.37**). This procedure was monitored by TLC analysis and found to proceed with full conversion. The resulting intermediate was not isolated and immediate formation of the xanthate ester from this secondary alcohol was performed. Finally, cleavage of this xanthate ester was attempted, using the previously synthesised NHC borane **340**. This step was found to proceed efficiently; unfortunately, however, the lipophilic nature of the deoxygenated material **339** prevented further purification. Despite this, the presence of the desired product **339** was confirmed through high resolution mass spectrometry (HRMS). It was thus decided that the material would be progressed further as it was believed that removal of the TES protecting group would provide the necessary polarity to allow successful purification.

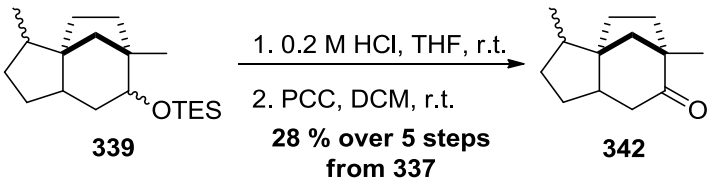


337 **339**

Scheme 3.51

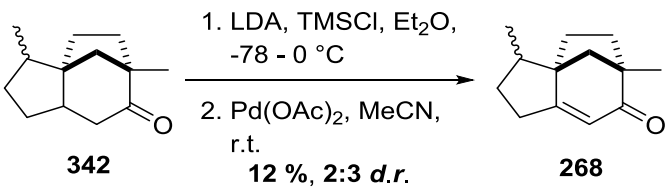
Deprotection of the TES group was attempted using conditions previously developed within our synthesis. To this end, the crude material containing compound **339** was stirred with 0.2 M HCl at r.t. (**Scheme 3.52**) In following this reaction by TLC analysis, complete conversion to the significantly more polar secondary alcohol was observed. Disappointingly, on attempting isolation, the residual silyl species was found to co-elute with the desired product. Once again, we decided progress the material through the next step. As such, oxidation of the secondary alcohol was mediated through reaction with PCC. Finally, at this stage, we were able to isolate the ketone **342** successfully, albeit as a complex mixture of isomers. The overall yield for this protocol was an impressive 28 % for these challenging 5 steps, which corresponds to almost 80 % per step. While isolation throughout these

transformations would have been preferable, it was felt that the expedited nature of the route was beneficial overall.



Scheme 3.52

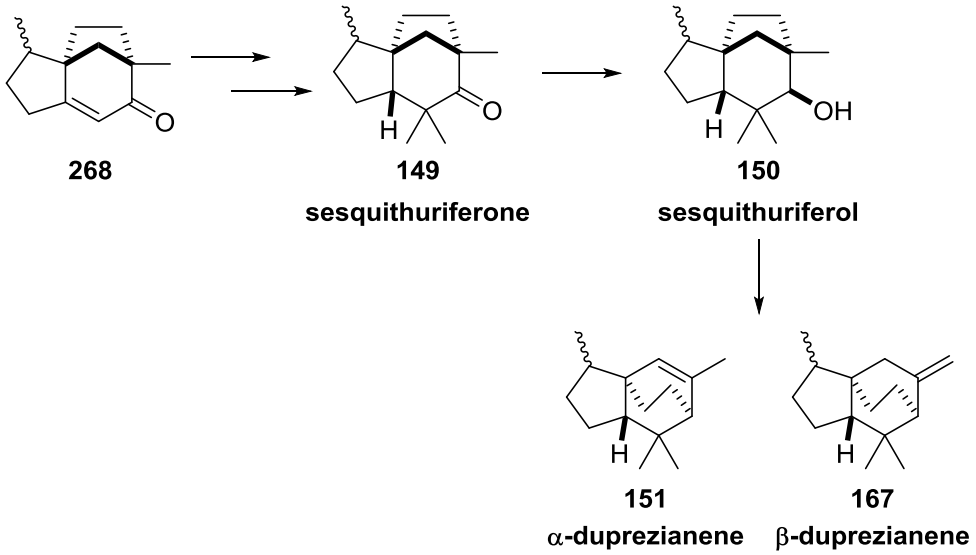
Having accessed ketone **342** successfully, we were finally in a position to attempt generation of the requisite 6-membered enone and achieve a formal total synthesis of sesquithuriferone **149**. To this end, a Saegusa-Ito oxidation protocol was selected to achieve this transformation. Thus, the ketone intermediate **342** was first subjected to deprotonation and silyl enol ether formation, and this silyl enol ether was then reacted with stoichiometric quantities of $Pd(OAc)_2$ (**Scheme 3.53**). To our delight, the desired 6-membered enone **268** was afforded, albeit in 12 % yield. Regrettably, at this point, with only one uncontrolled chiral centre remaining, it was evident that a 2:3 *d.r.* was present within this final compound **268**. This suggested that our epimerisation protocol had failed to converge on a single methyl stereochemistry within the molecule. Despite this mixture, we had reached a key intermediate in the synthesis of Subba Rao and co-workers, who also prepared enone **268** as a mixture of diastereomers.[207]



Scheme 3.53

It was at this point that synthetic investigations ceased. While a stereoselective synthesis had not been accomplished, a route had been developed which provided a

skeletal formal total synthesis of sesquithuriferone **149** (**Scheme 3.54**). Pleasingly, this in turn satisfies a skeletal formal synthesis of sesquithuriferol **150** and, in turn, the original target α-duprezianene **151**, mixed with its isomer β-duprezianene **167**. Chiefly, the key PKR employed in this strategy, to rapidly form the complex [5,6,5]-fused structure, had proved extremely successful, opening up the possibility to utilise this strategy in pursuit of other related sesquiterpene natural products.

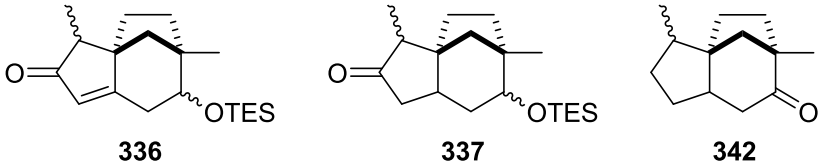


Scheme 3.54

3.3 NMR studies of key intermediates

Having successfully established a formal skeletal synthesis towards sesquithuriferone and the subsequent related sesquiterpenes, we were keen to develop greater understanding of the mixtures of isomers generated during the latter stages of the synthesis. Many of the compounds accessed had been afforded as complex mixtures of isomers which were extremely challenging to characterise. To this end, an NMR specialist was consulted and three key intermediates from the developed synthesis were identified for further analysis. These three intermediates were enone **336**, generated through alkylation of the PKR product, ketone **337**, afforded through hydrogenation and attempted epimerisation, and advanced ketone **342**, which was

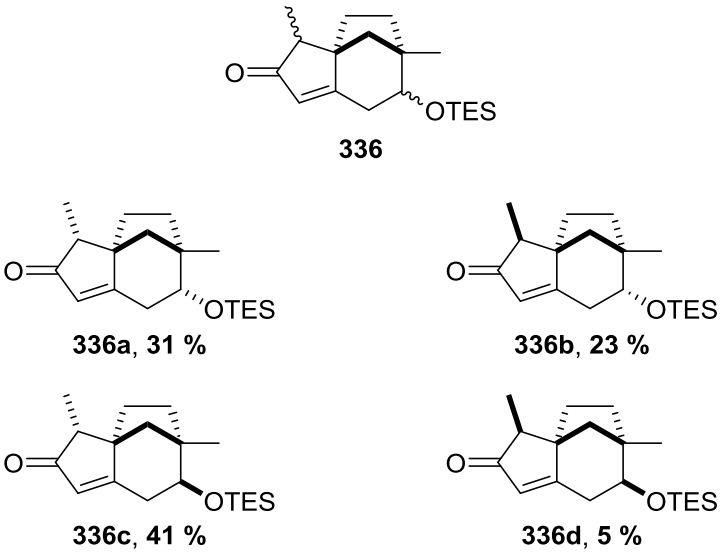
formed through a five step process from intermediate **337**, and was one step away from the final, 6-membered enone synthesised (**Figure 3.5**).



336 **337** **342**

Figure 3.5

The first of the three compounds to be further analysed was enone **336**. A series of NMR techniques were thus employed to provide greater insight towards the ratio of isomers present within this mixture. Further details of this analysis can be found within the appendix. Following this analysis, it was discovered that intermediate **336** was composed of a mixture of 4 isomers (**Figure 3.6**). Unfortunately, it appeared that the greater ratio of products (72 %, **336a** + **336c**) featured the α-methyl *anti*- to the bridging methylene unit. This was opposite to the orientation required to match natural sesquithuriferone.



336

336a, **31 %** **336b**, **23 %**

336c, **41 %** **336d**, **5 %**

Figure 3.6

Analysis of ketone **337** was then performed in a similar manner. To our surprise and delight, at this stage it was discovered that the hydrogenation had not only proceeded in entirely facially selective manner, but, also, the desired stereoselectivity had been achieved, contrary to expectation based on our previous work (**Figure 3.7**). As such, the hydrogen was found to have been delivered *syn* to the bridging methylene unit. Crucially, our hydrogenation conditions had proven to be successful in reducing a 5-membered ring of this type with the correct selectivity required to access sesquithuriferone and related natural products. This was considered to be the first example of such a process.

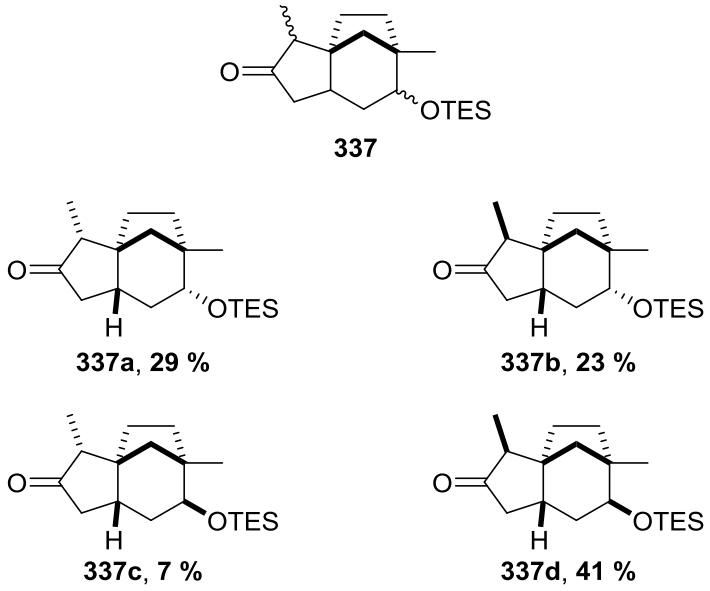


Figure 3.7

This extended NMR analysis also provided evidence that the attempted epimerisation was, at least, partially successful. On comparing the component isomer ratio of enone **336** with that of epimerised ketone **337**, an increase in the amount of correctly orientated α-methyl group was found. Interestingly, no epimerisation was observed in the diastereomer with the TES protected secondary alcohol *anti*- to the bridging methylene unit (23 % **337b** vs. 29 % **337a**). Pleasingly however, in the case of the *syn*- protected functionality, a significant increase in *syn* α-methyl orientation (41 % **337d** vs. 7 % **337c**) was observed. This suggests that the orientation of the TES unit plays a much greater role than had been originally considered.

Finally, similar extensive NMR analysis was performed on advanced ketone intermediate **342**. To this end, it was discovered that compound **342** had been afforded as a mixture of diastereomers with slight preference for the desired *syn* α-methyl functionality, as shown by compound **342a** (**Figure 3.8**). Crucially, the hydrogenation which, unknown to us, had occurred with the desired facial selectivity, provided the opportunity for synthetic route contraction. It was realised that as compound **342** comprised a mixture of **342a** and **342b**, the desired final compound sesquithuriferone **149** could actually be reached in one step according to Subba Rao and co-worker's synthetic strategy.[207] This negated the need to form the 6-membered enone, as had been performed (**c**.**f**. **Scheme 3.53**). Further to this, while not allowing a fully stereoselective synthesis of the target molecule, there would at least be a majority of the desired α-methyl diastereomer in this intermediate, and the subsequent achievable sesquiterpene products. Thus, it was discovered through these key NMR analyses that the developed synthetic strategy had proved significantly more successful than had originally been considered.

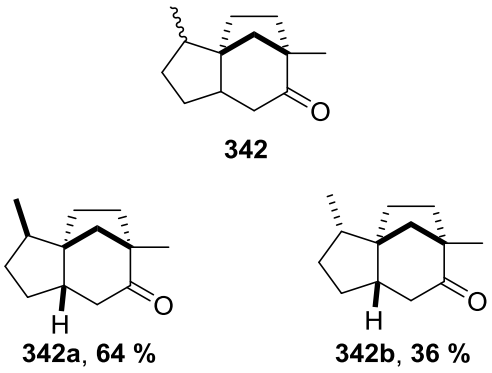
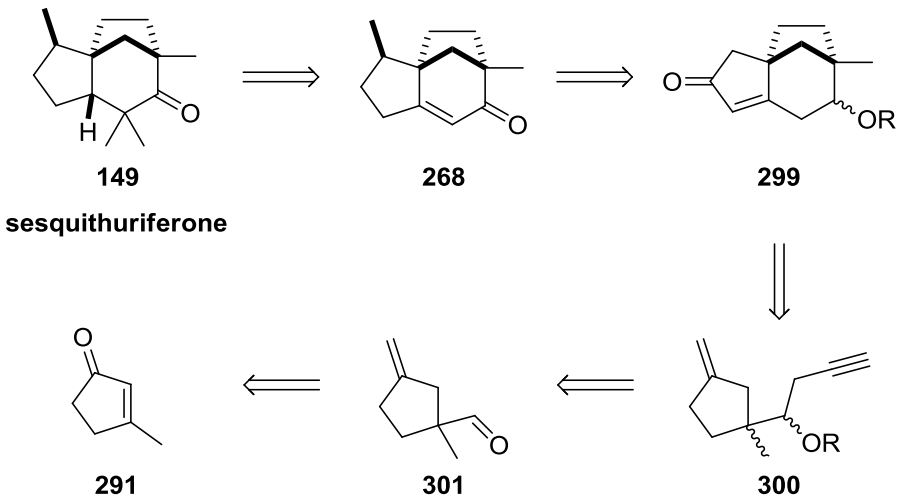


Figure 3.8

4 Summary

In summary, a novel synthetic strategy was devised and investigated towards stereoselective formation of the [5,6,5]-fused natural target, sesquithuriferone **159** (**Scheme 3.55**). It was envisioned that sesquithuriferone **159** could be constructed from the known enone **268**, with this intermediate previously shown to afford the final compound in two steps.[207] This key intermediate could, in turn, be furnished through transformation of a [5,6,5]-fused enone such as **299**. This cyclic enone would be accessed from an enyne of type **300** through use of the PKR, which would allow rapid generation of much of the required molecular complexity. The requisite enyne **300** would thus be generated from aldehyde **310**, which would, itself, be produced through a conjugate addition strategy from commercially available cyclopentenone **291**.



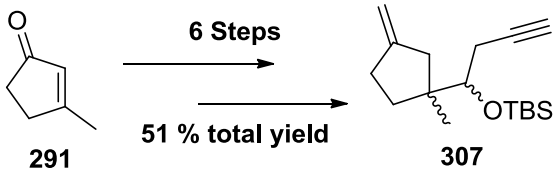
149 **268** **299**

sesquithuriferone

291 **301** **300**

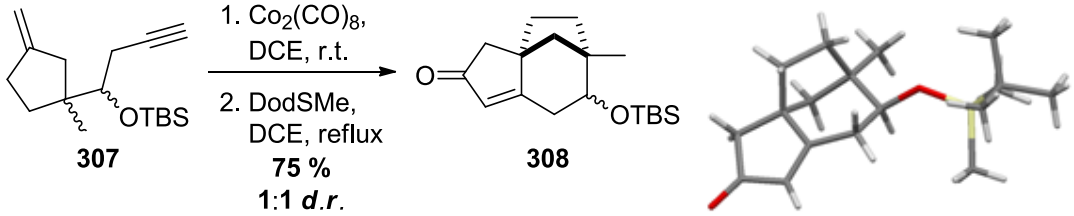
Scheme 3.55

Towards this aim, a route was developed to afford enyne **307**, in 6 steps and 51 % total yield, from the commercially available starting material **291** (**Scheme 3.56**). A TBS group was installed in the molecule as it was thought that this would prove suitable stable in the key PKR to follow while allowing relatively trivial removal when required. This developed route was robust, allowing generation of multigram quantities of the requisite enyne **307** and allowing investigation of the key PKR.



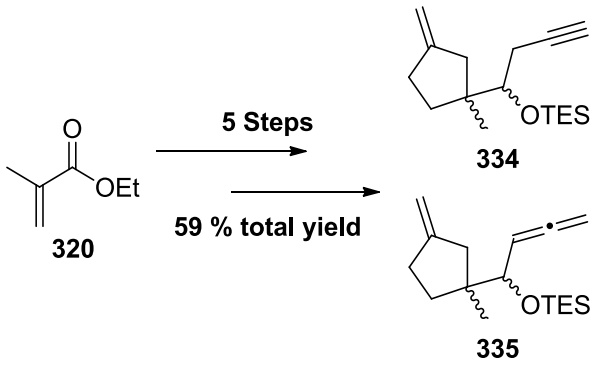
Scheme 3.56

On attempting the stoichiometric PKR, to our delight, the desired [5,6,5]-fused tricyclic compound **308** was found to form without incident. Thus, tricyclic enone **308** was afforded in as high as 75 % yield and as a 1:1 mixture of diastereomers. Further to this, a X-ray crystal structure of one of these diastereomers was secured, providing additional evidence of the complex 3-dimensional structure which had been formed through this key PKR. It was thus clear that this PKR strategy provided an elegant method towards construction of the skeletal framework of the tricyclic sesquiterpenes which were targeted.



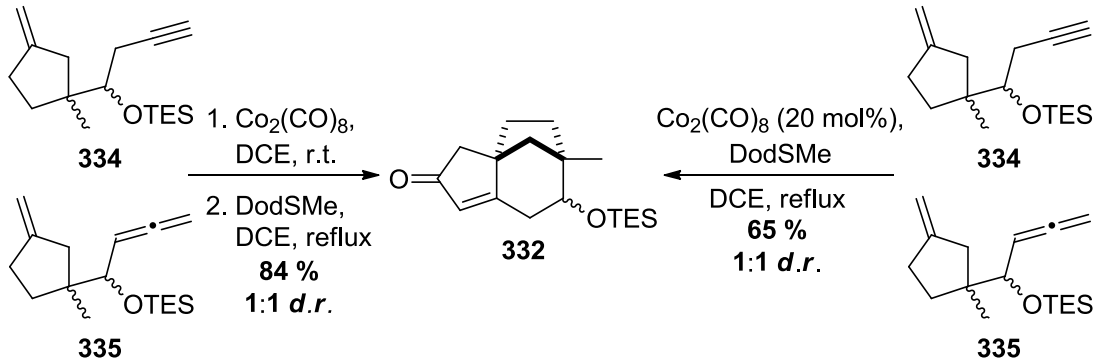
Scheme 3.57

Following successful formation of this [5,6,5]-fused species **308**, the proposed synthetic strategy was progressed. Regrettably, successful cleavage of the TBS protection on the secondary alcohol of intermediate **308** could not be achieved. An alternative TES protection strategy was considered, where, it was hoped, a suitable balance of stability and tractability would be afforded. As such, employing synthetic advancements developed within our previous investigations, an inseparable mixture of TES protected enyne **334** and allene **335** was generated in 5 steps and 59 % total yield from readily available ethyl methacrylate **320** (**Scheme 3.58**).



Scheme 3.58

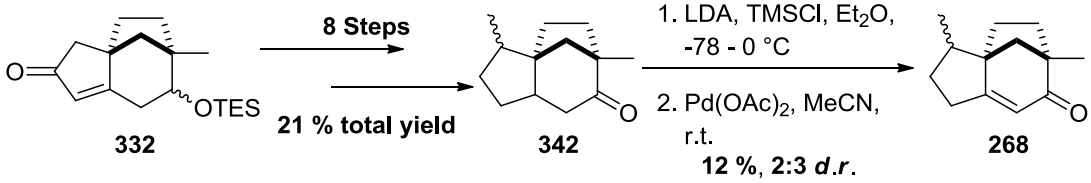
With the mixture of enyne **334** and allene **335** in hand, the key PKR was once again attempted. Pleasingly, the PKR, when performed under standard stoichiometric conditions, was found to proceed in even greater yield than before (**Scheme 3.59**). To our delight, on attempting catalytic conditions previously developed within our laboratories, the desired [5,6,5]-fused species **332** was furnished in only slightly reduced yields in a one pot fashion, employing a catalytic PKR.



Scheme 3.59

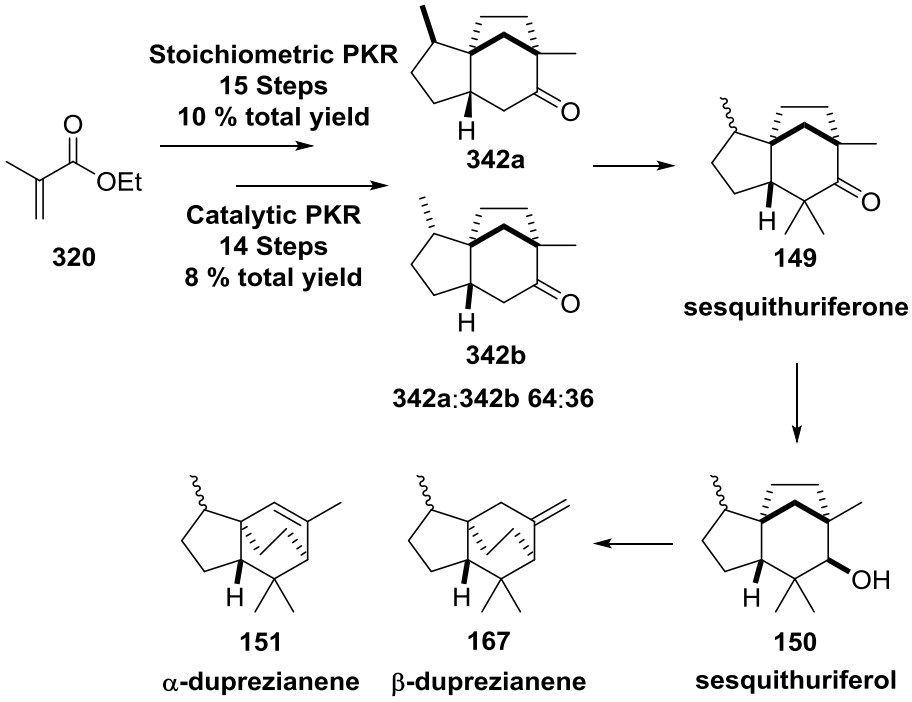
Having accessed compound **332**, our deprotection and oxidation strategy was once again attempted. Cleavage of the TES functionality was found to proceed efficiently but the subsequent oxidation could not be achieved. Consequently, an alternative strategy towards our target molecule was investigated. Accordingly, intermediate **332** was converted to advanced ketone intermediate **342** over 8 subsequent steps in 21 % total yield (**Scheme 3.60**). At this stage, due to previous synthetic attempts towards sesquithuriferone **159**, we believed that the hydrogenation we had performed

had proceeded with the undesired facial selectivity. Therefore, the 6-memebered enone **268**, previously described, was constructed from this advanced ketone in 12 % yield as an apparent 2:3 mixture of diastereomers. With formation of this compound, a formal skeletal synthesis of sesquithuriferone **159** had been achieved. Indeed, according to literature precedent it would now be possible to access the natural product target in two subsequent steps.[207]



Scheme 3.60

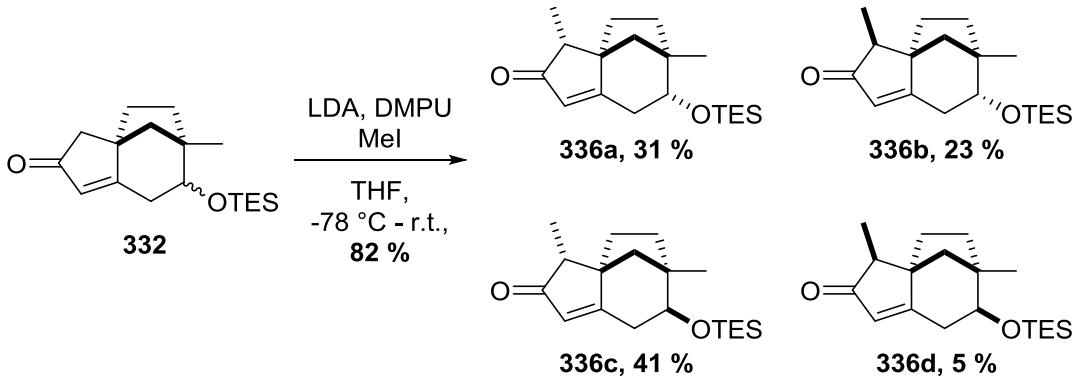
Due to the complexity of the compounds generated throughout this sequence much of the stereochemical subtelty could not be determined. In a final attempt to further understand these sterochemical consideration, and provide insight in how best to approach the desired steroeselctive synthesis, an NMR specialist was consulted who performed extensive analysis on a few key compounds. The results of these studies were extremly informative and, to our delight, it was discovered that our hydrogenation had, in fact, proceeded with complete desired faical selectivity. With this finding it was now realised that we had attained a formal skeletal synthesis of sesquithuriferone **159** with formation of ketone species **342** (**Scheme 3.61**).[207] Indeed, this advanced compound was actually one step closer to the final target molecule, with only a *gem*-dimethyl alkylation remaining to be performed. In assessing our route, it was thus discovered that we had achieved this formal synthesis in an impressive 10 % total yield over 15 steps, when employing a stoichiometric PKR strategy. When the catalytic variant was used, a slight reduction in overall yield was observed but the overall route was one step shorter. Further to this, with the formal skeletal synthesis of sesquithuriferone **159** realised, we had, in fact, also achieved a formal skeletal synthesis of sesquithuriferol **150**, and, in turn, the original target α-duprezianene **151** and its isomer β-duprezianene **167**.[149]


Stoichiometric PKR
15 Steps
10 % total yield
Catalytic PKR
14 Steps
8 % total yield
320
342a
342b
342a:342b 64:36
149
sesquithuriferone
150
sesquithuriferol
167
β-duprezianene
151
α-duprezianene

Scheme 3.61

5 Future work

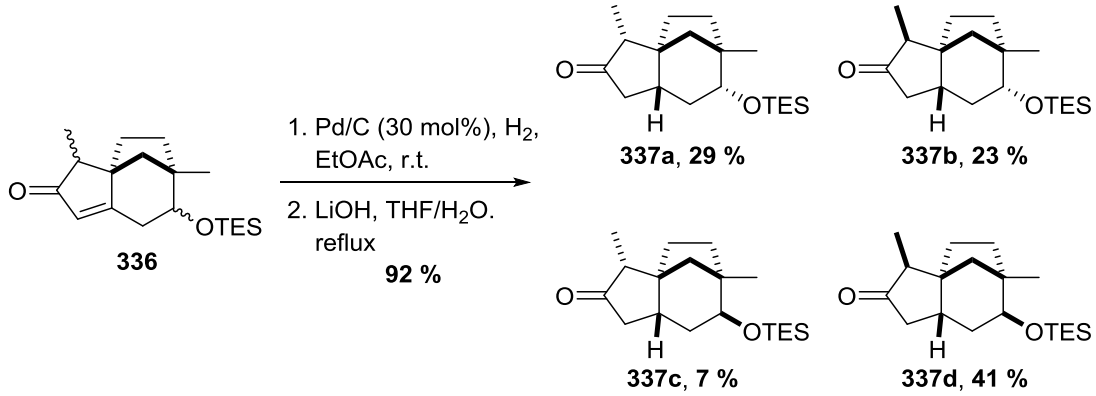
Having achieved a formal skeletal synthesis of sesquithuriferone **159**, the validity of a PKR strategy towards sesquiterpenes of this type has been proven without question. However, the overall goal of this project was, in fact, to develop a stereoselective synthesis of this target molecule, thus allowing, through further transformations, stereoselective access to a series of related natural products. In this regard, with the knowledge gained from our extensive NMR studies, it is clear that the alkylation is a key area for further focus within the synthetic strategy. Whilst the transformation was found to proceed in excellent yield, a mixture of isomers resulted (**Scheme 3.62**). With this in mind, further synthetic endeavour must focus on installation of the methyl unit with greater selectivity, *syn* to the bridging methylene unit. Many alternative protocols remain to trialled towards this goal; clearly a key challenge, however, will be analysis of the selectivities resulting.



Scheme 3.62

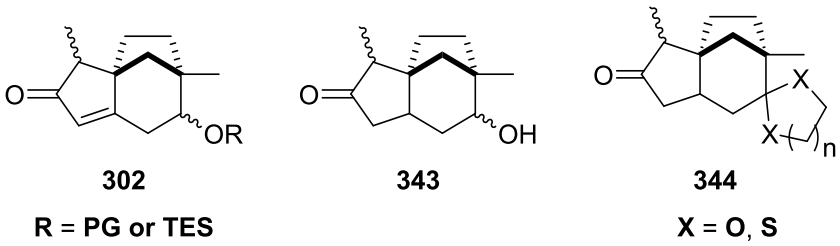
Through successful implementation of a selective alkylation, sesquithuriferone **159** and the related sesquiterpenes would be accessible in a fully stereoselective fashion. However, should this not prove possible, an alternative opportunity to set this compounds stereochemistry exists through an epimerisation strategy. Indeed, an epimerisation was attempted within our synthesis, however, in a similar manner to our alkylation, the extent of the isomeric mixture was not clarified until further NMR studies were performed. With this analysis in hand, it appeared that our

epimerisation protocol had proved partially successful, with no epimerisation observed for the isomers featuring protected alcohols *anti*- to the methylene bridge (**Scheme 3.63**).



Scheme 3.63

To establish a more efficient epimerisation, undoubtedly a number of potential conditions remain to be trialled. However, should these alternative conditions fail to afford the desired stereochemistry, alternative substrates for these epimerisation attempts could be formed and investigated. In the first instance, epimerisation could be attempted on the product of alkylation **302**, either protected or as the free alcohol, which would be accessible using the previously developed deprotection conditions (**Figure 3.9**). In a similar manner, the free alcohol of hydrogenated product **343** should also be considered, as the epimerisation may proceed quite differently in the absence of TES protection. Finally, removal of a stereogenic centre through formation of an acetal or thioacetal, such as in compound **344**, would again provide a significantly different environment in which to attempt the epimerisation. This final strategy would, however, require a far more circuitous route to form the initial substrates.



302 **343** **344**

R = PG or TES **X = O, S**

Figure 3.9

Finally, as previously mentioned, the completed formal skeletal synthesis served to highlight the potential of the PKR to form complex fused compounds of this type. Accordingly, with this strategic rationale, many other sesquiterpenes remain to be investigated. Though each individual target will of course present its own unique pitfalls and obstacles, we can now clearly see that the PKR provides a potent means towards their synthesis.

6 Experimental

6.1 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 argon atmosphere, unless otherwise stated. Purification was carried out according to standard laboratory methods.[195]

- Dry DCM, Et_2O, THF, and PhMe were obtained from an Innovative Technology, Pure Solv, SPS-400-5 solvent purification system. All other solvents were used as purchased unless required dry, wherein distillation under argon over calcium hydride was performed prior to use.
- TBAF was obtained as a 1.0 M solution in THF.
- Propargyl bromide was obtained as an 80 wt. % solution in toluene.
- *n*-BuLi was obtained as a solution in hexanes and was standardised using salicylaldehyde phenylhydrazone.[196]
- *i*-PrMgCl was obtained as a solution in THF and was standardised using salicylaldehyde phenylhydrazone.[196]
- NaHMDS was obtained as a 1 M solution in THF.
- BH_3·DMS was obtained as a 2 M solution in THF.
- Petroleum ether refers to petroleum ether in the boiling point (b.p.) range 40-60 °C unless otherwise stated.

Instrumentation and data

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV_{254}. Plates were 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.

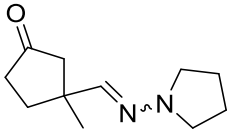
IR spectra were obtained on a Shimadzu IRAffinity-1 machine.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz and 101 MHz, respectively. ^{11}B NMR was recorded on a Bruker DPX 400 spectrometer at 128 MHz. Coupling constants are reported in Hz and refer to $^{3}J_{H\text{-}H}$ interactions, unless otherwise stated.

High resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap XL instrument, a Waters Xevo G2-S, and a Waters GCT Premier at the EPSRC Mass Spectrometry facility at the University of Wales, Swansea.

6.2 Experimental procedures and compound analyses

Preparation of 3-methyl-3-((pyrrolidin-1-ylimino)methyl)cyclopentan-1-one, **290**.



Chemical Formula: $C_{11}H_{18}N_2O$
Molecular Weight: 194.28

Scheme 3.20

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 3-methylcyclopent-2-en-1-one, **291** (3.37 mL, 34.06 mmol) in THF (50 mL), and the solution was cooled to -78 °C. To this solution was added TBSOTf (11.74 mL, 51.09 mmol) dropwise and the reaction mixture was then stirred at -78 °C for 30 min. A solution of *N*-(pyrrolidin-1-yl)methanimine, **214** (6.69 g, 68.11 mmol) in THF (18 mL) was then added to the reaction mixture dropwise and the resulting solution was then allowed to warm gradually to r.t., with stirring, over 16 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was dissolved in THF (34 mL) and TBAF (8.91 g, 34.06 mmol) was added. The reaction mixture was then allowed to stir at r.t. for 30 mins. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 3-methyl-3-((pyrrolidin-1-ylimino)methyl)cyclopentan-1-one, **290** (5.81 g, 88 % yield) as a colourless oil.

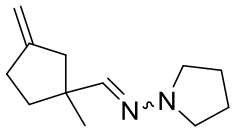
FTIR (**cm^{-1}**): 2955, 2872, 1734, 1597, 1460, 1402, 1341, 1252, 1163.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.43 (s, 1H, N=C<u>H</u>), 3.05-3.01 (m, 4H, NC<u>H</u>$_2$), 2.57 (d, 1H, ^2J = 17.4 Hz, alkyl C<u>H</u>), 2.29-2.17 (m, 2H, alkyl C<u>H</u>), 2.13-2.07 (m, 1H, alkyl C<u>H</u>), 1.97 (d, 1H, ^2J = 17.4 Hz, alkyl C<u>H</u>), 1.86-1.73 (m, 5H, alkyl C<u>H</u>), 1.20 ppm (s, 3H, alkyl C<u>H</u>$_3$)

^{13}C NMR (**101 MHz, $CDCl_3$**): 209.4, 141.3, 51.4, 50.0, 42.8, 37.0, 34.6, 25.6, 23.6 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{11}H_{19}N_2O$ (M^+ + H): 195.1492. Found: 195.1489.

Preparation of 1-(1-methyl-3-methylenecyclopentyl)-*N*-(pyrrolidin-1-yl)methanimine, **304**.



Chemical Formula: $C_{12}H_{20}N_2$
Molecular Weight: 192.31

Scheme 3.20

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added methyltriphenylphosphonium bromide (15.88 g, 44.46 mmol) and THF (40 mL). To this suspension was added KO*t*Bu (4.99 g, 44.46 mmol). The reaction mixture was allowed to stir at r.t. for 30 min before a solution of 3-methyl-3-((pyrrolidin-1-ylimino)methyl)cyclopentan-1-one, **290** (4.95 g, 25.94 mmol) in THF (20 mL) was added. The reaction mixture was then stirred for 4 h. After this time, the reaction mixture was diluted with saturated aqueous NH_4Cl solution (30 mL) and subsequent extraction was performed with Et_2O (30 mL × 3). The combined organics were then washed with water (25 mL × 2), and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give 1-(1-methyl-3-methylenecyclopentyl)-N-(pyrrolidin-1-yl)methanimine, **304** (4.71 g, 94 % yield) as a colourless oil.

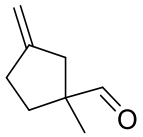
FTIR (**cm^{-1}**): 2951, 2864, 2826, 1659, 1599, 1460, 1429, 1341, 1202, 1101.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.55 (s, 1H, N=C<u>H</u>), 4.84-4.81 (m, 2H, vinylic C<u>H</u>) 3.08-3.05 (m, 4H, NC<u>H</u>$_2$), 2.50 (d, 1H, ^2J = 16.0 Hz, alkyl C<u>H</u>), 2.39-2.35 (m, 2H, alkyl C<u>H</u>), 2.12 (d, 1H, ^2J = 16.0 Hz, alkyl C<u>H</u>), 1.90-1.83 (m, 5H, alkyl C<u>H</u>), 1.57-1.50 (m, 1H, alkyl C<u>H</u>), 1.11 ppm (s, 3H, alkyl C<u>H</u>$_3$)

^{13}C NMR (**101 MHz, $CDCl_3$**): 152.1, 145.1, 105.9, 51.7, 45.8, 45.5, 38.1, 31.0, 24.3, 23.0 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{12}H_{21}N_2$ (M^+ + H): 193.1699. Found: 193.1695.

Preparation of 1-methyl-3-methylenecyclopentane-1-carbaldehyde, **301**.



Chemical Formula: $C_8H_{12}O$
Molecular Weight: 124.18

Scheme 3.20

To a round bottom flask fitted with a magnetic stirrer bar was added 1-(1-methyl-3-methylenecyclopentyl)-*N*-(pyrrolidin-1-yl)methanimine, **304** (4.71 g, 24.49 mmol) and acetone (61 mL). To this solution was added *p*-TSA·H_2O (9.32 g, 48.98 mmol) and water (0.4 mL). The reaction mixture was allowed to stir at r.t. for 5 h before being dried over Na_2SO_4, filtered, and concentrated at reduced pressure of 100 mbar and at 0 °C. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 1-methyl-3-methylenecyclopentane-1-carbaldehyde, **301** (2.75 g, 90 % yield) as a colourless oil.

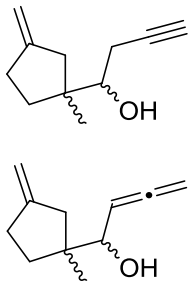
FTIR (**cm^{-1}**): 2957, 2932, 2872, 1724, 1696, 1456, 1429.

^{1}H NMR (**400 MHz, $CDCl_3$**,): 9.50 (s, 1H, CO<u>H</u>), 4.92-4.88 (m, 2H, vinylic C<u>H</u>), 2.68 (d, 1H, ^2J = 17.3 Hz, alkyl C<u>H</u>), 2.48-2.32 (m, 2H, alkyl C<u>H</u>), 2.10 (d, 1H, ^2J = 17.3 Hz, alkyl C<u>H</u>), 2.05-2.00 (m, 1H, alkyl C<u>H</u>), 1.55-1.48 (m, 1H, alkyl C<u>H</u>), 1.14 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 204.7, 149.9, 107.2, 53.8, 41.3, 34.0, 31.1, 19.8 ppm.

HRMS *m*/*z* (**EI**): Calc. for $C_8H_{12}O$ (M^+): 124.0888. Found: 124.0894.

Preparation of 1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, **305**, **& 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol**, **306**.



Chemical Formula: $C_{11}H_{16}O$
Molecular Weight: 164.25

Scheme 3.20

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added zinc powder (1.66 g, 6.33 mmol) to a mixture of DMF (20 mL) and Et_2O (20 mL). To this suspension was added propargyl bromide (2.11 mL, 18.99 mmol), after which the reaction mixture was stirred at r.t. for 15 min. To the reaction mixture was then added 1-methyl-3-methylenecyclopentane-1-carbaldehyde, **301** (786 mg, 6.33 mmol) in a mixture of DMF (12 mL) and Et_2O (12 mL). The resulting suspension was then allowed to stir at r.t. for 17 h before being diluted with EtOAc (30 mL) and filtered through celite. The filtrate was then washed with saturated aqueous NH_4Cl solution (30 mL) and brine (30 mL × 2), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give 1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol**,** **305**, & 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol, **306** (856 mg, 82 % yield, 7:1 **305**:**306**) as an inseparable mixture which appeared as a colourless oil.

1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, **305**, & 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol, **306** were isolated as a complex and inseparable mixture of isomers. The ratio of **305** and **306** was determined as 7:1 respectively. ^{1}H NMR spectroscopy was performed on this mixture, however, the ^{1}H NMR spectroscopic data has been separated for simplicity.

FTIR (**cm^{-1}**): 3469, 3302, 2958, 2936, 2875, 1656, 1428, 1377, 1061, 1022.

Compound 305 ^{1}H NMR

^{1}H NMR (**400 MHz, CDCl$_3$**): 4.88-4.82 (m, 2H, vinylic C<u>H</u>) 3.60-3.56 (m, 1H, OHC<u>H</u>), 2.42-2.26 (m, 5H, alkyl C<u>H</u>), 2.17 (brs, 1H, CHO<u>H</u>), 2.13 & 1.96 (d, 1H in total, ^{2}J = 16.3 Hz, alkyl C<u>H</u>, ratio 1:1), 2.06 (t, 1H, ^{4}J = 2.6 Hz, C≡C<u>H</u>), 1.77-1.61 (m, 1H, alkyl C<u>H</u>), 1.58-1.52 (m, 0.5H, alkyl C<u>H</u>), 1.40-1.34 (m, 0.5H, alkyl C<u>H</u>), 0.91 ppm (s, 3H, alkyl C<u>H</u>$_3$).

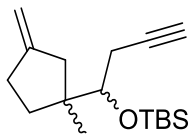
Compound 306 ^{1}H NMR

^{1}H NMR (**400 MHz, CDCl$_3$**): 5.29-5.23 (m, 1H, vinylic C<u>H</u>), 4.88-4.82 (m, 4H vinylic C<u>H</u>), 4.00-3.96 (m, 1H, OHC<u>H</u>) 2.42-2.26 (m, 3H, alkyl C<u>H</u>), 2.17 (brs, 1H, CHO<u>H</u>), 2.13 & 1.96 (d, 1H in total, ^{2}J = 16.3 Hz, alkyl C<u>H</u>, ratio 1:1), 1.77-1.61 (m, 1H, alkyl C<u>H</u>), 1.58-1.52 (m, 0.5H, alkyl C<u>H</u>), 1.40-1.34 (m, 0.5H, alkyl C<u>H</u>), 0.95 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, CDCl$_3$**): 151.64, 151.58, 106.4, 106.2, 92.3, 82.2, 76.94, 76.88, 70.7, 46.42, 46.39, 44.4, 44.1, 43.6, 35.8, 35.6, 35.4, 30.93, 30.86, 30.72, 30.65, 23.6, 23.5, 20.40, 20.36, 19.7, 19.5.

HRMS *m*/*z* (**EI**): Calc. for $C_{11}H_{16}O$ (M^+): 164.1201. Found: 164.1203.

Preparation of *tert*-butyldimethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **307**.



Chemical Formula: $C_{17}H_{30}OSi$
Molecular Weight: 278.51

Scheme 3.20

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added the inseparable mixture of 1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol, **305**, & 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol, **306** (1.15

g, 7.02 mmol, 7:1 **305**:**306**) in DCM (35 mL). The mixture was cooled to 0 °C and DMAP (258 mg, 2.11 mmol), Et_3N (2.00 mL, 14.35 mmol), and TBSOTf (2.10 mL, 9.14 mmol) were added. The reaction mixture was then allowed to gradually warm to r.t., with stirring, for 16 h. The reaction mixture was then washed with saturated aqueous NH_4Cl solution (30 mL), with further extraction with DCM (2 × 30 mL). The combined organics were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 10 % Et_2O in petroleum ether) to give *tert*-butyldimethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **307** (1.69 g, 98 % yield) as a colourless oil.

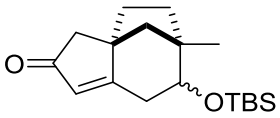
FTIR (**cm^{-1}**): 3314, 2958, 2930, 2857, 1655, 1435, 1254, 1090.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.86-4.81 (m, 2H, vinylic C<u>H</u>), 3.62 (t, 1H, *J* = 5.4 Hz, TBSOC<u>H</u>), 2.46-2.22 (m, 5H, alkyl C<u>H</u>), 2.10 & 1.99 (d, 1H in total, ^2J = 16.3 Hz, ratio 1:1), 1.98-1.96 (m, 1H, alkyl C<u>H</u>), 1.69-1.55 (m, 1.5H, alkyl C<u>H</u>), 1.43-1.37 (m, 0.5H, alkyl C<u>H</u>), 0.92 (s, 3H, alkyl C<u>H</u>$_3$), 0.91-0.89 (m, 9H, alkyl C(C<u>H</u>$_3$)$_3$), 0.15-0.14 (m, 3H, SiC<u>H</u>$_3$), 0.09-0.07 ppm (m, 3H, SiC<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 152.0, 106.1, 83.5, 78.8, 78.4, 50.5, 48.4, 45.9, 44.5, 37.4, 36.0, 30.4, 30.2, 26.2, 26.0, 24.4, 24.2, 19.7, 18.8, -3.4, -4.5.

HRMS *m*/*z* (**EI**): Calc. for $C_{17}H_{30}OSi$ (M^+): 278.2066. Found: 278.2054.

Preparation of (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308**.



Chemical Formula: $C_{18}H_{30}O_2Si$
Molecular Weight: 306.52

General procedure A

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, reflux condenser and an argon inlet was added *tert*-butyldimethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **307** (a) in DCE (b). To this was added Co_2CO_8 (c), with the resulting mixture stirred at r.t. for 2 h. Upon completion of the reaction, the mixture was filtered through celite, eluting with petroleum ether, and concentrated *in vacuo*. The crude product was dissolved in DCE (d) and DodSMe (e) was added. The mixture was heated to reflux and stirred for a period of time (f). The mixture was then filtered through celite, eluting with Et_2O, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308** (g) with specified *d.r.* (h).

Scheme 3.21

The following experiments were performed using **General procedure A**. Results are reported as: (a) amount of tert-butyldimethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **307**, (b) volume of DCE, (c) amount of Co_2CO_8, (d) volume of DCE, (e) volume of DodSMe, (f) time, (g) yield of (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308** as a pale pink oil, and (h) *d.r.*

Run 1: (a) 140 mg, 0.50 mmol, (b) 5 mL, (c) 188 mg, 0.55 mmol, (d) 5 mL, (e) 0.60 mL, 2.25 mmol, and (f) 17 h, (g) 95 mg, 62 % yield, and (h) 1:1.

Run 2: (a) 1.93 g, 6.93 mmol, (b) 70 mL, (c) 2.61 g, 7.62 mmol, (d) 70 mL, (e) 8.27 mL, 31.19 mmol, (f) 16 h, (g) 1.58 g, 75 % yield, and (h) 1:1.

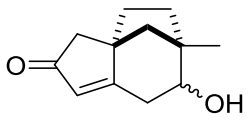
FTIR (**cm^{-1}**): 2951, 2928, 2857, 1709, 1676, 1622, 1470, 1254, 1094.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.68 & 5.63 (d, 1H in total, ^{4}J = 1.7 Hz, vinylic C<u>H</u>, ratio 1:1), 3.67-3.65 (m, 0.5H, TBSOC<u>H</u>), 3.55 (ddd, 0.5H, J = 6.1, 9.3 Hz, ^{4}J = 1.2 Hz, TBSOC<u>H</u>), 2.92 (dd, 0.5H, ^{2}J = 15.4 Hz, J = 6.2 Hz, alkyl C<u>H</u>), 2.63-2.61 (m, 1H, alkyl C<u>H</u>), 2.37-2.30 (m, 2.5H, alkyl C<u>H</u>), 2.12-2.05 (m, 0.5H, alkyl C<u>H</u>), 1.96-1.87 (m, 1.5H, alkyl C<u>H</u>), 1.77 (d, 0.5H, ^{2}J = 12.2 Hz, alkyl C<u>H</u>), 1.67-1.58 (m, 2H, alkyl C<u>H</u>), 1.46-1.34 (m, 1H, alkyl C<u>H</u>), 1.26-1.25 (m, 0.5H, alkyl C<u>H</u>), 1.06 & 1.05 (s, 3H in total, alkyl C<u>H</u>$_3$, ratio 1:1), 0.90 & 0.85 (s, 9H in total, alkyl SiCC<u>H</u>$_3$)$_3$, ratio 1:1), 1.51 & 1.57 (s, 3H, SiC<u>H</u>$_3$, ratio 1:1), 1.58 & 1.49 ppm (s, 3H in total, SiC<u>H</u>$_3$, ratio 1:1).

^{13}C NMR (**101 MHz, $CDCl_3$**): 208.8, 208.6, 186.1, 185.4, 125.5, 124.2, 76.8, 76.3, 52.1, 51.4, 48.7, 46.2, 46.0, 45.2, 44.9, 44.5, 36.2, 35.5, 35.0, 34.3, 34.2, 29.7, 25.9, 25.8, 24.1, 23.9, 18.1, 18.0, -4.0, -4.3, -4.76, -4.80 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{18}H_{31}O_2Si$ (M^+ + H): 307.2088. Found: 307.2088.

Attempted preparation of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310**.



Chemical Formula: $C_{12}H_{16}O_2$
Molecular Weight: 192.26

General procedure B

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308** (a) in THF (b). The solution was held at temperature (c) and TBAF (d) was added. The reaction mixture was allowed to stir at this temperature for an allocated period of time (e). The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** (f). Unfortunately, the desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** was not observed.

General procedure C

To a round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added additive (a) in THF (b), and the mixture was allowed to stir at r.t. for 30 min. To the mixture was added (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308** (c) in THF (d). The reaction mixture was then allowed to stir at temperature (e) for an allocated period of time (f). The mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give recovered SM (g) or the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** (h). Unfortunately, the desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** was not observed.

General procedure D

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (3*a*,6)-7-((*tert*-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308** (a) in acetone (b). The solution was held at temperature (c) and CBr_4 (d) and PPh_3 (e) were added. The reaction mixture was allowed to stir at this temperature for an allocated period of time (f). The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give recovered

SM (g) or the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** (h). Unfortunately the desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** was not observed.

Scheme 3.23, **Table 3.3**, **Entries 1 & 2**

The following experiments were performed using **General procedure B**. Results are reported as: (a) amount of (3*a*,6)-7-((tert-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308**, (b) volume of THF, (c) temperature, (d) volume of TBAF, (e) time, and (f) yield of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** as a colourless oil.

Entry 1: (a) 100 mg, 0.33 mmol, (b) 3 mL, (c) r.t., (d) 0.99 mL, 0.99 mmol, (e) 1 h, and (f) 45 mg, 79 % yield.

Entry 2: (a) 100 mg, 0.33 mmol, (b) 3 mL, (c) 0 °C, (d) 0.99 mL, 0.99 mmol, (e) 2 h, and (f) 39 mg, 68 % yield.

Scheme 3.23, **Table 3.3**, **Entries 3**, **4 & 5**

The following experiments were performed using **General procedure C**. Results are reported as: (a) additive employed and amount used, (b) volume of THF, (c) amount of (3*a*,6)-7-((tert-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308**, (d) volume of THF, (e) temperature, (f) time, (g) yield of recovered SM, and (h) yield of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** as a colourless oil.

Entry 3: (a) AcOH, 0.09 mL, 1.65 mmol, (b) 8 mL, (c) 100 mg, 0.33 mmol, (d) 7 mL, (e) r.t., (f) 4 h, (g) 100 mg, 100 % yield, and (h) 0 mg, 0 % yield.

Entry 4: (a) AcOH, 0.09 mL, 1.65 mmol, (b) 8 mL, (c) 100 mg, 0.33 mmol, (d) 7 mL, (e) reflux, (f) 7 h, (g) 49 mg, 49 % yield, and (h) 16 mg, 28 % yield.

Entry 5: (a) NH_4F, 61 mg, 1.65 mmol, (b) 8 mL, (c) 100 mg, 0.33 mmol, (d) 7 mL, (e) r.t., (f) 5 h, (g) 0 mg, 0 % yield, and (h) 27 mg, 47 % yield.

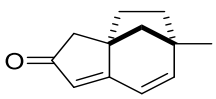
Scheme 3.24, **Table 3.4**

The following experiments were performed using **General procedure D**. Results are reported as: (a) amount of (3*a*,6)-7-((tert-butyldimethylsilyl)oxy)-6-methyl-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **308**, (b) volume of acetone, (c) temperature, (d) amount of CBr_4, (e) amount of PPh_3, (f) time, (g) yield of recovered SM, and (h) yield of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** as a colourless oil.

Entry 1: (a) 100 mg, 0.33 mmol, (b) 3 mL, (c) r.t., (d) 12 mg, 0.04 mmol, (e) 9 mg, 0.04 mmol, (f) 4 h, (g) 0 mg, 0 % yield, (h) 58 mg, 95 % yield.

Entry 2: (a) 100 mg, 0.33 mmol, (b) 3 mL, (c) 0 °C, (d) 12 mg, 0.04 mmol, (e) 9 mg, 0.04 mmol, (f) 3 h, (g) 98 mg, 98 % yield, (h) 0 mg, 0 % yield.

Product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3a,6-methanoazulen-2(4*H*)-one, **312**.



Chemical Formula: $C_{12}H_{14}O$
Molecular Weight: 174.24

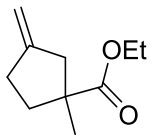
FTIR (**cm^{-1}**): 2949, 2934, 2872, 1697, 1670, 1608, 1570, 1263, 1161.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.39 (d, 1H, *J* = 9.2 Hz, vinylic C<u>H</u>), 6.34 (d, 1H, *J* = 9.2 Hz, vinylic C<u>H</u>), 5.62 (s, 1H, vinylic C<u>H</u>), 2.54 (d, 1H, ^{2}J = 18.4 Hz, alkyl C<u>H</u>), 2.42 (d, 1H, ^{2}J = 18.4 Hz, alkyl C<u>H</u>), 2.04-1.97 (m, 1H, alkyl C<u>H</u>), 1.85-1.79 (m, 1H, alkyl C<u>H</u>), 1.76-1.67 (m, 3H, alkyl C<u>H</u>), 1.64-1.61 (m, 1H, alkyl C<u>H</u>), 1.26 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 208.6, 180.6, 153.9, 120.93, 120.91, 51.2, 49.7, 46.6, 44.8, 39.6, 36.3, 24.3.

HRMS *m*/*z* (**ESI**): Calc. for $C_{12}H_{14}O$ (M^+ + H): 175.1123. Found: 175.1123.

Preparation of ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321**.



Chemical Formula: $C_{10}H_{16}O_2$
Molecular Weight: 168.24

General procedure E

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added ethyl methacrylate, **320** (a), 2-((trimethylsilyl)methyl)allyl acetate, **318**, (b), and $Pd(OAc)_2$ (c) in THF (d), and the solution was then degassed over 30 min. To the solution was added P(O*i*-Pr)$_3$ (e), the mixture was then heated to reflux and stirred for an allocated period of time (f). Following this time, the mixture was concentrated *in vacuo*, the residue was then dissolved in Et_2O (30 mL) and washed with water (30 mL × 2). The organics were further extracted with Et_2O (30 mL × 3) and washed with brine (30 mL). The combined organics were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 5 % Et_2O in petroleum ether) to give ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** (g).

Scheme 3.28, **Table 3.5**

The following experiments were performed using **General procedure E**. Results are reported as: (a) volume of ethyl methacrylate, **320**, (b) volume of 2-((trimethylsilyl)methyl)allyl acetate, **318**, (c) amount of $Pd(OAc)_2$, (d) volume of THF, (e) volume of $P(O\textit{i}\text{-}Pr)_3$, (f) time, and (g) yield of ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** as a colourless oil.

Entry 1: (a) 0.34 mL, 2.68 mmol, (b) 0.57 mL, 2.68 mmol, (c) 30 mg, 0.13 mmol, (d) 3 mL, (e) 0.17 mL, 0.67 mmol, (f) 2 h, and (g) 53 mg, 12 % yield.

Entry 2: (a) 0.34 mL, 2.68 mmol, (b) 0.57 mL, 2.68 mmol, (c) 30 mg, 0.13 mmol, (d) 3 mL, (e) 0.17 mL, 0.67 mmol, (f) 15 h, and (g) 117 mg, 26 % yield.

Entry 3: (a) 0.27 mL, 2.14 mmol, (b) 0.23 mL, 1.07 mmol, (c) 13 mg, 0.06 mmol, (d) 1.2 mL, (e) 0.06 mL, 0.26 mmol, (f) 20 h, and (g) 56 mg, 31 % yield.

Entry 4: (a) 2.00 mL, 16,10 mmol, (b) 1.14 mL, 5.37 mmol, (c) 60 mg, 0.27 mmol, (d) 6 mL, (e) 0.33 mL, 1.34 mmol, (f) 17 h, and (g) 469 mg, 52 % yield.

Entry 5: (a) 6.51 mL, 52.30 mmol, (b) 3.42 mL, 16.10 mmol, (c) 181 mg, 0.81 mmol, (d) 18 mL, (e) 1.00 mL, 4.03 mmol, (f) 18 h, and (g) 1.89 g, 70 % yield.

Entry 6: (a) 8.69 mL, 69.78 mmol, (b) 4.56 mL, 21.47 mmol, (c) 290 mg, 1.29 mmol, (d) 24 mL, (e) 1.38 mL, 5.58 mmol, (f) 20 h, and (g) 2.58 g, 72 % yield.

Entry 7: (a) 21.70 mL, 174.43 mmol, (b) 11.40 mL, 53.67 mmol, (c) 723 mg, 3.22 mmol, (d) 60 mL, (e) 3.44 mL, 13.95 mmol, (f) 18 h, and (g) 7.50 g, 83 % yield.

Entry 8: (a) 7.00 mL, 56.40 mmol, (b) 3.42 mL, 16.10 mmol, (c) 181 mg, 0.81 mmol, (d) 18 mL, (e) 1.00 mL, 4.03 mmol, (f) 16 h, and (g) 1.79 g, 66 % yield.

Entry 9: (a) 2.67 mL, 21.47 mmol, (b) 1.14 mL, 5.37 mmol, (c) 60 mg, 0.27 mmol, (d) 6 mL, (e) 0.33 mL, 1.34 mmol, (f) 17 h, and (g) 560 mg, 62 % yield.

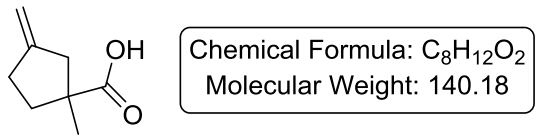
FTIR (**cm^{-1}**): 2981, 2973, 2953, 2938, 1727, 1662, 1234, 1177, 1109.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.88-4.83 (m, 2H, vinylic C<u>H</u>), 4.12 (q, 2H, *J* = 7.1 Hz, OC<u>H</u>$_2$), 2.79 (d, 1H, ^2J = 16.3 Hz, alkyl C<u>H</u>), 2.43-2.36 (m, 2H, alkyl C<u>H</u>), 2.21-2.12 (m, 2H, alkyl C<u>H</u>), 1.65-1.56 (m, 1H, alkyl C<u>H</u>), 1.25-1.22 ppm (m, 6H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 177.5, 150.5, 106.4, 60.4, 44.4, 36.7, 30.9, 26.9, 23.5, 14.2.

HRMS *m*/*z* (**ESI**): Calc. for $C_{10}H_{17}O_2$ (M^+ + H): 169.1223. Found: 169.1221.

Preparation of 1-methyl-3-methylenecyclopentane-1-carboxylic acid, **322**.



Scheme 3.29

To a round bottom flask fitted with a magnetic stirrer bar and a reflux condenser was added ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** (1.00 g, 5.94 mmol) in THF (6 mL). To this solution was added 2 M NaOH (14.86 mL, 29.70 mmol), and the reaction mixture was then heated to reflux and stirred for 17 h. The mixture was then concentrated *in vacuo*, then dissolved in Et_2O (30 mL). The mixture was then acidified with 2 M HCl, the organics were then extracted, with further extraction performed using Et_2O (30 mL × 2). The combined organics were

then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 50 % Et_2O in petroleum ether) to give ethyl 1-methyl-3-methylenecyclopentane-1-carboxylic acid, **322** (766 mg, 92 % yield) as a colourless oil.

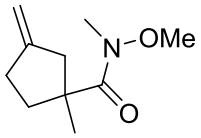
FTIR (**cm^{-1}**): 3075, 2968, 2938, 1697, 1466, 1408 1294.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.91-4.86 (m, 2H, vinylic C<u>H</u>), 2.84 (d, 1H, ^2J = 16.3 Hz, alkyl C<u>H</u>), 2.51-2.35 (m, 2H, alkyl C<u>H</u>), 2.25-2.16 (m, 2H, alkyl C<u>H</u>), 1.69-1.62 (m, 1H, alkyl C<u>H</u>), 1.28 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 184.5, 150.3, 106.8, 49.1, 44.4, 36.9, 31.1, 23.5

HRMS *m*/*z* (**ESI**): Calc. for $C_8H_{11}O_2$ (M^+ - H): 139.0765. Found: 139.0765.

Preparation of *N*-methoxy-*N*,1-dimethyl-3-methylenecyclopentane-1-carboxamide, **315**.



Chemical Formula: $C_{10}H_{17}NO_2$
Molecular Weight: 183.25

Scheme 3.29

To a flame dried round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added ethyl 1-methyl-3-methylenecyclopentane-1-carboxylic acid, **322** (1.71 g, 12.20 mmol) in MeCN (18 mL). To this solution was added DIPEA (4.26 mL, 24.40 mmol) and 2-(1H-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethylisouronium, tetrafluoroborate **323** (4.11 g, 12.81 mmol), and the mixture was then allowed to stir at r.t. for 30 min. In a separate flame dried flask fitted with an argon inlet and a magnetic stirrer bar, was added MeNHOMe·HCl (1.43 g, 14.64 mmol) and DIPEA (2.131 mL, 12.20 mmol) in MeCN (6.5 mL). This mixture was stirred at r.t. for 30 min before dropwise addition to the original reaction mixture. The combined mixture was then stirred at r.t. for 17 h. The mixture was then concentrated *in vacuo*,

then dissolved in EtOAc, washed with 0.5 M NaOH (20 mL, 0.5 M HCl (20 mL) and brine (30 mL) then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 70 % Et_2O in petroleum ether) to give *N*-methoxy-*N*,1-dimethyl-3-methylenecyclopentane-1-carboxamide, **315** (1.59 g, 71 % yield) as a colourless oil.

Scheme 3.30

To a flame dried round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** (500 mg, 2.97 mmol) and MeNHOMe·HCl (579 mg, 5.94 mmol) in THF (6 mL). The mixture was cooled to -20 °C and *i*-PrMgCl (5.94 mL, 11.88 mmol, 2 M) was added dropwise. Following this addition, the reaction mixture was stirred at -20 °C for 3 h, then allowed to warm slowly to r.t. over 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (30 mL × 3). The combined organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 70 % Et_2O in petroleum ether) to give *N*-methoxy-*N*,1-dimethyl-3-methylenecyclopentane-1-carboxamide, **315** (393 mg, 72 % yield) as a colourless oil.

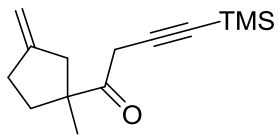
FTIR (**cm^{-1}**): 2965, 2958, 2937, 1694, 1465, 1374, 1358, 1175.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.89-4.84 (m, 2H, vinylic C<u>H</u>), 3.67 (s, 3H, NC<u>H</u>$_3$), 3.18 (s, 3H, OC<u>H</u>$_3$), 2.75 (d, 1H, ^2J = 16.3 Hz, alkyl C<u>H</u>), 2.40-2.31 (m, 3H, alkyl C<u>H</u>), 2.15-2.07 (m, 1H, alkyl C<u>H</u>), 1.81-1.74 (m, 1H, alkyl C<u>H</u>), 1.23 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 178.7, 150.7, 106.5, 60.8, 49.8, 44.3, 36.0, 33.6, 30.1, 22.8.

HRMS *m*/*z* (**ESI**): Calc. for $C_{10}H_{18}NO_2$ (M^+ + H): 184.1332. Found: 184.1329.

Preparation of 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325**.



Chemical Formula: $C_{14}H_{22}OSi$
Molecular Weight: 234.41

Scheme 3.31

To a flame dried round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added trimethyl(prop-1-yn-1-yl)silane, **324** (0.49 mL, 3.27 mmol) in THF (4 mL). The solution was cooled to -20 °C and *n*-BuLi (2.05 mL, 3.27 mmol, 1.6 M) was added dropwise. The reaction mixture was then cooled to -78 °C and stirred for 1 h then *N*-methoxy-*N*,1-dimethyl-3-methylenecyclopentane-1-carboxamide, **315** (300 mg, 1.64 mmol) in THF (1.5 mL) was added dropwise, and the mixture was then allowed to warm slowly to r.t. over 18 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with Et_2O (30 mL × 3). The combined organics were washed with saturated aqueous $NaHCO_3$ solution, and brine (30 mL) then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 5 % Et_2O in petroleum ether) to give 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (188 mg, 49 % yield) as a colourless oil.

Scheme 3.32

To a flame dried round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added trimethyl(prop-1-yn-1-yl)silane, **324** (0.88 mL, 5.94 mmol) in THF (8 mL). The solution was cooled to -20 °C and *n*-BuLi (3.72 mL, 5.94 mmol, 1.6 M) was added dropwise. The reaction mixture was then cooled to -78 °C and stirred for 1 h then ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** (500 mg, 2.97 mmol) in THF (2 mL) was added dropwise, the mixture was then allowed to warm slowly to r.t. over 19 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with Et_2O (30 mL × 3). The combined organics were washed with saturated aqueous $NaHCO_3$ solution, and brine (30 mL) then dried over Na_2SO_4,

filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 5 % Et_2O in petroleum ether) to give 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (515 mg, 74 % yield) as a colourless oil.

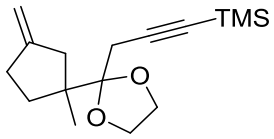
FTIR (**cm^{-1}**): 2959, 2179, 1709, 1456, 1431, 1250.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.92-4.86 (m, 2H, vinylic C<u>H</u>), 3.45 (s, 1H, alkyl C<u>H</u>), 3.44 (s, 1H, alkyl C<u>H</u>), 2.79 (d, 1H, ^2J = 16.3 Hz, alkyl C<u>H</u>), 2.43-2.34 (m, 2H, alkyl C<u>H</u>), 2.22-2.17 (m, 1H, alkyl C<u>H</u>), 2.15-2.10 (m, 1H, alkyl C<u>H</u>), 1.65-1.56 (m, 1H, alkyl C<u>H</u>), 1.25 (s, 3H, alkyl C<u>H</u>3), 0.16 ppm (s, 9H, Si(C<u>H</u>$_3$)$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 207.0, 149.9, 107.2, 98.7, 89.6, 55.6, 43.6, 35.9, 31.1, 30.8, 23.3, 0.0 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{14}H_{23}NO_2$ (M^+ + H): 235.1513. Found: 235.1511.

Attempted preparation of trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxolan-2-yl)prop-1-yn-1-yl)silane, **326**.



Chemical Formula: $C_{16}H_{26}O_2Si$
Molecular Weight: 278.47

Scheme 3.33, Table 3.6, **Entry 1**

To a flame dried, round bottom flask fitted with an argon inlet, a magnetic stirrer bar and a reflux condenser was added 4Å MS (30 mg), 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (100 mg, 0.43 mmol), ethylene glycol (0.1 ml, 1.72 mmol) and *p*-TsOH·H_2O (25 mg, 0.13 mmol), in PhMe (4 mL). The reaction mixture was then heated to reflux and allowed to stir for (18 h). The reaction mixture was then extracted with Et_2O (30 mL × 3) and the combined organics were washed with water (25 mL × 2), dried over Na_2SO_4, filtered, and

concentrated *in vacuo*. The desired product trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxolan-2-yl)prop-1-yn-1-yl)silane, **326**, was not isolated.

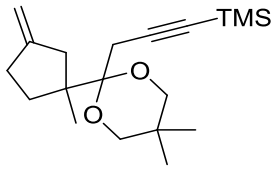
Scheme 3.33, Table 3.6, Entry 2

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (100 mg, 0.43 mmol), ethylene glycol (0.1 mL, 1.72 mmol), trimethylorthoformate (0.07 mL, 0.65 mmol), and *p*-TsOH·H_2O (74 mg, 0.39 mmol), in PhH (4 mL). The reaction mixture was then allowed to stir at r.t. for 20 h. The reaction mixture was then extracted with Et_2O (30 mL × 3) and the combined organics were washed with water (25 mL × 2), then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxolan-2-yl)prop-1-yn-1-yl)silane, **326**, was not isolated.

Scheme 3.34

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added DCM (1 mL), the solution was then cooled to -78 °C and TMSOTf (0.01 mL, 0.005 mmol) was added. This was followed by addition of 1,2-bis(trimethylsiloxy)ethane, **327** (0.17 mL, 0.68 mmol) and 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (80 mg, 0.34 mmol). The reaction mixture was stirred at -78 °C for 6 h, then quenched with pyridine (1 mL). The mixture was then washed with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (30 mL × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxolan-2-yl)prop-1-yn-1-yl)silane, **326**, was not isolated.

Attempted preparation of (3-(5,5-dimethyl-2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxan-2-yl)prop-1-yn-1-yl)trimethylsilane, **329**.

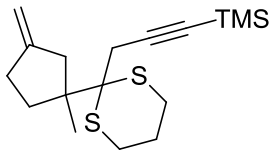


Chemical Formula: $C_{19}H_{32}O_2Si$
Molecular Weight: 320.55

Scheme 3.35

To a flame dried, round bottom flask fitted with an argon inlet, a magnetic stirrer bar and a Dean-Stark apparatus was added 1-(1-methyl-3-methylenecyclopentyl)-4-(trimethylsilyl)but-3-yn-1-one, **325** (136 mg, 0.58 mmol), 2,2-Dimethyl-1,3-propanediol, **328** (121 mg, 1.16 mmol) and PPTS (5 mg, 0.02 mmol) in PhH (4 mL). The reaction mixture was then heated to reflux and stirred for 18 h. The mixture was then washed with water (30 mL) and extracted with Et_2O (30 mL × 3). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3-(5,5-dimethyl-2-(1-methyl-3-methylenecyclopentyl)-1,3-dioxan-2-yl)prop-1-yn-1-yl)trimethylsilane, **329**, was not isolated.

Attempted preparation of trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dithian-2-yl)prop-1-yn-1-yl)silane, **331**.



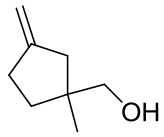
Chemical Formula: $C_{17}H_{28}S_2Si$
Molecular Weight: 324.62

Scheme 3.36

To a flame dried, round bottom flask fitted with an argon inlet, a magnetic stirrer bar and a Dean-Stark apparatus was added 1-(1-methyl-3-methylenecyclopentyl)-4-

(trimethylsilyl)but-3-yn-1-one, **325** (80 mg, 0.34 mmol), 1,3-propanedithiol, **330** (0.05 mL, 0.41 mmol) and *p*-TsOH·H_2O (13 mg, 0.07 mmol) in PhH (3 mL). The reaction mixture was then heated to reflux and stirred for 16 h. The mixture was then diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with Et_2O (30 mL × 3). The combined organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product trimethyl(3-(2-(1-methyl-3-methylenecyclopentyl)-1,3-dithian-2-yl)prop-1-yn-1-yl)silane, **331**, was not isolated.

Preparation of (1-methyl-3-methylenecyclopentyl)methanol, **333**.



Chemical Formula: $C_8H_{14}O$
Molecular Weight: 126.20

Scheme 3.39

To a flame dried, round bottom flask fitted with an argon inlet, a magnetic stirrer bar and a reflux condenser was added $LiAlH_4$ (2.77 g, 73.05 mmol) in THF (50 mL). The suspension was cooled to 0 °C and dropwise addition of a mixture of ethyl 1-methyl-3-methylenecyclopentane-1-carboxylate, **321** (4.01 g, 24.35 mmol) in THF (30 mL) was performed. The mixture was then to stirred at 0 °C for 1 h then allowed to warm to r.t. and stirred for a further 3 h. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous Na_2SO_4 solution, then allowed to warm to r.t. and stirred for a further 3 h. The resulting suspension was filtered and the filtrate was concentrated to dryness. The crude material was purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (1-methyl-3-methylenecyclopentyl)methanol, **333** (2.68 g, 87 % yield) as a colourless oil.

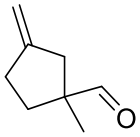
FTIR (**cm^{-1}**): 3333, 2950, 2934, 2889, 2869, 1660, 1429, 1033.

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.84-4.82 (m, 2H, vinylic C<u>H</u>), 3.41 (s, 2H, C<u>H</u>$_2$OH), 2.40-2.34 (m, 2H, alkyl C<u>H</u>), 2.24 (d, 1H, ^{2}J = 16.3 Hz, alkyl C<u>H</u>), 2.03 (d, 1H, ^{2}J = 16.3 Hz, alkyl C<u>H</u>), 1.68-1.61 (m, 1H, alkyl C<u>H</u>), 1.59 (br s, 1H, O<u>H</u>), 1.46-1.39 (m, 1H, alkyl C<u>H</u>), 1.01 ppm (s, 3H, alkyl C<u>H</u>$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 152.1, 106.2, 70.6, 44.3, 43.5, 35.2, 31.0, 23.1 ppm.

HRMS *m*/*z* (**EI**): Calc. for $C_8H_{14}O$ (M^+): 126.1045. Found: 126.1051.

Preparation of 1-methyl-3-methylenecyclopentane-1-carbaldehyde, **301**.



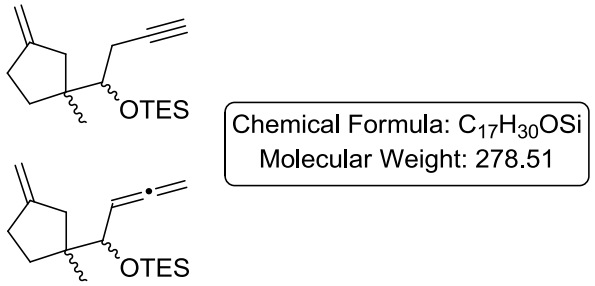
Chemical Formula: $C_8H_{12}O$
Molecular Weight: 124.18

Scheme 3.39

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added DMSO (6.45 mL, 90.65 mmol) in DCM (100 mL), the mixture was cooled to -78 °C and oxalyl chloride (3.85 mL, 45.32 mmol) was added. The solution was stirred at -78 °C for 1 h then (1-methyl-3-methylenecyclopentyl)methanol, **333** (4.77 g, 37.77 mmol) was added as a solution in DCM (25 mL). The reaction mixture was then stirred at -78 °C for 1 h before slow addition of Et_3N (21.05 mL, 151.08 mmol). The mixture was then allowed to warm slowly to r.t. over 16 h. Following this time the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extraction was performed with DCM (30 mL × 3). The combined organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 100 % Et_2O) to give 1-methyl-3-methylenecyclopentane-1-carbaldehyde, **301** (4.69 g, 100 % yield) as a colourless oil.

Associated characterisation data for this compound can be found on page 249.

Preparation of triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, **& triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-yl)oxy)silane**, **335**.



Scheme 3.39

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-ol**, 305**, & 1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-ol, **306** (2.00 g, 12.81 mmol, 7:1 **305**:**306**) in DCM (60 mL). The mixture was cooled to 0 °C and DMAP (373 mg, 3.05 mmol), Et_3N (4.25 mL, 30.45 mmol), and TESOTf (3.45 mL, 15.23 mmol) were added. The reaction mixture was then allowed to gradually warm to r.t. while stirring for 18 h. The mixture was washed with saturated aqueous NH_4Cl solution (30 mL), with the organic phase further extracted with DCM (2 × 30 mL). The combined organics were washed with brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 10 % Et_2O in petroleum ether) to give an inseparable mixture of triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, & triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-yl)oxy)silane, **335** (3.39 g, 100 % yield, 7:1 **334**:**335**) a colourless oil.

Triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, & triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-yl)oxy)silane, **335** were isolated as a complex and inseparable mixture of isomers. The ratio of **334** and **335** was determined as 7:1 respectively. ^{1}H NMR spectroscopy was performed on this mixture, however, the ^{1}H NMR analysis data has been separated for simplicity.

FTIR (**cm^{-1}**): 3312, 2953, 2911, 2876, 1661, 1458, 1238, 1096, 1005.

Compound 334 ^{1}H NMR

^{1}H NMR (**400 MHz, $CDCl_3$**): 4.86-4.81 (m, 2H, vinylic C<u>H</u>) 3.66 (ddd, 1H, *J* = 4.5, 7.0 Hz, ^{4}J = 1.1 Hz, OHC<u>H</u>), 2.44-2.21 (m, 5H, alkyl C<u>H</u>), 2.08 & 1.95 (d, 1H in total, ^{2}J = 15.6 Hz, alkyl C<u>H</u>, ratio 1:1), 1.98-1.97 (m, 1H, C≡C<u>H</u>), 1.70-1.60 (m, 1H, alkyl C<u>H</u>), 1.55-1.49 (m, 0.5H, alkyl C<u>H</u>), 1.41-1.27 (m, 0.5H, alkyl C<u>H</u>), 1.00-0.93 (m, 9H, $SiCH_2C\underline{H}_3$), 0.90 (s, 3H, alkyl $C\underline{H}_3$), 0.70-0.59 ppm (m, 6H, $SiC\underline{H}_2CH_3$).

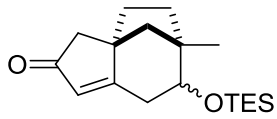
Compound 335 ^{1}H NMR

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.13-5.06 (m, 1H, vinylic C<u>H</u>), 4.86-4.81 (m, 2H vinylic C<u>H</u>), 4.72-4.68 (m, 2H vinylic C<u>H</u>), 3.94-3.92 (dd, 1H, *J* = 7.5 Hz, ^{4}J = 1.4 Hz, OHC<u>H</u>) 2.44-2.21 (m, 3H, alkyl C<u>H</u>), 2.08 & 1.95 (d, 1H in total, ^{2}J = 15.6 Hz, alkyl C<u>H</u>, ratio 1:1), 1.70-1.60 (m, 1H, alkyl C<u>H</u>), 1.55-1.49 (m, 0.5H, alkyl C<u>H</u>), 1.41-1.27 (m, 0.5H, alkyl C<u>H</u>), 1.00-0.93 (m, 9H, $SiCH_2C\underline{H}_3$), 0.91 (s, 3H, alkyl $C\underline{H}_3$) 0.70-0.59 ppm (m, 6H, $SiC\underline{H}_2CH_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 152.2, 152.07, 106.2, 106.1, 105.8, 105.7, 92.1, 83.50, 83.48, 78.9, 78.7, 78.3, 78.1, 75.02, 74.99, 69.98, 69.93, 48.3, 48.1, 48.01, 45.2, 44.4, 43.9, 43.6, 36.7, 36.0, 35.33, 35.29, 34.29, 30.8, 30.5, 24.5, 24.4, 20.9, 20.7, 19.5, 19.4, 14.2, 7.2, 7.0, 6.9, 6.6, 5.6, 5.2 ppm

HRMS *m*/*z* (**ESI**): Calc. for $C_{17}H_{31}OSi$ (M^+ + H): 279.2139. Found: 279.2137.

Preparation of (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332**.



Chemical Formula: $C_{18}H_{30}O_2Si$
Molecular Weight: 306.52

Scheme 3.40

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, reflux condenser and an argon inlet was added a mixture of triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, & triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-yl)oxy)silane, **335** (3.03 g, 10.87 mmol) in DCE (95 mL). To this was added Co_2CO_8 (3.35 g, 9.79 mmol), with the resulting mixture stirred at r.t. for 2 h. Upon complexation, the mixture was filtered through celite, eluting with petroleum ether, and concentrated *in vacuo*. The crude product was dissolved in DCE (95 mL) and DodSMe (11.00 mL, 41.47 mmol) was added. The mixture was heated to reflux and stirred for 18 h. The mixture was then filtered through celite, eluting with Et_2O, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (2.40 g, 84 % yield, *d.r*. 1:1) as a pale pink oil.

General procedure F

To a flame dried, round bottom flask fitted with a magnetic stirrer bar, reflux condenser and an argon inlet was added a mixture of triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, & triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-yl)oxy)silane, **335** (a) in DCE (b). To this was added Co_2CO_8 (c), and DodSMe (d) with the resulting mixture heated to reflux and stirred for the allocated period of time (e). The mixture was then filtered through celite, eluting with Et_2O, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (f) with specified *d.r*. (g).

Scheme 3.41, **Table 3.7**

The following experiments were performed using **General procedure F**. Results are reported as: (a) amount of triethyl((1-(1-methyl-3-methylenecyclopentyl)but-3-yn-1-yl)oxy)silane, **334**, & triethyl((1-(1-methyl-3-methylenecyclopentyl)buta-2,3-dien-1-

yl)oxy)silane, **335**, (b) volume of DCE, (c) amount of Co_2CO_8, (d) volume of DodSMe, (e) time, and (f) yield of (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332**, as a pale pink oil, and (g) *d.r.*

Entry 1: (a) 115 mg, 0.41 mmol, 7:1 **334**: **335**, (b) 10 mL, (c) 24 mg, 0.07 mmol), (d) 0.11 mL, 0.43 mmol, (e) 17 h, (f) 51 mg, 46 % yield, and (g) 1:1

Entry 2: (a) 115 mg, 0.41 mmol, 7:1 **334**: **335**, (b) 10 mL, (c) 24 mg, 0.07 mmol), (d) 0.33 mL, 1.26 mmol, (e) 17 h, (f) 65 mg, 59 % yield, and (g) 1:1

Entry 3: (a) 115 mg, 0.41 mmol, 7:1 **334**: **335**, (b) 10 mL, (c) 24 mg, 0.07 mmol), (d) 0.43 mL, 1.62 mmol, (e) 17 h, (f) 72 mg, 65 % yield, and (g) 1:1

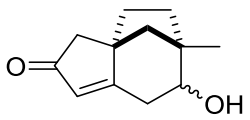
FTIR (**cm^{-1}**): 2949, 2911, 2874, 1709, 1624, 1452, 1098, 1074.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.69 & 5.64 (d, 1H in total, ^4J = 2.0 Hz, vinylic C<u>H</u>, ratio 1:1), 3.71-3.69 (m, 0.5H, TESOC<u>H</u>), 3.58 (ddd, 0.5H, J = 6.1, 9.4 Hz, ^4J = 1.1 Hz, TESOC<u>H</u>), 2.93 (dd, 0.5H, ^2J = 15.4 Hz, J = 6.1 Hz, alkyl C<u>H</u>), 2.65-2.62 (m, 1H, alkyl C<u>H</u>), 2.38-2.32 (m, 2.5H, alkyl C<u>H</u>), 2.14-2.06 (m, 0.5H, alkyl C<u>H</u>), 1.99-1.87 (m, 1.5H, alkyl C<u>H</u>), 1.78 (d, 0.5H, ^2J = 11.8 Hz, alkyl C<u>H</u>), 1.68-1.57 (m, 2H, alkyl C<u>H</u>), 1.44-1.35 (m, 1H, alkyl C<u>H</u>), 1.27-1.25 (m, 0.5H, alkyl C<u>H</u>), 1.08 & 1.07 (s, 3H in total, alkyl C<u>H</u>$_3$, ratio 1:1), 0.99-0.92 (m, 9H, $SiCH_2C\underline{H}_3$), 0.65-0.56 ppm (m, 6H, $SiC\underline{H}_2CH_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 208.9, 208.7, 186.1, 185.4, 125.6, 124.2, 76.9, 76.4, 52.2, 51.4, 48.8, 46.3, 46.1, 45.0, 44.6, 36.3, 35.5, 35.1, 34.3, 29.7, 24.0, 23.7, 7.06, 7.02, 5.3, 5.2 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{18}H_{31}O_2Si$ (M^+ + H): 307.2088. Found: 307.2082.

Preparation of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, 310.



Chemical Formula: $C_{12}H_{16}O_2$
Molecular Weight: 192.26

Scheme 3.43, Table 3.8, Entry 1

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (80 mg, 0.26 mmol) in MeOH (2.5 mL). To this solution was slowly added AcCl (0.005 mL, 0.08 mmol), the mixture was then stirred at r.t. for 16 h. The mixture was diluted with Et_2O (20 mL) and washed with brine (20 mL), and the aqueous phase was then further extracted with Et_2O (20 mL × 2). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 70 % Et_2O in petroleum ether) to give the product of elimination (3aR,6S)-6-methyl-5,6-dihydro-3H-3a,6-methanoazulen-2(4H)-one, **312** (29 mg, 64 % yield) as a colourless oil. Unfortunately, the desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** was not observed.

Scheme 3.43, Table 3.8, Entry 2

To a round bottom flask fitted with a magnetic stirrer bar was added (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (200 mg, 0.65 mmol) in THF (3 mL), and the mixture was then cooled to 0 °C. To the solution was added 0.2 M HCl (0.36 mL) the mixture was then stirred at 0 °C for 3 h, then allowed to warm to r.t. and stirred for a further 16 h. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and the subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 80 % Et_2O in petroleum ether) to (3*a*,6)-6-

methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (92 mg, 74 % yield, 2:3 *d.r.*) as a colourless oil.

Scheme 3.43, **Table 3.8**, **Entry 3**

To a round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added AcOH (0.19 mL, 3.25 mmol) in THF (8 mL), the mixture was allowed to stir at r.t. for 30 min then was cooled to 0 °C. To the mixture was added (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (200 mg, 0.65 mmol) in THF (4 mL). The reaction mixture was then allowed to stir at temperature 0 °C for 2 h, before allowing to warm to r.t. and stirring for a further 16 h. The mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 80 % Et_2O in petroleum ether) to give (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (95 mg, 76 % yield, 2:3 *d.r.*) as a colourless oil.

FTIR (**cm^{-1}**): 3426, 2947, 2926, 2868, 1701, 1674, 1618, 1570, 1067.

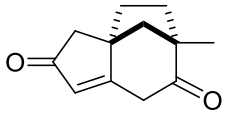
^{1}H NMR (**400 MHz, $CDCl_3$**): 5.71 (s, 0.4H, vinylic C<u>H</u>) 5.63 (d, 0.6H, ^4J = 2.0 Hz, vinylic C<u>H</u>,), 3.71-3.69 (m, 0.4H, OC<u>H</u>), 3.58 (dd, 0.6H, *J* = 6.4, 9.9 Hz, OC<u>H</u>), 3.02 (dd, 0.6H, ^2J = 15.6 Hz, *J* = 6.2 Hz, alkyl C<u>H</u>), 2.75 (br s, 0.6H, CHO<u>H</u>), 2.71-2.69 (m, 0.8H, alkyl C<u>H</u>), 2.57 (br s, 0.4H, CHO<u>H</u>), 2.35-2.28 (m, 2.6H, alkyl C<u>H</u>), 2.06-1.98 (m, 0.6H, alkyl C<u>H</u>), 1.95-1.85 (m, 1.4H, alkyl C<u>H</u>), 1.77 (d, 0.6H, ^2J = 12.2 Hz, alkyl C<u>H</u>), 1.67-1.60 (m, 1.8H, alkyl C<u>H</u>), 1.50-1.39 (m, 1H, alkyl C<u>H</u>), 1.27-1.23 (m, 0.6H, alkyl C<u>H</u>), 1.12 & 1.11 ppm (s, 3H in total, alkyl C<u>H</u>$_3$, ratio 2:3).

^{13}C NMR (**101 MHz, $CDCl_3$**): 209.1, 208.7, 185.7, 185.5, 125.8, 124.3, 76.2, 75.6, 52.2, 51.3, 48.7, 45.6, 45.3, 44.8, 44.5, 44.3, 35.4, 34.8, 34.6, 34.4, 34.1, 29.3, 23.4, 22.9 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{12}H_{17}O_2$ (M^+ + H): 193.1223. Found: 193.1220.

Characterisation data for the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312**, can be found on page 257.

Attempted preparation of (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**.



Chemical Formula: $C_{12}H_{14}O_2$
Molecular Weight: 190.24

Scheme 3.44, **Table 3.9**, **Entry 1**

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added DMSO (0.03 mL, 0.38 mmol) in DCM (0.5 mL), the mixture was cooled to -78 °C and oxalyl chloride (0.02 mL, 0.19 mmol) was added. The solution was stirred at -78 °C for 1 h then (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (30 mg, 0.16 mmol) was added as a solution in DCM (0.5 mL). The reaction mixture was then stirred at -78 °C for 1 h before slow addition of Et_3N (0.09 mL, 0.64 mmol). The mixture was then allowed to warm slowly to r.t. over 16 h. Following this the mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL), and extraction was performed with DCM (30 mL × 3). The combined organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified *via* column chromatography (petroleum ether to 60 % Et_2O) to give to give the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** (7 mg, 23 % yield) as a colourless oil. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Scheme 3.44, **Table 3.9**, **Entry 2**

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (35 mg, 0.18 mmol) in DCM (10 mL). To this mixture was added $NaHCO_3$ (60 mg,

0.72 mmol) followed by DMP (153 mg, 0.36 mmol). The reaction mixture was then stirred at r.t. for 16 h. Following this the mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL), extraction was performed with DCM (30 mL × 3). The combined organics were then washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Scheme 3.44, **Table 3.9**, **Entry 3**

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was activated powdered 4 Å MS (80 mg). To this was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (32 mg, 0.17 mmol) in DCM (3 mL), followed by addition of NMO (119 mg, 1.02 mmol) and TPAP (21 mg, 0.06 mmol). The reaction mixture was stirred at r.t. for 16 h, then filtered through celite eluting with EtOAc. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Scheme 3.44, **Table 3.9**, **Entry 4**

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (29 mg, 0.15 mmol) in DCM (1 mL). To this mixture was added TEMPO (2 mg, 0.02 mmol) and BAIB (55 mg, 0.17 mmol), the reaction mixture was then allowed to stir at r.t. for 16 h. The mixture was quenched with 10 % saturated aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with DCM (20 ml × 3). The combined organics were then washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL) dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Scheme 3.44, **Table 3.9**, **Entry 5**

To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added activated powdered 4 Å MS (80 mg). To this was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (30 mg, 0.16 mmol) in DCM (5 mL), followed by PDC (181 mg, 0.48 mmol). The reaction mixture was

stirred at r.t. for 16 h, then filtered through celite eluting with EtOAc. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed

Scheme 3.44, **Table 3.9**, **Entry 6**

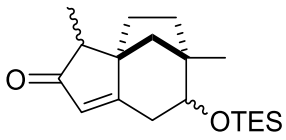
To a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar was added activated powdered 4 Å MS (80 mg). To this was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (30 mg, 0.16 mmol) in DCM (5 mL), followed by PCC (181 mg, 0.48 mmol) and NaOAc (26 mg, 0.32 mmol). The reaction mixture was stirred at r.t. for 16 h, then filtered through celite eluting with EtOAc. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Scheme 3.44, **Table 3.9**, **Entry 7**

To a flame dried, round bottom flask fitted with an argon inlet, a magnetic stirrer bar and a reflux condenser was added (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **310** (30 mg, 0.16 mmol) in acetone (1.5 mL). To this was added $(PPh_3)_3RuCl_2$ (2 mg, 0.02 mmol) and K_2CO_3 (2 mg, 0.02 mmol). The reaction mixture was then heated to reflux and stirred for 18 h, allowed to cool to r.t. and filtered through celite eluting with EtOAc. The crude material was purified *via* column chromatography (petroleum ether to 60 % Et_2O) to give to give the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312** (7 mg, 25 % yield) as a colourless oil. The desired product (3*a*,6)-6-methyl-5,6-dihydro-3H-3*a*,6-methanoazulene-2,7(4*H*,8*H*)-dione, **311**, was not formed.

Characterisation data for the product of elimination (3*a*,6)-6-methyl-5,6-dihydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **312**, can be found on page 257.

Preparation of (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, 336.



Chemical Formula: $C_{19}H_{32}O_2Si$
Molecular Weight: 320.55

Scheme 3.46

To a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (0.16 mL, 1.18 mmol) in THF (3 mL). The solution was cooled to 0 °C and *n*-BuLi (0.60 mL, 1.18 mmol, 2.0 M) was slowly added. The mixture was allowed to stir at 0 °C for 30 min before being cooled to -78 °C. At this point DMPU (0.14 mL, 1.18 mmol) was added and the mixture was allowed to stir at -78 °C for 1 h, before addition of (3*a*,6)-6-methyl-7-((triethylsilyl)oxy)-3,4,5,6,7,8-hexahydro-2*H*-3*a*,6-methanoazulen-2-one, **332** (300 mg, 0.98 mmol) in THF (2 mL). The solution was then stirred for a further 1 h before addition of MeI (0.08 mL, 1.18 mmol), and the mixture was then allowed to warm slowly to r.t. over 18 h. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then purified *via* column chromatography (petroleum ether to 60 % Et_2O in petroleum ether) to give (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **336** (259 mg, 82 % yield) as a colourless oil.

(3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **336**, was isolated as a complex and inseparable mixture of isomers.

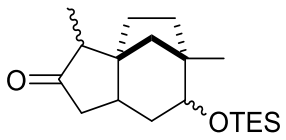
FTIR (**cm^{-1}**): 2951, 2911, 2874, 1701, 1626, 1458, 1094, 1076, 1005.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.71-5.70 & 5.66-5.65 (m, 1H in total, vinylic C<u>H</u>, ratio 1:1), 3.71-3.69 (m, 0.5H, TESOC<u>H</u>), 3.61-3.52 (m, 0.5H, TESOC<u>H</u>), 2.97-2.90 (m, 0.5H, alkyl C<u>H</u>), 2.65-2.61 (m, 1H, alkyl C<u>H</u>), 2.39-2.20 (m, 1.5H, alkyl C<u>H</u>), 2.14-2.05 (m, 0.5H, alkyl C<u>H</u>), 1.96-1.84 (m, 1.5H, alkyl C<u>H</u>), 1.79-1.53 (m, 2H, alkyl C<u>H</u>), 1.44-1.32 (m, 1.5H, alkyl C<u>H</u>), 1.19-1.16 (m, 0.5H, alkyl C<u>H</u>), 1.08 & 1.04 (m, 6H, alkyl C<u>H</u>$_3$), 0.99-0.92 (m, 9H, SiCH$_2$C<u>H</u>$_3$), 0.64-0.56 ppm (m, 6H, SiC<u>H</u>$_2$CH$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 211.84, 211.78, 211.2, 185.1, 184.5, 184.0, 124.4, 123.3, 123.0, 77.0, 76.5, 55.7, 55.2, 54.9, 49.2, 47.3, 47.0, 46.9, 45.8, 45.3, 44.8, 36.8, 36.6, 36.4, 35.3, 35.2, 35.0, 33.8, 30.8, 29.7, 29.14, 29.08, 24.2, 24.0, 23.9, 23.7, 13.0, 12.8, 10.6, 10.3, 7.1, 7.0 ppm.

HRMS *m*/*z* (ESI): Calc. for $C_{19}H_{33}O_2Si$ (M^+ + H): 321.2244. Found: 321.2237.

Preparation of (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)hexahydro-1*H*-3*a*,6-methanoazulen-2(3*H*)-one, **337**.



Chemical Formula: $C_{19}H_{34}O_2Si$
Molecular Weight: 322.56

Scheme 3.47

To a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)-5,6,7,8-tetrahydro-3*H*-3*a*,6-methanoazulen-2(4*H*)-one, **336** (50 mg, 0.16 mmol) and 10 wt. % Pd/C (57 mg, 0.05 mmol) in EtOAc (1.5 mL). The suspension was cooled to -78 °C and purged with H_2 gas. The reaction mixture was then allowed to warm to r.t. and stirred for 2 h at r.t. The reaction mixture was filtered through celite eluting with EtOAc, and the crude material was then purified *via* column chromatography (5 mL) and added to a flask fitted with a reflux condenser and magnetic stirrer bar. To this mixture was added H_2O (1 ml) and LiOH (18 mg, 0.75 mmol). The mixture was then heated to reflux and stirred for 72 h. The mixture was then diluted with water (20 mL) and

subsequent extraction was performed with Et_2O (20 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)hexahydro-1*H*-3*a*,6-methanoazulen-2(3*H*)-one, **337** (48 mg, 92 % yield) as a colourless oil.

(3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)hexahydro-1*H*-3*a*,6-methanoazulen-2(3*H*)-one, **337**, was isolated as a complex and inseparable mixture of isomers.

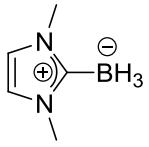
FTIR (**cm^{-1}**): 2951, 2934, 2874, 1742, 1672, 1452, 1094, 1078.

^{1}H NMR (**400 MHz, $CDCl_3$**): 3.58-3.50 (m, 1H, TESOC<u>H</u>), 2.50-2.22 (m, 1H, alkyl C<u>H</u>), 2.18-1.95 (m, 2.5H, , alkyl C<u>H</u>), 1.91-1.78 (m, 2H, alkyl C<u>H</u>), 1.74-1.52 (m, 2.5H, alkyl C<u>H</u>), 1.48-1.38 (m, 1H, alkyl C<u>H</u>), 1.31-1.08 (m, 2H, alkyl C<u>H</u>), 1.04-1.01 (m, 3H, alkyl C<u>H</u>$_3$), 1.00-0.91 (m, 12H, SiCH$_2$C<u>H</u>$_3$ + alkyl C<u>H</u>$_3$), 0.88-0.76 (m, 1H, alkyl C<u>H</u>), 0.62-0.54 ppm (m, 6H, SiC<u>H</u>$_2$CH$_3$).

^{13}C NMR (**101 MHz, $CDCl_3$**): 220.6, 219.6 77.0, 76.3, 75.2, 52.6, 52.06, 51.98, 51.61, 51.58, 51.2, 51.1, 48.1, 46.0, 44.6, 44.3, 42.8, 42.7, 41.9, 41.6, 41.1, 41.0, 39.5, 36.00, 35.97, 33.5, 33.2, 32.44, 32.36, 30.12, 30.07, 28.7, 25.4, 24.9, 23.83, 23.76, 7.8, 7.6, 7.3, 7.1, 6.7, 6.0 ppm.

HRMS *m*/*z* (**ESI**): Calc. for $C_{19}H_{38}O_2SiN$ ($M^+ + NH_4$): 340.2666. Found: 340.2666.

Preparation of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate, **340**.[228]



Chemical Formula: $C_5H_{12}BN_2$
Molecular Weight: 110.97

Scheme 3.50

To a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added 1,3-dimethyl-1*H*-imidazol-3-ium iodide, **341** (1 g, 4.46 mmol) in

THF (30 mL). The solution was cooled to -78 °C and NaHMDS (4.45 mL, 4.45 mmol) was added dropwise. The mixture was then allowed to stir at -78 °C for 1 h, then BH_3·DMS (2.20 ml, 4.40 mmol) was added and the mixture was allowed warm slowly to r.t. over 18 h. The mixture was then concentrated *in vacuo*, with the resulting white solid residue purified *via* column chromatography (DCM to 5 % MeOH in DCM) to give (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate, **340** (475 mg, 97 % yield) as a white solid.

Melting point: 134 - 136 °C

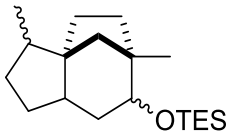
FTIR (**cm^{-1}**): 3129, 3048, 2940, 2328, 2270, 1574, 1476.

^{1}H NMR (**400 MHz, $CDCl_3$**): 6.79 (s, 2H, ArC<u>H</u>), 3.71 (s, 6H, NC<u>H_3</u>), 1.00 ppm (q, 3H, $^{1}J_{B\text{-}H}$ = 86.0 Hz, B<u>H_3</u>).

^{13}C NMR (**101 MHz, $CDCl_3$**): 120.0, 36.0 ppm.

^{11}B NMR (**128 MHz, $CDCl_3$**): -37.58 ppm (q, $^{1}J_{B\text{-}H}$ = 86.0 Hz, BH_3).

Preparation of (((3*a*,6)-3,6-dimethyloctahydro-1*H*-3*a*,6-methanoazulen-7-yl)oxy)triethylsilane, **339**.



Chemical Formula: $C_{19}H_{36}OSi$
Molecular Weight: 308.58

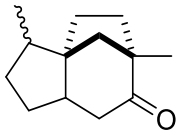
Scheme 3.51

To a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added (3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)hexahydro-1*H*-3*a*,6-methanoazulen-2(3*H*)-one, **337** (384 mg, 1.19 mmol) in MeOH (24 mL). The solution was cooled to 0 °C and $NaBH_4$ (58 mg, 1.53 mmol) was added. The mixture was allowed to stir at 0 °C for 30 min then allowed to warm to r.t. and stirred

for a further 2 h. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then passed through a plug of silica eluting with Et_2O. The filtrate was concentrated *in vacuo* then dissolved in THF (6 mL) and added to a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet. The solution was cooled to 0 °C and *n*-BuLi (0.49 mL, 1.07 mmol, 2.2 M) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 15 min then CS_2 (0.01 mL, 0.14 mmol) was added dropwise. The mixture was allowed to stir at 0 °C for a further 15 min, then allowed to warm to r.t. and stirred for 3 h. To the solution was added MeI (0.01 mL, 0.11 mmol) and the mixture was stirred at r.t. for a further 18 h. The reaction mixture was diluted with DCM (20 mL), washed with H_2O (30 mL), and the aqueous was further extracted with DCM (20 mL × 2). The combined organics were then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was then passed through a plug of silica eluting with petroleum ether. The filtrate was then concentrated, dissolved in PhH (10 mL) and added to a flame dried round bottom flask fitted with a magnetic stirrer bar, an argon inlet, and a reflux condenser. To this was added AIBN (159 mg, 0.97 mmol) and (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate, **340** (107 mg, 0.97 mmol). The resulting solution was then heated to reflux and stirred for 3 h. The mixture was then concentrated in vacuo and the crude material was passed through a plug of silica eluting with petroleum ether. The isolated yellow oil (187 mg) contained (((3*a*,6)-3,6-dimethyloctahydro-1*H*-3*a*,6-methanoazulen-7-yl)oxy)triethylsilane, **339**. The material was taken onto the subsequent step without further purification

HRMS *m*/*z* (EI): Calc. for $C_{19}H_{35}OSi$ (M^+ - H): 307.2461. Found: 307.2457.

Preparation of (3*a*,6)-3,6-dimethylhexahydro-1*H*-3*a*,6-methanoazulen-7(4*H*)-one, 342.[207]



Chemical Formula: $C_{13}H_{20}O$
Molecular Weight: 192.30

Scheme 3.42

To a round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added the material containing (((3*a*,6)-3,6-dimethyloctahydro-1*H*-3*a*,6-methanoazulen-7-yl)oxy)triethylsilane, **339** (187 mg) in THF (4 mL). To this was added 0.2 M HCl (0.12 mL), the mixture was then allowed to stir for 4 h. The reaction mixture was quenched through addition of saturated aqueous $NaHCO_3$ solution (30 mL) and subsequent extraction was performed with Et_2O (40 mL × 3). The combined organics were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was then dissolved in DCM (9 mL) and added to a flame dried, round bottom flask fitted with an argon inlet and a magnetic stirrer bar. To this solution was added celite (60 mg) and PCC (237 mg, 1.10 mmol). The resulting suspension was allowed to stir at r.t. for 16 h, then was filtered through celite eluting with EtOAc. The crude material was then purified *via* column chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (3*a*,6)-3,6-dimethylhexahydro-1*H*-3a,6-methanoazulen-7(4*H*)-one, **342** (65 mg, 28 % yield over 5 steps) as a colourless oil.

(3*a*,6)-3,6-dimethyl-7-((triethylsilyl)oxy)hexahydro-1*H*-3*a*,6-methanoazulen-2(3*H*)-one, **337**, was isolated as a complex and inseparable mixture of isomers.

FTIR (**cm^{-1}**): 2945, 2866, 1707, 1449, 1123.

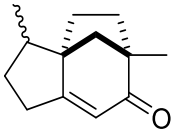
^{1}H NMR (**400 MHz, $CDCl_3$**): 2.58 & 2.39 (dd, 1H in total, ^2J = 16.6 Hz, J = 7.1 Hz, alkyl C<u>H</u>, ratio 3:2), 2.27-2.15 (m, 1H, alkyl C<u>H</u>), 2.07-1.21 (m, 12H, alkyl C<u>H</u>),

1.13 & 1.09 (s, 3H in total, alkyl C<u>H</u>$_3$, ratio 3:2), 0.93 & 0.91 ppm (d, 3H in total, ^3J = 6.4 Hz, C<u>H</u>$_3$, ratio 2:3).

^{13}C NMR (101 MHz, $CDCl_3$): 216.8, 215.4, 53.9, 53.6, 52.6, 52.0, 50.6, 47.3, 46.1, 42.3, 40.4, 39.2, 38.3, 38.0, 35.6, 34.9, 34.0, 32.3, 32.2, 30.5, 27.3, 22.7, 20.9, 20.1, 14.5, 14.4 ppm

HRMS *m*/*z* (ESI): Calc. for $C_{13}H_{21}O$ (M^+ + H): 193.1587. Found: 193.1583.

Preparation (3*a*,6)-3,6-dimethyl-2,3,5,6-tetrahydro-1*H*-3*a*,6-methanoazulen-7(4*H*)-one, 268.[207]



Chemical Formula: $C_{13}H_{18}O$
Molecular Weight: 190.29

Scheme 3.53

To a flame dried, round bottom flask fitted with a magnetic stirrer bar and an argon inlet was added DIPA (0.03 mL, 0.20 mmol), in Et_2O (3 mL). The solution was cooled to 0 °C and *n*-BuLi (0.11 mL, 0.23 mmol, 2.2 M) was slowly added. The mixture was allowed to stir at 0 °C for 30 min before being cooled to -78 °C. At this point (3a,6)-3,6-dimethylhexahydro-1*H*-3a,6-methanoazulen-7(4H)-one, **342** (34 mg, 0.18 mmol) in Et_2O (30 mL) was added and the mixture was stirred for 1 h. To the solution was added TMSCl (0.05 ml, 0.38 mmol) and the mixture was allowed to warm to 0 °C before stirring for a further 2 h. The reaction mixture was then quenched through addition of saturated aqueous NH_4Cl and subsequent extraction was performed with Et_2O (30 mL × 3). The combined organics were washed with water (30 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was then dissolved in MeCN (5 mL) and added to a flame dried round bottom flask fitted with a magnetic stirrer bar and an argon inlet. To this solution was added $Pd(OAc)_2$ (80 mg, 0.36 mmol) and the resulting suspension was allowed to stir at r.t. for 18 h. Following this time the mixture was filtered through celite eluting with Et_2O. The crude material was then purified *via* column

chromatography (petroleum ether to 40 % Et_2O in petroleum ether) to give (3*a*,6)-3,6-dimethyl-2,3,5,6-tetrahydro-1*H*-3*a*,6-methanoazulen-7(4*H*)-one, **268** (4 mg, 12 % yield, 2:3 *d.r.*) as a pale yellow oil.

FTIR (**cm^{-1}**): 2955, 2926, 2866, 1670, 1638, 1443, 1177.

^{1}H NMR (**400 MHz, $CDCl_3$**): 5.77 & 5.75 (s, 1H in total, vinylic C<u>H</u>, ratio 2:3), 2.69-2.47 (m, 2H, alkyl C<u>H</u>), 2.17-1.80 (m, 3H, alkyl C<u>H</u>), 1.75-1.59 (m, 4H, alkyl C<u>H</u>), 1.56-1.45 (m, 2H, alkyl C<u>H</u>), 1.24 & 1.23 (s, 3H in total, alkyl C<u>H</u>$_3$, ratio 2:3), 1.03 & 0.91 ppm (d, 3H in total, ^3J = 6.7 Hz, C<u>H</u>$_3$, ratio 3:2).

HRMS *m*/*z* (**EI**): Calc. for $C_{13}H_{19}O$ (M^+ + H): 191.1436. Found: 191.1438.

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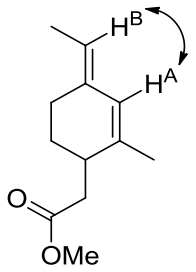
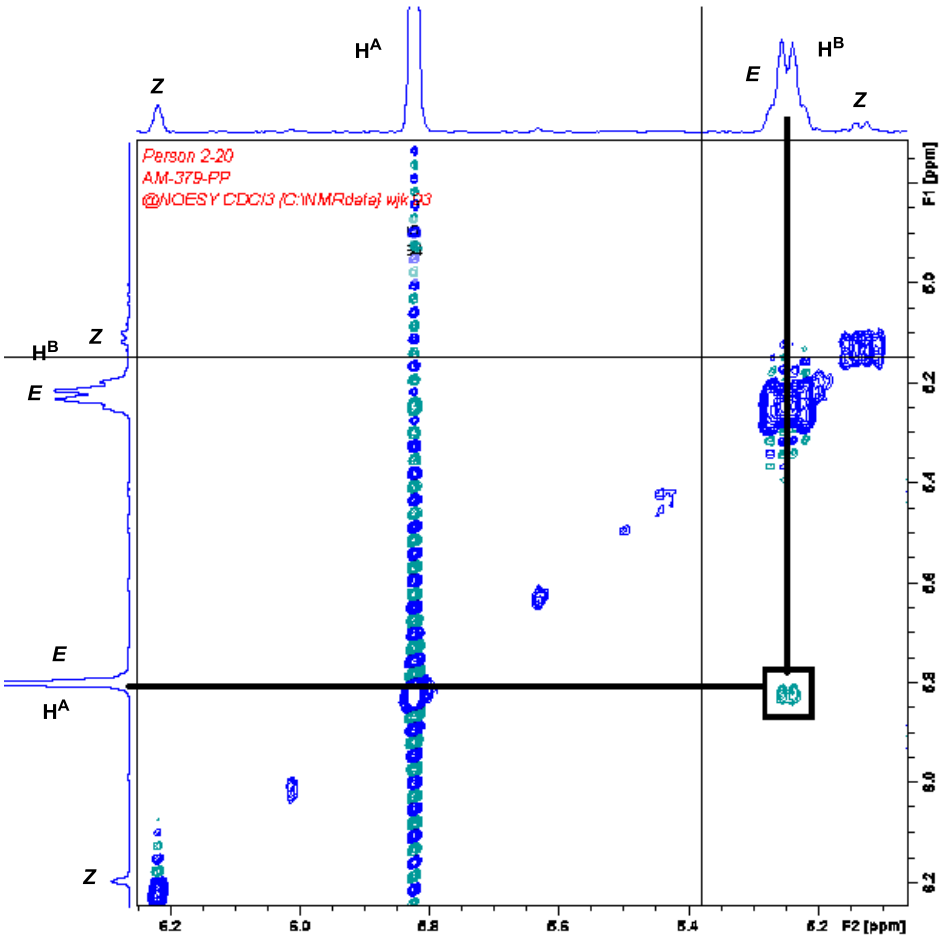
Appendix

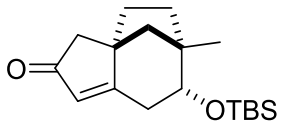
1 NOESY spectrum for compound 255

Key NOE correlation





2 X-ray crystallography data for compound 309



309

On attempting to separate the isomers *via* column chromatography crystals of isomer **309** were produced which proved suitable for diffraction.

Table 1. Crystal data and structure refinement

Empirical formula	$C_{18}H_{30}O_2Si$	
Formula weight	306.51	
Temperature	123(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 15.2459(7) Å	α = 90 °.
	b = 9.9639(3) Å	β = 115.852(6) °.
	c = 13.2878(7) Å	γ = 90 °.
Volume	1816.52(14) $Å^3$	
Z	4	
Density (calculated)	1.121 Mg/m^3	
Absorption coefficient	1.149 mm^{-1}	
F(000)	672	
Crystal size	0.30 × 0.20 × 0.06 mm^3	
Theta range for data collection	5.78 to 73.09°.	
Index ranges	-14<=h<=18, -10<=k<=12, -16<=l<=12	
Reflections collected	7366	
Independent reflections	3560 [R(int) = 0.0331]	
Completeness to theta = 70.00°	99.7 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.80577
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3560 / 0 / 197
Goodness-of-fit on F^2	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0467, wR2 = 0.1211
R indices (all data)	R1 = 0.0519, wR2 = 0.1258
Largest diff. peak and hole	0.408 and -0.452 e.Å^{-3}

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

	x	y	z	U(eq)
Si(1)	1495(1)	2426(1)	2082(1)	27(1)
O(1)	5601(2)	6874(2)	1034(2)	50(1)
O(2)	1838(1)	4016(2)	2187(2)	30(1)
C(1)	4978(2)	6634(3)	1364(3)	39(1)
C(2)	4899(2)	7331(3)	2336(3)	42(1)
C(3)	4017(2)	6685(3)	2421(2)	34(1)
C(4)	3653(2)	5693(3)	1467(2)	33(1)
C(5)	4192(2)	5652(3)	901(2)	37(1)
C(6)	4203(2)	5917(3)	3490(2)	32(1)
C(7)	3167(2)	5549(3)	3312(2)	31(1)
C(8)	2802(2)	4437(3)	2417(2)	29(1)
C(9)	2780(2)	4886(3)	1305(2)	35(1)
C(10)	3184(2)	7639(3)	2325(3)	43(1)
C(11)	2613(2)	6877(3)	2862(3)	38(1)
C(12)	3124(2)	5062(3)	4373(2)	39(1)
C(13)	2138(2)	1358(3)	1464(3)	39(1)
C(14)	1790(2)	1745(3)	3499(2)	41(1)

C(15)	144(2)	2463(2)	1152(2)	28(1)
C(16)	-357(2)	3523(3)	1559(3)	40(1)
C(17)	-314(2)	1085(3)	1141(3)	42(1)
C(18)	-31(2)	2817(3)	-47(2)	41(1)

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

Si(1)-O(2)	1.6547(17)
Si(1)-C(14)	1.863(3)
Si(1)-C(13)	1.863(3)
Si(1)-C(15)	1.884(2)
O(1)-C(1)	1.230(4)
O(2)-C(8)	1.428(3)
C(1)-C(5)	1.459(4)
C(1)-C(2)	1.517(5)
C(2)-C(3)	1.538(4)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.508(4)
C(3)-C(6)	1.528(4)
C(3)-C(10)	1.547(4)
C(4)-C(5)	1.335(4)
C(4)-C(9)	1.488(4)
C(5)-H(5)	0.9500
C(6)-C(7)	1.536(3)
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(12)	1.519(4)
C(7)-C(8)	1.541(3)
C(7)-C(11)	1.543(4)
C(8)-C(9)	1.530(4)
C(8)-H(8)	1.0000
C(9)-H(9A)	0.9900
C(9)-H(9B)	0.9900

C(10)-C(11)	1.544(4)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-H(12A)	0.9800
C(12)-H(12B)	0.9800
C(12)-H(12C)	0.9800
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-H(14A)	0.9800
C(14)-H(14B)	0.9800
C(14)-H(14C)	0.9800
C(15)-C(16)	1.533(4)
C(15)-C(18)	1.537(4)
C(15)-C(17)	1.539(3)
C(16)-H(16A)	0.9800
C(16)-H(16B)	0.9800
C(16)-H(16C)	0.9800
C(17)-H(17A)	0.9800
C(17)-H(17B)	0.9800
C(17)-H(17C)	0.9800
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800

O(2)-Si(1)-C(14)	109.58(12)
O(2)-Si(1)-C(13)	112.09(12)
C(14)-Si(1)-C(13)	107.23(15)
O(2)-Si(1)-C(15)	104.56(10)
C(14)-Si(1)-C(15)	112.54(13)
C(13)-Si(1)-C(15)	110.92(13)
C(8)-O(2)-Si(1)	123.88(15)

O(1)-C(1)-C(5)	126.9(3)
O(1)-C(1)-C(2)	125.1(3)
C(5)-C(1)-C(2)	108.0(3)
C(1)-C(2)-C(3)	105.5(2)
C(1)-C(2)-H(2A)	110.6
C(3)-C(2)-H(2A)	110.6
C(1)-C(2)-H(2B)	110.6
C(3)-C(2)-H(2B)	110.6
H(2A)-C(2)-H(2B)	108.8
C(4)-C(3)-C(6)	107.7(2)
C(4)-C(3)-C(2)	103.1(2)
C(6)-C(3)-C(2)	117.6(2)
C(4)-C(3)-C(10)	110.2(2)
C(6)-C(3)-C(10)	101.3(2)
C(2)-C(3)-C(10)	116.7(2)
C(5)-C(4)-C(9)	129.3(3)
C(5)-C(4)-C(3)	113.7(2)
C(9)-C(4)-C(3)	117.0(2)
C(4)-C(5)-C(1)	109.7(3)
C(4)-C(5)-H(5)	125.2
C(1)-C(5)-H(5)	125.2
C(3)-C(6)-C(7)	102.4(2)
C(3)-C(6)-H(6A)	111.3
C(7)-C(6)-H(6A)	111.3
C(3)-C(6)-H(6B)	111.3
C(7)-C(6)-H(6B)	111.3
H(6A)-C(6)-H(6B)	109.2
C(12)-C(7)-C(6)	113.1(2)
C(12)-C(7)-C(8)	109.8(2)
C(6)-C(7)-C(8)	107.0(2)
C(12)-C(7)-C(11)	113.3(2)
C(6)-C(7)-C(11)	101.9(2)
C(8)-C(7)-C(11)	111.4(2)
O(2)-C(8)-C(9)	107.0(2)

O(2)-C(8)-C(7)	111.6(2)
C(9)-C(8)-C(7)	112.6(2)
O(2)-C(8)-H(8)	108.5
C(9)-C(8)-H(8)	108.5
C(7)-C(8)-H(8)	108.5
C(4)-C(9)-C(8)	112.1(2)
C(4)-C(9)-H(9A)	109.2
C(8)-C(9)-H(9A)	109.2
C(4)-C(9)-H(9B)	109.2
C(8)-C(9)-H(9B)	109.2
H(9A)-C(9)-H(9B)	107.9
C(11)-C(10)-C(3)	105.6(2)
C(11)-C(10)-H(10A)	110.6
C(3)-C(10)-H(10A)	110.6
C(11)-C(10)-H(10B)	110.6
C(3)-C(10)-H(10B)	110.6
H(10A)-C(10)-H(10B)	108.8
C(7)-C(11)-C(10)	106.1(2)
C(7)-C(11)-H(11A)	110.5
C(10)-C(11)-H(11A)	110.5
C(7)-C(11)-H(11B)	110.5
C(10)-C(11)-H(11B)	110.5
H(11A)-C(11)-H(11B)	108.7
C(7)-C(12)-H(12A)	109.5
C(7)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(7)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
Si(1)-C(13)-H(13A)	109.5
Si(1)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
Si(1)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5

H(13B)-C(13)-H(13C)	109.5
Si(1)-C(14)-H(14A)	109.5
Si(1)-C(14)-H(14B)	109.5
H(14A)-C(14)-H(14B)	109.5
Si(1)-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(18)	108.6(2)
C(16)-C(15)-C(17)	108.9(2)
C(18)-C(15)-C(17)	108.8(2)
C(16)-C(15)-Si(1)	110.65(18)
C(18)-C(15)-Si(1)	109.32(18)
C(17)-C(15)-Si(1)	110.52(17)
C(15)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(15)-C(17)-H(17A)	109.5
C(15)-C(17)-H(17B)	109.5
H(17A)-C(17)-H(17B)	109.5
C(15)-C(17)-H(17C)	109.5
H(17A)-C(17)-H(17C)	109.5
H(17B)-C(17)-H(17C)	109.5
C(15)-C(18)-H(18A)	109.5
C(15)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(15)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$). 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}
Si(1)	28(1)	26(1)	24(1)	1(1)	10(1)	-1(1)
O(1)	45(1)	60(2)	52(1)	-6(1)	26(1)	-17(1)
O(2)	28(1)	29(1)	34(1)	-2(1)	13(1)	-2(1)
C(1)	36(1)	38(1)	38(2)	4(1)	13(1)	-5(1)
C(2)	40(1)	39(2)	48(2)	-5(1)	20(1)	-13(1)
C(3)	31(1)	30(1)	39(2)	-2(1)	13(1)	-4(1)
C(4)	34(1)	33(1)	28(1)	2(1)	10(1)	-1(1)
C(5)	41(1)	39(1)	31(1)	-1(1)	16(1)	-7(1)
C(6)	30(1)	30(1)	30(1)	-5(1)	9(1)	-1(1)
C(7)	28(1)	31(1)	33(1)	-3(1)	12(1)	2(1)
C(8)	27(1)	28(1)	31(1)	-1(1)	10(1)	-2(1)
C(9)	36(1)	36(1)	30(1)	-4(1)	11(1)	-8(1)
C(10)	46(2)	30(1)	50(2)	1(1)	19(1)	3(1)
C(11)	36(1)	30(1)	48(2)	-4(1)	17(1)	4(1)
C(12)	36(1)	47(2)	32(1)	-7(1)	13(1)	-4(1)
C(13)	38(1)	31(1)	47(2)	-2(1)	20(1)	4(1)
C(14)	46(2)	47(2)	25(1)	10(1)	12(1)	-7(1)
C(15)	27(1)	26(1)	27(1)	-1(1)	7(1)	-2(1)
C(16)	34(1)	40(2)	48(2)	-3(1)	19(1)	5(1)
C(17)	39(1)	34(1)	49(2)	-2(1)	16(1)	-8(1)
C(18)	37(1)	44(2)	34(2)	2(1)	7(1)	2(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$).

	x	y	z	U(eq)
H(2A)	4796	8307	2194	50
H(2B)	5500	7192	3037	50
H(5)	4081	5072	290	44
H(6A)	4534	6489	4160	38
H(6B)	4601	5104	3568	38
H(8)	3248	3648	2700	35
H(9A)	2747	4084	850	42
H(9B)	2186	5427	889	42
H(10A)	3451	8489	2728	51
H(10B)	2756	7846	1532	51
H(11A)	2590	7410	3479	46
H(11B)	1938	6697	2300	46
H(12A)	3495	4226	4623	58
H(12B)	2443	4900	4222	58
H(12C)	3404	5745	4958	58
H(13A)	2066	1752	756	58
H(13B)	1856	455	1327	58
H(13C)	2832	1306	1983	58
H(14A)	2492	1823	3971	61
H(14B)	1598	799	3437	61
H(14C)	1435	2255	3835	61
H(16A)	-80	4408	1553	60
H(16B)	-255	3305	2321	60
H(16C)	-1057	3532	1062	60
H(17A)	-289	906	1879	63
H(17B)	48	387	962	63
H(17C)	-995	1083	576	63
H(18A)	-733	2877	-525	61
H(18B)	253	2119	-334	61
H(18C)	276	3682	-46	61

Table 6. Torsion angles [°].

C(14)-Si(1)-O(2)-C(8)	85.0(2)
C(13)-Si(1)-O(2)-C(8)	-33.9(2)
C(15)-Si(1)-O(2)-C(8)	-154.2(2)
O(1)-C(1)-C(2)-C(3)	-179.8(3)
C(5)-C(1)-C(2)-C(3)	0.4(3)
C(1)-C(2)-C(3)-C(4)	-1.3(3)
C(1)-C(2)-C(3)-C(6)	117.0(3)
C(1)-C(2)-C(3)-C(10)	-122.2(3)
C(6)-C(3)-C(4)-C(5)	-123.1(3)
C(2)-C(3)-C(4)-C(5)	1.9(3)
C(10)-C(3)-C(4)-C(5)	127.2(3)
C(6)-C(3)-C(4)-C(9)	55.3(3)
C(2)-C(3)-C(4)-C(9)	-179.6(2)
C(10)-C(3)-C(4)-C(9)	-54.4(3)
C(9)-C(4)-C(5)-C(1)	-180.0(3)
C(3)-C(4)-C(5)-C(1)	-1.8(3)
O(1)-C(1)-C(5)-C(4)	-179.0(3)
C(2)-C(1)-C(5)-C(4)	0.8(3)
C(4)-C(3)-C(6)-C(7)	-69.3(3)
C(2)-C(3)-C(6)-C(7)	174.9(2)
C(10)-C(3)-C(6)-C(7)	46.4(2)
C(3)-C(6)-C(7)-C(12)	-166.4(2)
C(3)-C(6)-C(7)-C(8)	72.6(2)
C(3)-C(6)-C(7)-C(11)	-44.4(3)
Si(1)-O(2)-C(8)-C(9)	101.8(2)
Si(1)-O(2)-C(8)-C(7)	-134.66(19)
C(12)-C(7)-C(8)-O(2)	56.9(3)
C(6)-C(7)-C(8)-O(2)	179.9(2)
C(11)-C(7)-C(8)-O(2)	-69.5(3)
C(12)-C(7)-C(8)-C(9)	177.2(2)
C(6)-C(7)-C(8)-C(9)	-59.7(3)
C(11)-C(7)-C(8)-C(9)	50.9(3)

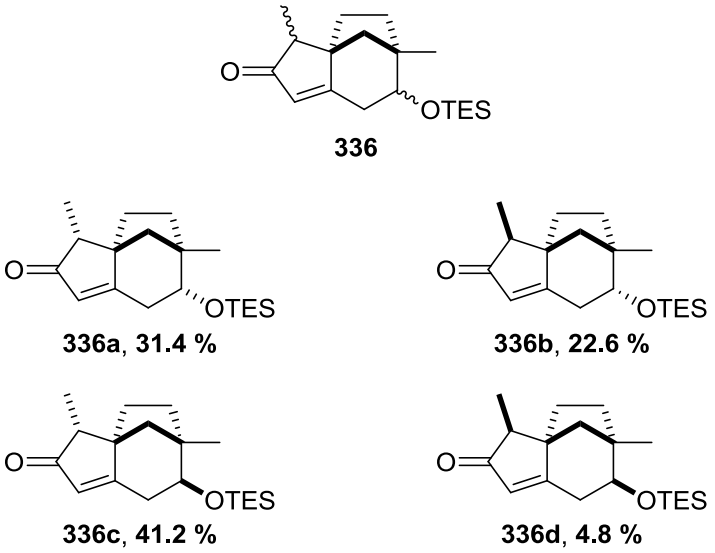
C(5)-C(4)-C(9)-C(8)	138.5(3)
C(3)-C(4)-C(9)-C(8)	-39.6(3)
O(2)-C(8)-C(9)-C(4)	164.1(2)
C(7)-C(8)-C(9)-C(4)	41.1(3)
C(4)-C(3)-C(10)-C(11)	83.6(3)
C(6)-C(3)-C(10)-C(11)	-30.3(3)
C(2)-C(3)-C(10)-C(11)	-159.4(3)
C(12)-C(7)-C(11)-C(10)	146.7(2)
C(6)-C(7)-C(11)-C(10)	24.9(3)
C(8)-C(7)-C(11)-C(10)	-88.9(3)
C(3)-C(10)-C(11)-C(7)	3.3(3)
O(2)-Si(1)-C(15)-C(16)	-49.4(2)
C(14)-Si(1)-C(15)-C(16)	69.5(2)
C(13)-Si(1)-C(15)-C(16)	-170.4(2)
O(2)-Si(1)-C(15)-C(18)	70.2(2)
C(14)-Si(1)-C(15)-C(18)	-170.9(2)
C(13)-Si(1)-C(15)-C(18)	-50.8(2)
O(2)-Si(1)-C(15)-C(17)	-170.0(2)
C(14)-Si(1)-C(15)-C(17)	-51.2(2)
C(13)-Si(1)-C(15)-C(17)	68.9(2)

Symmetry transformations used to generate equivalent atoms:

3 Assignment and stereochemical consideration for compound 336

Further analysis of compound **336** was performed using a variety of NMR techniques by Dr. John Parkinson at the University of Strathclyde, Glasgow.

Four diastereoisomers are mixed and exist as:



Based on integration of the PSYCHE (Pureshift) 1D ^{1}H NMR spectrum in the alkene proton resonance region of the NMR spectrum, the ratio of products for **a:b:c:d** is:

a (31.4%) : b (22.6%) : c (41.2%) : d (4.8%)

Table 1. NMR assignments for diastereoisomer **a** of compound **336**

Assignment	**δ ^{1}H (ppm)**	**Assignment**	**δ ^{13}C (ppm)**
9	1.006	1	53.79
21	?	2	183.5
23	2.165	3	35.3
24	1.813	4	75.88
25	1.528	5	44.26

26	1.285	6	48.09
27	2.030	7	27.96
28	5.590	8	33.89
29	1.111	9	22.62
30	1.712	18	45.83
31	2.880	19	210.7
32	2.269	20	121.9
33	3.528	21	11.64

Table 2. NMR assignments for diastereoisomer **b** of **336**

Assignment	**δ ^{1}H (ppm)**	**Assignment**	**δ ^{13}C (ppm)**
9	1.018	1	54.10
21	0.979	2	182.9
23	2.169	3	35.45
24	1.857	4	76.08
25	1.307	5	44.77
26	?	6	43.66
27	2.018	7	29.10
28	5.598	8	?
29	0.969	9	22.87
30	1.592	18	45.95
31	2.861	19	210.10
32	2.293	20	122.20
33	3.474	21	9.54

Table 3. NMR assignments for diastereoisomer **c** of **336**

Assignment	**δ ^{1}H (ppm)**	**Assignment**	**δ ^{13}C (ppm)**
9	?	1	54.58
21	0.997	2	184.1
23	2.202	3	34.13
24	1.544	4	75.31
25	1.510	5	44.23

26	1.334	6	44.20
27	1.850	7	28.54
28	5.642	8	32.65
29	1.363	9	22.93
30	1.832	18	46.20
31	2.561	19	210.7
32	2.561	20	123.3
33	3.637	21	11.94

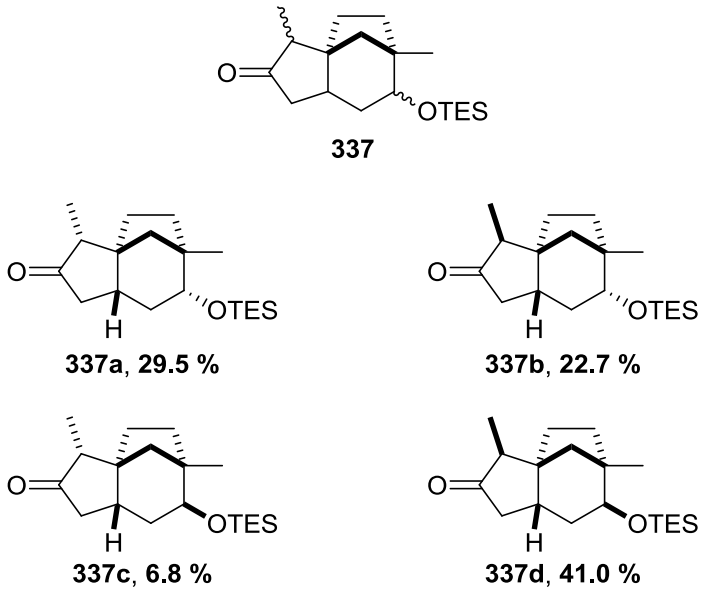
Table 4. NMR assignments for diastereoisomer **d** of **336**

Assignment	**δ ^{1}H (ppm)**	**Assignment**	**δ ^{13}C (ppm)**
9	?	1	54.89
21	1.004	2	183.80
23	2.170	3	?
24	?	4	75.69
25	?	5	44.67
26	?	6	?
27	?	7	?
28	5.646	8	?
29	?	9	?
30	?	18	46.19
31	2.603	19	210.0
32	2.603	20	123.6
33	3.638	21	9.134

4 Assignment and stereochemical consideration for compound 337

Further analysis of compound **337** was performed using a variety of NMR techniques by Dr. John Parkinson at the University of Strathclyde, Glasgow.

Four diastereoisomers are mixed and exist as:



Critical assessment of the standard 1D ^{1}H and pureshift (PSYCHE) 1D ^{1}H NMR spectrum in comparison with the same data for the reduced material before attempted epimerisation P assists in significantly identifying the stereochemical orientation of the four required diastereoisomers. A comparison of a region of the ^{1}H NMR data showing the resonance for the methine proton adjacent to the attached $OSi(Et_3)$ group is shown in **Figure 1** along with assignment of the signals to the respective structures shown as **a-d**.

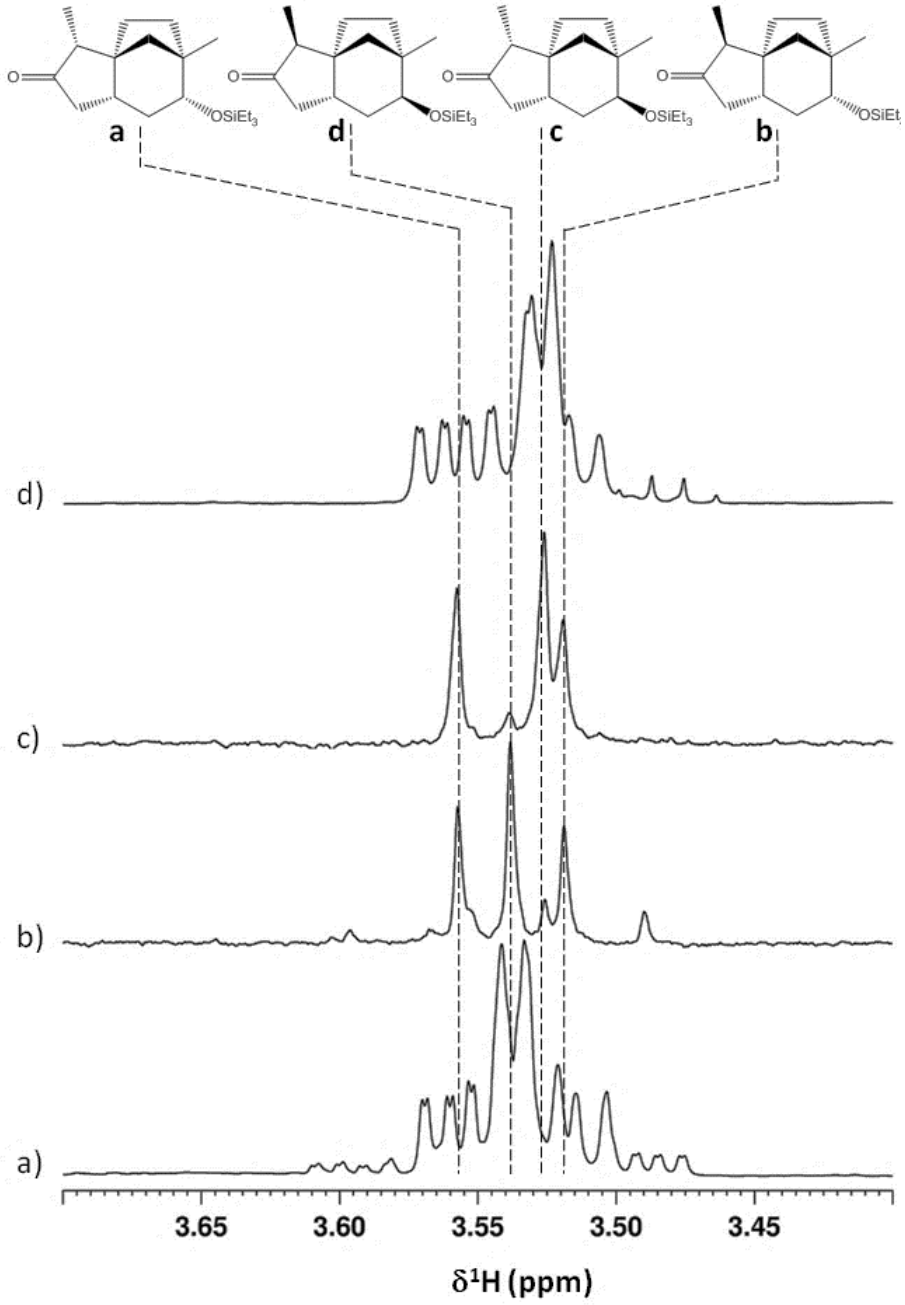


Figure 1. a) 1D ^{1}H NMR spectrum for **337** "post-epimerization". b) Pureshift (PSYCHE) 1D ^{1}H NMR spectrum for **337**. c) Pureshift (PSYCHE) 1D ^{1}H NMR spectrum for material "pre-epimerisation". d) 1D ^{1}H NMR spectrum for material "pre-epimerisation". Structures for the respective diastereoisomers are shown assigned to specific methine signals following exhaustive data assignment strategies.

NMR data assignments for the diastereotopic mixture of molecules presented is particularly challenging even at a magnet field strength of 14.1 T owing to the

considerable crowding in the proton NMR spectrum. Hence, whilst NOE data is traditionally acceptable for determining the structures of small molecules, this is not possible in all cases for these molecules and other features of the NMR data must be considered as well as the use of other types of NMR data. In particular, this work has been carried out with respect to Pureshift NMR data.

Comparison of the data in the region shown in **Figure 1** for compound **337** and the material before attempted epimerisation holds a vital clue regarding the orientation of the stereo centre at the carbon bearing the $–OSiEt_3$ protecting group. In each set of data there clearly exists two types of resonances. The most intense signals appear as narrow doublets (probably realistically double doublets, although the finer of the small couplings is lost in the lineshape of the data acquired). The lesser signals appear as double double doublets with at least two large couplings and one long-range coupling. In the former case, the narrow splitting is due to the small couplings arising from the methine proton (position labelled 33) being orientated in a pseudo-equatorial manner with respect to both of the adjacent methylene protons (attached to carbon labelled 3). This places the protecting group in an orientation out of the plane as shown. In the cases of the larger couplings, the stereo centre has the opposite configuration, with the protecting group going into the plane as shown. The large coupling to the methine proton is due to the axial-axial coupling from one of the adjacent methylene protons.

The data confirm that epimerization occurs at the carbon centre adjacent to the carbonyl group on the 5-membered ring, altering the structure of **c** to **d**. It is not clear or apparent that the same epimerization occurs for **a**/**b** since the data for these two compounds appear similar in each case along with the relative ratio of diastereoisomers.

In the case of compound **337** the relative ratio of diastereoisomers by integration of the Pureshift (PSYCHE) NMR data shown in **Figure 1** is:

Appendix

a (**29.5 %**) : **b** (**22.7 %**) : **c** (**6.8 %**) : **d** (**41.0 %**)

These structures are confirmed by both ^{1}H-^{1}H NOE data and by chemical shift considerations.

Table 1. NMR assignments for isomer **d** of **337**:

Assignment	**δ ^{1}H (ppm)**	**Assignment**	**δ ^{13}C (ppm)**
9	0.955	1	n/a*
21	0.884	2	39.97
23	2.018	3	28.92
24	n/a	4	75.09
25	n/a	5	43.19
26	n/a	6	32.03
27	n/a	7	n/a
28	2.196	8	n/a
29	0.735	9	24.26
30	1.546	18	50.83
31	1.595	19	219.5
32	1.912	20	41.58
33	3.467	21	6.126
34	2.401		
35	1.797		

Identified NOEs consistent with the structure shown for **d** are shown in **Figure 2**.

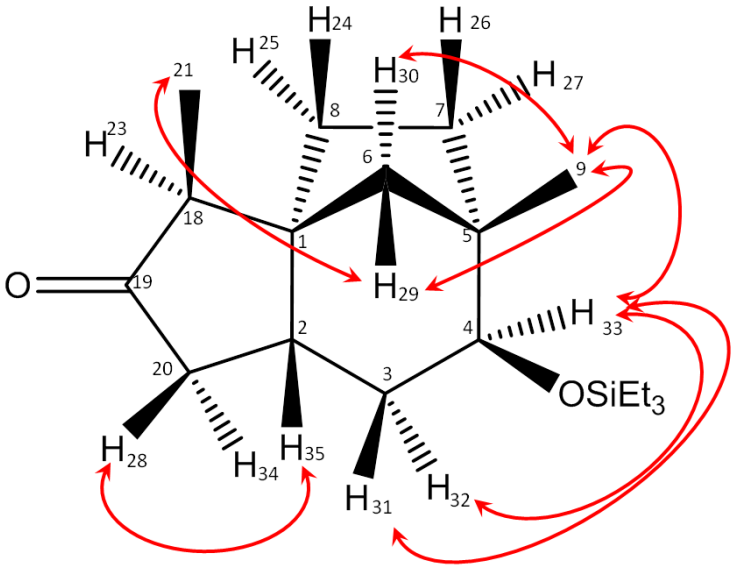


Figure 2. Structure of **337 "d"** as defined by NMR data assignment, chemical shift considerations and NOE data as shown by the red double-headed arrows.

Representative data showing assignment of signals for the **d** diastereoisomer in **337** are shown in **Figure 3** below.

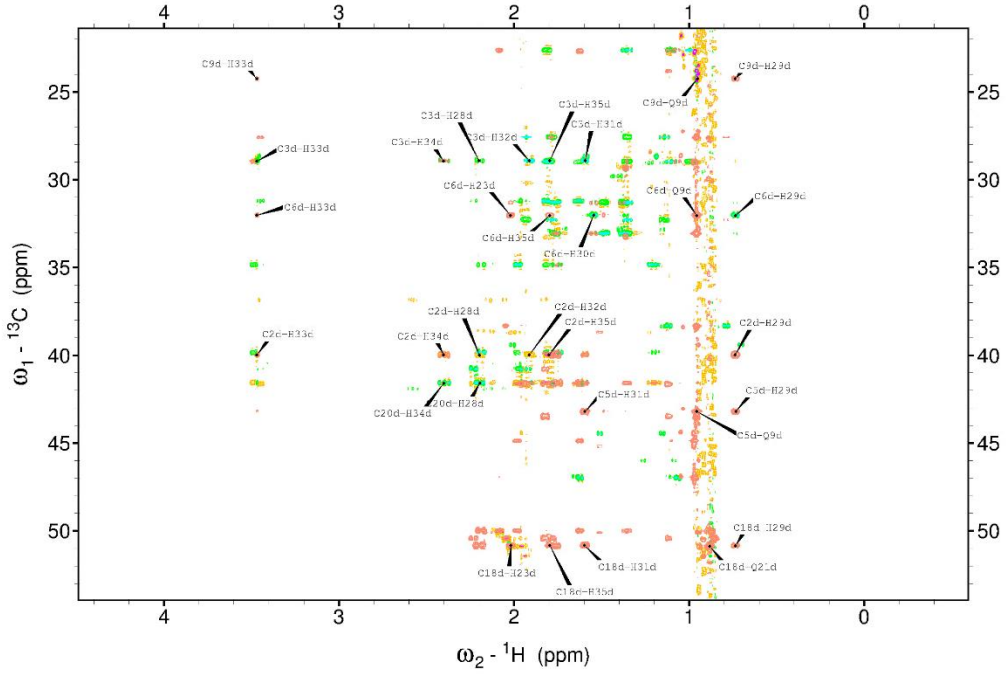
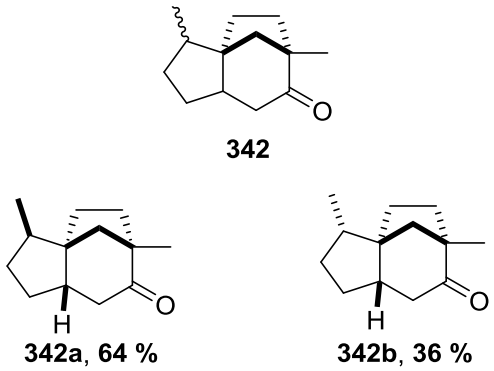


Figure 3. Representative 2D [^{1}H, ^{13}C] correlation data used in the assignment of structure **d** of **337**. Green/Yellow – 2D [^{1}H, ^{13}C] HSQC-TOCSY NMR data. Coral – 2D [^{1}H, ^{13}C] HMBC NMR data. Magenta/Cyan – 2D [^{1}H, ^{13}C] HSQC NMR data. Only those signals identified for structure **d** show assignments from the mixture. Signals from the other diastereoisomers are not annotated or assigned in this instance.

5 Assignment and stereochemical consideration for compound 342

Further analysis of compound **342** was performed using a variety of NMR techniques by Dr. John Parkinson at the University of Strathclyde, Glasgow.

Two diastereoisomers are mixed and exist as:



Based on integration of the proton resonances for the isolated methyl groups within the two structures, the ratio of isomers was found to be:

a (**64%**) : **b** (**36%**)

The numbering scheme used for these structures is shown in **Figure 1** and differs to other numbering schemes used for other structures.

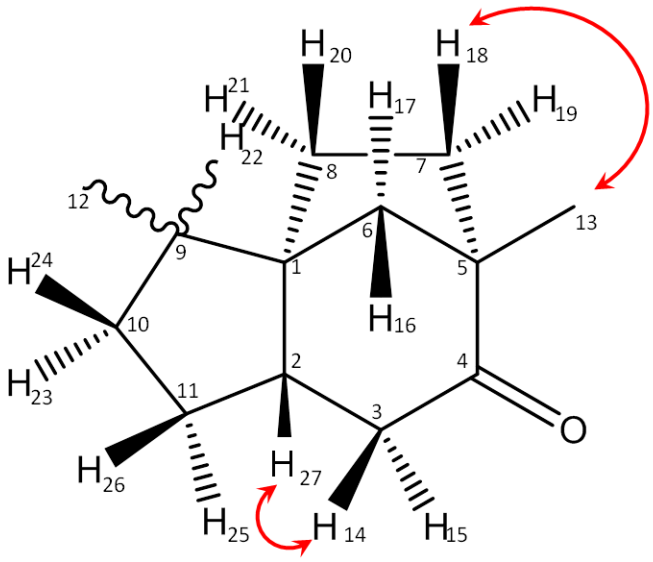


Figure 1. Numbering scheme used in the NMR data assignment of **342**

Table 1. NMR assignments for isomer **a** of **342**:

Assignment	δ ^{1}H (ppm)	Assignment	δ ^{13}C (ppm)
12	0.843	1	52.59
13	1.066	2	44.89
14	2.514	3	39.27
15	2.120	4	215.28
16	1.285	5	50.88
17	1.430	6	37.10
18	1.520	7	33.78
19	1.772	8	32.90
20	1.354	9	38.03
21	1.876	10	31.11
22	1.811	11	29.33
23	1.198	12	13.31
24	1.789	13	19.80
25	1.264		
26	1.775		
27	1.957		

Table 2. NMR assignments for isomer **b** of **342**:

Assignment	δ ^{1}H (ppm)	Assignment	δ ^{13}C (ppm)
12	0.869	1	52.68
13	1.028	2	49.47
14	2.324	3	41.10
15	2.168	4	213.84
16	1.242	5	51.43
17	1.725	6	46.19
18	1.510	7	34.46
19	1.615	8	21.58
20	1.397	9	36.84
21	1.675	10	31.17
22	1.759	11	26.15
23	1.209	12	13.22
24	1.839	13	18.99
25	1.273		
26	1.656		
27	1.817		

Making the assumption that the conformation across carbons 1-2 is *trans*, the conformation at position 9 is determined by NOE along with the chemical shifts of carbons 8 and 6 in particular. In structure **a** the chemical shift of carbon 8 is significantly deshielded with respect to the same carbon in structure **b** (a difference $\Delta\delta^{13}C_{(8a-8b)}$ = 11.32 ppm). In structure **b**, the methyl group labelled 12 eclipses carbon 8 and the attached protons, thereby causing shielding of carbon 8. This places methyl group 12 on the same face of the structure as carbon 8. In a similar vein, the opposite shielding effects are observed at carbon 6. In structure **a** the carbon at position 6 is more shielded than in structure **b** ($\Delta\delta^{13}C_{(6a-6b)}$ = -9.09 ppm). Thus, in structure **a** the methyl group at position 12 is on the same face of the molecule as carbon 6 whereas the opposite is true for structure **b**. NOE data confirm this by showing through space correlation between H22 and H21 in structure **a** which is feasible only if H22 is on the same face as C8, as is the case in structure **a**.

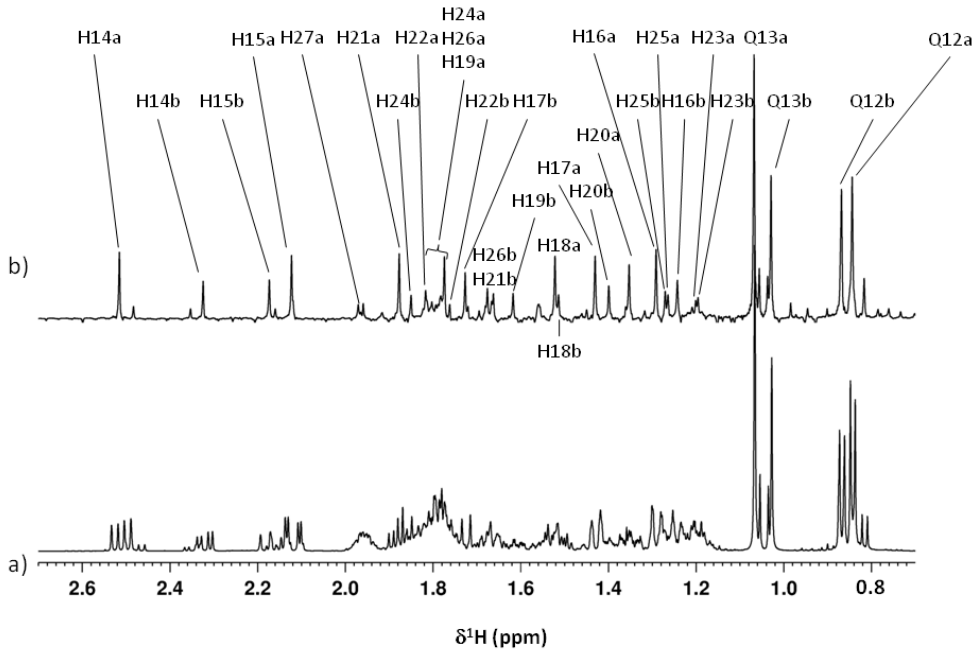


Figure 2: 600 MHz 1D ^{1}H NMR spectra for **342**. a) Standard spectrum. b) Pureshift (PSYCHE) 1D ^{1}H NMR spectrum showing a singlet for each type of proton in the molecule with assignments shown above each signal (below for H18b).

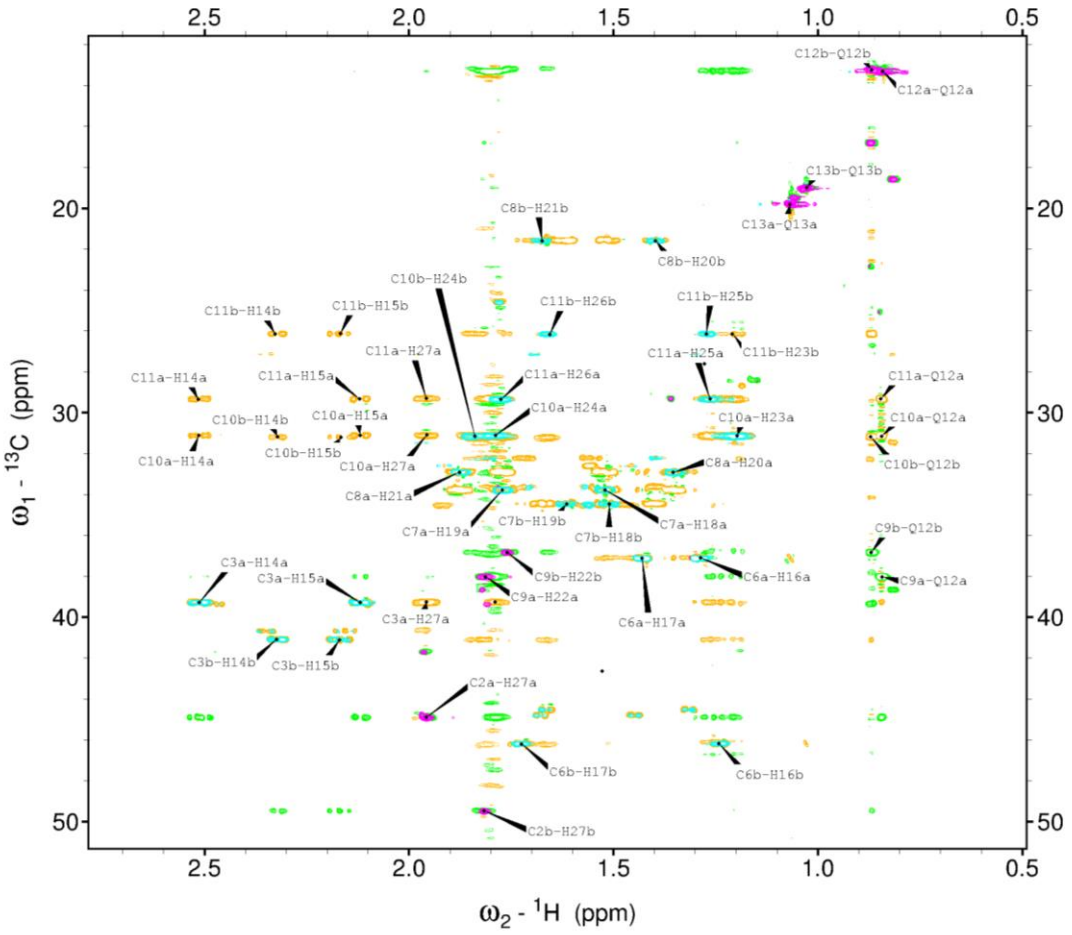


Figure 3: 2D [^{1}H, ^{13}C] correlation data for **342**. Magenta (CH, CH_3 – positive contours) and cyan (CH_2 – negative contours) cross-peaks from the 2D [^{1}H, ^{13}C] HSQC NMR data acquired at 14.1 T. Yellow and green contours: overlay of 2D [^{1}H, ^{13}C] HSQC-TOCSY NMR data acquired at the same magnetic field strength. Assignments of cross-peaks are shown as C*xn*-H/Q*yn*, where C indicates carbon chemical shift and H/(Q) indicates proton (methyl group) chemical shift and *x* / *y* correspond to the numbering scheme for the structure of **342** shown in **Figure 1** and "a" or "b" refer to the specific stereochemistry described for the two possible structures of **342** shown.