The use of Silyl Enol Ethers as Alkene Equivalents in the Pauson-Khand Reaction

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Author Declaration

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Date: 26/03/2020

Abstract

Over the past two decades, work within our laboratories has focused on the development of the Pauson-Khand reaction to deliver novel methodologies for the construction of flexible cyclopentenone scaffolds. To date, the Pauson-Khand reaction has been widely used to synthesise cyclopentenone motifs in natural product synthesis and beyond. However, there is a distinct lack of examples which use functionalised reacting partners to form diverse cyclopentenones. To address this notable deficiency, we employed, for the first time, silyl enol ethers as alkene equivalents for the intramolecular Pauson-Khand reaction to generate oxygenated cyclopentenones. Using this method, 17 novel cyclopentenones have been synthesised, which feature oxygenation on the cyclopentenone ring. Furthermore, two oxygenated cyclopentenones were readily converted into their fluorinated analogues in one step.

In addition to the methodology development, we sought to employ this novel Pauson-Khand reaction in the arena of total synthesis of natural products. In this regard, we selected Xeromphalinone C, a natural product isolated in 2010, which is part of a family of natural products featuring oxygenated cyclopentenone motifs. A novel synthetic sequence to Xeromphalinone C was established, which used our novel Pauson-Khand reaction methodology as a key step, completing the first total synthesis of Xeromphalinone C in **1.6%** yield over 16 steps. This highlighted the utility of our novel methodology as a useful step for the synthesis of complex, functionalised cyclopentenone molecules.

“There is light but there’s a tunnel to crawl through”

-Frightened Rabbit

The Oil Slick

Acknowledgements

I wish to begin the acknowledgements section by thanking Professor William J. Kerr. Particularly for choosing me to work on this interesting research project but also for helping me to develop my skills as a researcher and communicator. I am grateful for the opportunities you have afforded me and for helping me secure a job at the end of my PhD.

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A special thanks goes to the technical staff at the University of Strathclyde, in particular Craig Irving, Gavin Bain and Patricia Keating. Thanks also to Lindsay McCulloch for organising the 1st year teaching laboratories and having the interminable ability to shrug off yet another glassware breakage.

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Abbreviations

))):	ultrasound
Bu:	butyl
DCE:	1,2-dichloroethane
4 Å MS:	4 Å molecular sieves
Ac:	acetic
Atm.:	atmospheres
BINAP:	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc:	*tert*-butyloxycarbonyl
Bn:	benzyl
Conc.:	concentrated
Cp:	cyclopentadienyl
Cy:	cyclohexyl
d:	days
DBU:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM:	dichloromethane
DFT:	density functional theory
DIPEA:	di*iso*propylethylamine
DMAP:	dimethylaminopyridine
DME:	1,2-dimethoxyethane
DMF:	*N*,*N*-dimethylformamide
DMP:	Dess-Martin Periodinane
DMSO:	dimethyl sulfoxide

DodSMe:	dodecyl methyl sulfide
dr:	diastereomeric ratio
DSAC:	dry state absorption conditions
EDG:	electron-donating group
EWG:	electron-withdrawing group
ee:	enantiomeric excess
Eq.:	equivalents
Et:	ethyl
EtOH:	ethanol
EWG:	electron-withdrawing group
h:	hours
HOMO:	highest occupied molecular orbital
HPLC:	high performance liquid chromatography
HSQC:	heteronuclear single quantum coherence
HMBC:	heteronuclear multiple bond correlation
HRMS:	high resolution mass spectrometry
IR:	infrared
LUMO:	lowest unoccupied molecular orbital
M:	molar
Me:	methyl
Min:	minutes
MS:	mass spectrometry
MW:	microwave irradiation

NBO:	natural bond order
^{n}Bu:	^{n}butyl
NMO:	*N*-methylmorpholine *N*-oxide
NMR:	nuclear magnetic resonance
	s: singlet
	d: doublet
	t: triplet
	q: quartet
	m: multiplet
Pet. ether:	petroleum ether
Ph:	phenyl
PG:	protecting group
PPTS:	pyridinium *p*-tolunesulfonate
Quant.:	quantitative
rt:	Room temperature
s:	seconds
TBAI:	tetrabutylammonium iodide
TBAF:	tetrabutylammonium fluoride
TBS:	*tert*-butyldimethylsilyl
^{t}Bu:	*tert*-butyl
TES:	triethylsilyl
Temp.:	temperature
TIPS:	triisopropylsilyl

TLC: thin-layer chromatography

TMANO: trimethylamine *N*-oxide

TMTU: tetramethylthiourea

Ts: *p*-toluenesulfonyl

TS: transition state

Contents

Chapter 1

Synthesis of Oxygenated Cyclopentenones *via* the Pauson-Khand Reaction

1.1 Introduction

Cyclopentenones are prevalent structural motifs in the field of organic chemistry, they feature in many bioactive molecules, and are common among an array of natural products (**Figure 1**).[1–5] Furthermore, they are widely used as key intermediates and building blocks for the synthesis of more complex structures. As a result, cyclopentenones are the subject of many extensive reviews cataloguing their synthesis and characteristics.[6–10] One such method of synthesis that is of particular interest to our research group is the Pauson-Khand reaction.[11–19]

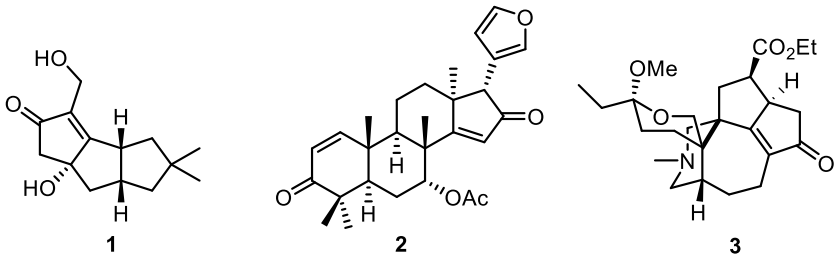
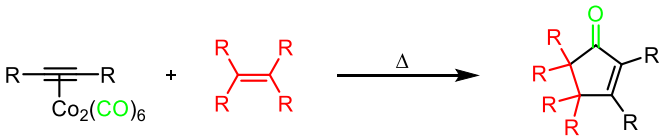


Figure 1

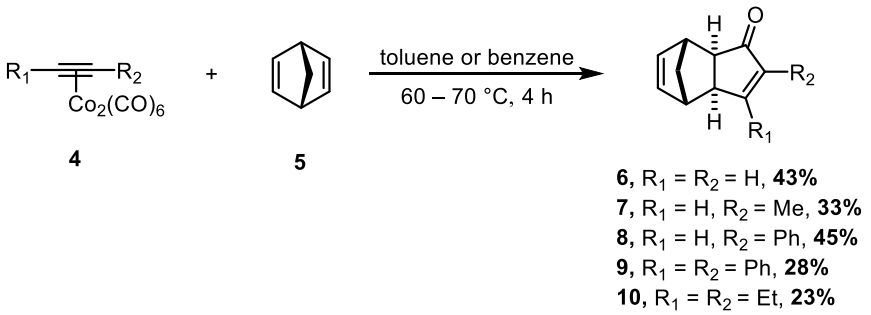
1.1.1 Pauson-Khand Reaction

The Pauson-Khand reaction is formally a [2 + 2 + 1] cycloaddition, featuring an alkene, an alkyne, and carbon monoxide as the three coupling components. The reaction is a transition metal-mediated process whereby, traditionally, the alkyne is administered in the form of a dicobalt hexacarbonyl complex. However, many protocols using other transition metals such as titanium,[20–23] rhodium,[24–26] and ruthenium[27,28] have been developed. Since its discovery, the reaction has found common application in synthetic organic chemistry, and, in particular, in the synthesis of natural products, which will be discussed with selected examples in Chapter 3. A general reaction scheme for the cobalt-mediated process is shown in **Scheme 1.**



Scheme 1

The reaction itself was initially discovered in the 1970s by Peter L. Pauson and Ihsan U. Khand when attempting to develop methods for cyclotrimerisation using cobalt-alkyne complexes of type **4** and norbornadiene **5** as an additive (**Scheme 2**).[29] It was noted that a cyclopentenone product was observed and that this could be replicated for a number of different substrates. This resulted in a series of publications, chartering some of the initial discoveries and applications of the newly-discovered reaction.[29–31]



Scheme 2

Although the yields of these early examples may seem modest, the reaction builds up impressive complexity from relatively simple starting materials. Pauson and Khand noted a few observations from their initial publications which hold true for most applications of this reaction. Specifically, they saw that it was predominantly the *exo*-product which was formed and that, in the case of unsymmetrical alkynes, the larger alkyne substituent would be featured in the α-position of the product (compounds **7** and **8**). Furthermore, Pauson rightly asserted that the regioselectivity was due to a steric interaction *(vide infra*). After this initial furore, there was a brief period of inactivity due to lack of interest by other researchers at the time; that is until Schore published the intramolecular Pauson-Khand reaction in the early 1980s.[32] This was followed by Magnus' proposed mechanism,[33] which is still accepted today, and since then many studies have probed the different variations and promotion methods available to turn the Pauson-Khand reaction into a broadly applicable methodology to reach a challenging cyclopentenone ring system. Each of these variations and promotion methods will be discussed throughout this introductory section.

1.1.2 Cobalt-alkyne Complex

In order to fully understand the mechanism of the Pauson-Khand reaction it is necessary to appreciate the properties of the catalyst dicobalt octacarbonyl, $Co_2(CO)_8$, and the cobalt-alkyne complex which forms as a result of mixing $Co_2(CO)_8$ and an alkyne. Dicobalt octacarbonyl is a transition metal carbonyl complex; it exists as a dimer of which there are varying isomeric forms in solution (**Figure 2**).[34–36] The left hand structure (**11a**) features a Co—Co bond and four terminal carbon monoxide ligands attached to each cobalt atom which has a trigonal bipyramidal geometry. The right-hand structure (**11b**) has two bridging carbonyl ligands and a metal—metal bond. Bimetallic complexes with carbonyl ligands are commonly bridged due to the polarisation of the strongly π-accepting/σ-donating carbonyl ligand which can be susceptible to nucleophilic attack at the carbon. Cobalt, however, is a mid-to-late transition metal, hence relatively electronegative, and allows dissociation of these carbonyl ligands, which is a significant feature of the Pauson-Khand mechanism (*vide infra*).

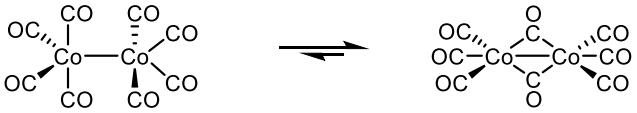


Figure 2

The cobalt-alkyne complexes are surprisingly stable compared to the dicobalt octacarbonyl starting material species; $Co_2(CO)_8$ is known to convert to $Co_4(CO)_{12}$ at 50 °C.[37] Formed by stirring dicobalt octacarbonyl and the alkyne together, in an inert solvent, at room temperature the formation of the dicobalt hexacarbonyl alkyne complex occurs rapidly. The complex can then be purified by chromatography on silica gel or alumina and stored under inert atmosphere in the freezer for extended periods. It forms by displacing the two bridging carbonyl ligands, releasing two molecules of carbon monoxide, and, as a result, maintaining a bridge structure with the alkyne as the bridging ligand (**Figure 3**).

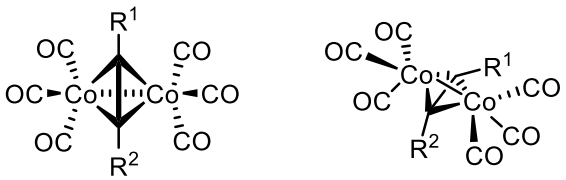


Figure 3

As mentioned above, cobalt is a group 9 element and so it means it is a relatively electronegative transition metal. In the cobalt-alkyne complexes described here, the cobalt is overall in the 0 oxidation state, so the *d*-orbitals required for effective back-donation are of sufficient energy to form strong bonds with the alkyne ligand.[38] interestingly, if the cobalt-alkyne complex is of an unsymmetrical alkyne then the complex itself can be de-symmetrised by the addition of a ligand (**Figure 4**). This forms the basis of some examples of stereoselective Pauson-Khand variations (*vide infra*) and can be clearly explained by considering the cobalt-alkyne complex as *pseudo*-tetrahedral. In this model, the central "atom" will be made chiral by the addition of a ligand to one cobalt atom by making each cobalt atom inequivalent. Thus, the complex is prochiral.[39,40]

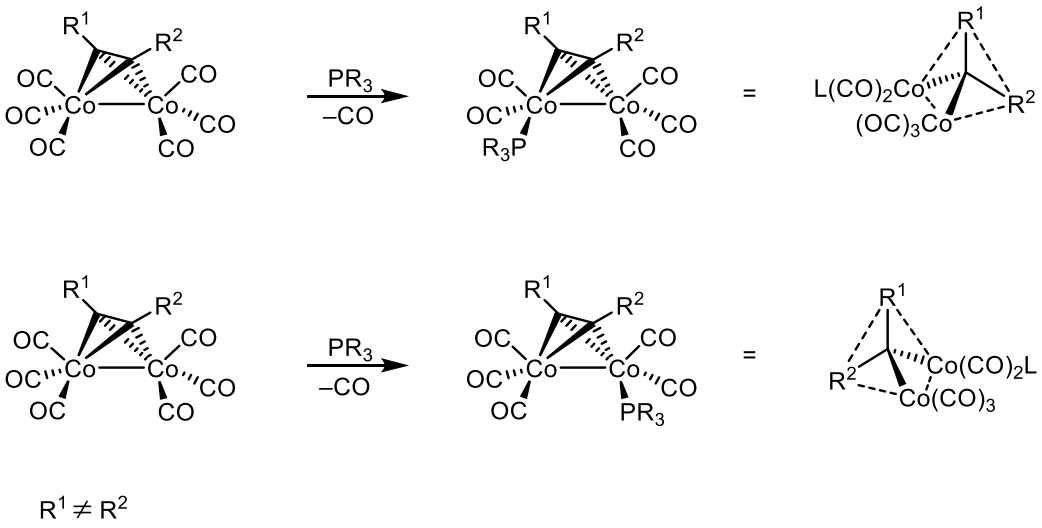
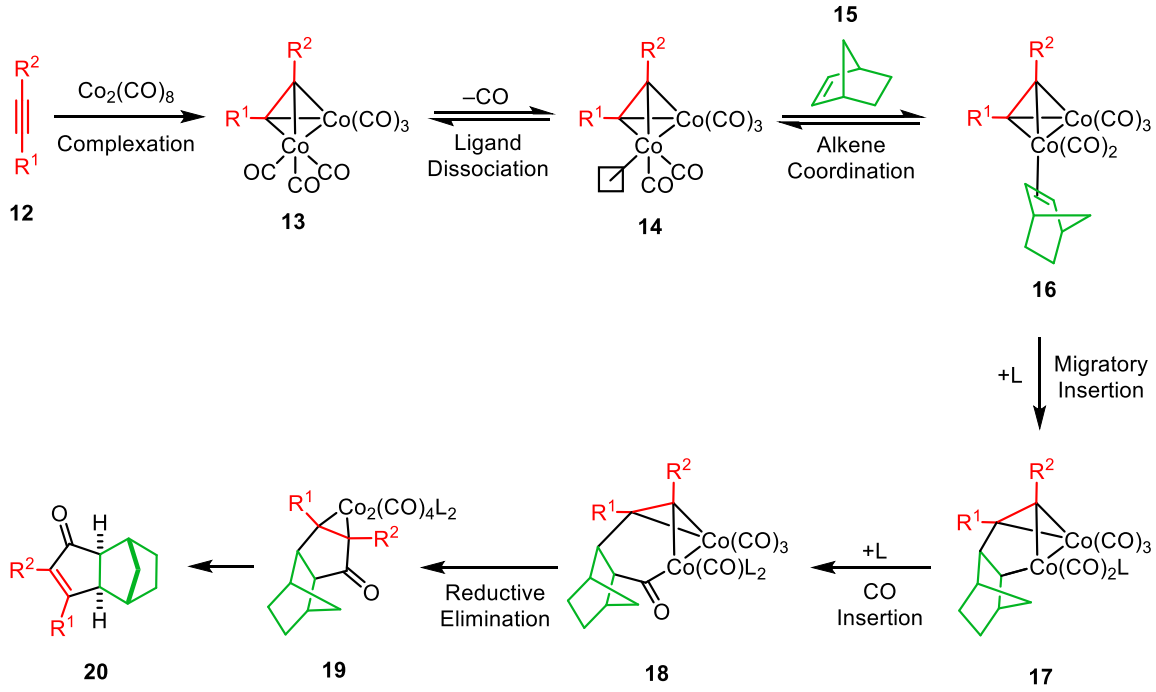


Figure 4

1.1.3 Mechanism of the Pauson-Khand Reaction

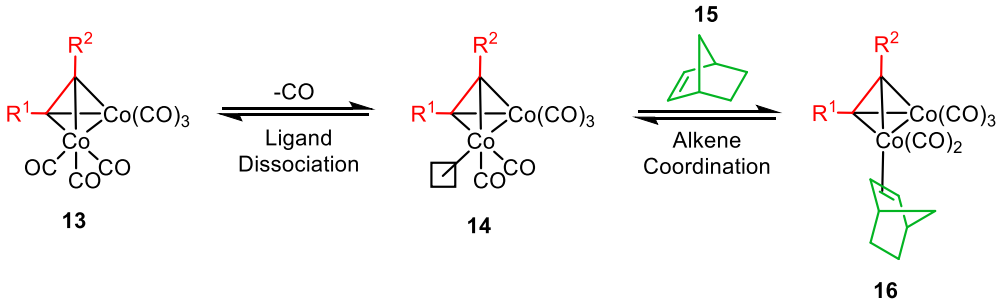
The mechanism of the Pauson-Khand reaction was first postulated by Magnus in 1985[33] though, since no intermediate beyond the cobalt-alkyne complex has been isolated, this has never been confirmed. An example mechanism is shown in **Scheme 3** using norbornene **15** as the alkene component of the reaction. This mechanism is widely accepted due to the prediction of regio- and diastereoselectivity seen in a wide range of examples. Additionally, several theoretical calculations have been conducted on this mechanism and agree with its plausibility, which has improved our overall understanding of this complex mechanism.[41–50]



Scheme 3

This is a rather complex reaction mechanism with several important features which will be described individually in the following sections. The four main components of the reaction are: i) ligand substitution; ii) cobaltacycle formation; iii) CO insertion; and iv) reductive elimination.

1.1.3.1 Ligand Substitution

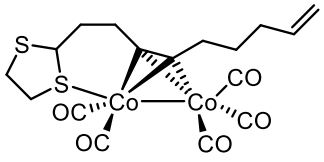


Scheme 4

Ligand substitution is the two-step process that occurs after formation of the cobalt-alkyne complex **13**. In order to facilitate the cyclisation, both the alkene and alkyne coupling partners must be coordinated to the catalyst. For this to happen, there must be substitution of one of the CO ligands to accommodate the coordination of the alkene component (**Scheme 4**). This

occurs *via* a dissociative mechanism, whereby the carbonyl ligand will be released from the metal complex resulting in a coordinatively unsaturated metal centre (compound **14**). This is a reversible process and the carbonyl ligand can detach and recombine until the alkene component can coordinate to the metal (compound **16**). The initial dissociation of the carbonyl ligand is widely-accepted as most energetically demanding step for the thermal Pauson-Khand reaction.[41] Often, methods for reaction promotion are focused on accelerating this initial dissociation, and stabilisation of the coordinatively unsaturated species, since the subsequent steps do not have the same activation energy requirements and represent, generally, an energetically downhill process to the product (*vide infra*). Indeed, this explains the difficulty in observing any intermediates beyond this ligand substitution because the process towards the products will be very rapid. Furthermore, the steps to this point have been reversible as the alkene binds much more weakly to the cobalt than the alkyne does and so can simply dissociate again, returning unsaturated intermediate **14**. High pressures of carbon monoxide will lower the rate of reaction as this system will disfavour the initial dissociation of a carbonyl ligand. Moreover, Lewis basic solvents and additives such as DME or cyclohexylamine will increase the rate of reaction due to the stabilisation of the coordinatively unsaturated species formed after the initial loss of CO.

The pentacarbonyl species **14** has been observed by photoexcitation and trapping in an argon/nitrogen matrix at 12 K[51] and in frozen nujol at 90 K.[52] Similarly, Krafft *et al.* isolated a sulfur-stabilised pentacarbonyl-cobalt complex **21** during their studies (**Figure 5**), which they found could be rapidly converted back to the cobalt-alkyne complex when treated with carbon monoxide.[53]

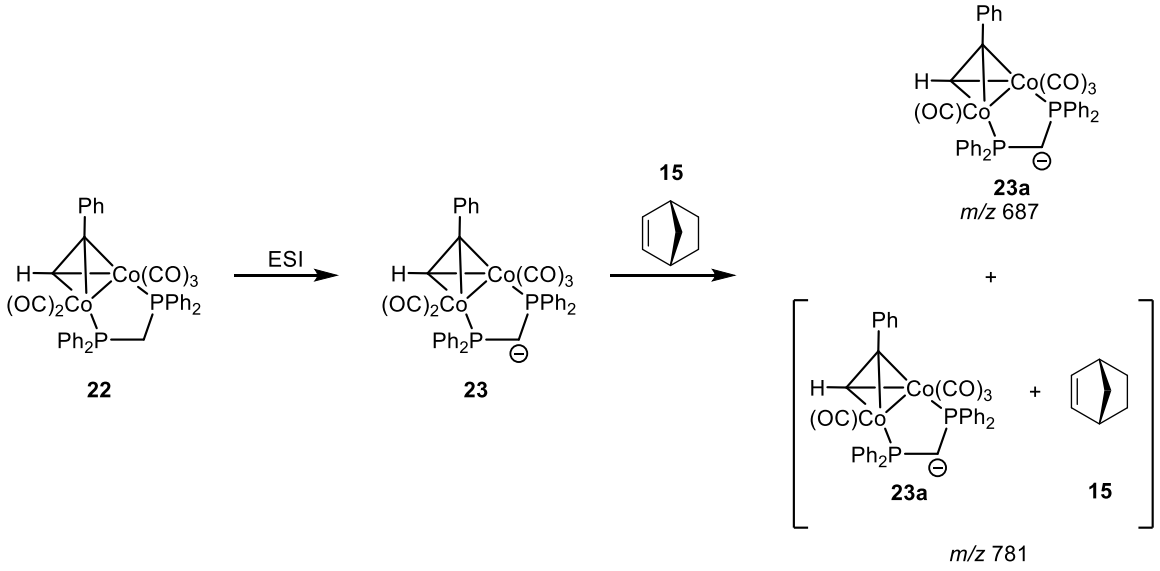


21

Figure 5

Gimbert, Greene, and Milet have conducted mass spectrometry experiments with regard to the ligand substitution stage of the Pauson-Khand reaction mechanism.[49] Specifically, the authors attempted to detect a reactive intermediate in the Pauson-Khand reaction

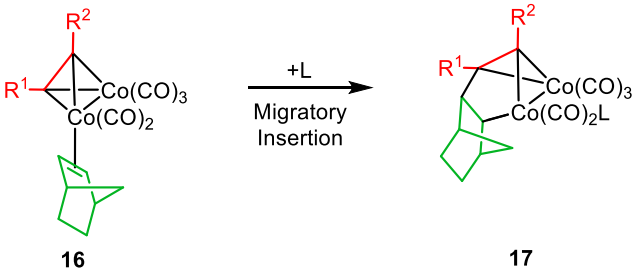
mechanism by electrospray ionisation followed by a reactive-collision process. Using cobalt-alkyne complex **22** containing a bridging bisphosphine ligand, electrospray ionisation was used to yield the anion **23**, which was subjected to reactive collisions with norbornene (**Scheme 5**). A mass ion peak corresponding to a coordinatively unsaturated cobalt-alkyne complex **23a** and another peak corresponding to that of the alkene-coordinated complex at m/z 781 were observed. There was distinctly no observation of the coordinatively saturated complex with coordination of the alkene which would have formed *via* an associative mechanism.



Scheme 5

Further DFT studies were carried out to ascertain whether the mass ion corresponded to the alkene-associated complex as shown above or whether it was actually the post-norbornene insertion cobaltacycle. Through evaluation of the respective energies, the authors stated that the mass corresponded to the more advanced cobaltacycle as this was significantly lower in energy; the possibility that mass corresponded to the yet more advanced carbon monoxide insertion product was deemed improbable. Ultimately, this research confirmed that the initial ligand substitution mechanism occurs *via* a dissociative mechanism with loss of the carbonyl ligand prior to association of the alkene component.

1.1.3.2 Cobaltacycle Formation



Scheme 6

Cobaltacycle formation (**Scheme 6**) is another important step in the mechanism of the Pauson-Khand reaction as this is the product-determining step. It is at this stage that the regio- and stereoselectivity of the process is set, and from this point onwards all reactivity occurs at one cobalt centre. The other cobalt centre remains attached to the alkyne and exerts an electronic influence on the overall reaction.[41] This alkene insertion step occurs in a migratory insertion-like fashion where the alkene inserts into one of the carbon—cobalt bonds and a new carbon—carbon bond is formed. Commonly, this is facilitated by an incoming ligand – which may be a dissociated carbonyl ligand or a Lewis basic additive. Alkenes are π-acceptors and will receive electron density from a filled *d*-orbital on the metal centre in order to strengthen the coordination. These orbitals play an important role in the reactivity of the olefin at this stage and are pivotal in forming the cobaltacycle.[42] An orbital representation of this insertion step is shown is shown in **Figure 6**. The amount of back-donation afforded to the LUMO (π*) of the alkene is directly related to the barrier to cobaltacycle formation, the higher the degree of back-donation the lower the barrier to cobaltacycle formation. This LUMO will also be directly involved in the formation of the new carbon—carbon bond and the HOMO (π) will be involved in forming the new carbon—cobalt bond. The HOMO of the $Co_2(CO)_5$-alkyne complex, will interact with the LUMO of the alkene to form the new carbon—carbon bond. The HOMO of the $Co_2(CO)_5$-alkyne complex was formed as a result of the orbital interaction of the unfilled π* of the alkyne and the filled *d*-orbitals of the metal. This generated a new filled π-orbital and it is this HOMO orbital which interacts with the alkene LUMO (π*) to form the new carbon-carbon bond. The alkene HOMO (π) does not receive the same degree of back-bonding as the alkyne portion and so will interact with the *d*-orbital of the cobalt to form the new σ-bond, thus creating the cobaltacycle.

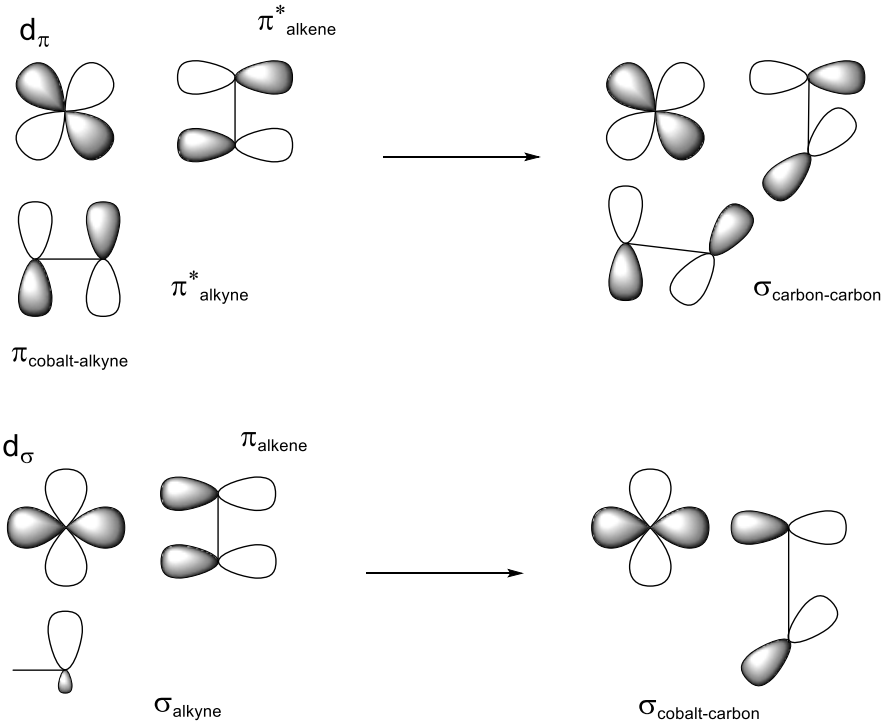
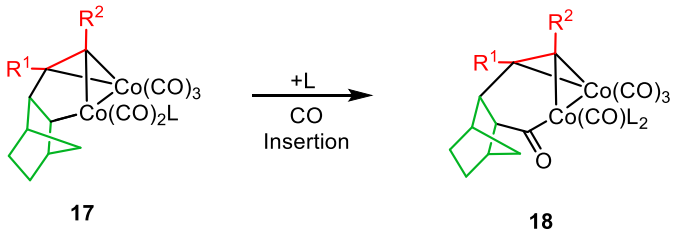


Figure 6

The alkene will typically, though not exclusively, insert into the least hindered cobalt—carbon bond and this is what gives rise to the regioselectivity, which Pauson and Khand initially reported in the seminal studies. However, this regioselectivity is with respect to the alkyne substituents only. There is no inherent regioselectivity with respect to the alkene substituents (*vide infra*). Energetically, this phase of the reaction is often endothermic or thermoneutral and, therefore, is potentially reversible. Some Lewis bases, such as cyclohexylamine and *n*-butyl methyl sulfide, have been purported to render this step irreversible and for this reason they find application as promoters for the reaction.[50] Further elaboration on the action of Lewis basic promoters will be discussed in a later section.

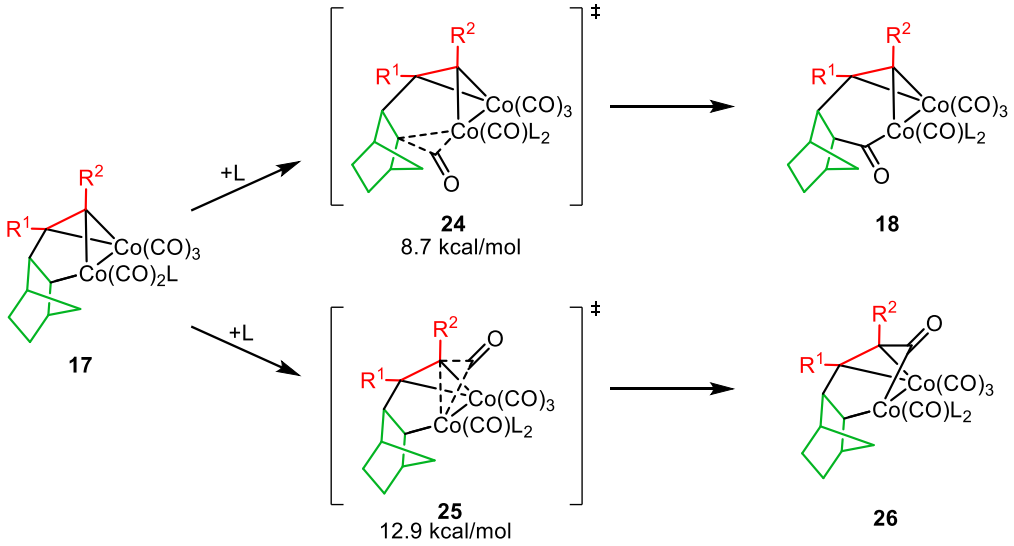
1.1.3.3 CO Insertion



17 **18**

Scheme 7

The insertion of a carbonyl ligand into the newly formed cobalt—carbon bond (**Scheme 7**) occurs in a similar fashion to the above-described alkene insertion. This incorporates the carbonyl ligand of the cyclopentenone product and generates a cobalt-acyl complex **18**. As shown in **Scheme 8**, there is thought to be a discrimination between which cobalt—carbon bond the carbonyl ligand will insert into based on theoretical calculations by Nakamura.[41] In theory, and in relation to that shown in **Scheme 7** above, the carbonyl ligand could insert into the other cobalt—carbon bond resulting in a different transition state **25** and an alternative cobalt-acyl complex **26**. Insertion into the newly formed carbon-cobalt bond (via **24** to deliver **18**) is the more favoured pathway given that the transition state energy barrier to this cobalt-acyl complex is 8.7 kcal/mol, which is significantly lower than insertion into the alkyne carbon-cobalt bond, which has an activation energy of 12.9 kcal/mol. Ultimately, this has no bearing on the product of the reaction as subsequent reductive elimination gives the same cyclopentenone. In concordance with the alkene insertion, the CO insertion is facilitated by an incoming ligand.



Scheme 8

In an effort to determine the precise origin of the CO group represented in the cyclopentenone product, Gimbert, Milet, and Greene recently published a similar study to their work on the alkene insertion step, which involved the use of ^{13}CO as a labelled collision gas in mass spectrometry analysis.[48] The results produced a product mass ion which did not contain any ^{13}C atoms and so they concluded that the carbonyl ligands must originate in the cobalt complex. Essentially, this suggests that the coordinatively saturated cobalt centre,

which facilitates the insertion of the carbonyl ligand into one of the cobalt—carbon bonds, does not become saturated *via* association of a ligand but instead through intramolecular transfer of a carbonyl. Following this suggestion, they produced some DFT calculations shown in **Figure 7.**

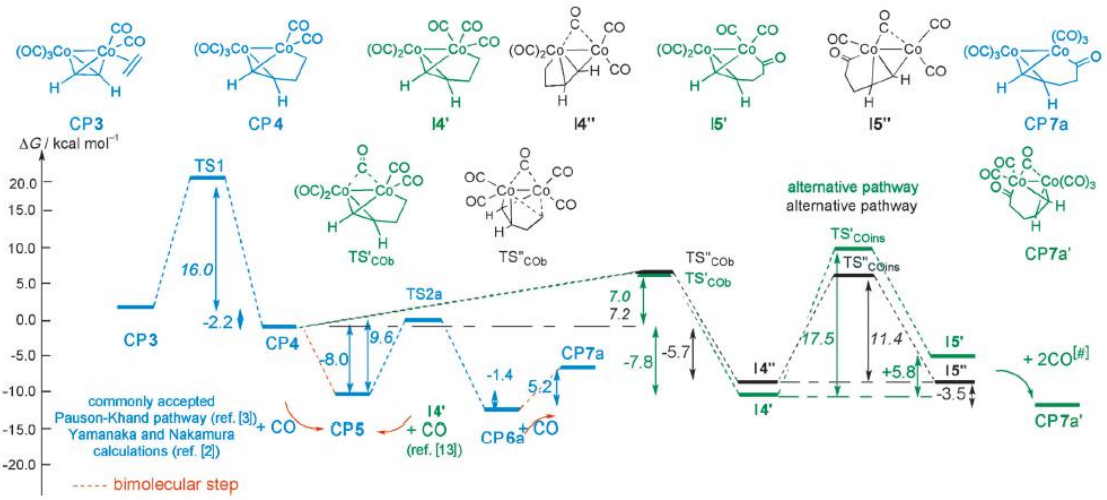
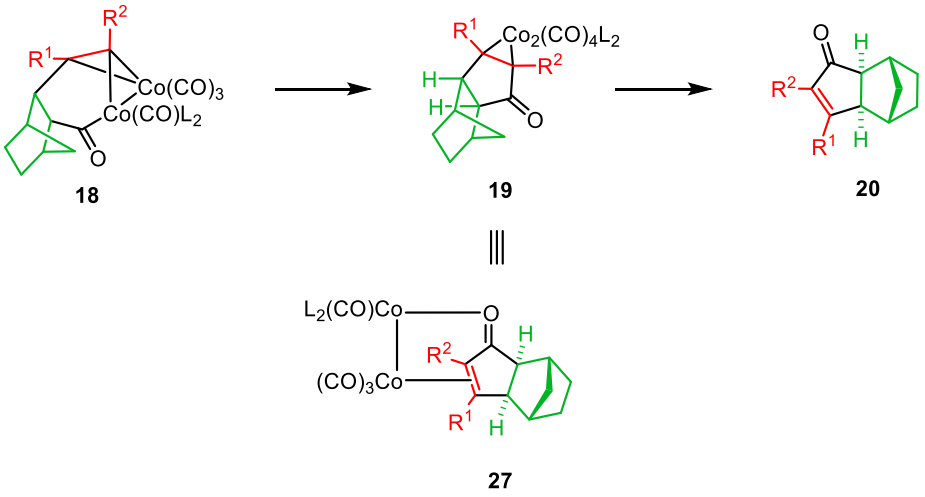


Figure 7[48]

The pathway in blue is the pathway calculated by Nakamura[41] which is the traditionally accepted pathway. The two parallel pathways are two alternative routes to the product; the authors comment that both pathways are possible. Following the green pathway, after the insertion of the alkene to generate the cobaltacycle CP4, Gimbert, Milet, and Greene propose that an intramolecular transfer of CO will occur *via* TS'$_{COb}$ to give I4', which can insert a CO into the cobalt—carbon bond to give I5'. Another alternative transition state (black pathway, TS''$_{COb}$), which has a similar energy, was computed. This transition state arises when the cobaltacycle switches to the other cobalt atom upon bridging of a carbonyl and after the CO insertion event produces I5''.

1.1.3.4 Reductive Elimination



Scheme 9

The final stage of the Pauson-Khand reaction mechanism is reductive elimination followed by ligand exchange of the cobalt catalyst (**Scheme 9**). This ligand exchange step only occurs as a formal ligand exchange in the catalytic variant of the Pauson-Khand, exchanging with another alkyne fragment to restart the catalytic cycle. However, in the stoichiometric Pauson-Khand this is unnecessary and so the coordinated enone-cobalt complex will disproportionate to yield the Pauson-Khand product and cobalt residues.[18,41]

The theoretical experiments conducted on the overall mechanism of the Pauson-Khand reaction were undertaken quite some time after the initial proposal by Magnus. It is from these experiments that most of the information regarding the mechanism can be gleaned, particularly with regard to which steps are the most energetically demanding. Thus, producing a reason for the inability to isolate any intermediates of the mechanism: dissociation of the carbonyl ligand and insertion of the alkene are the highest energy transition states and thereafter the reaction is energetically downhill. The fully calculated reaction energy profile by Yamanaka and Nakamura is shown in **Figure 8**.

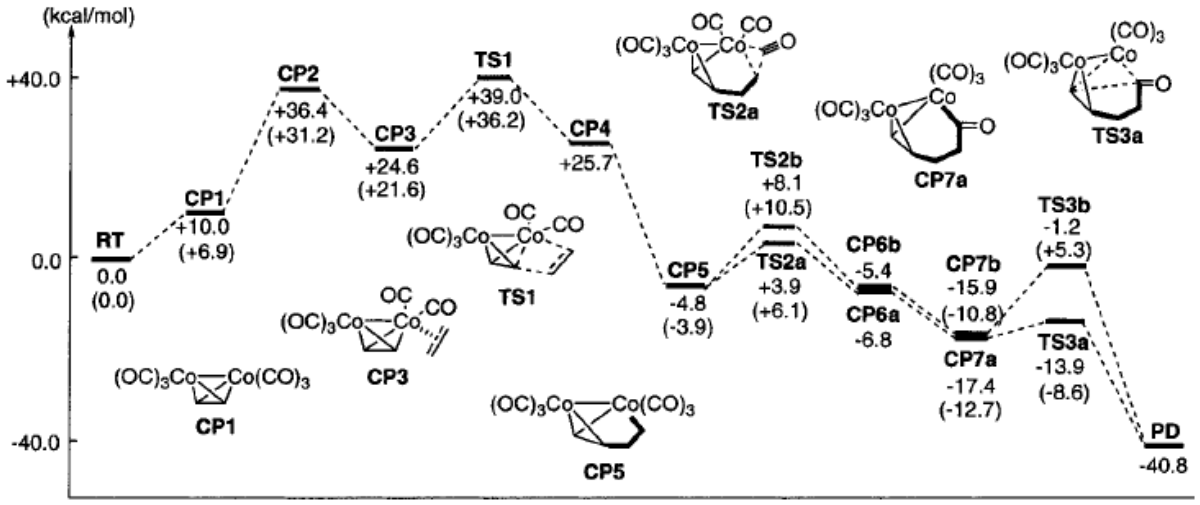
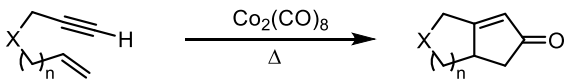


Figure 8[41]

This energy profile shows clearly that coordinatively unsaturated cobalt species (CP2) and TS1 are the high energy stationary points of the computed mechanism. The energy of CP2 can be lowered by the addition of an additive to stabilise the unsaturated species (*vide infra*). After TS1 the process is strongly exothermic, irreversible and product formation is fast.

1.1.4 General Substrate Reactivity

There are two distinct varieties of the Pauson-Khand reaction with respect to the reactants involved, the intra- and intermolecular variations. Many of the initial studies were conducted on the intermolecular Pauson-Khand reaction, whereby regiochemical issues arise when using unsymmetrical alkyne and alkene components. In general, terminal alkynes react more efficiently than internal alkynes. Similarly, un-, mono-, di- and trisubstituted alkenes[31,54] react with decreasing efficiency and there are no examples of tetrasubstituted alkenes. Strained alkenes react most efficiently as release of the strain can promote the insertion step.[42] In general, the intramolecular Pauson-Khand cyclisation is more efficient than its intermolecular counterpart, and is usually aided by a Thorpe-Ingold effect. Most common examples include substituted enynes that cyclise to form 5,5-fused bicyclic systems, as generalised in **Scheme 10.**



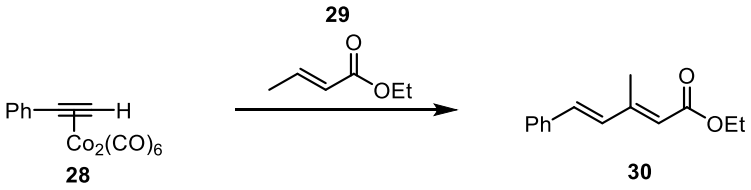
X = $C(CO_2Me)_2$, NTs, O

Scheme 10

The first intramolecular Pauson-Khand example was showcased by Schore in the early 1980s.[32] The Pauson-Khand reaction had begun to stagnate prior to this publication; it being widely regarded as a low-yielding and inapplicable reaction. This publication, and the subsequent proposal of the mechanism, generated more interest in the Pauson-Khand and thus the development of several methods of promotion, which will be discussed in detail in *Section 1.6*.

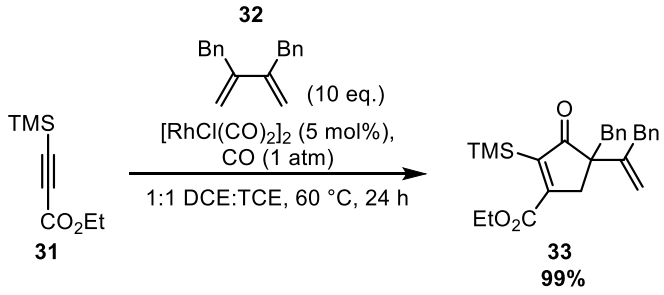
With regards substrate applicability, the Pauson-Khand reaction has, thus far, only been shown with simple alkyl-substituted substrates, with only limited examples of more functionalised substrates such as vinyl esters and vinyl fluorides (*vide infra*), and the electronics of these substituents affect the viability of the reaction.

A particular example of poorly reactive substrates are olefins containing electron-withdrawing groups, such as conjugated dienes, and α,β-unsaturated nitrile, ketone, and aldehyde functional groups. Indeed, these were originally thought to be unsuitable substrates for the Pauson-Khand reaction, often generating only conjugated diene products such as **30** (**Scheme 11**). [11,48] Such products arise from the lack of CO insertion within the typical Pauson-Khand reaction pathway.



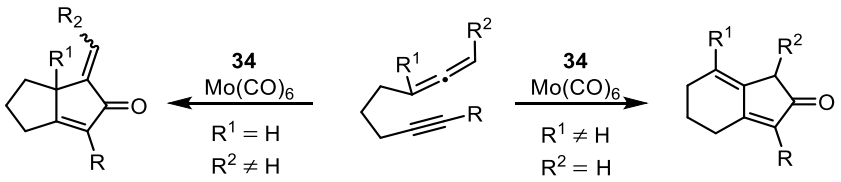
Scheme 11

However, since this initial work, several academic groups have studied the scope of electron-deficient olefins in the Pauson-Khand reaction.[56,57] Wender *et al*. have made the largest strides in this area by employing a Rh-catalysed process to cyclise conjugated dienes.[58–62] One such example is shown in **Scheme 12**, whereby Wender's chemistry delivered the desired product almost exclusively, albeit requiring 10 equivalents of the alkene.[60]



Scheme 12

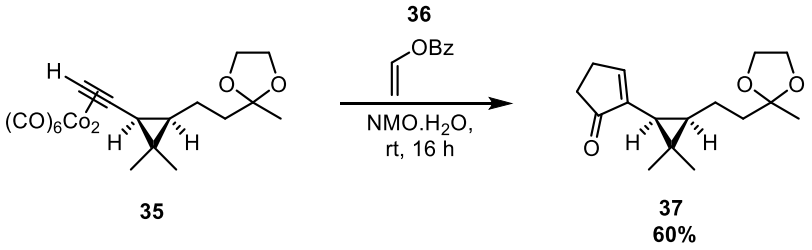
Another substrate type which received attention from Wender *et al.*,[61] and others,[63–66] were allenes. The use of allenes as alkene coupling partners for the Pauson-Khand reaction was initially developed by Brummond,[63] whose research highlighted that the substitution pattern of allenes was the determining factor on the selectivity of the products. It can be envisaged that the allene would cyclise through either of the double bonds of the allene. Brummond described that it was possible to induce cyclisation through one double bond over the other depending on whether an internal or terminal allene was used. A generalised reaction is shown in **Scheme 13** below. This protocol utilised molybdenum hexacarbonyl in place of the more common $Co_2(CO)_8$ which strangely proved to be inefficient in these types of Pauson-Khand cyclisation.[63] The terminal allene showed selective cyclisation through the terminal π-bond in most cases and *vice versa* for the internal allene. This was evidence that the π-bond selectivity could be attributed to sterics and that the reaction would proceed through the more accessible π-bond.[66] In cases where both R^1 and R^2 are hydrogen atoms then the cyclisation would occur through the internal π-bond to provide a 5,5-fused system.



Scheme 13

As mentioned previously, increasing substitution on the alkene component decreases the reactivity. Therefore, ethylene is a particularly reactive alkene component. However, its use requires high pressures of ethylene gas, typically using an autoclave.[24,67–69] Clearly, these reaction conditions presented significant impracticalities and an elegant protocol was discovered in our lab which overcame this issue.[70,71] This procedure used vinyl esters as

ethylene equivalents was employed as a key step in the total synthesis of (+)-taylorione shown in **Scheme 15**.[71] It is assumed that the ester is reduced by the residual cobalt species produced at the end of the reaction. This is a rare example of a functionalised alkene being used as a reacting partner in the Pauson-Khand reaction.

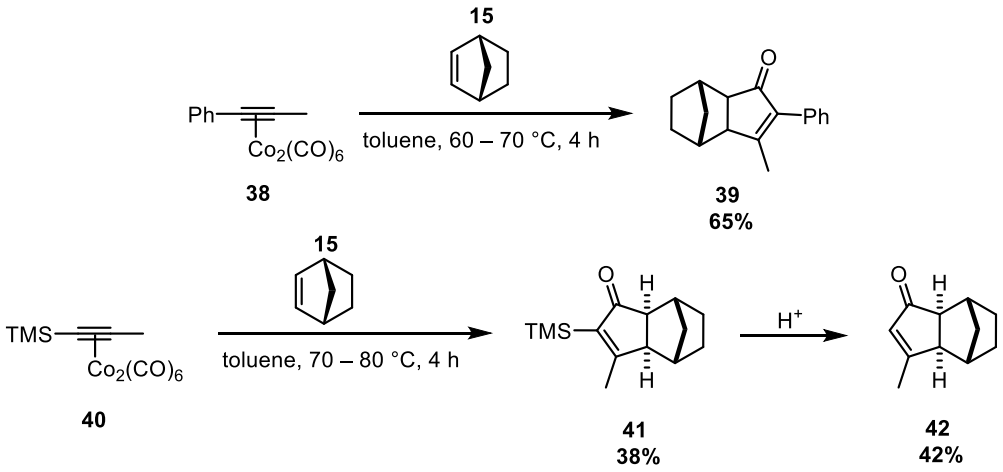


Scheme 14

1.1.5 Regioselectivity of the Pauson-Khand Reaction

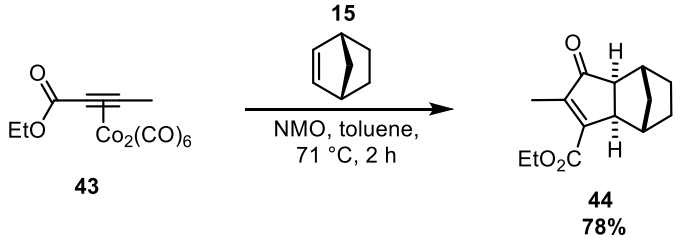
1.1.5.1 Alkyne Regioselectivity

The Pauson-Khand reaction is inherently regioselective for the alkyne component. Pauson and Khand asserted that the regioselectivity with respect to the alkyne was a result of sterics.[31] Highlighted in **Scheme 15**, the reaction between propynylbenzene cobalt complex **38** and norbornene **15** delivered compound **39** exclusively, containing the bulky phenyl substituent in the α position with respect to the carbonyl moiety. In an effort to generate β-substituted products, the same authors used a silyl-substituted alkyne which was subsequently hydrolysed to give β-substituted products.[31]



Scheme 15

Following this, Krafft *et al.* noticed that the alkyne regioselectivity could not be solely attributed to a steric interaction and proposed that electronics also played a role.[72,73] Krafft emphasised this by using electron-deficient alkynes in the reaction; previously there had been no reported successful examples using such substrates. The authors reported a successful *N*-methylmorpholine *N*-oxide (NMO)-promoted cyclisation with an interesting regiochemical outcome, showing that sterics are not entirely responsible for the regioselectivity (**Scheme 16**).[72] The sterically smaller methyl substituent was found exclusively at the α-position of the cyclopentenone product. It was expected that the steric differences between the two groups should not be sufficient enough to produce one regioisomer exclusively.[73] This was followed closely by a publication by Hoye showcasing the same results.[74]



Scheme 16

The rationale proposed for this novel regioselectivity was based on the electronic configuration of the alkyne C—C bond. Electron-withdrawing groups will polarise this bond and result in the formation of the favoured cobaltacycle **A** over **B** (**Figure 9**). The polarisation of the C—C bond makes alkene insertion into the carbon containing the electron-withdrawing group more favoured. This reasoning explains the regiochemical outcome of these reactions. However, if the R group in **Figure 9** is a hydrogen atom then steric interactions outweigh the electronic influence and a mixture of regioisomers is observed with incorporation of the larger EWG in the α-position as the major product.[73] This shows that the regiochemistry is dictated by a combination of steric and electronic effect but underlines that steric effects prevail.

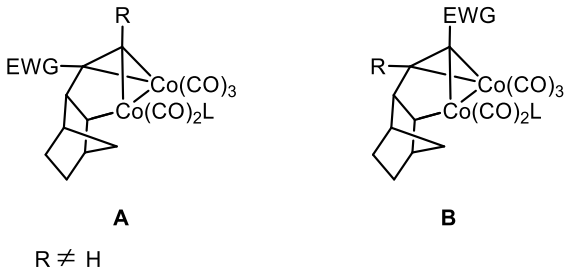
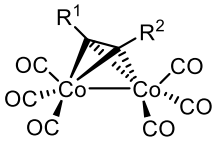


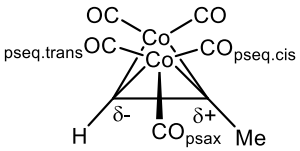
Figure 9

DFT calculations and experimental work conducted by Milet, Gimbert, and Greene have shown further reasoning for this selectivity switch governed by electronics.[43,47,75] In particular, carbon-13 NMR analysis of cobalt-alkyne complexes shows the change in the chemical shift of the acetylenic carbons upon complexation depending on the substituents, which is correlated to a polarisation of the bond.[76] It is stated that this polarisation is more marked in the cobalt-alkyne complex than in the free alkyne and that this extends to the carbonyl ligands attached to the cobalt itself, albeit less intensely. Considering this, they deduced that since polarisation of the alkyne ligand has an effect on the carbonyl ligands, this may result in selective decarbonylation.[43] Milet, Gimbert, and Greene hypothesised that electron-withdrawing groups on the alkyne increase its acceptor properties and so will decrease the overall back-donation afforded to the carbonyl ligands. This results in an accumulation of electron density on one of the carbons of the alkyne which is discharged back through the metal and onto the carbonyl ligands strengthening the metal-ligand bond. However, this electron density is not distributed equally to the carbonyls. Due to a *trans*-effect, the $CO_{pseq.trans}$ ligand (*trans* relative to EWG of alkyne) will be more receptive to electron density thereby making the $CO_{pseq.cis}$ ligand more labile by comparison. Testing this hypothesis, Milet, Gimbert, and Greene computed the geometries of the selected cobalt complexes shown in **Figure 10**. The electron densities due to polarisation of the alkyne were varied by careful choice of the substitution on the alkyne. Propyne-complex **45** was polarised towards the C—H bond due to the electron-donating properties of the methyl group. Complex **46** showed no polarisation of the alkyne bond as the hydrogen substituent on one side of the alkyne does not donate electron density as the alkyl group does and so cannot participate in the polarisation of this bond. The methyl-substituted version **47** was polarised towards the carbon containing the ester group, the electron-withdrawing nature of the ester group and electron-donating nature of the methyl group working in conjunction. Measuring the bond

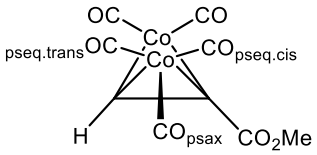
lengths of the carbonyl ligands for each computed structure it was clear that a *trans*-effect was in play. In compound **45**, the carbonyl with the longest M—CO bond length was $CO_{pseq.trans}$ as the *trans*-effect would benefit the $CO_{pseq,cis}$ ligand. In compound **46**, there was no distinct polarisation and so bond lengths for each ligand were almost identical. Finally, compound **47** displayed elongation of the M—$CO_{pseq.cis}$ bond.



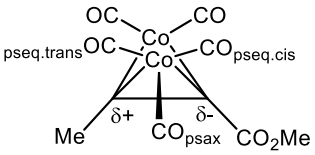
45, R^1 = H, R^2 = Me
46, R^1 = H, R^2 = CO_2Me
47, R^1 = Me, R^2 = CO_2Me



45



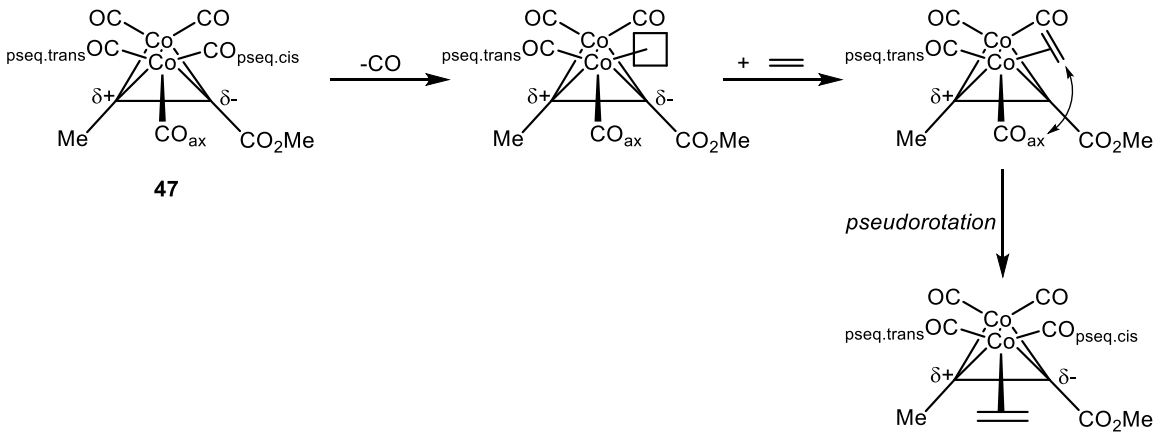
46



47

Figure 10

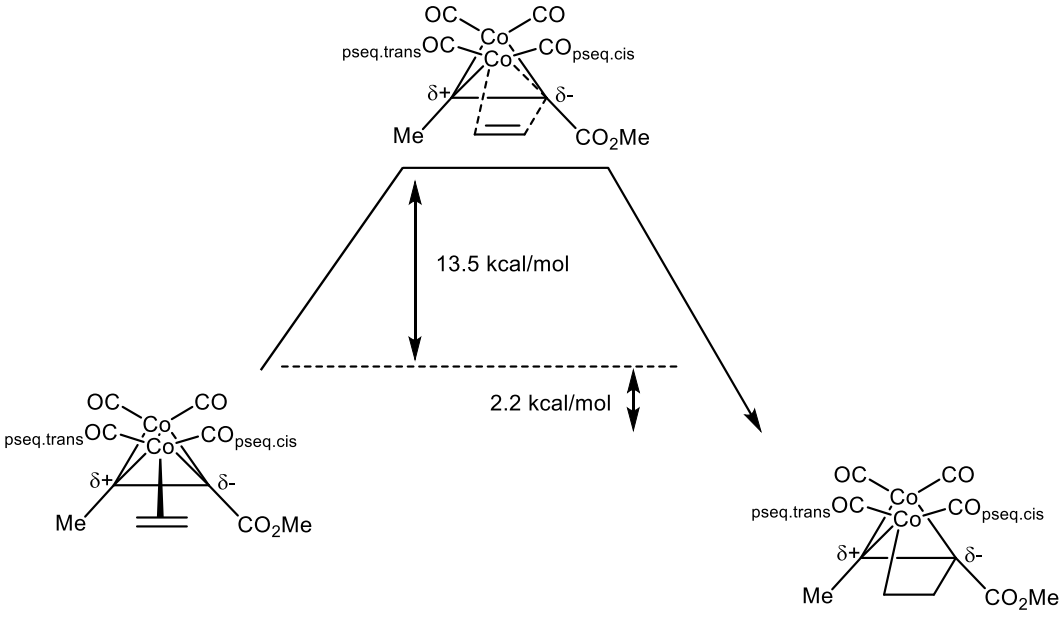
Considering alkene coordination and insertion, a further publication by the same authors showed the ability of the alkene component to undergo pseudorotation at room temperature.[47] Compound **47** (**Figure 10**) displays significant polarisation of the alkyne bond and so the $CO_{pseq.cis}$ carbonyl ligand will be the most labile and will dissociate most readily (**Scheme 17**). The free site can be coordinated by an alkene molecule, which will undergo pseudorotation to the axial position, resulting in the lowest energy transition state for the alkene insertion step.



47

Scheme 17

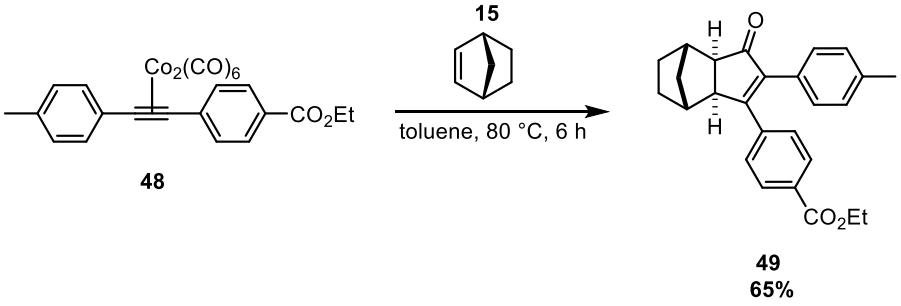
Therefore, the cobaltacycle may not be formed from the position of initial alkene coordination but from a position which will result in the lowest energy transition state (**Scheme 18**). This transition state is formed when the alkene is coordinated in the axial position and an NBO charge analysis of electronically-polarised alkyne complexes suggest the insertion will occur at the carbon bearing the electron-withdrawing substituent.[75] It is expected that the alkene will coordinate in the equatorial position as described above and then through pseudorotation will be able to insert from the axial position into the Co—C bond. This results in the lowest energy transition state compared to all other modes of insertion and is the transition state that yields the product with the electron-withdrawing substituent in the β-position.



Scheme 18

To summarise, a combination of the *trans* effect described in **Figure 10** and the alkene insertion step shown in **Scheme 18** are the contributing factors to the regioselectivity of the Pauson-Khand reaction with regard to the alkyne component.

The results discussed above were confirmed experimentally by cyclising an internal alkyne with no distinct steric bias but a clear electronic bias, compound **48**, with norbornene **15** (**Scheme 19**). This resulted in exclusive incorporation of the electron-withdrawing substituent in the β-position.

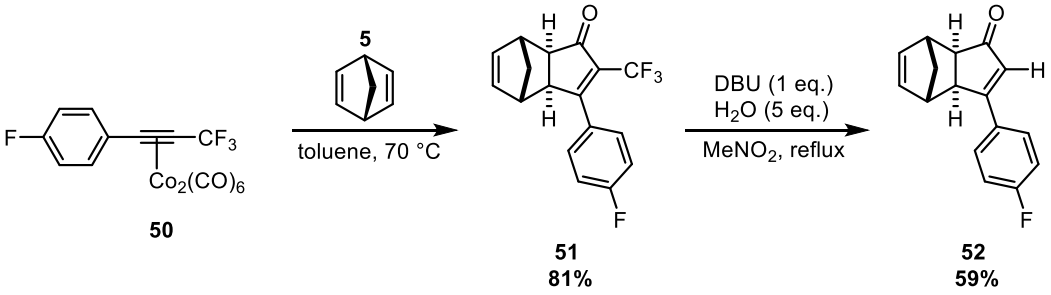


48

49
65%

Scheme 19

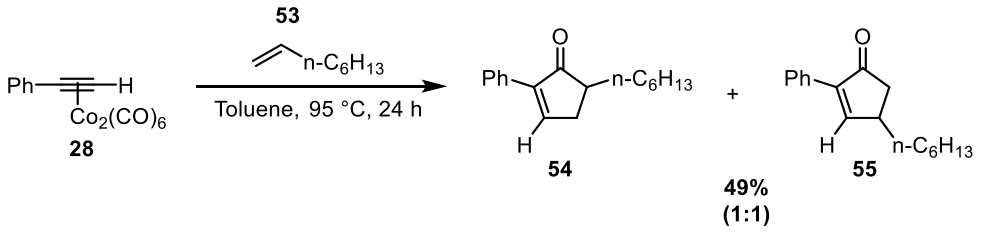
In an attempt to probe this regioselectivity further, Riera *et al.* synthesised CF_3-substituted alkynes as coupling partners for the reaction (**Scheme 20**).[77,78] Due to the highly electron-withdrawing nature of the CF_3 substituent, products with this group in the β-position were expected, however, it was the opposite products which were isolated. This type of alkyne was shown to be regioselective for these products regardless of the size or electronics of the substituent on the other side of the alkyne. The authors reasoned that the electronic effect of the CF_3 group must be less significant than expected or this electronic effect is overridden by its steric effect. Riera *et al.* showed that the $–CF_3$ group could be removed by refluxing the substrate with DBU, water, and nitromethane. The example shown below highlights the selectivity for the α-CF_3 product versus another electron-withdrawing yet bulkier substituent. After removal of the CF_3, the inherent alkyne steric selectivity of the Pauson-Khand reaction has, rather neatly, been switched. This product **52** would be complementary to the product of the reaction with terminal alkyne bearing a 4-fluorophenyl- substituent, which would result in the α-substituted product.



Scheme 20

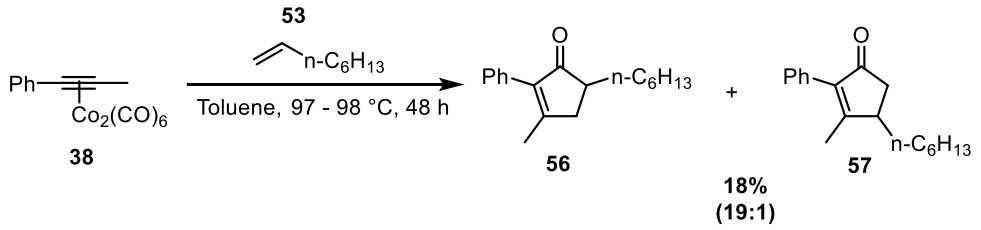
1.1.5.2 Alkene Regioselectivity

In contrast to the alkyne partner, there is no inherent regioselectivity for the alkene component, an insight which was noticed in the initial studies by Pauson and Khand.[79] Often, the products of the cyclisation would be almost 1:1 mixtures of the two corresponding regioisomers (**Scheme 21**). The example shown below uses phenylacetylene and long chain alkene, 1-octene, delivering equimolar amounts of both regioisomers, whilst maintaining the high degree of selectivity for the alkyne component.[73]



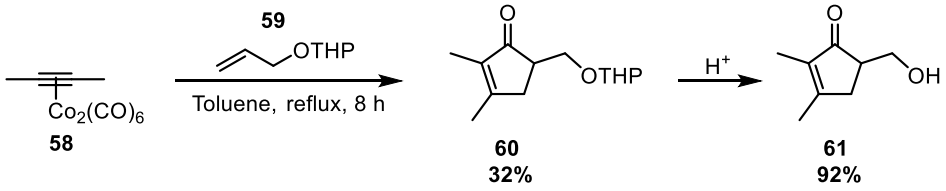
Scheme 21

Krafft showed that the use of internal alkynes improved the alkene regioselectivity drastically and surmised that this must arise from a steric interaction (**Scheme 22**).[81] The improved regioselectivity was at the expense of the yield reported in all cases. The increase in regioselectivity was attributed to the insertion of the least hindered alkene carbon into the least hindered alkyne carbon-cobalt bond to minimise the steric impact.



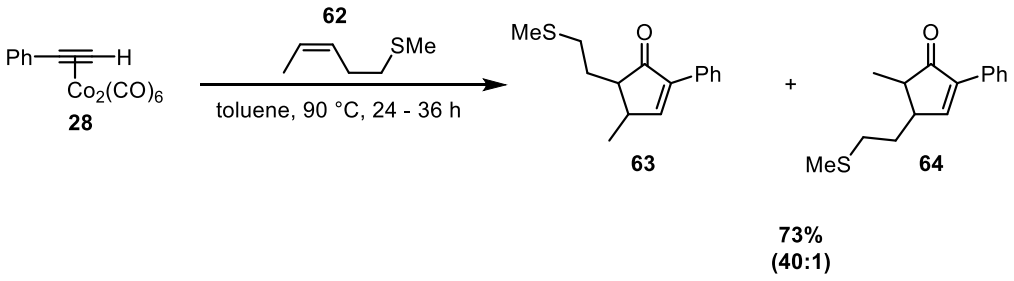
Scheme 22

Prior to this discovery by Krafft, Pauson had shown selectivity of the olefinic portion.[82] In the synthesis of methylenomycin B, Pauson used an olefin containing a THP-protected alcohol substituent, which was, subsequently, deprotected to the free alcohol (**Scheme 23**). In the cyclisation reaction only one regioisomer was observed. Reminiscent of Pauson's previous work using a silyl-protecting group to reverse the regioselectivity of the alkyne, this strategy induced regioselectivity in the alkene (**Scheme 15**).



Scheme 23

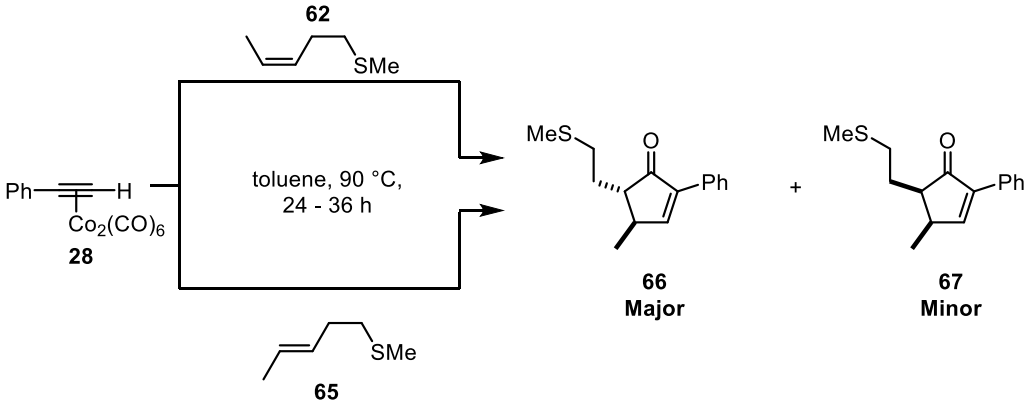
Following on from this result, Krafft produced a publication where the regioselectivity of the olefin could be controlled by the use of heteroatom substituents in the alkene chain.[80] By consideration of the mechanism, Krafft predicted that a heteroatom would be able to coordinate to the unsaturated cobalt species, which is generated through the reaction pathway, and, as a result, would direct the regiochemistry of the product. Krafft employed the use of homoallylic and bishomoallylic alcohols, ethers, amines, and sulfides to test this hypothesis. Overall, the homoallylic alcohols and ethers showed no improvement in the selectivity, though the amines showed good improvement of the regioselectivity. The most versatile of these was the sulfur substituted versions as illustrated in **Scheme 24**, and this showcases not only drastic regioselectivity improvements but also yield improvements.



Scheme 24

Krafft also noted for internal olefins that the major product in each case was determined to be the *trans* isomer.[80] An example is highlighted in **Scheme 25** where both *cis* and *trans*

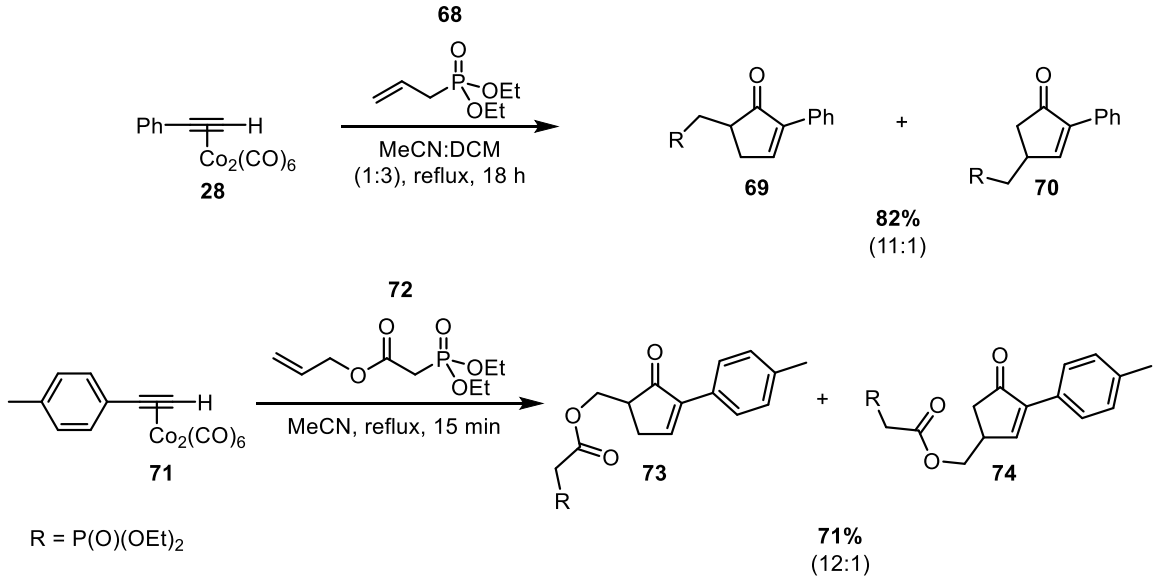
isomers were used in separate reactions and under the same conditions both achieved the same major product.



Scheme 25

This was further elaborated on by heating a 4:1 *trans*:*cis* mixture of the cyclopentenone products in toluene for 12 hours and the resulting ratio was 11:1 *trans*:*cis* in a 95% yield. This shows that there is significant epimerisation of the α-position and this would account for the more thermodynamically favoured *trans* isomer being the major product.

Work within our own research group has successfully expanded on the idea of using directing substituents on the olefin to control the regiochemical outcome.[83,84] The use of allylphosphonates as the olefin coupling partner in the Pauson-Khand cyclisation with phenylacetylene cobalt complex resulted in excellent regiocontrol when used with acetonitrile as a promoter.[83] Furthermore, a similar study using β-functionalised phosphonates, such as **72**, as olefin partners was conducted and resulted in high regioselectivity.[84] Representative examples of both of these protocols are contained in **Scheme 26**.



Scheme 26

The regioselectivity of these protocols was attributed to the phosphonate group in the former example and a combination of the phosphonate and carbonyl groups in the latter. Indeed, the replacement of the ester in **72** with a ketone resulted in a decrease in regioselectivity. Both of these protocols expanded the scope of the Pauson-Khand reaction and the phosphonate ester motif added the potential for further derivatisation of the products.

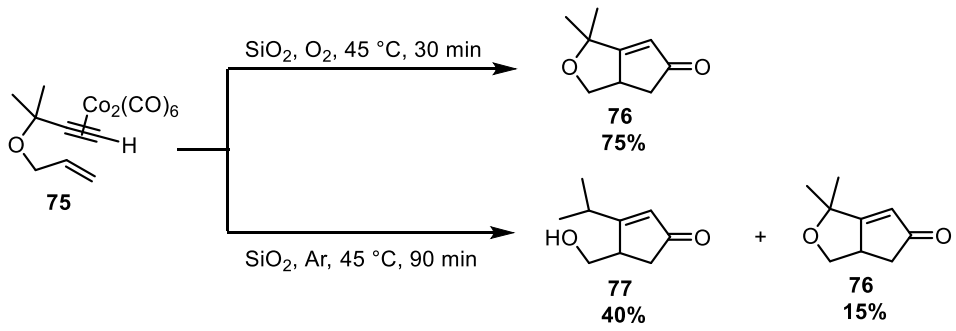
1.1.6 Improving the Pauson-Khand Reaction

The traditional conditions for the Pauson-Khand reaction required heating to high temperatures for long periods of time. This led to fairly low yields of the desired products alongside several by-products and cobalt residues that made separation of the crude material tricky. Since then, a myriad of improvements have been made to the reaction to improve its efficiency and generality. Details of the most major improvements that have turned the Pauson-Khand reaction into a broadly applicable methodology are described in the following sub-sections.

1.1.6.1 Dry State Absorption Conditions

In the mid-1980s, Smit and Caple described an appreciable improvement of the intramolecular Pauson-Khand reaction.[85,86] Specifically, loading of the cobalt-alkyne complex onto silica and heating conventionally under a stream of O_2 resulted in cyclised products in high yields and in short reaction times. This protocol not only increased the efficiency of the

reaction itself but it ensured easier purification by washing the silica with ether to isolate to the product, leaving the cobalt residues behind.



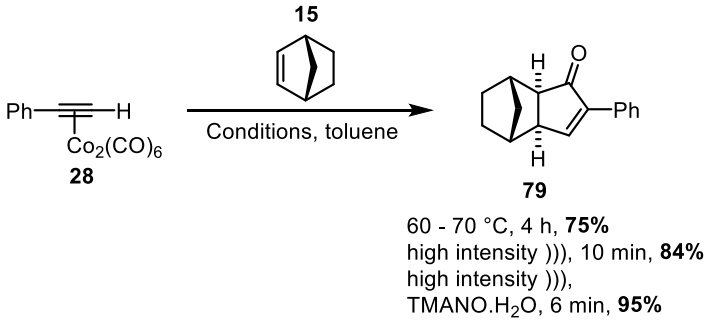
Scheme 27

As highlighted in **Scheme 27** above, the inclusion of the O_2 atmosphere was necessary to produce cyclised Pauson-Khand products, with reactions carried out under argon delivering undesired cyclopentenone **77** in appreciable yield. Overall, this dry state absorption method provided drastic improvements in the reaction time and temperature with cyclised products now being delivered in a little as 30 minutes at just 45 °C. Having said this, the scope of this methodology was limited to substrates that contained distinct hydrophilic and hydrophobic centres. The hydrophilic centres would bind to the silica and the hydrophobic reacting centres would be repulsed by the silica and pushed together lowering the entropy barrier.

1.1.6.2 Ultrasound

Pauson *et al.* published a study where they used low-powered ultrasonication methods, such as an ultrasonic cleaning bath, to facilitate the Pauson-Khand cyclisation by aiding in the dissociation of a carbonyl ligand.[60] Whilst this protocol showed improvement in the rate of reaction it had no effect on the yield of the cyclopentenone, and, in some cases, had a negative impact on the efficiency when compared with thermal conditions.[88] Improvements within our own laboratory showed that high powered ultrasound could be used in conjunction with other promotion methods to great benefit.[89] Outlined in **Scheme 28** is a comparison of different methods of promotion on the same substrate. The original thermal Pauson-Khand conditions provided a **75%** yield over 4 hours of reaction time, whilst with the high-intensity ultrasound promotion this was significantly decreased to just 10 minutes with an improved yield of **84%**. Furthermore, the use of this high-intensity ultrasonication in conjunction with an amine *N*-oxide promoter (*vide infra*) decreased the reaction time even further to just 6

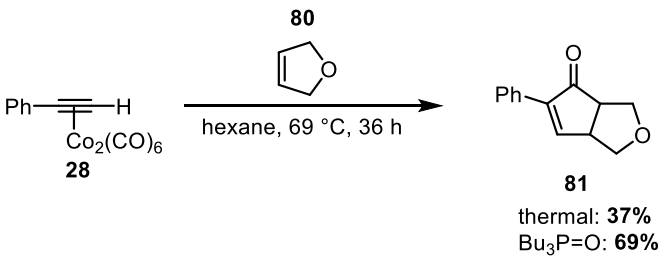
minutes and resulted in an outstanding yield of **95%**. These results showcase the effectiveness that the improved conditions have on the Pauson-Khand reaction, when compared directly with the original thermal conditions, resulting in an appreciably lowered reaction time while improving upon the yield of the transformation.



Scheme 28

1.1.6.3 Phosphine Oxides

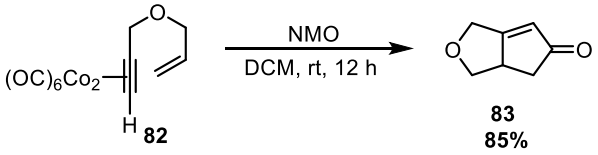
Phosphines, phosphine oxides, and phosphites have also been used as additives to good effect by Pauson and co-workers.[67] These were incorporated either in the form of ligands on the cobalt catalyst or as components of the reaction mixture. It was noted that when phosphines and phosphites were added as ligands the yields or rate of reaction were reduced when compared with traditional methods. However, when a phosphine oxide was added, this resulted in an appreciable increase in the yield of the reaction compared with the purely thermal conditions as highlighted in a representative example in **Scheme 29**. It is important to note that the phosphine oxide only improved the reaction yield in certain cases and was not broadly applicable. Indeed, when used in conjunction with the low-powered ultrasound, it did not improve the reaction yields.



Scheme 29

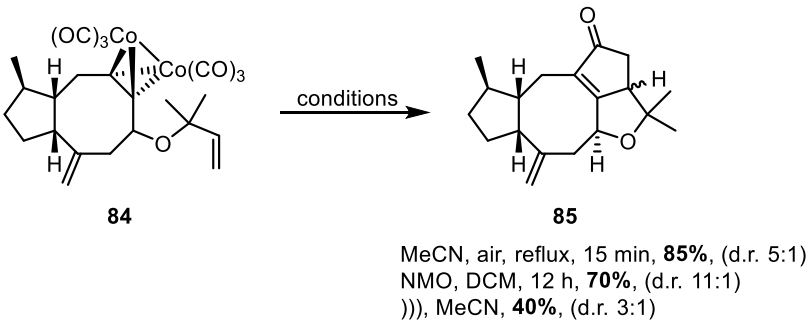
1.1.6.4 Amine *N*-Oxides

One of the most important discoveries in the context of Pauson-Khand reaction promotion was the use of tertiary amine *N*-oxides. It was the discovery of this promotion technique that brought the Pauson-Khand reaction to the fore and made it a widely applicable cyclisation methodology. This development was built on the known ability of tertiary amine *N*-oxides to decarbonylate metal carbonyl complexes by oxidising carbonyl monoxide ligands to carbon dioxide.[90,91] The Pauson-Khand reaction, which requires the dissociation of a carbonyl ligand at the rate-determining step, was thought to be able to harness this capability as a means for improving the reaction. That the carbonyl ligand would be removed and oxidised would be invaluable to this reactivity as the equilibrium of dissociation would favour the loss of CO_2. The first application of this methodology was by Schreiber *et al.* using *N*-methylmorpholine *N*-oxide (NMO) (**Scheme 30**).[92] This was the first promotion method which allowed the Pauson-Khand reaction to be conducted at room temperature. Furthermore, these conditions allowed facile purification of the cyclopentenone product, often requiring a simple filtration or short silica plug.



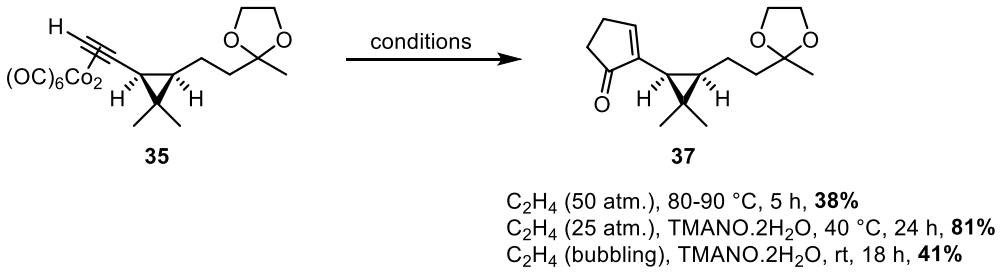
Scheme 30

This methodology was further expanded to intermolecular variants by Jeong and co-workers by using trimethylamine *N*-oxide (TMANO).[93] Krafft also utilised amine *N*-oxides in studies on trapping a reactive intermediate as shown previously in **Figure 5** (*vide supra*).[53] As shown in **Scheme 31** below, Schreiber showcased the methodology in the total synthesis of (+)-epoxydictymene and compared the reactivity of the other known promoters at the time.[88,92,94]



Scheme 31

The lower temperatures necessary for the cyclisation meant that the reaction was much more stereoselective than the comparative thermal or ultrasound-promoted Pauson-Khand cyclisations. Furthermore, this example highlighted an occasion where ultrasound actually hindered the reaction compared to the thermally-promoted version. The use of *N*-oxide additives also results in much cleaner reactions resulting in more facile product isolations. In addition to the above, many studies on the *N*-oxide promoted Pauson-Khand reaction have been conducted within our laboratory.[69–71,95–97] It was interesting to note that, in most cases, the use of NMO.H_2O or TMANO.$2H_2O$ resulted in greater yields than the equivalent anhydrous promoters, which was also noted by Krafft.[72] However, some instances have shown that the anhydrous promoters are necessary when used with less reactive substrates.[98] In a particular study, the use of amine *N*-oxide promoters has been utilised in our lab to improve efficiency when using ethylene as the alkene coupling partner. Complementary to the use of vinyl esters as ethylene equivalents, as illustrated previously in **Scheme 15**, the use of ethylene gas in an autoclave in conjunction with an amine *N*-oxide resulted in much more favourable conditions for the cyclisation than the comparative thermal conditions. This was highlighted as a key step in the synthesis of (+)-taylorione, where traditional conditions using high pressures of ethylene gas could be improved upon by the addition of an amine *N*-oxide (**Scheme 32**).[95] The addition of the amine *N*-oxide allowed the pressure of ethylene to be halved and the temperature reduced to 40 °C, resulting in an appreciable improvement in the yield. In addition, bubbling ethylene through the reaction mixture at atmospheric pressure and room temperature resulted in formation cyclopentenone product albeit in lower yield than the equivalent reaction at 25 atm of ethylene.[69,99] This milder process has the benefit of being more operationally simple than the corresponding high pressure example and gave comparable yield to the purely thermally-promoted example.



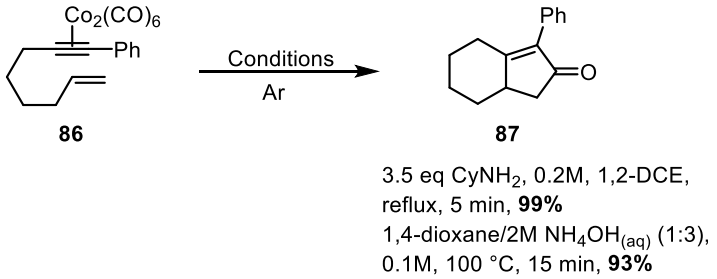
Scheme 32

Considering the above, one of the perceived problems with the use of amine *N*-oxides is the large excess in which they are usually required (3 – 8 eq.). To address this, work in our laboratory developed a reusable polymer-supported amine *N*-oxide to circumvent this issue.[100,101] After the reaction, the *N*-oxide could be regenerated by oxidation using Davis' oxaziridine and the polymer-bound substrate reused up to 5 times.[100] This methodology also had the added benefit of sequestering the cobalt residues in the polymer support thus simplifying purification of the final product.[101]

1.1.6.5 Lewis Bases

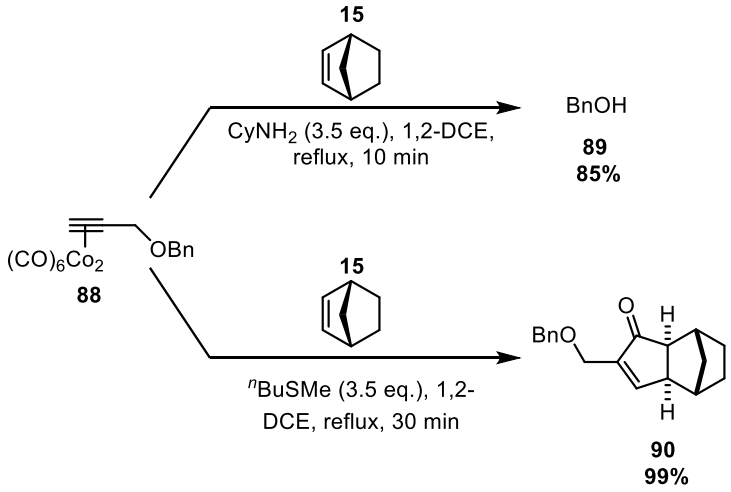
It was proposed by Sugihara *et al.* that the use of a hard Lewis basic additive would facilitate the Pauson-Khand cyclisation by labilising a carbonyl ligand.[102,103] The electron-donating properties of the hard ligand would increase the electron density on the metal centre thus weakening the M—CO σ-bond. In addition, the coordinatively unsaturated intermediate thus formed would be stabilised by interaction with the Lewis base so would be longer-lived. The first promoter of this type to be described in the literature, by Sugihara and Yamaguchi, was the use of primary amines.[102] A number of different primary amines were screened with both cyclohexylamine ($CyNH_2$) and ammonium hydroxide proving considerably better than the others. Thus, two sets of conditions were established using cyclohexylamine or ammonium hydroxide as the amine promoter and these were employed in the development of a scope of substrates. A challenging intramolecular example (**86**) is illustrated in **Scheme 33** where there is no Thorpe-Ingold effect to aid the cyclisation. The developed conditions provided the desired product in excellent yields over short reaction times, however, this process required much more forcing conditions than other promotion methods. There are other limitations of this protocol as excess amines have shown to disproportionate $Co_2(CO)_8$ and break the Co—Co bond generating an inactive cobalt species.[104,105] In addition, less reactive alkenes in the

intermolecular variant do not couple well under amine promotion conditions and carbon—heteroatom bonds have been known to cleave under these conditions.



Scheme 33

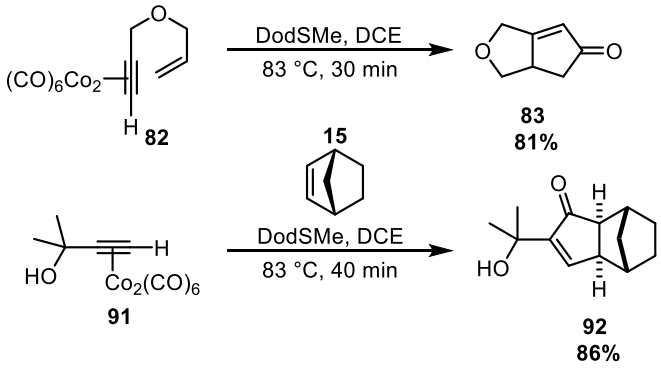
In addition to the above, sulfides were also employed as Lewis basic promoters for the Pauson-Khand reaction, again by Sugihara and Yamaguchi.[106] Indeed, sulfides were expected to be better ligands than amines due to their greater π-accepting ability and so cleavage of carbon—heteroatom bonds would be minimised as the metal centre would be less electron dense. Several sulfides were shown to be effective promoters for the reaction, with *n*butyl methyl sulfide shown to be most effective at room temperature. The optimal conditions were then applied to a range of substrates and it was found that, overall, the sulfide promoters performed better than the amines, particularly in examples with reducible α-substituents as shown in **Scheme 34**.



Scheme 34

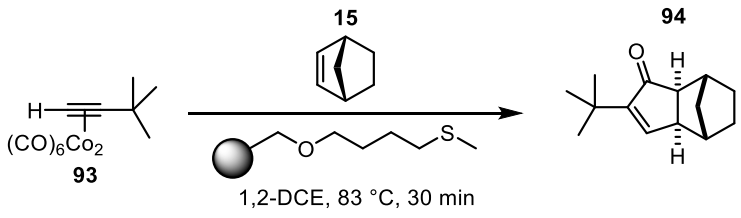
As shown above, cyclisation attempts using alkyne **88** with cyclohexylamine resulted in reduction of the benzyl ether group to the corresponding alcohol. Comparatively, the sulfide-promoted protocol gave the corresponding cyclopentenone in almost quantitative yield in a

short reaction period. This sulfide-promoted method often requires heating to reflux but in all other aspects can be considered complementary to the amine *N*-oxide technique. The drawback of this method, however, is the sulfide promoter itself. Infamously, alkyl sulfides possess a strong and unpleasant smell and they also exhibit lachrymatory properties. In an effort to develop a more amenable sulfide promoter, the longer chain sulfide, dodecyl methyl sulfide (DodSMe), was employed in our lab.[107] This cheap and odourless alternative to *n*butyl methyl sulfide was shown to be an efficient promoter for both the inter- and intramolecular Pauson-Khand reaction (**Scheme 35**).



Scheme 35

In each case attempted, the longer-chain sulfide was at least comparable with the shorter-chain derivative and is much easier to handle. In addition to the development of this methodology, a polymer-supported sulfide was also utilised as a promoter in the Pauson-Khand reaction in our lab.[108] This involved a similar method to the polymer supported *N*-oxide though there was no need to regenerate the active material and the resin simply required an acidic wash to remove metal residues. The material was shown to be recycled up to 5 times without a sacrifice in product yield (**Scheme 36** and **Table 1**). Additionally, the amount of sulfide could be lowered to 1 equivalent without any reduction in yield, though, there was a significant drop in the cobalt residue retention by the resin.



Scheme 36

Table 1

Run	Yield of Product (%)
1	**89**
2	**92**
3	**87**
4	**86**
5	**88**

Milet, Gimbert, and Greene proposed that coordination of the Lewis base does not increase the rate by enabling more facile dissociation of a carbonyl ligand, contrary to the hypothesis of Sugihara *et al*.[109] Comparison of the relative energies of dissociation of a carbonyl ligand on a simple carbonyl-substituted complex with a complex where one carbonyl ligand had been replaced by water or ammonia showed that there was no stark energy difference between them (**Figure 11**).[50]

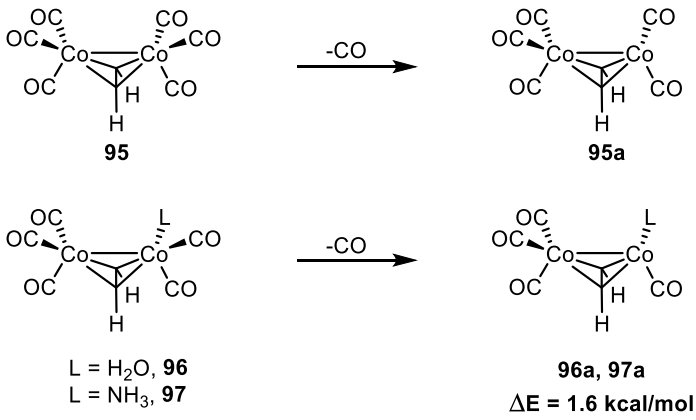


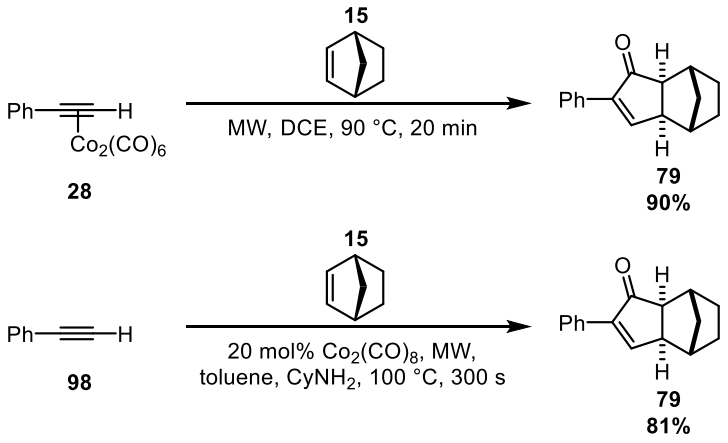
Figure 11

Milet, Gimbert, and Greene proposed that the reason for the increase in rate and yield of the Lewis base-promoted Pauson-Khand reaction was actually a result of stabilising the cobaltacycle. This, in turn, lowered the energy of this species and makes the overall process more exothermic when compared with the simple carbonyl-substituted complex. Thus, this step is made effectively irreversible.

1.1.6.6 Microwave Irradiation

Microwave irradiation has found its place in synthetic organic chemistry as a means of lowering reaction times over conventional heating methods.[110] Naturally, attention was turned to microwave heating as a means of lowering Pauson-Khand reaction times whilst

maintaining reaction efficiency. A publication by Evans *et al.* provided evidence of the effectiveness of microwave technology on shortening reaction times with typically reactive substrates.[111] The scope was expanded to a catalytic protocol by Groth *et al.* in the same year which used cyclohexylamine as an additive.[112] Both of these publications compared the polarity of the solvents used and surmised that less polar solvents worked well due to the quantitative absorption of the energy by the reagents. The catalytic protocol was interesting in that unlike other catalytic Pauson-Khand processes (*vide infra*) it did not require an external CO source to achieve catalyst turnover. Examples of both methodologies are contained in **Scheme 37**.

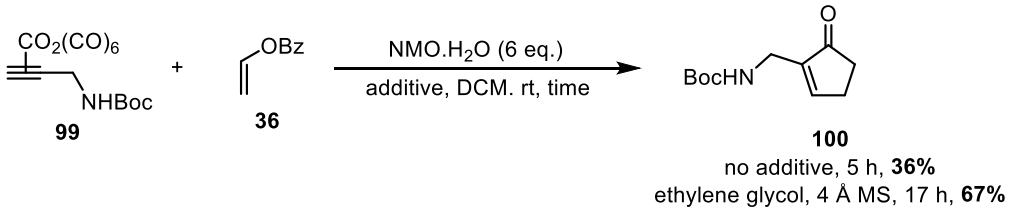


Scheme 37

1.1.6.7 Ethylene Glycol

A recent total synthesis published by the Baran group utilised a neat intramolecular Pauson-Khand reaction between a propargyl guanidine and bis-allylic trimethyl silyl ether species.[113] This was an interesting publication as it used a promotion method, ethylene glycol, which had not been disclosed prior to this publication. This was used in conjugation with more common promoters NMO and 4Å molecular sieves but the authors commented that the ethylene glycol was imperative to achieve reproducibly good yields. Verdaguer *et al*. investigated the aptitude of this combination of promoters to improve the yields of a series of intermolecular Pauson-Khand reactions.[114] In this study, they employed reactive coupling partner norbornene, medium ring *trans* alkenes, cyclopentene, 2,3-dihydrofuran, ethylene, and ethylene equivalents with terminal and internal alkynes. The reactions were conducted with and without the addition of ethylene glycol and it was found that, in most cases, ethylene glycol increased the yield of the reaction. An example is shown in **Scheme 38** where they used

vinyl benzoate as an ethylene equivalent (*vide supra*), and the dicobalt hexacarbonyl complex of boc-protected propargyl amine **99**. In this example, the addition of ethylene glycol increases the isolated yield significantly, though with a slight drawback of a much increased reaction time. In general, the addition of ethylene glycol resulted in an increase in reaction time and so indicates the additive may not increase the rate of reaction but stabilise intermediate species and thus prevent decomposition pathways from coinciding with productive pathways.



Scheme 38

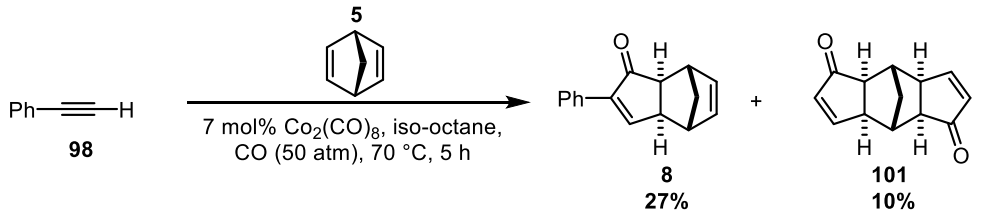
In summary, the described methods to promote the Pauson-Khand reaction have revolutionised its capacity. Such methods have allowed the construction of desired cyclopentenone frameworks in high yields over short reaction periods. This changed the views of the chemistry community on the reaction and solidified its position as one of the most useful, complexity-generating, reactions in a synthetic chemist's toolkit. It is now unthinkable to conduct a Pauson-Khand reaction without using one or more of the promoters described in this section.

1.1.7 Catalytic Pauson-Khand Reaction

Until this point, the discussion has mainly been focused on the stoichiometric Pauson-Khand reaction where the cobalt complex is usually pre-formed and purified before being subjected to the cyclisation conditions. Attempts to improve the output of metal-catalysed reactions by lowering waste are widespread across chemistry and a common way to do this is by lowering the number of equivalents of the employed metal reagent. This improvement can broaden the reach of a methodology and make it an industry-viable process. Additionally, the lowering of the equivalents of a reactive metal complex is often beneficial for synthesis with regards reaction selectivity and the ability to isolate pure products.

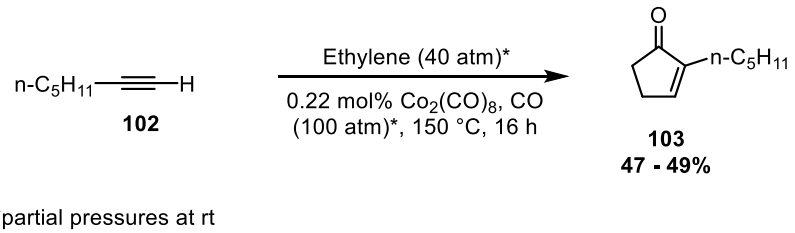
The catalytic Pauson-Khand reaction was first reported in early Pauson-Khand studies by Pauson[29] and later by Magnus.[37] They both noted that the yields of these catalytic reactions

were much lower than the corresponding stoichiometric variations. Pauson also noted that the catalytic version provided tricyclic by-products (**Scheme 39**) and this proved to be a concise means of accessing such molecules in one step. Initially utilising an acetylene:carbon monoxide mixed gas stream, attention was turned to the use of an autoclave to maintain the high pressure of carbon monoxide. In order to facilitate a cyclisation, 50 atm. pressure of carbon monoxide was necessary and this could be used with a 7% catalyst loading of $Co_2(CO)_8$. This was an encouraging preliminary result, despite the low yield and appearance of several by-products, as it provided proof of concept for the catalytic Pauson-Khand reaction.



Scheme 39

In 1990, Rautenstrauch *et al.* produced another catalytic protocol for the Pauson-Khand reaction.[115] Again, very harsh conditions were required to facilitate the cyclisation and the yields achieved were only slightly better than those seen by Pauson.[29] The methodology utilised very low amounts of $Co_2(CO)_8$ (0.22 mol%) but required very high pressures of gas (**Scheme 40**). This mixture was then heated in an autoclave for 16 hours to give a total pressure of 310 – 360 bar.

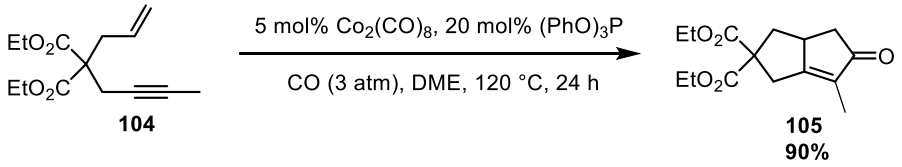


Scheme 40

The scope for both of Pauson and Rautenstrauch's work were not extensive but provided the preliminary results for further work on the catalytic Pauson-Khand reaction.

The mechanism of the catalytic Pauson-Khand is assumed to follow that for the stoichiometric variant. This makes it necessary, in most cases, for the reaction to be conducted under a pressure of carbon monoxide to regenerate the active catalyst at the end of the cycle. The

development of a synthetically useful catalytic protocol was not an easy process, due to the fact that the coordinatively unsaturated species [$Co_2(CO)_6$], which is released at the end of the cycle, can react with CO to restart the cycle or can dimerise to the inactive $Co_4(CO)_{12}$.[18,115] Thus, to achieve the necessary activity, it was thought that stabilisation of this coordinatively unsaturated species was an important aspect. Jeong employed triphenylphosphine and triphenylphosphite as stabilising additives for the coordinatively unsaturated cobalt species in a catalytic intramolecular protocol (**Scheme 41**).[116] Triphenylphosphite was the most effective in this role and, when used in the Lewis basic solvent DME, resulted in an efficient cyclisation process. This process used 5 mol% of $Co_2(CO)_8$ and required the use of 3 atmospheres of carbon monoxide to regenerate the catalytically active species. This was an improvement on Rautenstrauch's conditions, despite the fact a larger amount of catalyst was required, as it could be conducted at much lower pressures of carbon monoxide compared with the 100 atmospheres necessary for Rautenstrauch's protocol. It was determined that the triphenylphosphite was serving to stabilise the coordinatively unsaturated species as a control reaction without this additive produced only **4%** of the cyclopentenone product. The Lewis basic solvent likely aids the reaction in a similar manner to that described above.

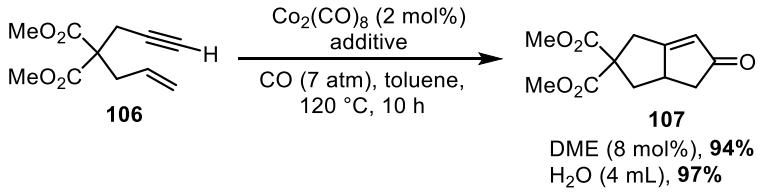


Scheme 41

This was the first synthetically useful catalytic protocol of the Pauson-Khand reaction limited only by the lack of intermolecular examples in the scope. In address of this fact, Jeong went on to utilise a (cod)(indenyl)Co(I) complex as the catalyst for the intermolecular variant of the Pauson-Khand cyclisation.[117] The protocol used relatively high pressures and temperatures to facilitate the cyclisation and was only tested with highly strained alkene partners.

In addition to Jeong's research, Sugihara and Yamaguchi described an effective catalytic Pauson-Khand protocol which also utilised Lewis basic additives (**Scheme 42**).[109] Indeed, a range of additives were tested including those that were known to work with the stoichiometric variant, such as cyclohexylamine, however these produced only low levels of the cyclopentenone product. Having said this, as shown in the example below, water or DME

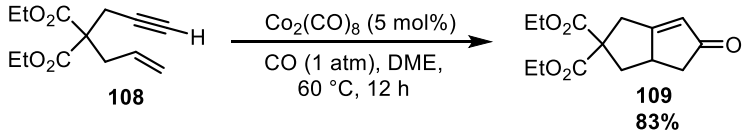
were incredibly effective, producing the desired product **108** in outstanding yields using only 2 mol% of catalyst.



Scheme 42

Like the other catalytic protocols, this required high pressures and temperatures to aid the cyclisation. It was noted that pressures of CO higher than 3 atmospheres were necessary for high yields of product. In the same publication, the authors also presented a few examples of intermolecular Pauson-Khand reactions, which cyclised with similar efficiency to that above.

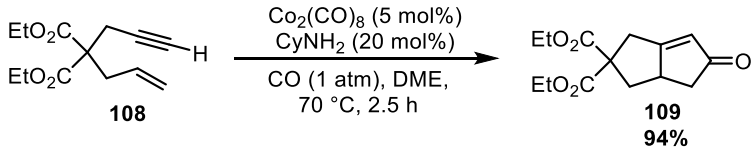
In 1996, Livinghouse proposed that the purity of the cobalt complex was the determining factor in the possibility of cyclisation at catalytic levels. Initially describing a visible light-mediated reaction methodology,[118] this was revised to be purely thermal with the inclusion of DME as a Lewis basic promoter and purified $Co_2(CO)_8$.[119] This protocol only required a blanket of CO at 1 atmosphere and proceeded at the relatively low temperature of 60 °C, a great improvement on the previous examples at the time (**Scheme 43**). Livinghouse described the importance of controlling the reaction temperature noting that temperatures outside the range of 50 – 70 °C were detrimental to reaction efficiency. In order to make a more accessible high-purity catalyst, Livinghouse used a cobalt—alkyne complex, as a catalyst surrogate, which could be purified by column chromatography and reduced *in situ* with Et_3SiH to give [$Co_2(CO)_6$], the active species.[120]



Scheme 43

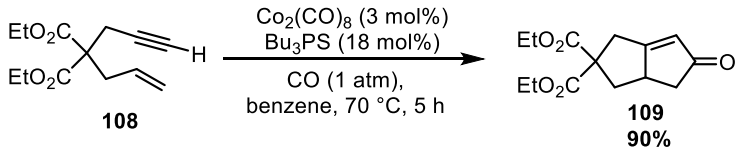
Krafft improved on both of these observations by using carefully base-washed glassware, which negated the need for ultra-pure $Co_2(CO)_8$, employing three separate commercial samples without purification (**Scheme 44**).[121] The protocol used cyclohexylamine as an additive, with careful adherence to the catalyst:additive ratio, and DME as the solvent, which

undoubtedly aided cyclisation. This process only required an atmosphere of carbon monoxide for it to proceed efficiently.



Scheme 44

Tributylphosphane sulfide was also highlighted as an efficient promoter of the catalytic Pauson-Khand reaction by Hashimoto and Saigo in 2000 (**Scheme 45**).[122] The role of the sulfur was not elucidated though it was noted that the analogous phosphine oxide and phosphane selenide did not promote the reaction as effectively. This protocol used low catalyst loadings of 3 mol% and favourable pressures of only 1 atmosphere of carbon monoxide. Intra- and intermolecular variations of the Pauson-Khand reaction were described for these conditions, though the intermolecular variation required excess of highly reactive norbornene as a reactant.

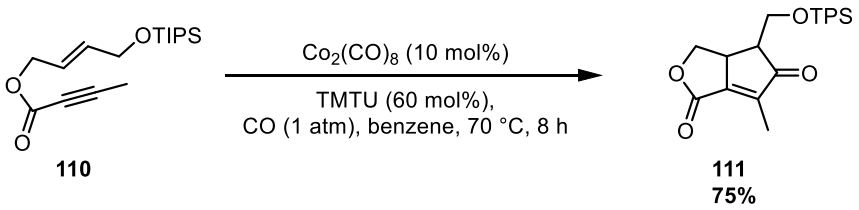


Scheme 45

The reaction above is a representative example of the methodology exhibiting the high yields achieved over short reaction times with low catalyst loading and low carbon monoxide pressures. The authors highlighted that the ratio of the catalyst to promoter is very important and, as observed by Livinghouse, that the reaction works efficiently only over a short temperature range; the reaction does not proceed below 50 °C and catalyst decomposition competes above 70 °C.

In a similar manner, some thiourea additives were tested as promoters for the catalytic Pauson-Khand cyclisation.[123] Tetramethylthiourea (TMTU) was the most effective additive tested and, as seen previously, it was highlighted in this study that careful control of the ratio of additive to catalyst is important for efficiency. When testing the scope, mainly intramolecular cyclisation substrates were used, however, one example of an intermolecular

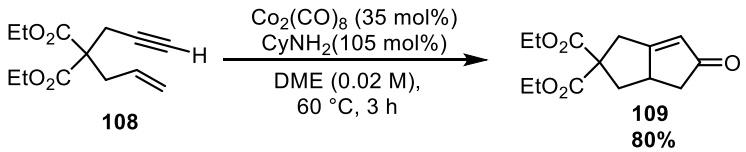
Pauson-Khand was conducted attaining high yields. This result was promising although it required an excess of a highly reactive alkene coupling partner as with Hashimoto and Saigo's work described above. An example of a densely-functionalised cyclopentenone (**111**) is shown in **Scheme 46**, which was cyclised from a challenging internal alkyne under such TMTU-promoted conditions. The role of the additive is not clarified by the authors though a direct link to the Lewis basic promoters previously described can be made.



Scheme 46

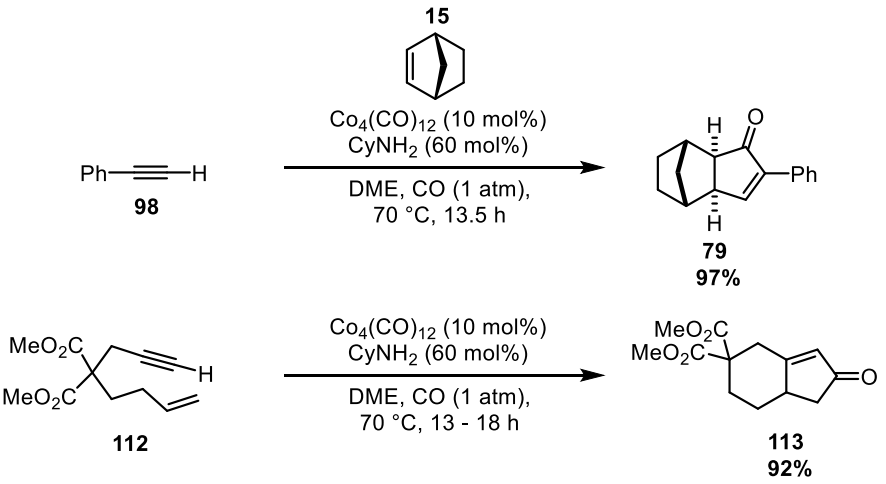
When considering the active species within the catalytic Pauson-Khand reaction, it is accepted that this is $Co_2(CO)_6$, which can dimerise to form $Co_4(CO)_{12}$ and become inactive. The Pauson-Khand-active $Co_2(CO)_6$ can be regenerated from $Co_4(CO)_{12}$ under high pressures of CO and such conditions also disfavour initial $Co_2(CO)_6$ dimerisation and so should be considered when conducting catalytic Pauson-Khand reactions. Unfortunately, the use of high pressures of toxic CO gas is not compatible with a mild and readily applicable methodology therefore this unproductive dimerisation process presents a significant challenge in the development of such procedures.

In an effort to identify mild and safe catalytic Pauson-Khand methodology, Krafft published a study on a catalytic protocol that did not require an external source of CO, and instead was conducted under an atmosphere of nitrogen (**Scheme 47**).[124] After screening a range of promoters it was found that cyclohexylamine was optimal when compared to other Lewis bases. Having said this, for this protocol to be effective, relatively high catalyst loadings of 35 mol% of $Co_2(CO)_8$ and a slight excess of cyclohexylamine were required.



Scheme 47

Developing this catalytic protocol even further in a separate publication, Krafft used substoichiometric amounts of $Co_4(CO)_{12}$ as a pre-catalyst with the addition of cyclohexylamine to promote the Pauson-Khand reaction.[125] In order to uncover the desired reactivity, the inactive $Co_4(CO)_{12}$ is converted to $Co_2(CO)_6$ *via* disproportionation, facilitated by the cyclohexylamine. This process was showcased using intramolecular and intermolecular cyclisations (**Scheme 48**) employing just 1 atmosphere of carbon monoxide and a catalyst loading of 10 mol%. The effective loading of active species is slightly higher than some of the previous examples given that the pre-catalyst will disproportionate into two moles of $Co_2(CO)_6$, becoming effectively 20 mol% of the active catalyst. Nonetheless, the yields for these cyclisations are exceptionally high.



Scheme 48

This publication proved that the dimer $Co_4(CO)_{12}$ could be activated as a catalyst for the Pauson-Khand reaction. This also confirmed the ability of cyclohexylamine to disproportionate the dimer to the active species and preserve it through the catalytic cycle. This would explain the superiority of cyclohexylamine for catalytic Pauson-Khand processes compared with other Lewis basic promoters which are superior in the stoichiometric variant.

The catalytic Pauson-Khand reaction has been developed successfully for a range of intra- and intermolecular substrates. Typically, the intramolecular substrates react more readily and under milder conditions than the intermolecular counterparts. Initially, the process required high pressures of carbon monoxide and relatively high catalyst loadings, however, improvements made by several researchers have brought both of these parameters down to more favourable levels, in some instances negating the need for an external source of carbon

monoxide entirely. There are several further examples of catalytic Pauson-Khand cyclisations using metals aside from cobalt and these will be discussed further throughout *Section 1.8*.

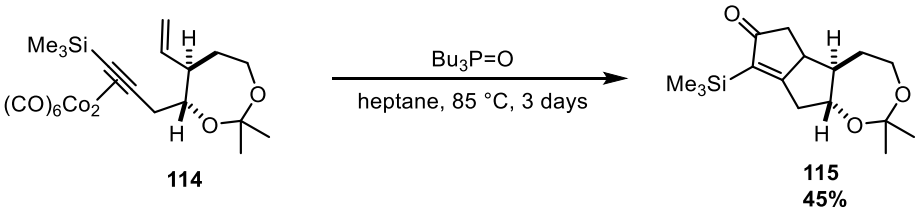
1.1.8 Asymmetric Pauson-Khand Reactions

The area of synthetic chemistry is abound with ways of controlling stereochemistry in organic transformations and this is an imperative part of complex molecule synthesis and drug discovery with the ever-increasing need for 3-dimensional drug molecules driving this area of medicinal chemistry.[126] The Pauson-Khand reaction's ability to generate complexity in a single step has wide application in the areas of medicinal chemistry and natural product synthesis due to the prevalence of the cyclopentenone motif.

Several commonly-used methods for inducing asymmetry have been applied to the Pauson-Khand reaction: chiral pool substrates, chiral auxiliaries, chiral metal complexes, and chiral ligands. Indeed, this area is very extensive and so will not be covered in the detail required to give a full review of the subject matter. Attention should be drawn to certain published reviews,[13,15,16,19] and, in particular, the book The Pauson-Khand Reaction: Scope, Variations and Applications, which has three chapters dedicated to this area of the reaction.[18] The following section describes some particularly elegant examples in this overall area.

1.1.8.1 The Use of a Chiral Substrate

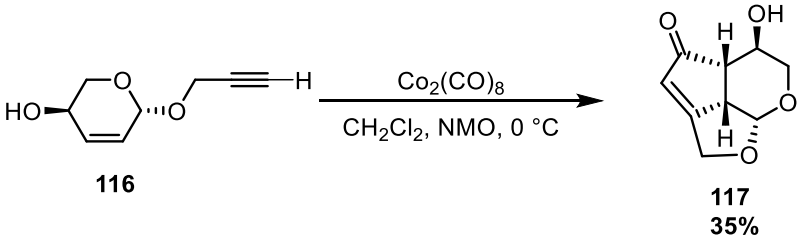
A chiral pool strategy is perhaps the most obvious way to generate chiral products. The first example of this in the context of the Pauson-Khand reaction was described by Magnus in the stereospecific formation of a carbocycline analogue (**Scheme 47**).[127]



Scheme 49

Another example comes from Marco-Contelles *et al.* who produced two methodological studies which cyclised chiral carbohydrates to form iridoid skeletons.[128,129] Using NMO-promoted methods, they generated a scope of chiral products, an example of which is shown in **Scheme 50**. This example starts with a relatively simple monocyclic molecule and in one

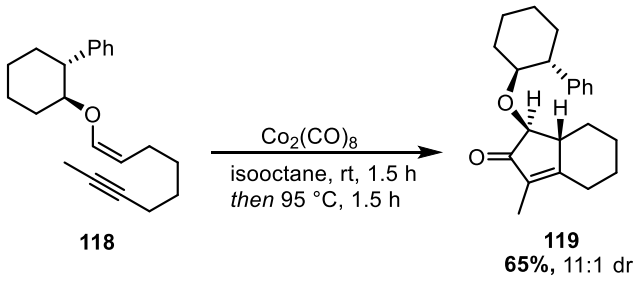
step generates a very complex, fused, tricyclic system containing four chiral centres. This exhibits the complexity-generating nature of the Pauson-Khand reaction elegantly alongside its stereospecific features.



Scheme 50

1.1.8.2 The Use of a Chiral Auxiliary

Most of the stereoselective Pauson-Khand methodologies published to date involve the use of a chiral auxiliary to induce asymmetry. The chiral auxiliary can be attached to the alkyne, alkene, or located in the enyne chain of the intramolecular variant. The most common examples attach the chiral auxiliary directly to the alkene or alkyne. One of the initial usages in this area was by Pericàs and Moyano in the intramolecular Pauson-Khand annulation using an alkene substituted with a (1*S*,2*R*)-2-phenylcyclohexanol group (**Scheme 51**).[130] This auxiliary was expected to protect one face of the molecule and so cyclisation could only occur on the other face. Indeed, the reaction proceeded in just 1.5 h to deliver the product in an appreciable **65%** yield with impressive 11:1 dr.

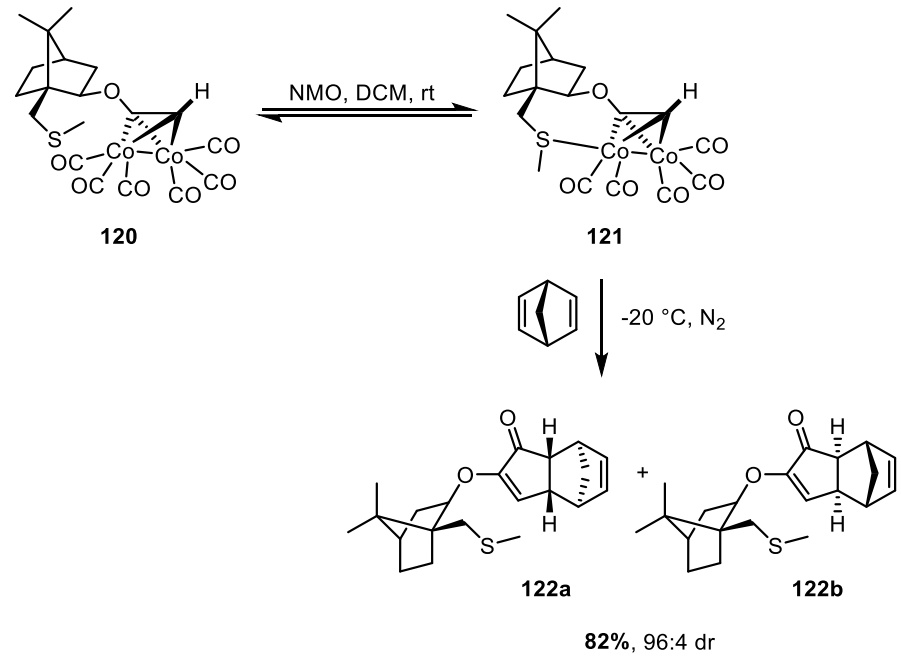


Scheme 51

The authors subsequently use SmI_2 to remove the auxiliary, however, it is important to highlight that this is a rare example of the use of a functionalised alkene in the Pauson-Khand reaction, namely an enol ether, to generate an oxygenated cyclopentenone. This is distinct from the previous examples shown so far as it shows the ability of the reaction to generate

decorated cyclopentenones through the Pauson-Khand reaction by using functionalised starting materials, which relates to the research within this thesis.

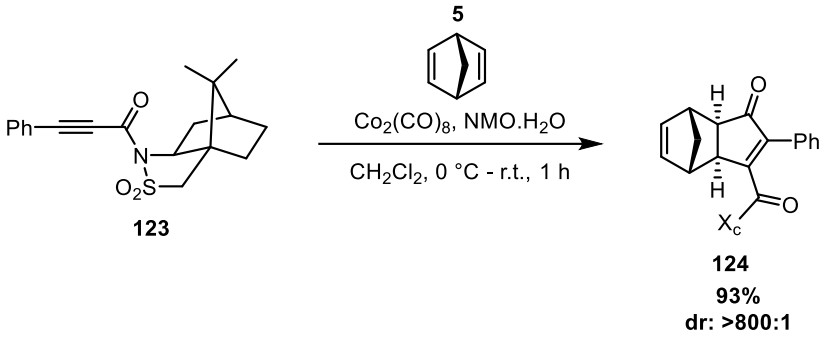
Improvements were made upon the asymmetric Pauson-Khand reaction by Pericàs and Riera by considering the influence of the sulfur atom on the regioselectivity, as described by Krafft *et al.* (*vide supra*).[80] Pericàs and Riera neatly produced a chiral auxiliary that contained a sulfur atom capable of coordinating the unsaturated cobalt species and anchoring the complex in two positions (**Scheme 52**). The authors attached the chiral auxiliary to the alkyne and then generated the alkyne-cobalt complex **120**.[131] This complex then undergoes decarbonylation at which point the sulfur can attach onto the coordinatively unsaturated cobalt atom as in complex **121**. The diastereoselectivity in this example arises from the coordination of the chiral auxiliary to the cobalt centre as this distinguishes between the faces of the cobalt-alkyne complex and coordination of the alkene will occur at the cobalt with the coordinated sulfur atom.[44] This is an effective protocol as evidenced in the example shown below where the authors achieved an exceptionally high diastereoselectivity. Having said this, whilst incredibly effective in imparting selectivity, such auxiliaries required prior synthesis and the process becomes atom uneconomic due to the large group which is ultimately removed.



Scheme 52

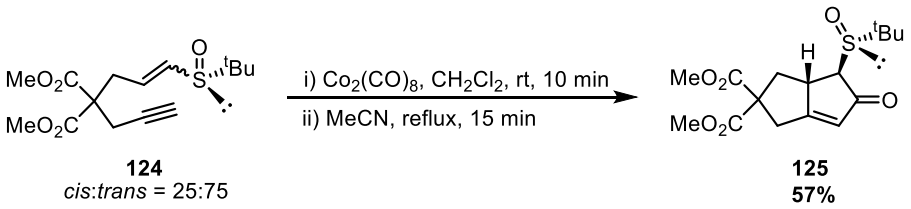
Oppolzer's 2,10-bornanesultam was also utilised by Pericàs and Riera as an efficient auxiliary achieving extremely high stereoselectivities (**Scheme 53**).[132] The asymmetric induction of this

auxiliary is similar to that described above, whereby, in this example, coordination occurs through the sulfone oxygen.



Scheme 53

A further case by Carretero *et al.* describes examples of a chiral sulfoxide moiety attached to the alkene component of the cyclisation substrate.[133–135] The most relevant example was the intramolecular process shown in **Scheme 54**, whereby a single enantiomer was produced from an isomeric mixture of the substrate. Again, this represents an example of a functionalised alkene being employed in the Pauson-Khand reaction to provide a heteroatom-substituted cyclopentenone. Having said this, again, the authors cleaved this heteroatom functionality post cyclisation.



Scheme 54

The theoretical reasoning for the asymmetric induction described above is the dihedral angle of the C=C—S—O. In the *trans* substrate it was determined to be close to 0 ° by theoretical and computational experiments, which means that the *tert*-butyl group hinders the Si face of the substrate when the complex is formed (**Figure 12**). Thus, attack must happen from the Re face resulting in the observed stereochemistry. However, the opposite must happen for the *cis* starting material, yet only a single enantiomer was isolated from the cyclisation of the mixture. It is expected that a thermodynamically driven epimerisation of the α-centre of the cyclopentenone containing the chiral auxiliary occurs after cyclisation to generate a single

enantiomer. The *tert*-butylsulfinyl group could be removed by treatment with activated zinc to give highly enantiopure cyclopentenone products.

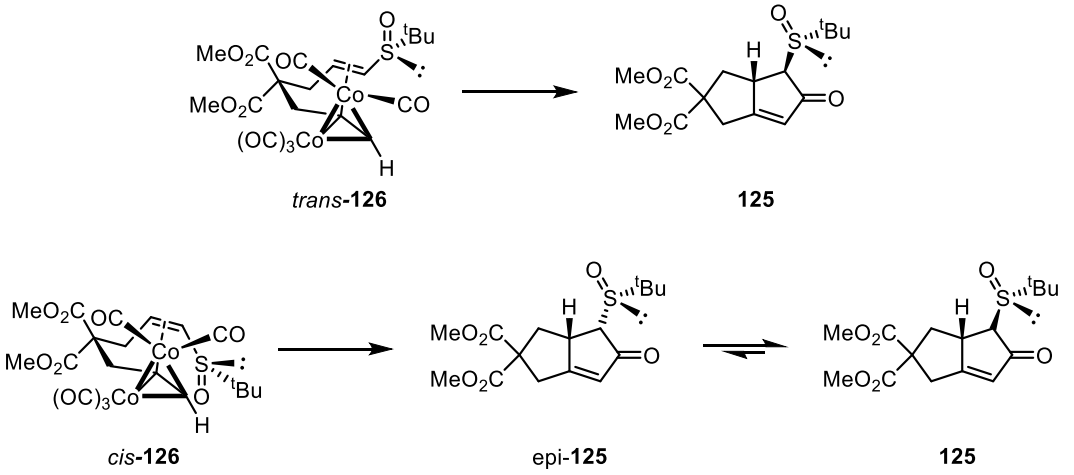
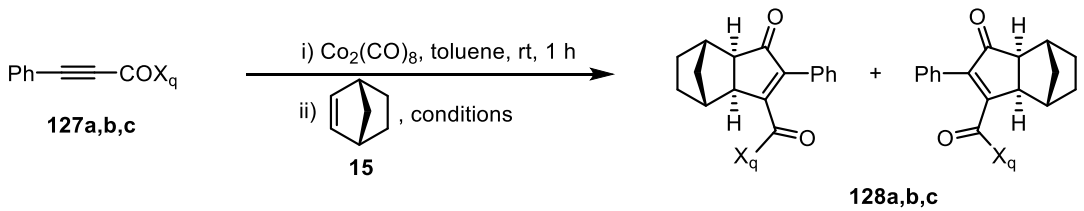


Figure 12

In relation to the above, a similar strategy by Pericàs and Riera involved placing the sulfoxide auxililary on to the *alkyne* component of the substrate as opposed to the alkene component.[136] In contrast, this had a surprising complete lack of efficacy in inducing diastereoselectivity in the cyclisation. This was traced to a racemisation of the cobalt complex, which could occur at room temperature.

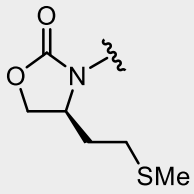
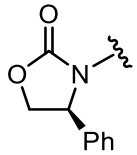
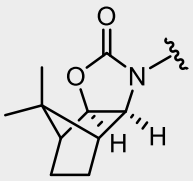
The use of chiral oxazolidinones, common chiral auxiliaries in asymmetric organic synthesis, was also explored by Pericàs and Moyano.[137] The stereoselectivity of these reactions is thought to arise from coordination of the chiral auxiliary to a cobalt atom in the reaction, controlling the face at which the alkene coordinates. In the study, the authors selected a range of different chiral oxazolidinones to determine the effect of bulk on stereoselectivity. This drew a comparison of the steric bulk at the C_4 position of the oxazolidinone as the determining factor in the stereoselectivity of the reaction. The authors compared various chiral oxazolidinones containing an *S*-configured chiral centre (**Scheme 55**) each requiring bespoke reaction conditions, highlighted in **Table 2**, for optimum diastereoselectivity. This resulted in good diastereomeric excesses and high yields where camphor-derived auxiliary **129c** was most proficient. Notably, this process was only effective for disubstituted alkynes containing a sterically comparable group opposite the chiral auxiliary. The use of a methyl group instead of the phenyl group in **127** resulted in a mixture of α- and β-substituted

products where the steric influence of the oxazolidinone overrode the electronic influence in the insertion step.



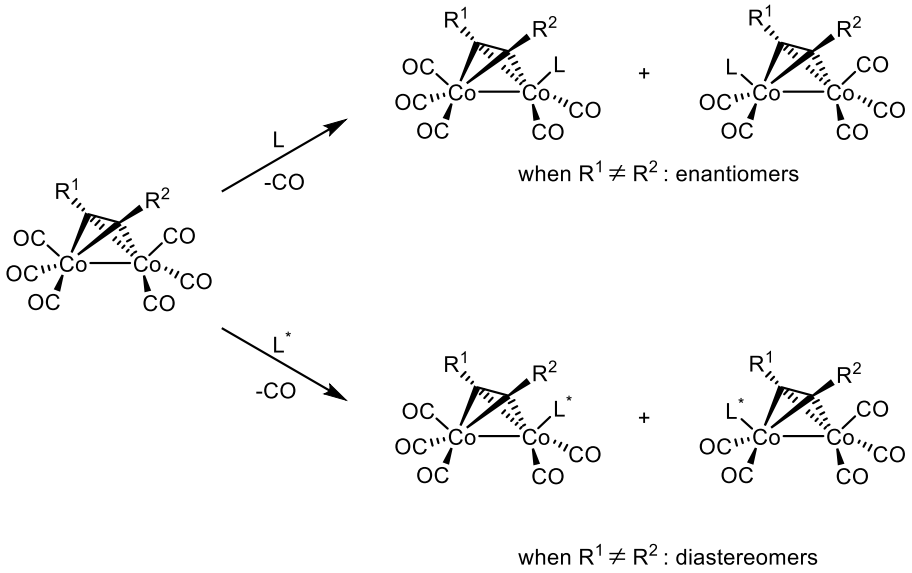
Scheme 55

Table 2

Auxiliary (Xq)	Conditions	Yield	Diastereomeric Ratio
	NMO, DCM, 0 °C – rt, 15 h	**81%**	1.8:1
	toluene, rt, 21 h	**96%**	5.2:1
	toluene, 45 °C, 42 h	**Quant.**	9.2:1

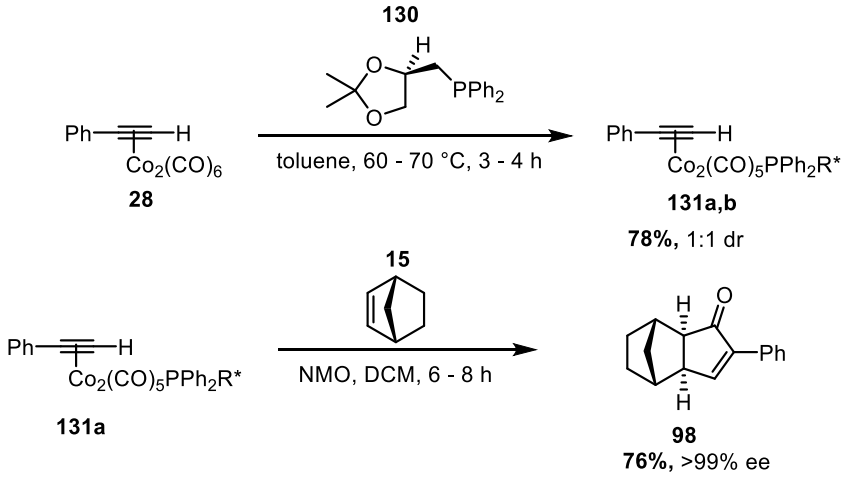
1.1.8.3 The Use of Chiral Complexes

Stereochemistry of products can arise from the cobalt complex itself. The central C_2Co_2 atomic arrangement can be considered prochiral as discussed briefly in *Section 1.2* (*c.f* **Figure 4**). Coordination of a Lewis basic ligand can result in a chiral complex, if the ligand itself is chiral or if the alkyne is unsymmetrical (**Scheme 56**).



Scheme 56

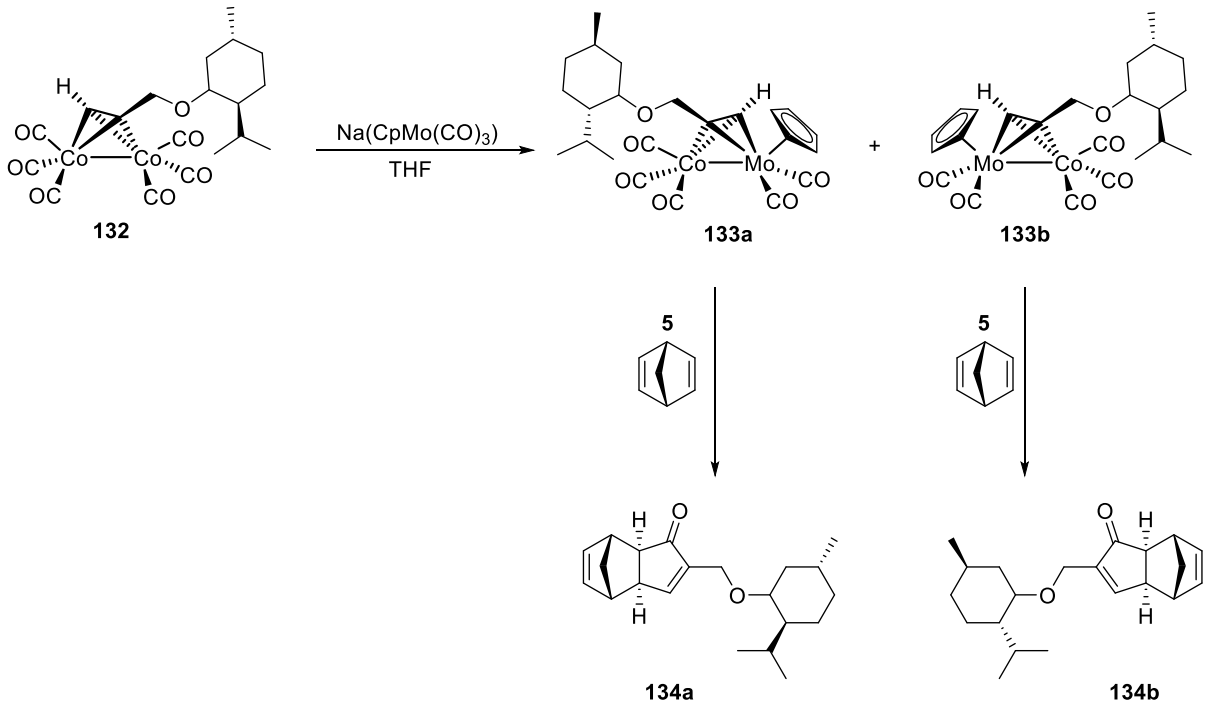
Considering the above, when an achiral Lewis base (L) is used then an enantiomeric mixture of complexes is produced if the alkyne is unsymmetrical. However, when a chiral Lewis base (L^*) is used then a diastereomeric mixture of complexes is produced when an unsymmetrical alkyne is used. Lewis basic promoters often labilise the carbonyl ligands on the distal cobalt atom,[138] therefore selective olefin coordination can arise. Inducing selective olefin insertion then gives rise to enantiomerically-pure products. Work conducted in our own laboratory has provided some insight into this aspect of the Pauson-Khand reaction. Building on an initial publication by Pauson and Brunner,[139] which used (+)-Glyphos (**130**) as a chiral ligand and phenyl acetylene as the unsymmetrical alkyne, our method produced a diastereomeric mixture of complexes that could be separated by column chromatography and subjected to the Pauson-Khand reaction conditions separately to give single-enantiomer products (**Scheme 57**).[98] Specifically, NMO was used as a mild decarbonylation reagent to generate such diastereomeric complexes, **131a,b**, that were then separated using preparative HPLC and subjected to the Pauson-Khand conditions to give the first enantioselective Pauson-Khand protocol.



Scheme 57

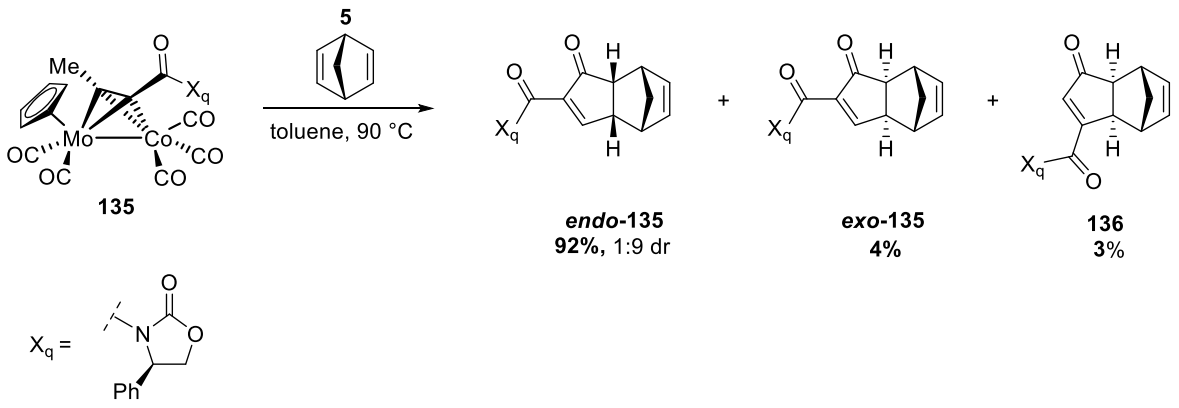
The ability of this protocol to be able to produce either enantiomer of the product despite the fixed chirality of the (+)-Glyphos ligand suggests that the asymmetric induction does not arise from the ligand but from the C_2Co_2 core itself. Expanding on this, brucine *N*-oxide, a chiral amine *N*-oxide, was employed to selectively decarbonylate one cobalt atom in the complex.[140] These conditions were used to generate highly enantioenriched products in high yields (**44**–**75%**, 72–78% *ee*).[40] This was employed in conjunction with a phosphine or phosphite ligand, which would trap the decarbonylated cobalt complex, and then the use of an achiral *N*-oxide could generate enantioenriched products.[39] It was a prerequisite of this protocol that the alkyne have an alcohol group in the propargylic position and replacing this with a methyl group or protected with a silyl group resulted in a loss of enantioselection. Laschat *et al.* employed several different chiral *N*-oxide promoters[141,142] though did not achieve the same levels of enantioselectivities seen previously.

Heterobimetallic complexes have also been developed as a means of inducing stereoselectivity in the Pauson-Khand reaction. The first example of this was described by Christie *et al*.[143,144] These complexes could be synthesised from their corresponding alkyne-dicobalt complex by subjecting it to $Na(CpMo(CO)_3)$ (**Scheme 58**). This resulted in a mixture of diastereomeric complexes which were then separated and, when heated with norbornadiene, produced a single diastereoisomer of the cyclopentenone Pauson-Khand product.



Scheme 58

Pericàs *et al.* noticed an interesting result when performing studies on Co—Mo and Co—W heterobimetallic complexes of alkynes with chiral auxiliary substituents.[145,146] On conducting intermolecular studies of these complexes, it was observed that the formation of the *endo* isomer was preferred to the traditionally obtained *exo* isomer (**Scheme 59**).

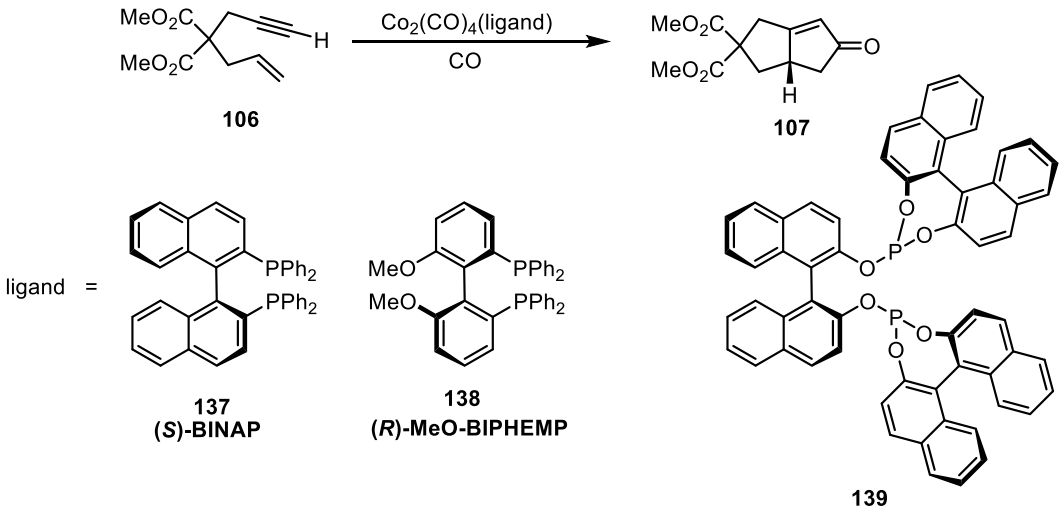


Scheme 59

Interestingly, when the analogous dimolybdenum complex was used, no cyclised product was observed. Thus, the reactive centre must be the cobalt atom. The authors hypothesised that the resulting stereochemistry arises from a steric influence of the cyclopentadienyl ligand on the molybdenum and the chiral auxiliary.

1.1.8.4 The Use of Chiral Ligands

Certain chiral ligands have been used to induce asymmetry in the Pauson-Khand reaction. The initial work was carried out by Hiroi *et al.*[147,148] in a catalytic Pauson-Khand reaction, and, since then, the groups of Riera and Verdaguer have produced several studies on this.[149–152] Hiroi *et al.* achieved high levels of enantiomeric excess (*ee*) when using bidentate phosphine (*S*)-BINAP (**137**) as a ligand in their catalytic protocol. They suggested that the (*S*)-BINAP coordinates to both cobalt atoms and directs the olefin coordination onto the most sterically accessible cobalt atom. However, a crystal structure of a cobalt complex with bound (*S*)-BINAP, generated by Gibson *et al.,* confirmed that, in fact, the phosphine only binds to one cobalt atom when generated from $Co_2(CO)_8$.[153] By comparison, when the complex is formed by mixing $Co_4(CO)_{12}$ and (*S*)-BINAP with heating, the bridged complex was formed and this proved to be inactive to many different cyclisation conditions. This was backed up by computational studies on the mechanism of this system by Pericàs and Maresas.[154] Further work by Consiglio achieved similar enantiomeric excesses using a similar bidentate ligand, (*R*)-MeO-BIPHEP (**138**).[155] Further still, Buchwald employed a sterically bulky BINOL-derived phosphite ligand (**139**) to achieve modest enantiomeric excesses.[156] A summary of these examples is contained in **Scheme 60** and **Table 3**.



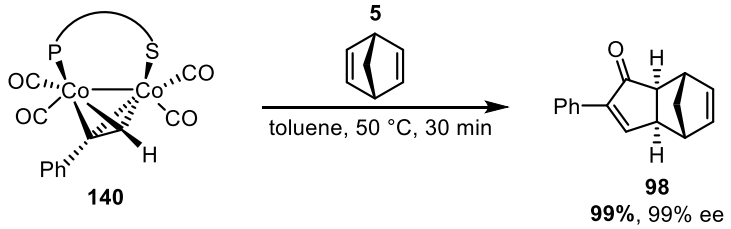
Scheme 60

Table 3

Ligand	Yield	ee (%)
BINAP	55	90
MeO-BIPHEMP	86	91
139	87	22

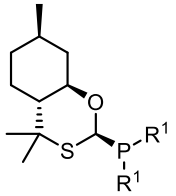
The drawbacks of these systems were their lack of applicability, working only with intramolecular systems and with minimal substitution on the alkene or alkyne.

Phosphine ligands are known to slow the Pauson-Khand reaction due to the increased π-backdonation to the carbonyl ligands. Since alkyl sulfides are shown in many cases to be effective promoters for the Pauson-Khand reaction, Pericàs and Riera developed a novel chiral bidentate ligand derived from (+)-pulegone, PuPHOS (**141**, **Figure 13**).[149] Considering that the decarbonylation event occurs at the cobalt distal to a phosphine ligand then it was imperative that this ligand bridges the two cobalt atoms so that the sulfide can coordinate to this distal cobalt and enhance reactivity. This ligand was confirmed to have a bridged structure X-Ray diffraction analysis of the corresponding complex (**140**), which required column chromatographic separation from its diastereomer. Employing this in the intermolecular Pauson-Khand reaction resulted in outstanding yield and *ee* (**Scheme 61**).

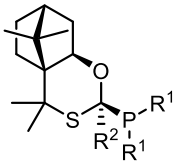


Scheme 61

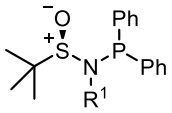
This prompted the development of several analogous bidentate ligands, namely, derivatives of PuPHOS and the novel CamPHOS (**143**) (developed from (+)-camphorsulfonic acid).[157] Furthermore, the chirality can be centred on the heteroatom rather than the backbone of the ligand, this hypothesis resulted in the development of the PNSO bidentate ligands (**148-150**),[150–152] where a chiral sulfoxide motif is employed. The structure of each of these ligands is outlined in **Figure 13**.



PuPHOS: R^1 = Ph, **141**
CyPuPHOS: R^1 = Cy, **142**



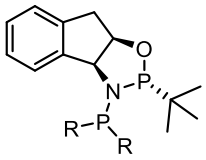
CamPHOS: R^1 = Ph, R^2 = H, **143**
MeCamPHOS: R^1 = Ph, R^2 = Me, **144**
CyCamPHOS: R^1 = Cy, R^2 = H, **145**
^{t}BuCamPHOS: R^1 = ^{t}Bu, R^2 = H, **146**
TolCamPHOS: R^1 = o-Tol, R^2 = H, **147**



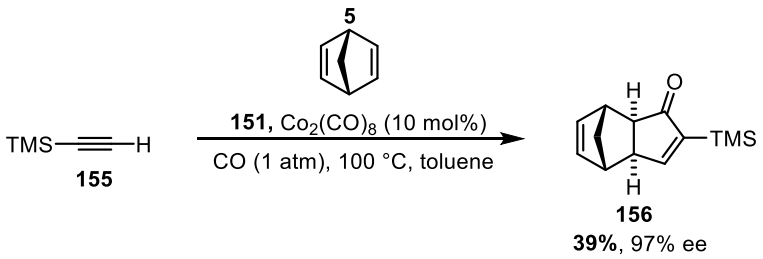
148: R^1 = Bn
149: R^1 =p-MeO-Bn
150: R^1 = p-F-Bn

Figure 13

These ligands were employed effectively in the intra- and intermolecular Pauson-Khand reactions, though none worked efficiently in the catalytic asymmetric Pauson-Khand. The use of CamPHOS gave the best enantiomeric excesses of 28%.[158] Until recently, sufficient catalytic asymmetric Pauson-Khand conditions had not been developed for use with dicobalt octacarbonyl. Verdaguer, Riera *et al.* developed a new type of phosphine ligand in 2015 for this purpose.[159] The so-called ThaxPHOS series of ligands (**151-154**) were screened against a range of substrates and conditions for catalytic Pauson-Khand, an example of which is seen below in **Scheme 62**. This example is the highest enantiomeric excess seen for this system and few others achieved the same level.



151: R = Ph
152: R = p-$CF_3C_6H_4$
153: (m-CF_3)$_2C_6H_3$
154: ^{i}Pr

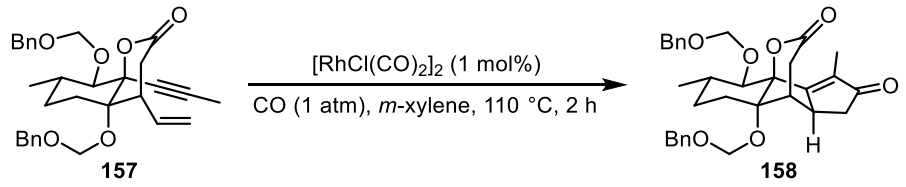


Scheme 62

1.1.9 Functionalised Alkenes in the Pauson-Khand Reaction

The Pauson-Khand reaction is a supremely successful reaction for delivering polycyclic molecules. It has been employed widely in the synthesis of bicyclic small molecules but, further to this, it is commonly used in the synthesis of natural products, a notable example

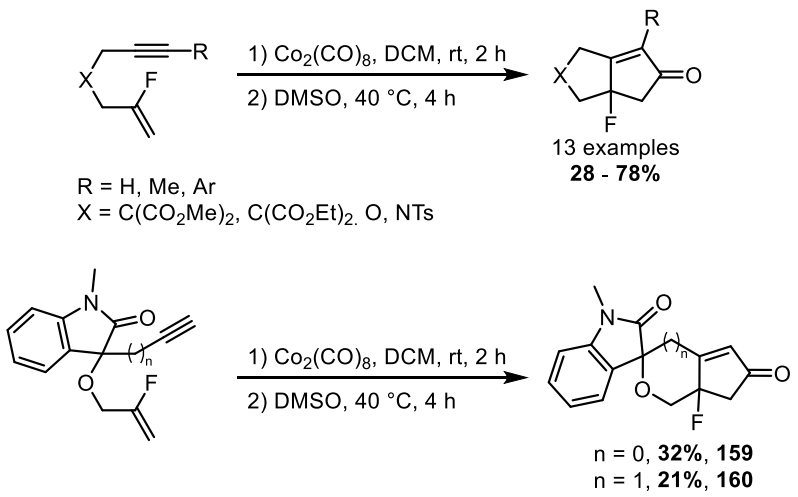
being the recent total synthesis of Ryanodol which used the Pauson-Khand reaction as a key step to form the tetracyclic core of the final product (**Scheme 63**).[160] This is a prime example of the reaction being used to build up a complex polycyclic ring system from a comparatively accessible starting material.



Scheme 63

Having said this, it can be seen in this example and, indeed, throughout this introductory chapter, that there are few instances where diversely functionalised cyclopentenones are accessed directly through the Pauson-Khand reaction. As touched upon previously, typically, the most effective Pauson-Khand reactions are conducted with simple alkyl substituents on the reacting centres and examples which feature heteroatom functionality are few. Two such examples were noted in the previous section, though these heteroatoms were being used to instil chirality in the molecule and the heteroatom was removed after the cyclisation. The lack of functionalised reaction partners presents a distinct limitation in the cyclisation scope as it restricts the achievable diversity of the products. Functionalised polycyclic systems are desirable structural motifs for organic synthesis and methods for accessing these are still highly sought after.

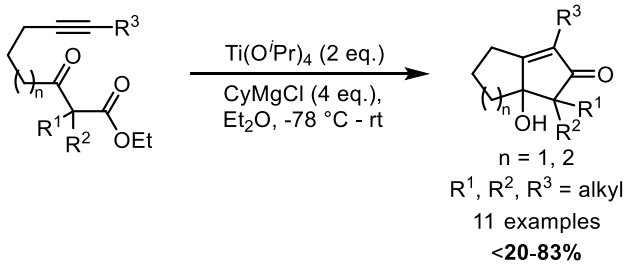
This limitation of the Pauson-Khand reaction was highlighted in recent work conducted by Barrio and co-workers, where the authors utilised vinyl fluorides as the olefinic component in the Pauson-Khand reaction (**Scheme 64**).[161] Implementing a one-pot complexation-cyclisation process, with DMSO as the promoter, 16 substrates were cyclised to good effect in many cases. This resulted in bicyclic small molecules which featured a tertiary fluorine substituent, a potentially difficult functionality to install *via* other methods. However, yields were typically poor and a common side reaction was the elimination of hydrogen fluoride, thus losing the precious heteroatom functionality. In addition to simple bicyclic molecules, the authors applied more complex spirocyclic substrates to this methodology due to their biological relevance as isatin derivatives. Such substrates also worked well to deliver compounds **159** and **160** in moderate yields.



Scheme 64

The authors followed this publication with further research into the fluoro-Pauson-Khand by employing chiral substrates to deliver enantioenriched bicyclic structures featuring a tertiary fluorine heteroatom at the ring junction.[162]

An interesting process, complementary to the Pauson-Khand reaction, was disclosed recently by Micalizio *et al.* (**Scheme 65**).[163] This protocol utilised a β-ketoester and an internal alkyne with 4 eq. of a Grignard reagent and 2 eq. of $Ti(O^iPr)_4$ as a Lewis acid to access synthetically challenging oxygenated cyclopentenones featuring a tertiary alcohol at the ring junction. A clear drawback to this protocol is the use of superstoichiometric quantities of a strong Lewis acid and a strong base thus making the process poorly tolerable to sensitive functional groups through which side reactions may occur. Additionally, the methodology was only effective when the carbon situated between the carbonyl groups was quaternary and efficacy decreased when longer chain systems were employed. A further obstacle of the methodology with certain substrates was proto-deoxygenation. Despite these limitations, the methodology was developed well to deliver highly functionalised cyclopentenones from simple and easily-accessible starting materials.



Scheme 65

The above examples from Micalizio show the clear desire for access to functionalised cyclopentenone molecules, and highlight the lack of versatile methodologies to access these compounds. As part of our ongoing research, we are constantly striving to develop the Pauson-Khand reaction to deliver adaptable methodology through which desirable and functionalised scaffolds can be obtained. Whilst we have explored the use of vinyl esters as functionalised reacting partners (*vide supra*), the heteroatom was cleaved under the reaction conditions. Nonetheless, this set precedent for the use of enol equivalents as the alkene component in the Pauson-Khand reaction and such techniques form the basis of this PhD Thesis (*vide infra*).

1.1.10 Summary

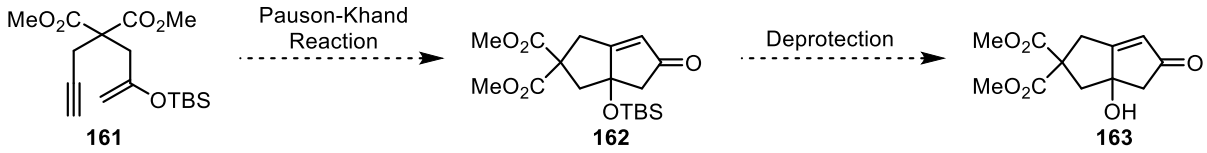
From humble beginnings, the Pauson-Khand reaction has evolved and improved over the decades since its discovery. Initially requiring very forcing conditions over long periods of time, a myriad of enhancements have made the reaction a viable and synthetically useful transformation. The Pauson-Khand reaction is a tailorable method for constructing cyclopentenones, which are prevalent motifs in drug and natural product molecules. It can be employed in a stoichiometric, catalytic or asymmetric manner to build up a variety of diverse polycyclic rings. However, there are few examples of the Pauson-Khand reaction tolerating heteroatom functionality on the reacting partners and as a result decorated cyclopentenone scaffolds cannot be accessed directly through the Pauson-Khand reaction. Mechanistically, the process is not fully understood; other than the dicobalt hexacarbonyl-alkyne complex, no distinct intermediate has been isolated in the mechanistic pathway. Thus, this makes it difficult to determine why certain substrates perform less well than others and how to improve their efficiency. Despite these drawbacks, the Pauson-Khand reaction has found many applications in natural product synthesis and medicinal chemistry. Though, clearly the

reaction has certain limitations, emerging methodologies continue to improve the process and explore the untapped potential of this powerful reaction.

1.2 Previous and Proposed Work

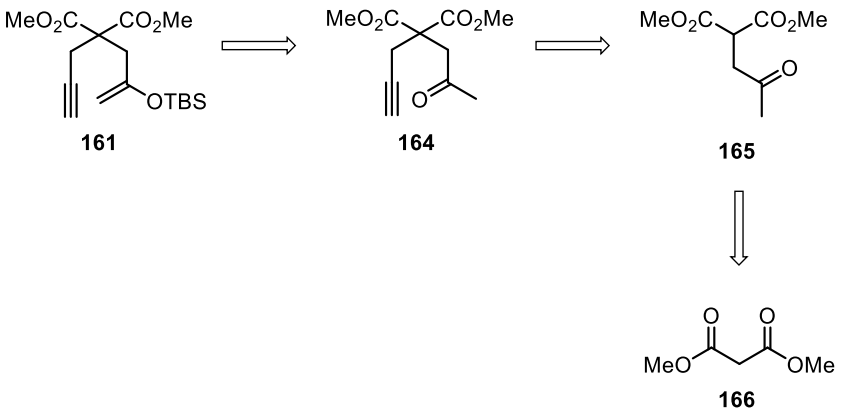
The need to access novel, diverse, and pharmaceutically-relevant chemical scaffolds is continuous within the synthetic community. Methods for accessing such molecules are constantly being researched and developed, yet, so far, the approaches for accessing oxygenated cyclopentenone motifs are limited (*vide supra*). As discussed in the previous section, the Pauson-Khand reaction has incredible potential as a viable method for accessing oxygenated cyclopentenones through the use of novel alkene reacting partners. These novel reacting partners could be enol equivalents, such as silyl enol ethers, which would broaden the scope of the substrates that are applicable, whilst delivering a practically accessible route to desirable compounds and strengthening the overall impact of the Pauson-Khand cyclisation as the optimal method for the synthesis of cyclopentenones.

In relation to the above, preliminary investigations within our laboratory has focused on the use of tethered alkyne-silyl enol ether substrates, such as **161**, to generate functionalised cyclopentenones *via* an intramolecular Pauson-Khand reaction (**Scheme 66**).[164] It was expected that the heteroatom functionality would be retained in these examples, contrary to the use of vinyl esters as alkene components.[71] The overall programme of work would comprise of subsequent desilylation after the key Pauson-Khand cyclisation to deliver the corresponding free alcohol moiety, now available as a new functional handle to generate further complexity.



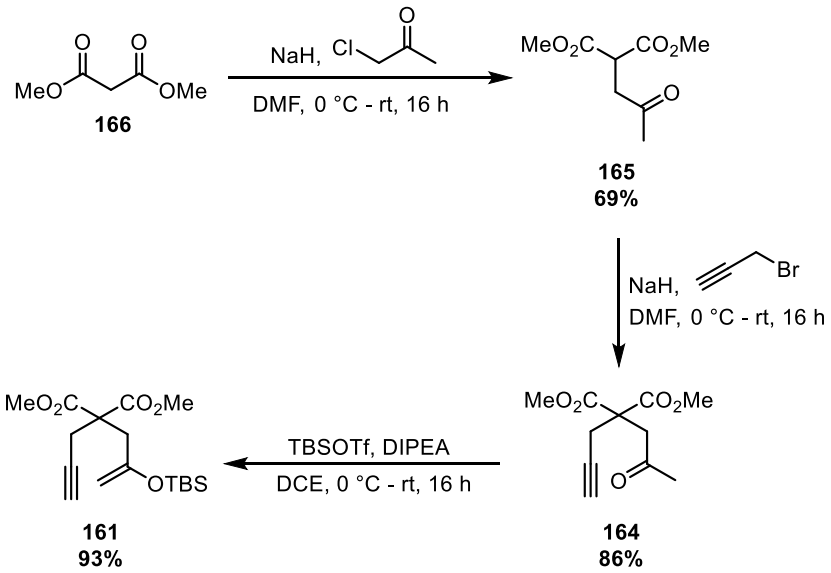
Scheme 66

To this end, the Pauson-Khand reaction shown in **Scheme 66** above was proposed as a benchmark reaction against which optimal conditions could be established. Retrosynthetically, the requisite substrate **161** could be accessed in a few steps from simple, commercially available, starting materials as shown in **Scheme 67** below. More specifically, **161** was envisaged *via* kinetic deprotonation of compound **164**, which could be afforded by two subsequent alkylations from dimethyl malonate **166**.



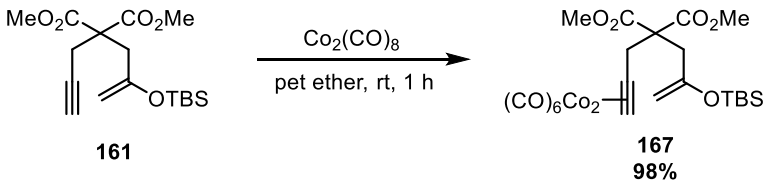
Scheme 67

This strategy was successfully pursued in the synthesis of TBS (*tert*-butyldimethylsilyl) enol ether **161** and the forward synthesis is shown in **Scheme 68**. Starting from dimethyl malonate, two alkylation reactions provided the key ketone intermediate **164** in a good yield over the 2 steps. Following this, a kinetic deprotonation and trap with TBSOTf allowed the exclusive preparation of desired enol ether, and Pauson-Khand precursor **161**, in an excellent 93% yield.



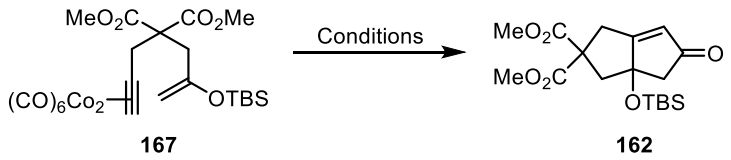
Scheme 68

To investigate the Pauson-Khand reaction with this compound, the dicobalt hexacarbonyl complex was generated in almost quantitative yield using well-established conditions (**Scheme 69**).



Scheme 69

The applicability of silyl enol ether substrates in Pauson-Khand methodology was thus investigated for the first time (**Scheme 70** and **Table 4**). The initial conditions tested involved the use of an amine *N*-oxide promoter, TMANO.2H_2O. This is known to be an excellent promoter for the Pauson-Khand reaction (*vide supra*) and, pleasingly, the novel Pauson-Khand product was generated in **32%** yield (**Table 4**, **Entry 1**). Interest was then turned toward the use of a sulfide promoter, DodSMe, at refluxing temperatures in an attempt to increase the yield of this reaction (**Table 4**, **Entry 2**). Under these conditions, the reaction yield was significantly increased to **74%**, an excellent yield for the transformation. Subsequent reactions showed that a lowering of the reaction time had no detrimental effect on the yield and lowering of the temperature to 70 °C, in fact, improved the yield of isolated product to **88%** (**Table 4**, **Entries 3 & 4**).



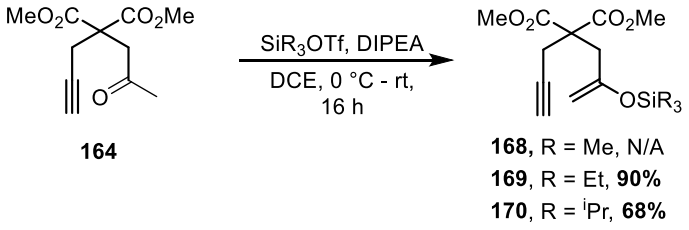
Scheme 70

Table 4

Entry	Conditions	Yield
1	TMANO.2H_2O, DCE, rt, 16 h	**32%**
2	DodSMe, DCE, reflux, 16 h	**74%**
3	DodSMe, DCE, reflux, 2 h	**74%**
4	DodSMe, DCE, 70 °C, 2 h	**88%**

With these encouraging results, attention was turned to alternative silyl protecting groups to determine what the effects of changing this group would have on reactivity (**Scheme 71**). Research focused on whether a bulkier group such as TIPS (triisopropylsilyl) would hinder the reactivity through steric effects and on whether the more labile TMS (trimethylsilyl) group

would be stable enough to survive the reaction conditions. These silyl enol ethers could be generated from compound **164**, and whilst the TIPS analogue could be isolated in good yield the TMS analogue proved to be too unstable to be isolated. The TES (triethylsilyl) analogue was also synthesised in excellent yield, and was anticipated to afford a similar steric bulk to the TBS group.

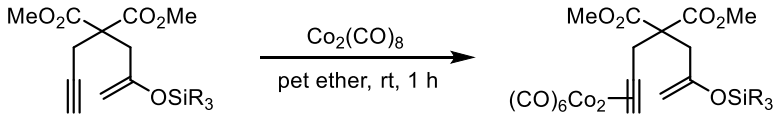


164

168, R = Me, N/A
169, R = Et, **90%**
170, R = ^{i}Pr, **68%**

Scheme 71

With the success of formation of the TES and TIPS analogues, the complexation of these substrates was carried out effectively (**Scheme 72**). Isolation of the $Co_2(CO)_6$-complex of the TES analogue was achieved in similarly high yields to those seen previously, however, the respective complex of the TIPS analogue was isolated with a slightly decreased yield in comparison.

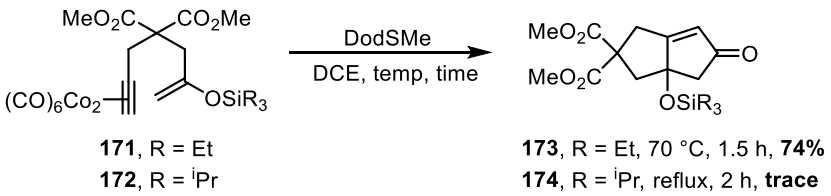


169, R = Et
170, R = ^{i}Pr

171, R = Et, **92%**
172, R = ^{i}Pr, **64%**

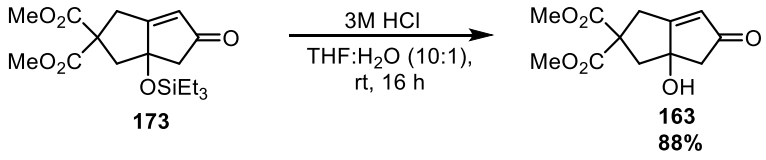
Scheme 72

With these complexes in hand, investigation of their applicability in the Pauson-Khand cyclisation was carried out using the previously optimised conditions. (**Scheme 73**). As expected, the TES analogue cyclised with similar efficiency to that seen with the TBS silyl enol ether, however, when the reaction with the TIPS enol ether was carried out, significant decomposition of the starting material occurred and only trace amounts of impure bicyclic product were obtained. This apparent failure of the reaction was rationalised due to the increase in steric bulk which slows the rate of cyclisation and decomposition occurs before reaction can proceed to completion.



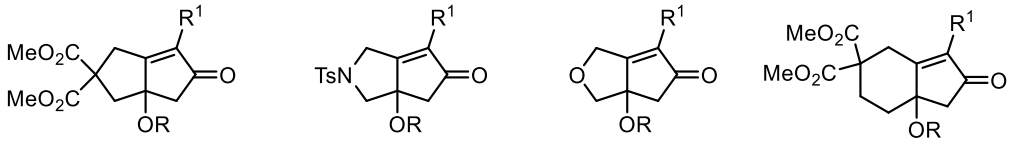
Scheme 73

In addition to the development of a Pauson-Khand protocol, mild deprotection conditions were also developed for the silyl ether bicyclic systems (**Scheme 74**). Conditions were developed using the TES protected ether and the isolated alcohol **163** was delivered in an excellent **88%** yield. This step is crucial in accessing the additional functionality which is afforded by this methodology. The success of this step confirmed the utility of the process while generating a tertiary alcohol (and quaternary carbon) centre, a motif which would be tricky to synthesise through other means.



Scheme 74

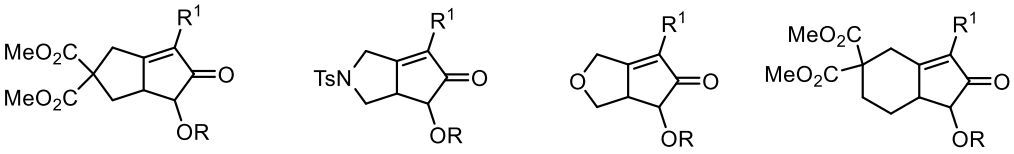
Having established proficient reaction conditions which effect the cyclisation of silyl enol ether substrates for the first time, the research described above provided the background to the programme of work which will be described as part of this PhD Thesis. It is proposed that further utilisation of silyl enol ethers derived from an array of ketone intermediates in the intramolecular Pauson-Khand reaction would serve to deliver interesting fused bicyclic products containing a quaternary carbon centre. Thus, it was envisaged that a scope of cyclisation substrates could be generated utilising both TBS and TES enol ethers. Exploring the use of terminal and, the typically more challenging, internal alkynes would provide proof of concept that this methodology can be used for more complex substrates (**Figure 14**). Indeed, further diversity will also be explored *via* the tether in the form of nitrogen or oxygen linkers. Indeed, nitrogen and oxygen heterocycles such as those products shown below appear in many natural products and are commonly explored substrates for the more traditional Pauson-Khand cyclisations, and thus would provide a benchmark for the described reaction methodology.



R = TES, TBS
R^1 = H, alkyl, aryl, silyl

Figure 14

In addition to the compounds shown above, a natural extension to this methodology would be to explore silyl enol ethers derived from aldehydes as coupling partners. This would generate a class of complementary compounds where the additional heteroatom functionality is incorporated in the α-position with respect to the carbonyl moiety (**Figure 15**). Indeed, α-oxygenated cyclopentenones (and their saturated counterparts) are present in a spectrum of biologically-important frameworks and related natural product systems.



R = TES, TBS
R^1 = H, Me

Figure 15

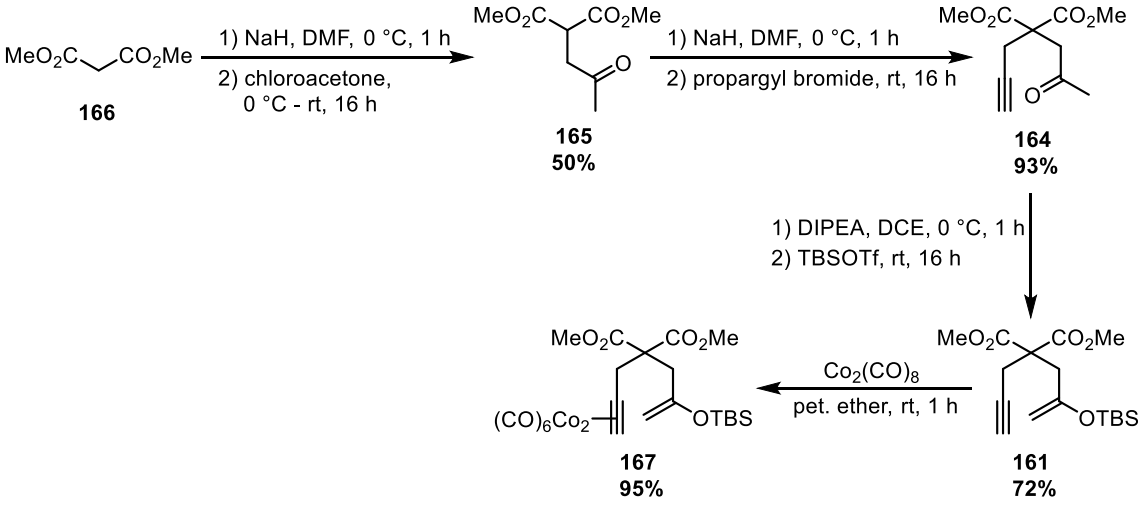
In relation to that above, the initial programme of work will include the synthesis of a range of novel silyl enol ether substrates for their application in the Pauson-Khand reaction. Such investigations will explore the scope and overall capabilities of this developing methodology. Additionally, we will endeavour to discover the structural limits of our novel methodology by attempting to employ sterically-taxing substrates in the reaction to better understand this variation of the Pauson-Khand reaction.

1.3 Results and Discussion

1.3.1 Alternative Promotion Methods

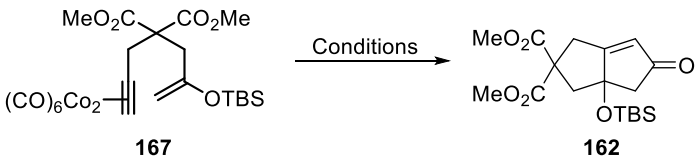
Building upon the preliminary investigations conducted within our laboratory, attempts to broaden the substrate scope were undertaken in order to develop an appreciation for the applicability of silyl enol ethers as alkene components in the Pauson-Khand cyclisation. Initially, it was necessary to determine that the conditions which had been used in the benchmark reaction of dicobalt hexacarbonyl complex **167** were the optimal conditions for the reaction. At this stage, only two distinct promotion methods had been employed in the reaction, namely a sulfide in DodSMe and an amine *N*-oxide in TMANO (*c.f* **Scheme 70**). To enable a direct comparison of other promotion methods, it was necessary to conduct these studies with standard substrate **167**.

The synthesis of complex **167** was conducted according to the procedure described by the previous researcher in our laboratory (**Scheme 75**).[164] First, alkylation of dimethyl malonate with chloroacetone proceeded in a good yield of **50%**, followed by a second alkylation with propargyl bromide to give **166** in an excellent **93%** yield. The TBS enol ether **161** was prepared readily in a very good **72%** yield and subsequent dicobalt hexacarbonyl formation allowed the isolation of **167** in an excellent **98%** yield.



Scheme 75

With compound **167** in hand, it was possible to explore various promotion methods in an effort to reach the optimal conditions for the synthesis of oxygenated cyclopentenones *via* the Pauson-Khand reaction (**Scheme 76** and **Table 5**).



Scheme 76

Table 5

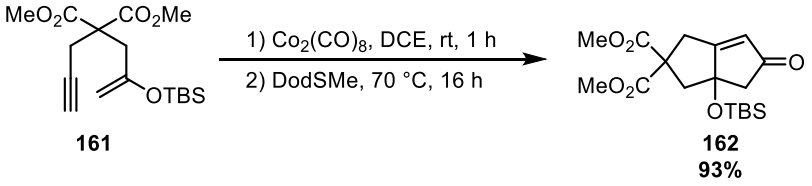
Entry	Conditions	Yield (%)	Starting material (%)	Decomplexed starting material (%)
1	$CyNH_2$, DCE, 70 °C, 16 h	2	5	23
2	TMTU, DCE, 70 °C, 16 h	21	-	29
3	No additive, DCE, 70 °C, 16 h	18	-	-
4	DodSMe, DCE, 70 °C, 2 h	81	-	-

Thus far, there had been no attempts using an amine promoter, which has been shown to be efficacious for the more traditional Pauson-Khand starting substrates. Cyclohexylamine was chosen as this has been shown to be the most effective amine promoter when tested against a range of others.[102] This achieved only a **2%** yield of isolated product with **5%** of starting complex **167** and decomplexed starting material **161** also recovered (**Table 5**, **Entry 1**). Another common Lewis base promoter is TMTU.[123] In our system, TMTU did promote cyclisation, and was more effective in this regard than cyclohexylamine, achieving the cyclopentenone product in **21%** yield (**Table 5**, **Entry 2**). Alongside this, decomplexed starting material was recovered in **29%** yield. Furthermore, the reaction was conducted in the absence of any additives (**Table 5**, **Entry 3**). Pauson-Khand reactions can be conducted under thermal promotion methods, though typically these reactions are less efficient, and, indeed, this was the case with substrate **167** as the products were delivered in a poor **18%** yield. Clearly, these additional conditions were not an improvement on the DodSMe protocol. For comprehensiveness, a comparative reaction using the previously described optimal conditions was conducted (**Table 5**, **Entry 4**). This furnished the cyclopentenone product in an excellent **81**% yield after only 2 h.

Confident that the DodSMe protocol applied to our system were the ideal set of reaction conditions for such silyl enol ether starting substrates, a more expansive substrate scope

could be embarked upon to broaden the application of this new methodology. In this regard, internal alkynes commonly present a greater challenge as substrates for the Pauson-Khand reaction when compared to their terminal analogues and so expansion of the methodology to these compounds would test the limits of this developing methodology.

To further strengthen the methodology, the idea of a one-pot protocol where the alkyne complexation and Pauson-Khand reaction are carried out in one vessel, was considered. Until this stage, each complex had been purified and isolated before it was subjected to the optimised Pauson-Khand reaction conditions. However, a one pot protocol would render the overall system more practically accessible due to the difficult isolation of the alkyne-cobalt complexes themselves. To explore this possibility, standard test substrate compound **167** was employed (**Scheme 77**). This was subjected to the complexation conditions, however DCE was used as solvent in this case to facilitate the one-pot reaction. This step proceeded efficiently, as monitored by TLC analysis, and the cobalt-alkyne complex was formed after 1 h. DodSMe was subsequently added to this reaction mixture and upon heating to 70 °C for 16 h, gratifyingly, the cyclopentenone product was delivered in an excellent **93%**. This is an improvement on the yield of the analogous stepwise reactions in which the cyclopentenone product was obtained in **86%** from the silyl enol ether **161**.

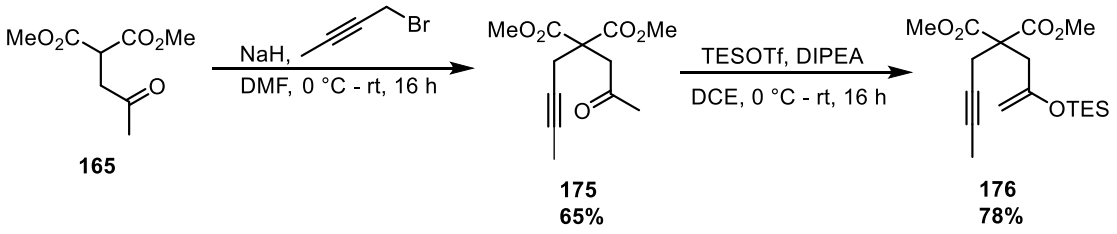


Scheme 77

1.3.2 The Use of an Internal Alkyne

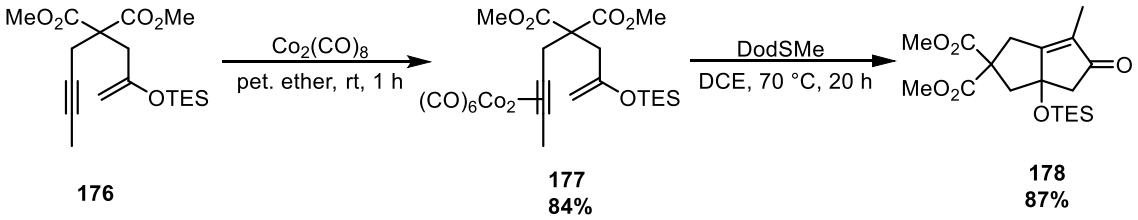
It was envisaged that an internal alkyne substrate analogous to compound **167** would provide a useful comparison with regard to the efficacy of internal alkynes in our protocol. To achieve this goal, the internal alkyne moiety was incorporated from common intermediate **165** using butynyl bromide (**Scheme 78**). This alkylation reaction proceeded to compound **175** in **65%** yield and the product was pleasingly isolated as a white solid. From compound **175** the corresponding TES enol ether was synthesised in the typically described manner, using TESOTf and DIPEA. It is important to note that previous research with substrate **167** showed that both TBS and TES silyl enol ether substrates worked equally well within this developing Pauson-

Khand methodology. Pleasingly, TES enol ether **176** was accessed in **78**% yield, which is comparable with the corresponding terminal alkyne substrate **167** (*c.f.* **Scheme 71**).



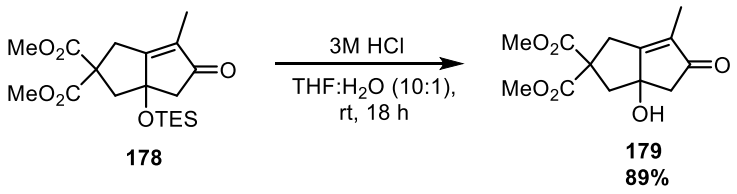
Scheme 78

Complexation of this substrate with $Co_2(CO)_8$ proceeded rapidly and efficiently as with the previous examples (**Scheme 79**). Gratifyingly, the Pauson-Khand reaction also proceeded excellently for this substrate and the cyclopentenone product was accessed in **87%** yield, albeit over a slightly longer reaction time of 20 h compared with the 2 h required for the terminal analogue. This result set the precedent for the use of the more challenging internal alkynes alongside the terminal substrates, and demonstrated potential for a broad application of the methodology.



Scheme 79

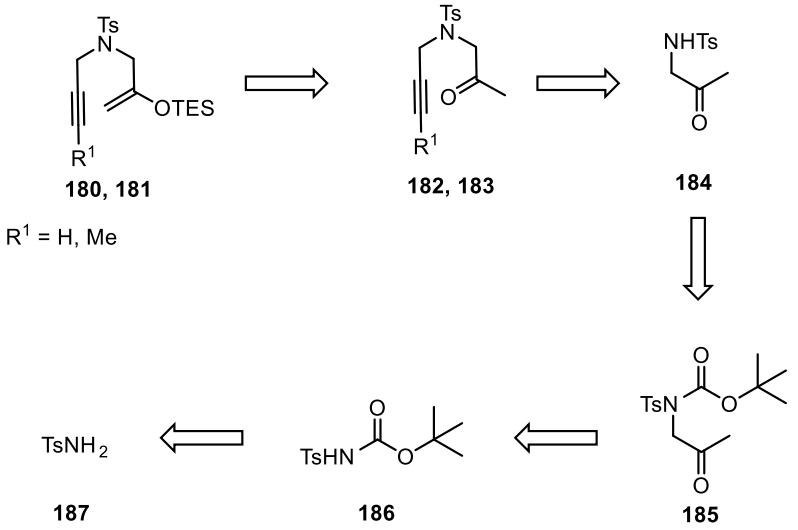
With this pleasing result, our focus was turned to facilitating the deprotection of the silyl ether to yield the free hydroxyl group. This would generate a further functional handle in the cyclopentenone molecules, aside from those created from the Pauson-Khand reaction itself, with which even more molecular complexity can be built. Previously established conditions involved the use of 3 M $HCl_{(aq)}$ and a THF:H_2O (10:1) mixed solvent system. With our particular compound **178**, such conditions furnished the free hydroxyl product **179** in an excellent **89%** yield (**Scheme 80**).



Scheme 80

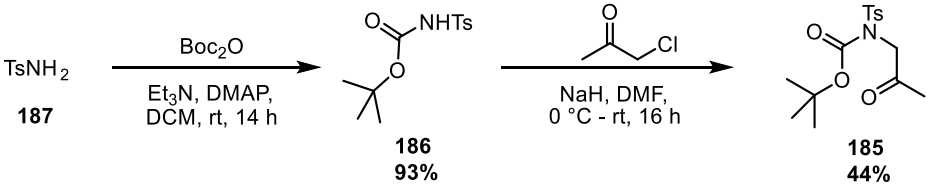
1.3.3 Expansion to N-linked Substrates

Buoyed by the applicability of the methodology to both terminal and internal alkynes, an extension to further intramolecular Pauson-Khand reaction substrates was initiated. The first of these substrates explored were compounds which contained a nitrogen atom in the chain. Such *N*-linked substrates are desirable compounds as a protecting group, such as a tosyl, can be attached to the nitrogen throughout the synthesis and this could be ultimately unmasked in the cyclised final product, thus, generating an additional functional handle. Furthermore, the bond angles afforded by the nitrogen substituent in the tether helps to push the reacting centres together. As such, synthesis of *N*-linked silyl enol ether substrates **178** and **179** was anticipated as described in **Scheme 81**. As standard, the silyl enol ether Pauson-Khand precursor (TES in this case) could be formed from the corresponding ketones **182** and **183**, which, in turn, would be prepared *via* alkylation of amino-ketone **184**. This compound could be made through a series known transformations from *p*-toluenesulfonamide **187**, a cheap and readily-available starting material. Over-alkylation of this material was highlighted as a potential issue if attempting to prepare **184** from **187** directly, therefore, the Boc group was incorporated to prevent this outcome.



Scheme 81

This pathway started with a Boc protection of *p*-toluenesulfonamide **187**, which was achieved in a high **93**% yield using di-*tert*-butyl carbonate (**Scheme 82**). The product was easily purified by trituration to give a white solid. The following step involved alkylation using distilled chloroacetone and sodium hydride as the base (**Scheme 82**, **Table 6**). Despite a somewhat moderate yield of **44%** in the first instance (**Table 6**, **Entry 1**), repetition of this reaction resulted in a significant drop in efficiency to **19%** (**Table 6**, **Entries 2** and **3**). The unpredictable nature of this step proved to be problematic when attempting to build sufficient quantities of this intermediate for subsequent steps.

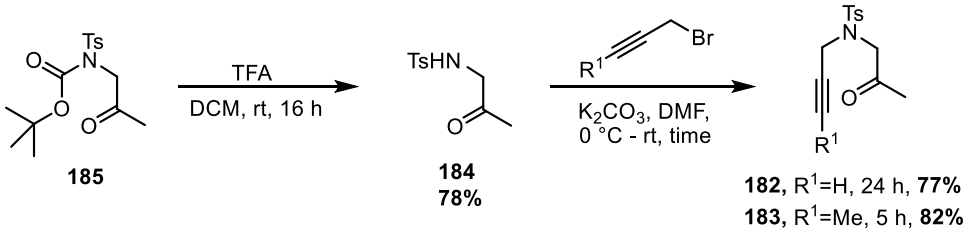


Scheme 82

Table 6

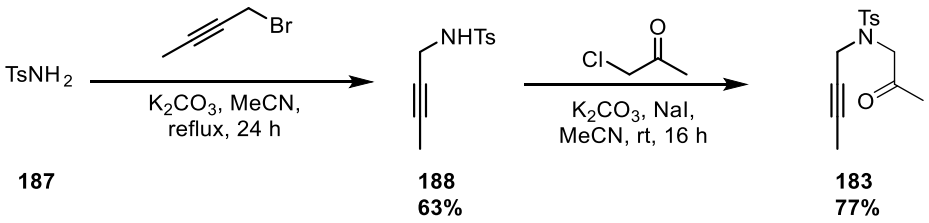
Entry	Scale	Yield
1	5.53	**44%**
2	5.03	**19%**
3	26.20	**19%**

The next step required Boc deprotection, which was realised in a good **78%** yield using TFA in DCM for 16 hours (**Scheme 83**). At this stage, **184** was alkylated further using propargyl bromide and butynyl bromide to form **182** and **183**, respectively. Whilst this described synthetic pathway delivered the key ketone intermediates, the overall yield was far from desirable. Additionally, the required protection and deprotection steps added a cumbersome nature to this overall sequence and **78%** yield for the Boc-deprotection is a good yield for a chemical transformation.



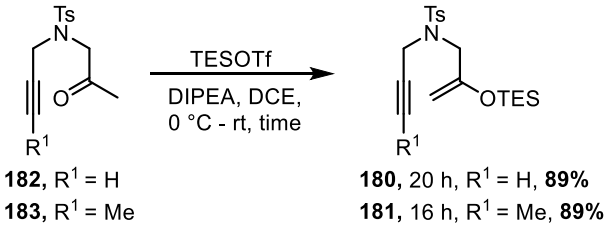
Scheme 83

In relation to the above, a literature search uncovered a route where *p*-toluenesulfonamide **187** could be alkylated directly using an alkynyl electrophile.[165] With respect to our targeted compounds, these conditions were applied using butynyl bromide as the electrophile in an attempt to synthesise further quantities of **183** (**Scheme 84**). In order to prevent overalkylation of the sulfonamide starting material, a large excess of 4 equivalents was employed. The desired product was achieved in a good yield of **63%**, though this material required two column chromatography purifications due to the large excess of *p*-toluenesulfonamide and the poor separation by TLC. Nonetheless, with this compound in hand, it was further alkylated using chloroacetone, K_2CO_3, and sodium iodide as an additive. Sodium iodide is commonly used as a reagent for the Finkelstein reaction – an S_N2 reaction where one halogen is replaced by another. The newly formed iodoacetone will be much more susceptible to nucleophilic attack by compound **188**. This resulted in an excellent yield of **77%** of compound **183**, which constituted an improved overall yield (**49%**) from *p*-toluenesulfonamide compared with the previous pathway (**26%** at best).



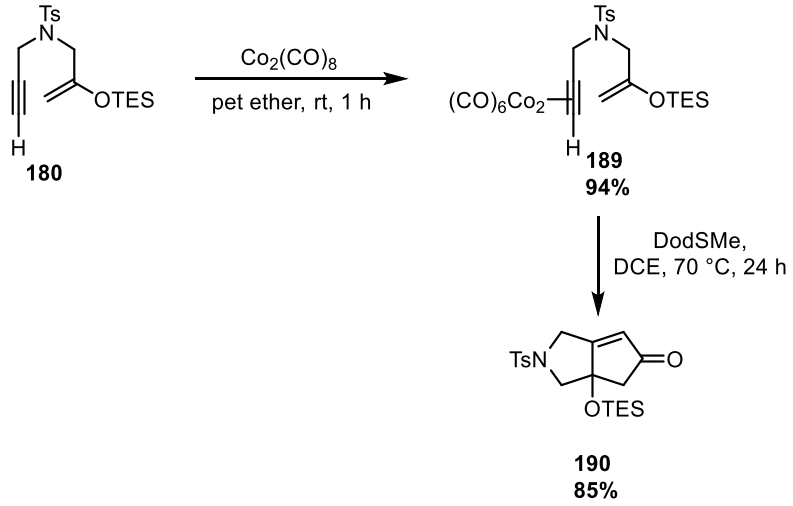
Scheme 84

The formation of the desired silyl enol ethers **178** and **179** was then achieved in excellent yield from substrates **182** and **183** (**Scheme 85**) in **89%** for both compounds. The overall pathway to the required Pauson-Khand precursors was now robust and reliable.



Scheme 85

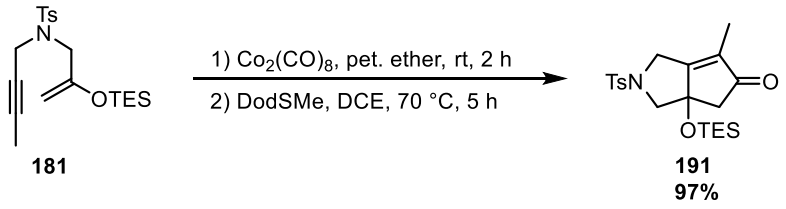
Complexation of the terminal alkyne substrate proceeded efficiently to the alkyne-cobalt complex **189** which was delivered in **94%** yield (**Scheme 86**). Pleasingly, when this complex was subjected to the Pauson-Khand reaction conditions the cyclopentenone **190** was obtained in **85%** yield.



Scheme 86

At this point we turned our focus to the internal alkyne analogue of the *N*-linked target, compound **179**. It was theorised that the complexation and cyclisation could be conducted as

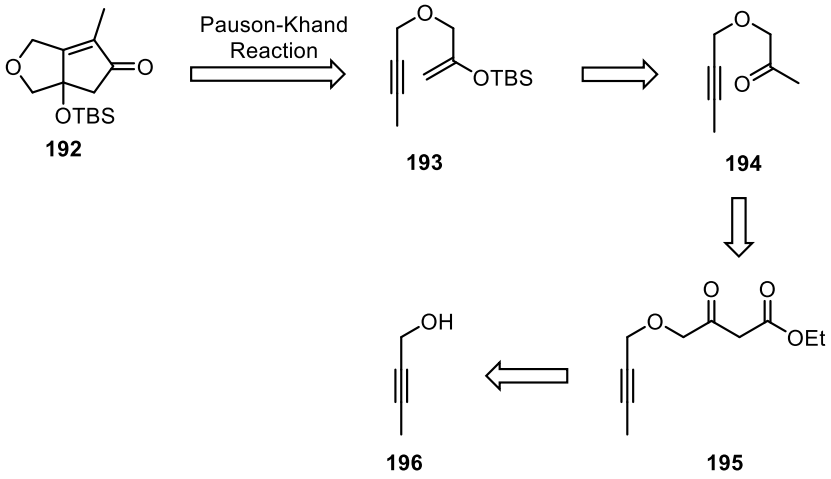
a telescoped process. This method involved the formation of the dicobalt hexacarbonyl complex in pet. ether and then filtration and solvent switch before subjection to Pauson-Khand conditions (**Scheme 87**). While this is a less practically-accessible procedure than the one-pot protocol (*c.f*. **Scheme 79**), the filtration removes unreacted $Co_2(CO)_8$ and cobalt residues which are formed in the complexation step. This provided a cleaner reaction medium for the Pauson-Khand reaction step and proved to be particularly efficacious, generating the cyclopentenone product **191** in **97%** yield directly from the silyl enol ether. Regarding the one-pot protocol *versus* the telescoped process, both protocols delivered the functionalised cyclopentenone product in excellent yields and, therefore, one process need not be favoured over the other. However, unreacted $Co_2(CO)_8$ and cobalt residues may hinder the progress of the reaction for certain sensitive systems and result in a diminished yield. This can be circumvented by employing the telescoped process, which includes the filtration step, without a significant loss in practical efficiency.



Scheme 87

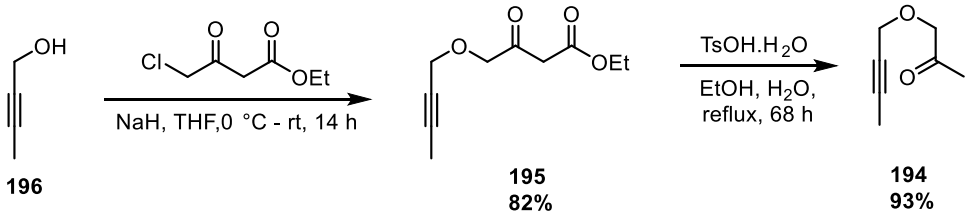
1.3.4 Synthesis of an oxygen-linked Cyclopentenone

To this point, our developing methodology has shown success in achieving efficient cyclisation of a varied range of silyl enol ether compounds to oxygenated cyclopentenones for the first time. Thus far, fully carbon-linked and nitrogen-linked examples have been utilised to showcase the procedure. Expansion of the methodology to incorporate oxygen-linked substrates was envisaged as another achievable goal. Retrosynthetic analysis of the synthetic route to oxygen-linked cyclopentenone **192** is contained in **Scheme 88**. In a similar vein to the synthetic procedures already described, novel target **192** could be prepared *via* the Pauson-Khand reaction from the corresponding silyl enol ether **193**, which is derived from ketone **194**. This ketone could be accessed by decarbonylation of the β-ketoester **195**, which could be prepared by alkylation of alkynol **196**.



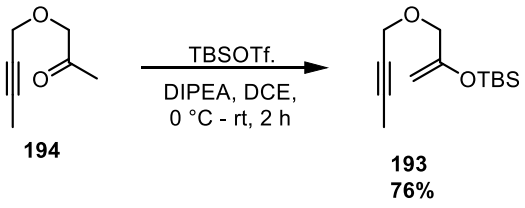
Scheme 88

The initial alkylation reaction proceeded in an excellent yield of **82%** (**Scheme 89**). Due to the number of side reactions which could occur with this process, the β-ketoester electrophile was added to a stirring suspension of excess NaH, followed by the nucleophile over 2 h. The subsequent decarboxylation reaction proceeded very efficiently to **93%**, albeit under forcing conditions over a long reaction period.



Scheme 89

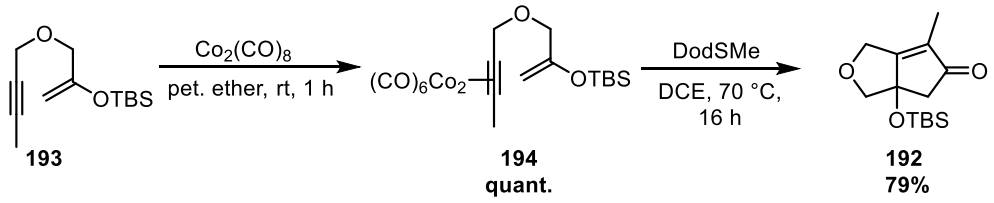
With **194** in hand, formation of the silyl enol ether substrate proceeded rapidly, and in good yield, to the corresponding silyl enol ether **193** (**Scheme 90**).



Scheme 90

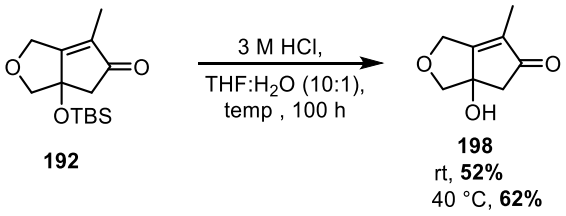
The complexation of substrate **193** was achieved in a quantitative yield and required minimal purification *via* a short silica plug to generate the pure product (**Scheme 91**). The key Pauson-

Khand cyclisation was then carried out and produced the functionalised cyclopentenone product **192** in a very good yield of **79%** over 16 h, which is consistent with previous cyclisation results. We were pleased to widen the scope of our methodology, delivering an interesting bicyclic structure containing a densely oxygenated small molecule. This cyclisation also represents the use of a more challenging internal alkyne.



Scheme 91

Deprotection of this silyl ether yielded the free alcohol in **52%**, a pleasing result for this important reaction (**Scheme 92**). Unexpectedly, complete conversion of the starting material was not reached, even after 100 h, and **33%** of **192** was recollected. It was hypothesised that increasing the reaction temperature may increase the rate of reaction to enable an improved yield of product. However, when the reaction was conducted at 40 °C, the product **198** was obtained in only a slightly increased **62%** yield over 100 h, though complete conversion of **192** was obtained.



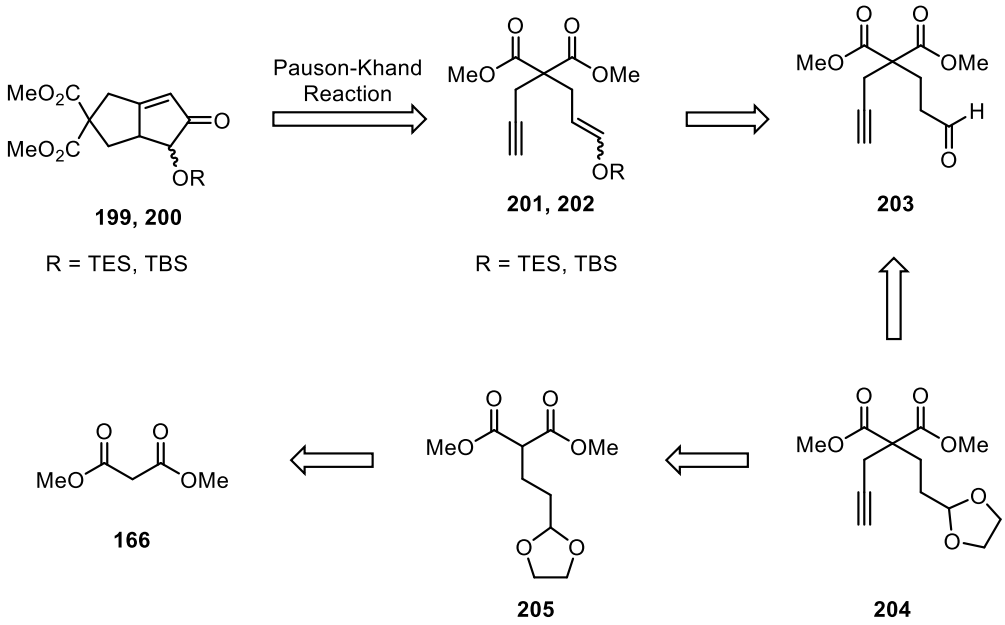
Scheme 92

1.3.5 Expansion to α-oxygenated Cyclopentenones

Utilising silyl enol ethers derived from ketones, a range of 5,5-fused bicyclic systems, which feature oxygenation at the ring junction, have been accessed. A class of related substrates are silyl enol ethers deriving from aldehydes; employing these as alkene components in the Pauson-Khand reaction would deliver divergent products where the oxygenation is adjacent to the ketone. The requisite alkene coupling partners, i.e. the silyl enol ethers, would represent 1,2-disubstituted olefins, which is the key structural difference from the 1,1-disubstituted examples that have been successful so far. Synthesis of cyclopentenones with

α-functionalisation would highlight the versatility of the developing methodology and emphasise how careful substrate design can be used to tailor the site of the functionality in the final cyclopentenone. Furthermore, the final molecule would contain an additional chiral centre, a useful 3-dimensional functional handle.

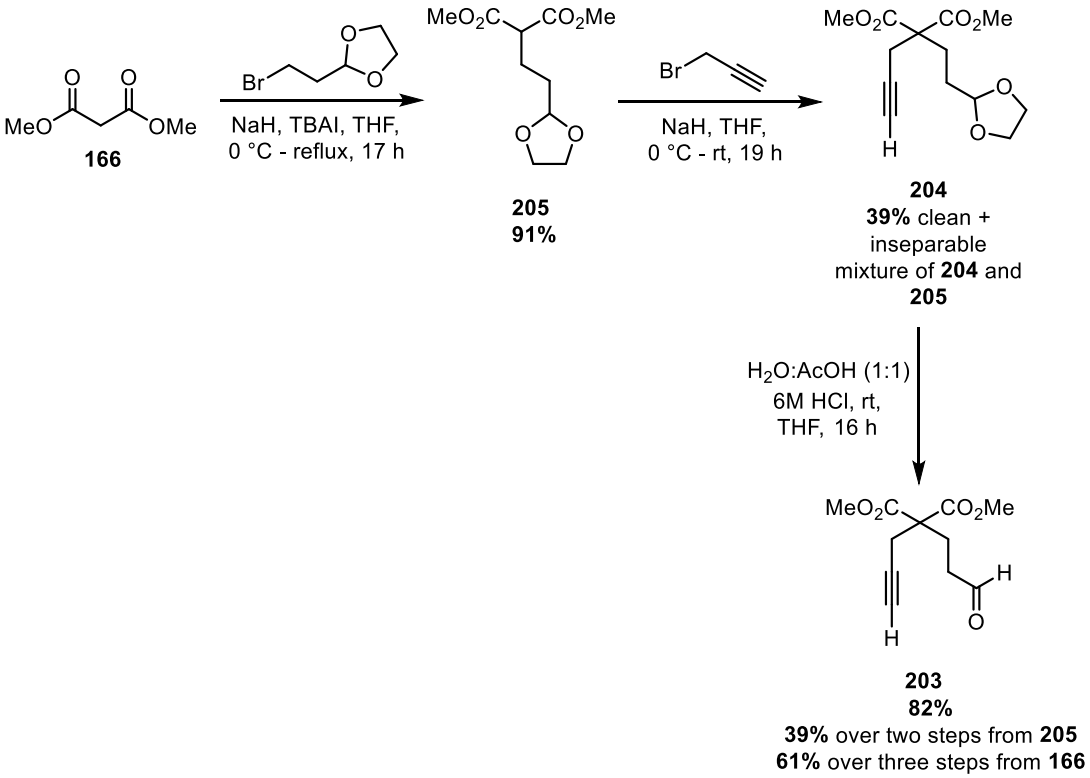
Target molecules would be prepared *via* the Pauson-Khand reaction of substrates of type **199** and **200** (**Scheme 93**). The Pauson-Khand reaction is similar to the previously shown examples, though, at this stage, it was unclear whether these silyl enol ethers would react in such an efficient manner. Retrosynthetically, silyl enol ethers **201** and **202** are derived from aldehyde **203**. Notably, the silyl enol ether compounds now have the potential to exhibit a mixture of *cis* and *trans* geometry. With aldehyde compounds notorious for their reactivity, it was deemed necessary to reveal this centre late in the synthetic pathway to prevent side reactions in earlier steps. As such, the masked aldehyde group could be installed as a cyclic acetal, as in **204**, as this can be easily removed to reveal the required aldehyde motif downstream. Compound **204** was envisaged *via* two alkylation reactions from readily available starting material dimethyl malonate **166**.



Scheme 93

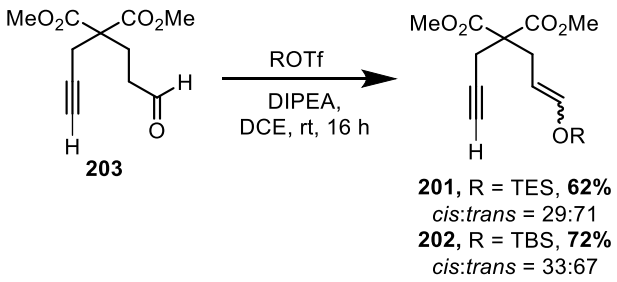
This route began with a simple alkylation of dimethyl malonate, affording compound **205** in **91%** yield after 17 h (**Scheme 94**). The next step was an alkylation with propargyl bromide, which, surprisingly, did not reach completion even after 19 hours, and only **39%** of the product could be collected cleanly. In addition to this, an inseparable mixture of product **204**

and starting material **205** was also isolated. The mixture of compounds **204** and **205** was subjected to the acidic conditions required for deprotection of the acetal and this permitted the isolation and purification of **203**. The overall yield for both of these steps was **39%**. This was an acceptable yield over 2 steps; however, it was necessary to repeat this synthetic route in an effort to build sufficient quantities of intermediate **203**. To accelerate the process, the reactions were telescoped and each compound was taken, in turn, onto the next step in its crude form without further purification. Pleasingly, this generated the aldehyde compound **203** in **61%** yield overall yield from dimethyl malonate **166** over three steps, which was a significant improvement over the equivalent stepwise process.



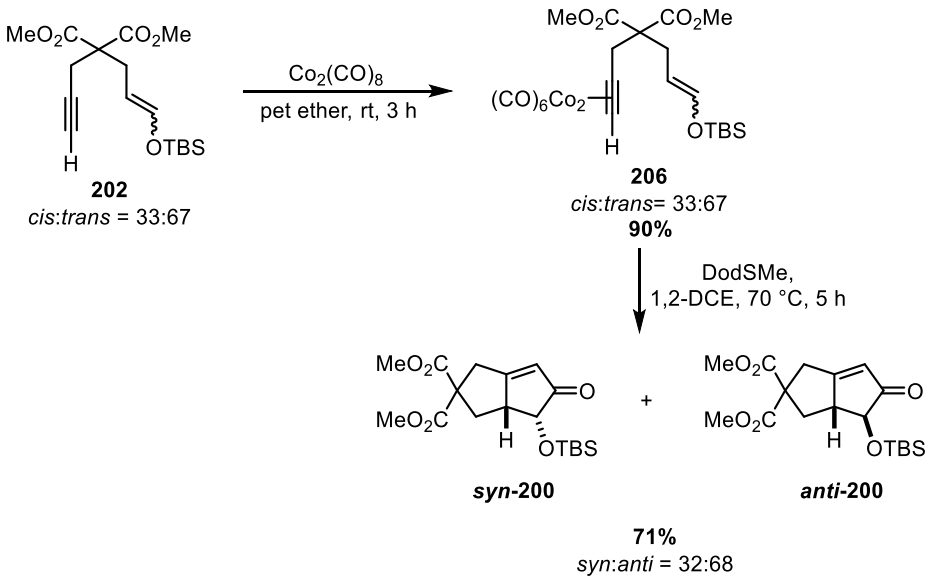
Scheme 94

With key aldehyde **203** in hand, it was possible to progress to the silyl enol ether preparation. TES enol ether **201** was delivered in a good **72%** yield using the standard conditions (**Scheme 95**). Notably, compound **201** was isolated as a 29:71 mixture of *cis*:*trans* isomers, with respect to the alkyl and *O*-silyl functional groups. Synthesis of the TBS analogue **202** resulted in similar observations, where this compound was isolated as a 33:67 *cis*:*trans* mixture. In both cases, separation of the isomers was impossible by column chromatography, and, the assignment of each compound was determined by ^{1}H NMR spectroscopy.



Scheme 95

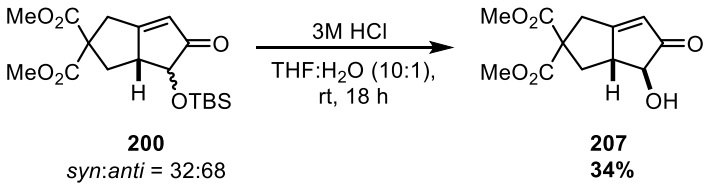
Dicobalt hexacarbonyl complex **206** was subsequently prepared from TBS enol ether **202** in an excellent yield of **90%** and the *cis*:*trans* ratio was retained through this reaction (**Scheme 96**). Applying complex **206** to the standard Pauson-Khand reaction conditions delivered cyclopentenone **200** in an excellent **71%** yield as a 32:68 mixture of *syn*:*anti* diastereomers. This result established that 1,2-substituted silyl enol ethers can be applied to the Pauson-Khand reaction in addition to their 1,1-substituted counterparts. Furthermore, α- and β-functionalised cyclopentenones can be accessed through our expanding methodology by altering the silyl enol ether motif employed in the cyclisation. This underlines the versatility of this method and emphasises its ability to synthesis a range of diversely functionalised cyclopentenones.



Scheme 96

When the 32:68 mixture of *syn*:*anti* diastereomers of **200** were applied to our common deprotection conditions, **34%** of the corresponding alcohol was isolated and it was found to be the single *(anti*) diastereomer **207** (**Scheme 97**). This was confirmed by single-crystal X-ray

diffraction (for full details see the *Appendix Section*). Whilst **207** was isolated along with **25%** of the starting material, none of the *syn* epimer was observed. Energy minimisation calculations discovered that this diastereomer is 2.88 kcal/mol lower in energy than the corresponding *syn* epimer due to a stabilising hydrogen bonding interaction (for full computational details see the *Experimental Section*). Since this is known to be an epimerisable centre, it is possible that this could be a thermodynamic effect.

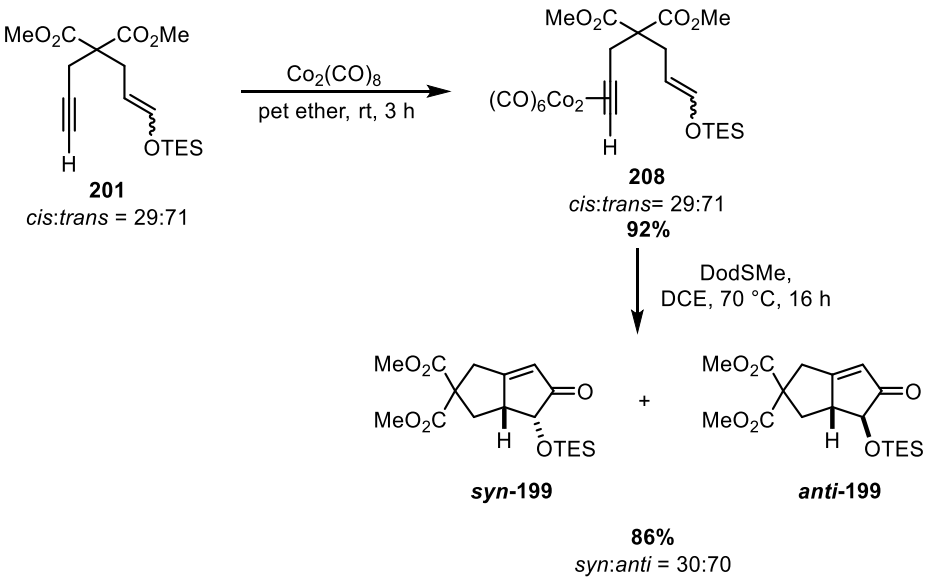


200
syn:*anti* = 32:68

207
34%

Scheme 97

Now our focus turned to the corresponding TES enol ether **208**. Both TES and TBS enol ethers performed excellently in the previous 1,1-substituted olefin examples. It was prudent to determine if this applicability could be extended to these 1,2-substituted olefins. The formation of the dicobalt hexacarbonyl complex proceeded well and the *cis*:*trans* ratio of the silyl enol ether as retained (**Scheme 98**). This complex was applied to the Pauson-Khand reaction and the cyclopentenone was obtained in an excellent **86%** yield and the *syn*:*anti* ratio reflected the *cis*:*trans* ratios of the silyl enol ether and dicobalt hexacarbonyl complex.



201
cis:*trans* = 29:71

208
cis:*trans*= 29:71
92%

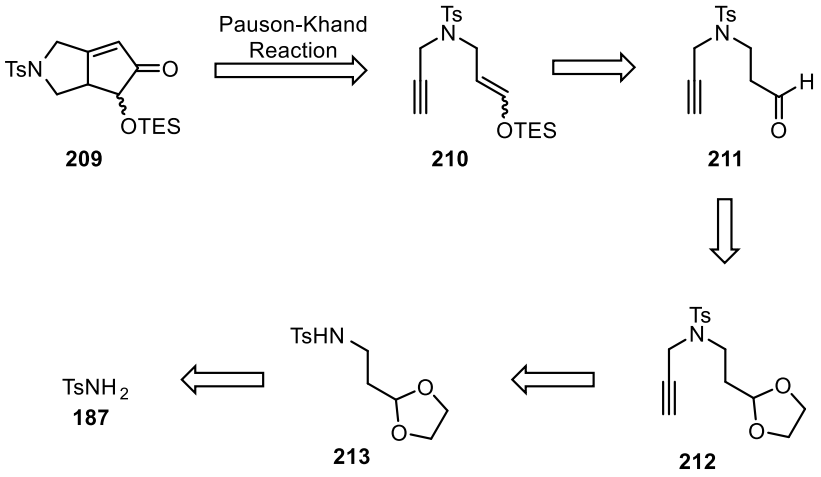
***syn*-199**

***anti*-199**

86%
syn:*anti* = 30:70

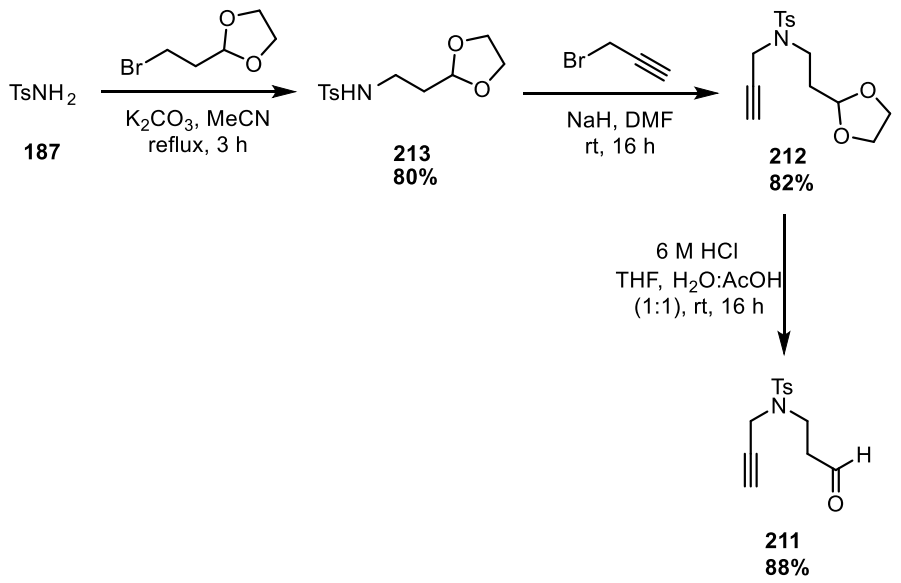
Scheme 98

Pleased that the reaction had proven to be successful in delivering α-oxygenated cyclopentenones, our attention was subsequently focused on exploring the applicability of other aldehyde-derived silyl enol ether substrates. Variation in the alkyl chain as a pertinent place to commence the investigation of other aldehyde-derived silyl enol ethers and, as such, the synthesis of *N*-linked α-oxygenated cyclopentenone **209** was sought (**Scheme 99**). It was envisaged that compound **209** could be generated *via* the Pauson-Khand reaction of the corresponding silyl enol ether **210**. This silyl enol ether is derived from aldehyde **211**, prepared by deprotection of the cyclic acetal in **212**, which can be generated *via* two alkylation reactions from readily-available *p*-toluenesulfonamide **187**.



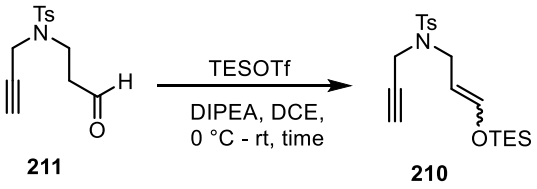
Scheme 99

Due to the previous shortcomings of using a Boc protecting group, we looked to circumvent any issues by alkylating **187** directly to deliver **213** (**Scheme 100**). In this case, 2 equivalents of *p*-toluenesulfonamide were used and, pleasingly, this resulted in the product being isolated in a high yield of **80%**. Subsequent alkylation of **213** with propargyl bromide provided compound **212** in **82%** yield. Complete conversion of the starting material was achieved in this reaction, which had been problematic in the analogous synthesis of compound **205** (*vide supra*), which made for a simplified purification and isolation procedure. Deprotection of the acetal to yield the key aldehyde **211** was conducted using strong acid, and this delivered the desired product in an excellent **88%** yield with high overall yield (**58%** from **187**) to this key intermediate.



Scheme 100

Following this, TES enol ether **210** was readily prepared from aldehyde **211** using our standard conditions (**Scheme 101** and **Table 7**). Initially, the previous reaction conditions were replicated completely and a 29:71 mixture of *cis*:*trans* silyl enol ethers were isolated in **72%** yield after 16 h (**Table 7, Entry 1**). The *cis*:*trans* ratio of the product was assigned by ^{1}H NMR analysis and with each subsequent synthesis (with varying reaction times) a different *cis*:*trans* ratio of the product was observed. With a shorter reaction time of 6 h, the observed *cis*:*trans* ratio was 45:55, though the isolated yield was comparable at **78%** (**Table 7, Entry 2**). A further attempt, which was conducted over an intermediate reaction time of 8 h, provided the products with a *cis*:*trans* ratio of 48:52 (**Table 7, Entry 3**). The expectation had been that a longer reaction time would afford more of the *trans* isomer, however, the ratio observed in **Entry 3** is comparable to the ratio observed in **Entry 2**.

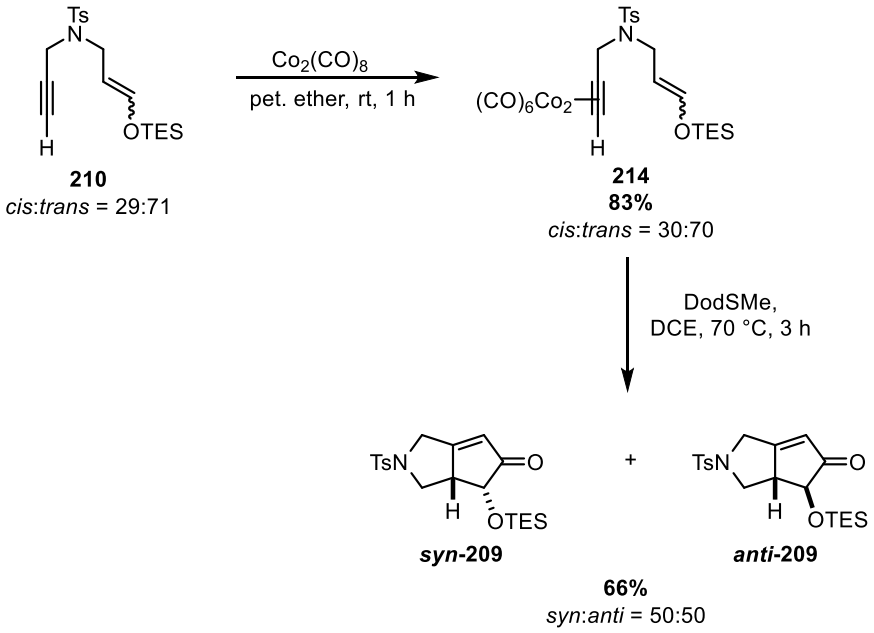


Scheme 101

Table 7

Entry	Yield (%)	Reaction time (h)	*cis*:*trans* ratio
1	72	16	29:71
2	78	6	45:55
3	68	8	48:52

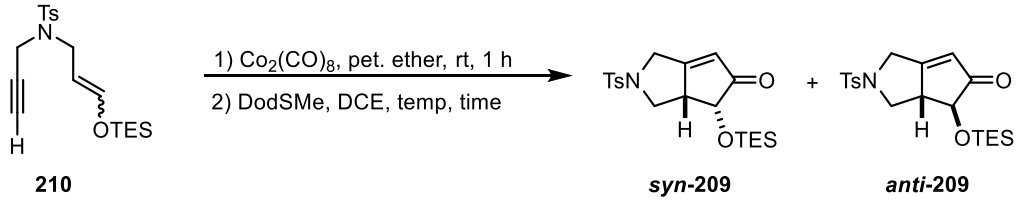
From the mixture of *cis* and *trans* isomers (29:71) in **Table 7**, **Entry 1**, the dicobalt hexacarbonyl complex was formed (**Scheme 102**). The *cis*:*trans* ratio was retained from the starting silyl enol ether with the desired cobalt complex being isolated in **83%** yield. When this mixture was subjected to the Pauson-Khand conditions, complete conversion was observed and the cyclised product **209** was obtained in a good **66%** yield, however, the ratio of *syn*:*anti* products was now 50:50. This result provided an interesting conundrum and raised the question: what dictates the ratio of isomers and could this be harnessed to provide a single diasteromeric product from the Pauson-Khand reaction? A myriad of factors could dictate the ratio of isomers: cyclisation of one isomer preferentially and decomposition of the other; rearrangement before cyclisation; epimerisation after cyclisation; or equilibration after cyclisation.



Scheme 102

As the yield of **66%** could correspond to **100%** conversion of one isomer and low conversion of the other to reach this ratio, it was not clear whether there was indeed an epimerisation process. Improvement of the yield would shed further light on whether epimerisation does, in fact, occur. To this end, it has been shown previously that preparing the dicobalt hexacarbonyl complex and subjecting this to the Pauson-Khand reaction without significant purification has delivered the cyclopentenone in an excellently high yield (*c.f*. **Scheme 87**).

Thus, in an effort to improve the yield of this particular cyclisation, such telescoped complexation-cyclisation conditions were employed using substrate **210** (**Scheme 103**, **Table 8**). Employing the same reaction time and temperature as the two-step process above, unfortunately, the telescoped procedure did not provide a significant improvement of the yield, though it was noticed that the *syn*:*anti* ratio was different in this instance; now heavily favouring the *syn* isomer (**Table 8**, **Entry 1** *vs* **Scheme 102**). Maintaining all other conditions, the reaction time was shortened to 1.5 h (**Table 8**, **Entry 2**). This was an attempt to increase the yield of the reaction in the event that decomposition of products was occurring post-cyclisation. Curiously, this afforded the product **209** in **52**% yield with a differing ratio of *syn*:*anti*, once more. This time, the *syn*:*anti* ratio slightly favoured the *anti* isomer. The conditions detailed in **Table 8**, **Entry 3** were employed following the discovery that isolated cyclopentenone product, which is a solid, decomposes over the temperature range of 60 – 68 °C. It is understood that solution behaviour is often divergent from solid state behaviour, however, given that the reaction proceeded rapidly at 70 °C, it was envisaged that this drop in temperature would not affect the efficacy of this particular reaction. The reaction reached complete conversion in 8 h, though there was no significant improvement in yield. Interestingly, the ratio of *syn:anti* did not change from the silyl enol ether starting substrate to the cyclopentenone products in this example, which may mean that, at 55 °C, there is not sufficient energy in the system to cause epimerisation. These attempts at increasing the yield of the products through tuning the reaction conditions proved ineffective. As a result, it remains unclear whether the observed *syn*:*anti* ratio of the cyclopentenone is a result of more effective cyclisation of one isomer of silyl enol ether **210** over the other or epimerisation of the cyclopentenone product post-cyclisation. To determine whether we could control the *syn*:*anti* ratio of the products our focus was turned to attempting to alter the *syn*:*anti* ratio post-cyclisation through epimerisation of the α-keto chiral centre.



210 ***syn*-209** ***anti*-209**

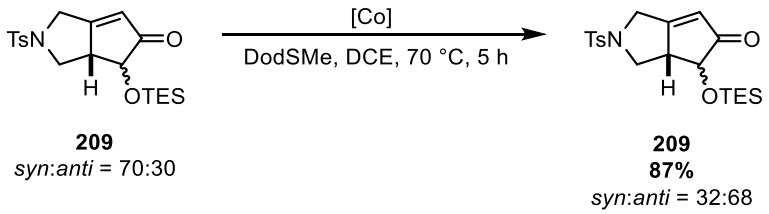
Scheme 103

Table 8

Entry	Ratio of SM (*cis*:*trans*)	Reaction temp. (°C)	Reaction time (h)	Yield (%)	Ratio of Products (*syn*:*anti*)
1	45:55	70	3	58	70:30
2	48:52	70	1.5	52	41:59
3	48:52	55	8	60	48:52

As the *syn*:*anti* ratio observed in the previous experiments were considerably divergent, though the *cis*:*trans* ratios of the starting material and isolated yields of the products were similar, it was theorised that an epimerisation event may be occurring under the reaction conditions. It was envisaged that the ability to epimerise the chiral centre through careful selection of the reaction conditions could be utilised as a means to generate a single diastereomer of α-functionalised cyclopentenones from a *cis*:*trans* mixture of silyl enol ethers. In order to examine this possibility, determination of the root cause of the epimerisation was necessary so that conditions may be developed to induce this epimerisation in the reaction mixture. To test if the epimerisation occurs after the formation of the cyclopentenone, the product was re-subjected to the reaction conditions (**Scheme 104**). However, over the course of the Pauson-Khand reaction, black cobalt residues form as a by-product as the dicobalt hexacarbonyl complexes convert to cyclopentenone products and the leftover cobalt coalesces to form the aforementioned cobalt residues. These residues must be considered as a component in the recreation of the reaction conditions as, though their structure is not well-defined, they may not be inert and may contribute to the epimerisation of the cyclopentenone by acting as a Lewis acid. The cobalt residues in question could be collected by filtration, through a fritted glass funnel, of the Pauson-Khand reaction used to synthesise **209** and were added to a solution of **209** and DodSMe in DCE. This mixture

was heated to 70 °C to determine whether epimerisation or alteration of the *syn*:*anti* ratio could be observed. Curiously, these conditions resulted in an almost direct flip in the stereochemistry of the cyclopentenone from *syn*:*anti* 70:30 to 32:68.

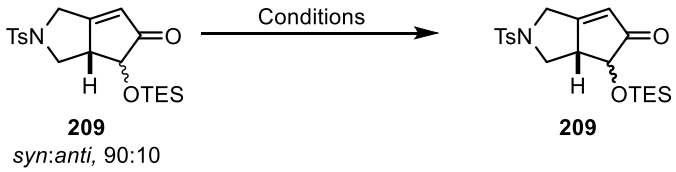


209
syn:*anti* = 70:30

209
87%
syn:*anti* = 32:68

Scheme 104

This intriguing result led to attempts being made to identify the cause of the epimerisation; indeed, it is possible the process could be cobalt-mediated, DodSMe-mediated, or simply a spontaneous process facilitated by temperature. Several different reaction conditions were employed to test these hypotheses (**Scheme 106** and **Table 9**) using a *syn*-enriched sample of **209**. As the example in **Scheme 105** converted from high-*syn* ratio to a high-*anti* ratio it was expected that the use of a diastereomerically-enriched sample would make any significant change in the ratio easier to monitor. Initially, individual reactants were excluded in turn to assess which of these causes the observed stereochemical shift (**Table 9**, **Entries 1-3**). Simple heating of the *syn*-enriched sample afforded no change in the stereochemistry and all of the material was recovered (**Entry 1**). Recreation of the Pauson-Khand reaction conditions, without a source of cobalt, was attempted (**Entry 2**) and this also afforded no change in the stereochemical information. Subsequently, DodSMe was excluded and 1 eq. of $Co_2(CO)_8$ was used as a well-defined source of cobalt this time the ratio was changed to a *syn*:*anti* ratio of 80:20 (**Entry 3**). However, only **61%** of the starting material was recovered and this was not a significant change to assert that epimerisation had occurred. Following this, the full set of Pauson-Khand reaction conditions were recreated using 1 eq. $Co_2(CO)_8$ as the source of cobalt, however, as before, **209** was isolated with an unchanged *syn*:*anti* ratio. It is important to note that, the conditions which included $Co_2(CO)_8$ resulted in a significantly diminished recovery of **209**, which may indicate that the product is sensitive to the reaction conditions and prolonged exposure could result in decomposition.



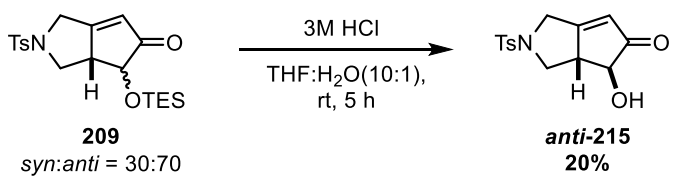
Scheme 105

Table 9

Entry	Conditions	Yield (%)	Ratio of products (*syn*:*anti*)
1	70 °C, 5 h	100	90:10
2	DodSMe (4.75 eq.), 70 °C, 5 h	87	90:10
3	$Co_2(CO)_8$, 70 °C, 5 h	61	80:20
4	$Co_2(CO)_8$, DodSMe (4.75 eq.), 70 °C, 5 h	67	90:10

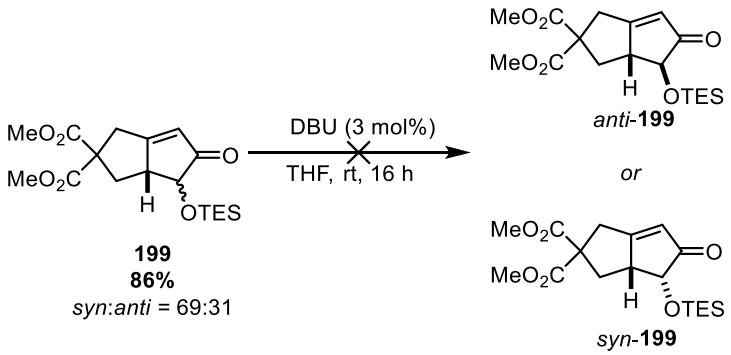
Experiments showed that the *syn*:*anti* ratio of cyclopentenone **209** did not remain constant throughout the Pauson-Khand reaction (**Scheme 29**). The ratio of isomers of the cyclopentenone at the end of the reaction was altered from the ratio at the start, thus showing that an epimerisation event can occur through our Pauson-Khand reaction conditions. Unfortunately, attempts to identify which component afforded this epimerisation were fruitless and as a result the epimerisation could not be controlled to deliver a single diastereomer from the Pauson-Khand reaction.

Following on from the experiments above, deprotection of the silyl ether of α-oxygenated cyclopentenone **209** was achieved in the disappointing yield of **20%** and like the previous example this was a single diastereomer (**Scheme 106**). The stereochemistry of this product was confirmed as the *anti*-isomer by single crystal X-Ray diffraction (*for full details see the Appendix Section*). This is further evidence of the sensitivity of this product that these mild conditions delivered a poor yield.



Scheme 106

A commonly-used method for epimerising centres adjacent to carbonyl functionality is to react them with a small amount of base. This should epimerise the centre of the least thermodynamically stable isomer to that of the most stable thus affording a single diastereomer. This was attempted using a 69:31 *syn*:*anti* mixture of compound **198** and DBU (**Scheme 107**). It was envisaged that a catalytic quantity (3 mol%) would be sufficient to faciitate this epimerisation process. Unfortunately, even under these mild conditions, this reaction resulted in a complete decomposition of the starting material. This is yet more evidence that the α-oxygenated cyclopentenones explored in this study are highly sensitive as mildly acidic and basic conditions have resulted in either a poor molecular recovery or no recovery at all.



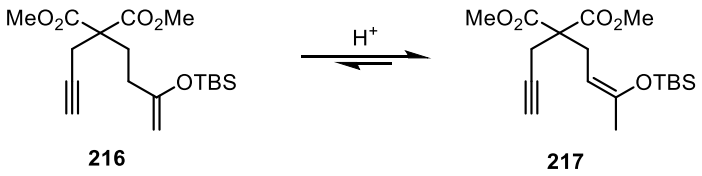
Scheme 107

There is evidence of epimerisation of the α-oxygenated cyclopentenones under the reaction conditions for the Pauson-Khand reaction. However, it was not possible to induce this epimerisation or determine which component of the reaction caused this to occur. Additionally, it is clear that the α-oxygenated cyclopentenone products from seems to be highly sensitive to acidic and basic media and so Lewis acidic cobalt residues may contribute to the decomposition of this product after the cyclisation. Irrespectively of stereoselectivity, it was pleasing to afford high reaction yields from these novel transformations.

1.3.6 Synthesis of a 6,5,-fused Cyclopentenone

The formation of highly-strained, functionalised 5,5-fused rings in a facile manner is of great benefit to the synthetic community and access to the complementary 6,5-fused rings would be equally desired. This would pose a new challenge to the developing methodology and, if successful, enhance its potential applications. It is important to note that, in traditional Pauson-Khand chemistry, preparation of 6,5-analogues are generally represented as more

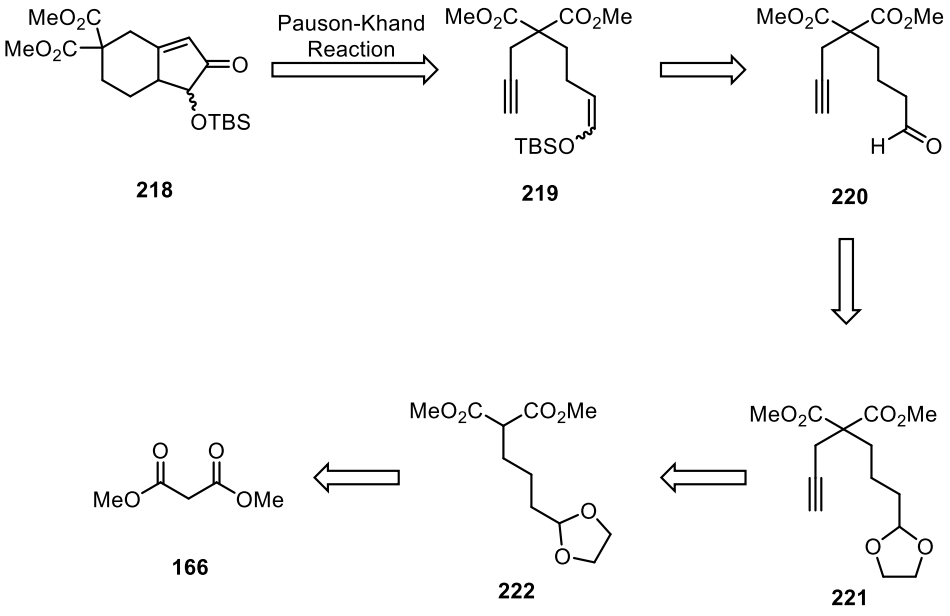
challenging transformations than their 5,5-counterparts. In relation to our targets, 6,5,-fused rings could be prepared from **216**, a ketone-derived silyl enol ether, though, it was envisaged there may be significant isomerisation to the thermodynamic silyl enol ether with an internal double bond **217** (**Scheme 108**).



216 **217**

Scheme 108

As such, attempts were not made to access **216** and work, instead, focused on the synthesis of compound **218** (**Scheme 109**). It was envisaged that **218** could be formed *via* the Pauson-Khand reaction using silyl enol ether **219**. This silyl enol ether cannot isomerise in the manner described above, though is likely to exist as a mixture of *cis* and *trans* isomers as observed previously with similar compounds (*vide supra*). Enyne **219** could be prepared from the corresponding aldehyde **220** and the formation of this compound was planned using a similar approach to the aldehyde compounds described above (*c.f.* **Schemes 3.18** and **3.23**) using a one carbon homologated electrophile in the first instance. Ultimately, dimethyl malonate was the starting point for this overall synthetic sequence.

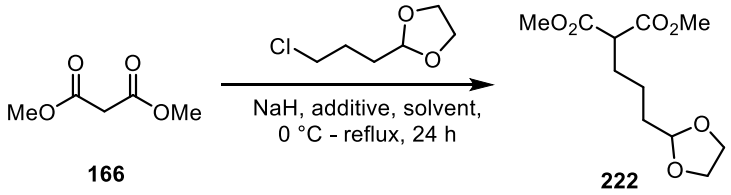


218 **219** **220**

166 **222** **221**

Scheme 109

The first step was an alkylation reaction, as described previously, though required the use of a homologated alkyl chloride (**Scheme 110** and **Table 10**). This reaction proved to be problematic as alkylation with such an unactivated electrophile failed to proceed without an additive (**Table 8**, **Entry 1**). Attempting an *in situ* Finkelstein reaction with sodium iodide afforded the product in **6%** yield (**Table 8**, **Entry 2**). Whilst a great improvement in yield to **30%** was achieved by switching to a more soluble iodide source, TBAI, changing the solvent from THF to a THF:NMP mixture afforded an even better yield of product **222** of **64%** (**Table 8**, **Entry 4**), a pleasing result given the inefficiency of the initial attempts.

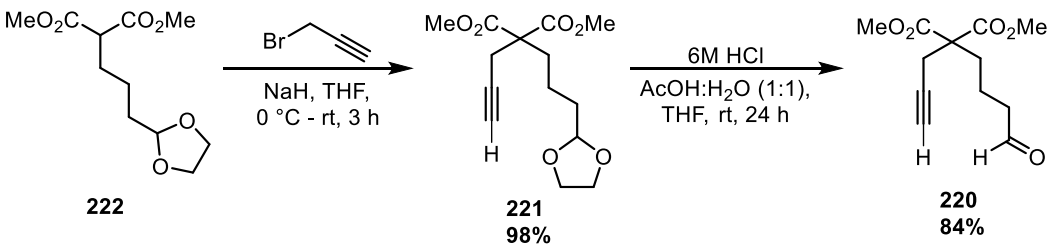


Scheme 110

Table 10

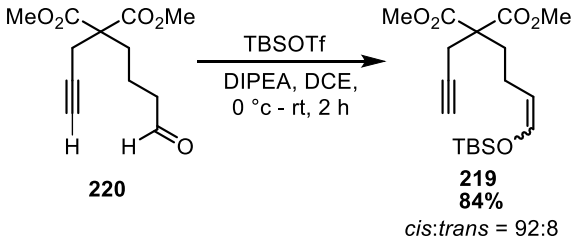
Entry	Additive	Solvent	Yield
1	No additive	THF	-
2	NaI	THF	6%
3	TBAI	THF	30%
4	TBAI	THF:NMP (3:1)	64%

The next step was alkylation with propargyl bromide, which proceeded excellently, followed by an acid-mediated deprotection of the acetal to reveal aldehyde **220** in a very good yield of **84%** (**Scheme 111**).



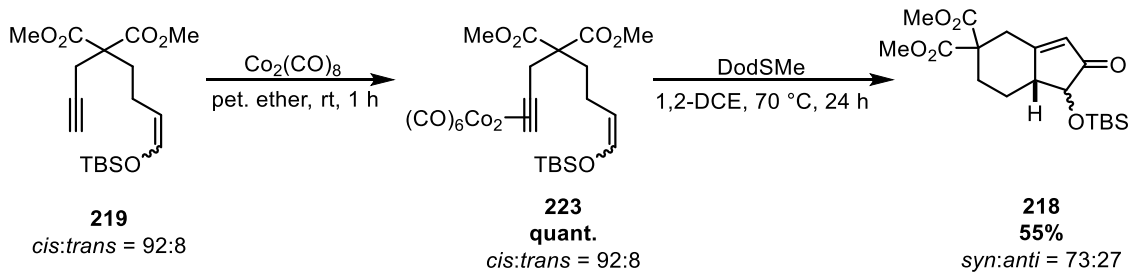
Scheme 111

Preparation of the silyl enol ether occurred over a short reaction period and yielded a *cis*:*trans* mixture of 92:8 in **87%** (**Scheme 112**). The isolation of a mixture of isomers correlates the results previously obtained for the formation of silyl enol ethers from aldehydes. Curiously, this time the *cis* isomer is much more strongly favoured than in the previous examples (*c.f*. compounds **200** and **210**), which could be attributed to the shorter reaction time, though there is no further experimental evidence to support this.



Scheme 112

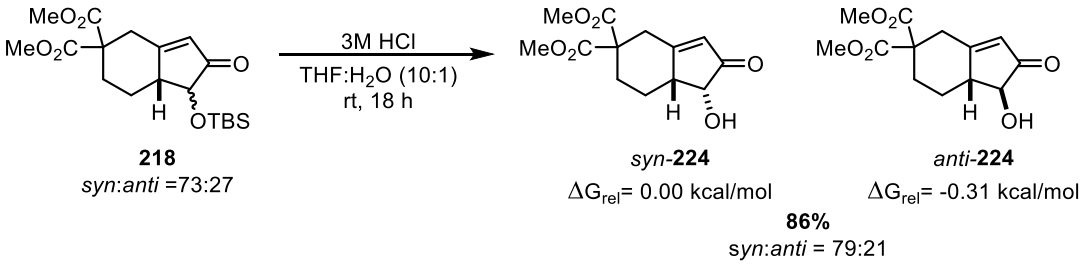
The isomeric ratio of the silyl enol ether was retained, as expected, upon complexation with dicobalt octacarbonyl (**Scheme 113**). The resulting hexacarbonyl complex was afforded in quantitative yield and did not require any purification further to filtering through a silica plug. Complex **223** was subjected to the Pauson-Khand reaction conditions and the desired cyclopentenone was obtained in a very good **55**% yield after 24 h. Importantly, a 73:27 ratio of *syn*:*anti* products was obtained, which indicates that a small amount of epimerisation of the *syn* product had occurred in this instance. This is somewhat expected due to the epimerisable nature of this centre, though, confirms that epimerisation can occur under the Pauson-Khand reaction conditions.



Scheme 113

Deprotection of compound **218** delivered the free hydroxyl compound **224** in a pleasingly high yield of **86**% (**Scheme 114**). Previously, the α-oxygenated cyclopentenones, such as **198** and

209, had been isolated from the Pauson-Khand reaction as a mixture of diastereomers and upon deprotection had resolved to a single diastereomer. Interestingly, the deprotected compound **224** was isolated as a 79:21 *syn*:*anti* mixture of diastereomers. The structure of the *syn* isomer of **224** was confirmed by single crystal X-Ray diffraction (for full details see the *Appendix Section*). Using these coordinates energy minimisation calculations were conducted on both diastereomers and, remarkably, there was only a small difference in energy (0.31 kcal/mol) between both isomers. This corroborates the experimental result and lends more evidence towards the theory that the single diastereomer isolated from the deprotection reactions is a result of a thermodynamic favourability of one isomer over the other.



Scheme 114

We were pleased to add this compound to our developing scope of cyclopentenone compounds prepared through our novel methodology. This is further evidence of the great potential that this synthetic protocol has for accessing a range of varied, functionalised cyclopentenones.

1.3.7 Pushing the Limits of the Methodology

It is well documented that steric bulk around the reacting centres can place limitations on the Pauson-Khand reaction. We have direct evidence that our process is not immune to these steric effects, for example when the TIPS enol ether was employed as the alkene component this reaction failed to produce any cyclopentenone products (*vide supra*). Establishing the steric boundaries of the reaction would deepen our understanding of the methodology and identify precisely how restrictive this key limitation is.

There are two key areas in which steric bulk may have a significant effect on the efficacy of the cyclisation. These areas are in the substitution around the alkyne and the alkene (**Figure 16**). The alkyne and the alkene are the reacting centres therefore it seems intuitive that increasing the size of the substituents around these sites will have a detrimental effect on the

cyclisation. To further our understanding of this novel process, and determine which site has the most profound effect on the reactivity, it was envisaged that steadily increasing the bulk at each section would provide useful insight into how cyclisation efficiency is affected by the size of the substituents at the reacting centres. So far, only a methyl substituent in the alkyne position had been examined, and while this provides evidence that internal alkynes can cyclise well, it does not sterically encumber the reaction considerably. A phenyl ring at this position would be a suitable alternative substituent as this would be helpful in determining the ability of the reaction to tolerate a relatively bulky, 2-dimensional substituent. In addition, silyl groups work effectively as protecting groups for terminal alkynes, therefore, exploring the tolerance of a TES alkyne would represent a useful probe for establishing whether our reaction can overcome this considerable steric hindrance. With regards to the alkene component, bulk could be increased by increasing the number of substituents; to this point only di-substituted alkenes have been employed in the methodology, however, *tri-* and *tetra-*substituted alkenes may be included. It is key to point out that there are few examples of trisubstituted alkenes being employed in the traditional Pauson-Khand.[54] Determining these key boundaries would help to provide a clear picture of how flexible the methodology is.

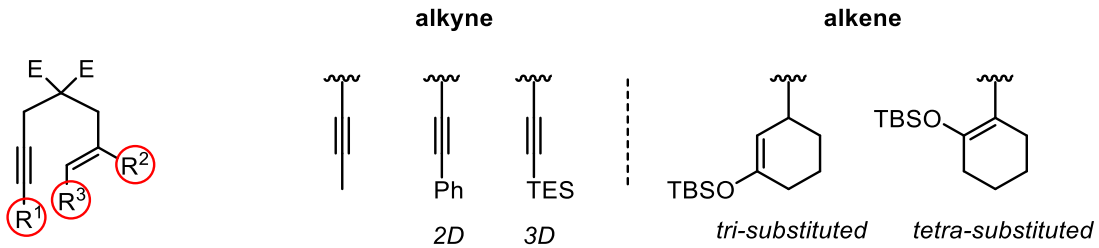
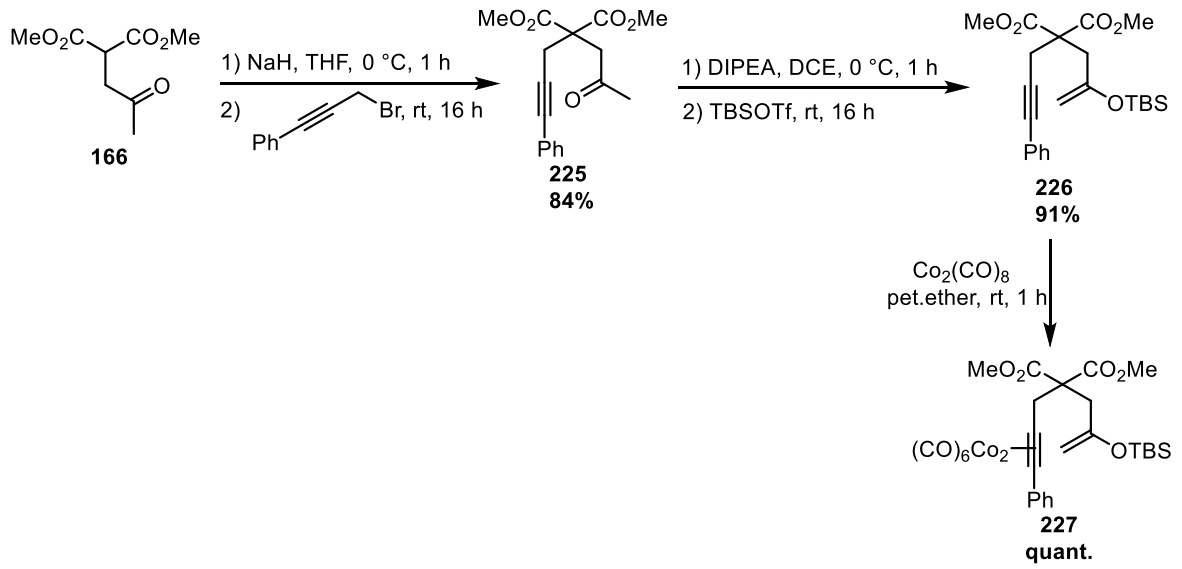


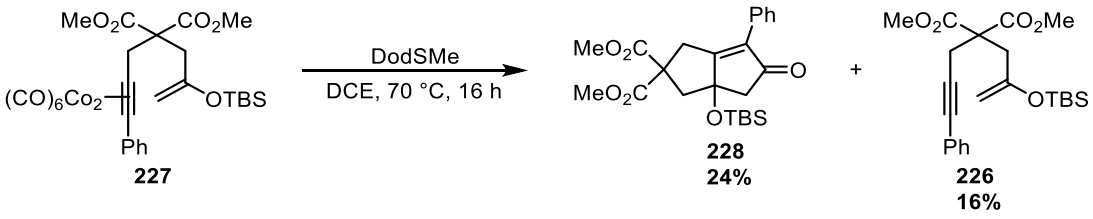
Figure 16

In relation to the above, phenyl substituted alkyne **227** was the first substrate to be targeted. This could be accessed from previously prepared ketone **166** (**Scheme 115**). The first alkylation gave an excellent **84%** yield of **225** from **166**. The next step was preparation of the silyl enol ether which proceeded in a high yield of **91%**, followed by complexation which gave the product in quantitative yield.



Scheme 115

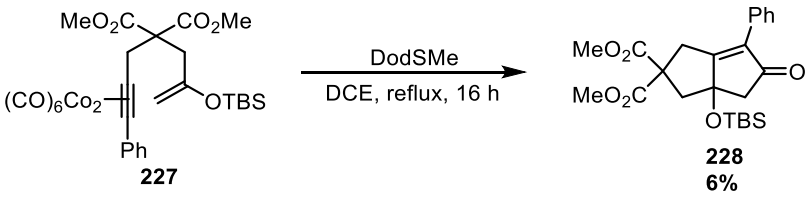
With the first of the bulkier substrates in hand, the Pauson-Khand reaction was attempted (**Scheme 116**) using our standard conditions. Pleasingly, the 2-dimensional bulk of the phenyl ring was tolerated, although, the product was isolated in a reduced **24%** yield. With respect to previous examples, it was expected that, after 16 h, the reaction would have reached completion, however, **13%** of starting material **227** was collected from the reaction mixture, alongside **12%** of the silyl enol ether **226**, which is re-formed from simple decomplexation of the starting material.



Scheme 116

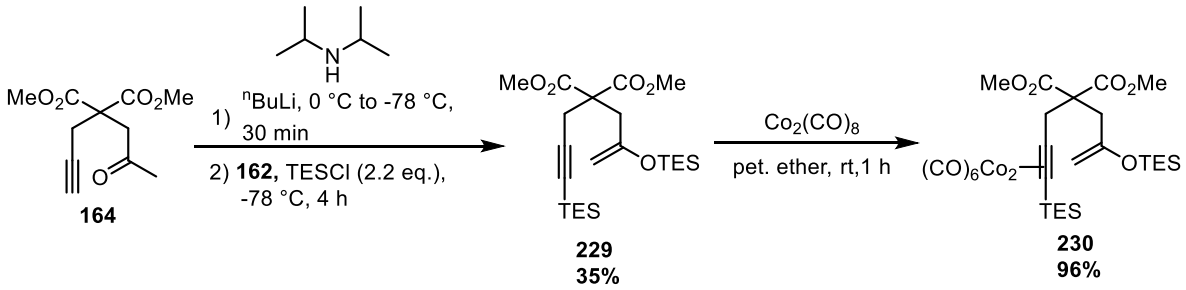
With this knowledge, it was theorised that the bulk considerably slows the reaction and that the low yield is a result of decomposition of the starting material which may be a competing reaction. Thus, if the rate could be increased then more productive reactions may take precedence. The more energy present in the system; the more feasible the Pauson-Khand reaction may be for the bulkier substrate and so the reaction was re-attempted with an increase of the temperature to reflux (**Scheme 117**). In this case, the reaction still produced cyclopentenone **228**, however, the yield was considerably lower than the previous example

at only **6%**. There was no evidence of starting material **227** or silyl enol ether **226** from this reaction suggesting these conditions increased the rate of decomposition rather than the rate of the Pauson-Khand reaction.



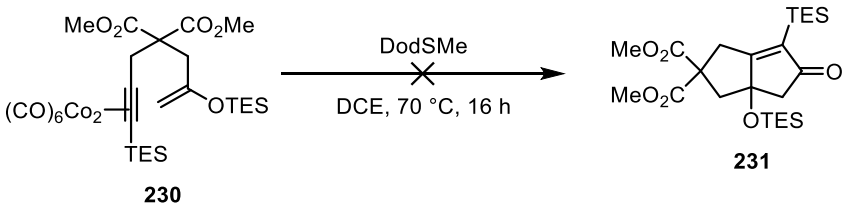
Scheme 117

To continue the investigation into the steric limitations of our developing methodology, the synthesis of silyl-substituted substrate **230** was carried out (**Scheme 118**). Starting with compound **164**, *bis*-silylation to provide compound **229** was carried out in **35%** yield, which was subsequently complexed as its dicobalt hexacarbonyl analogue in an efficient manner to give **230** in **96%** yield.



Scheme 118

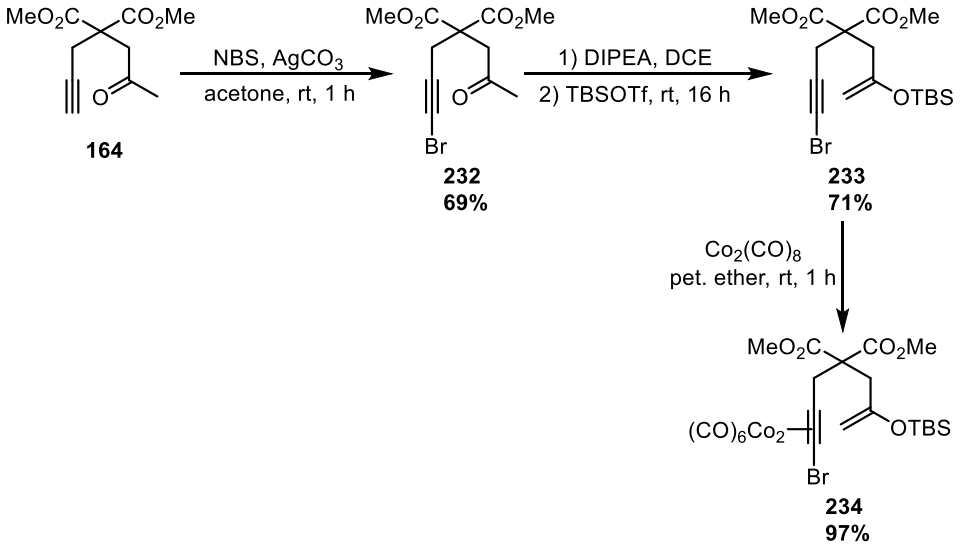
This compound was subjected to the optimal Pauson-Khand reaction conditions (**Scheme 119**). Unfortunately, no cyclopentenone product was obtained from this reaction. This result is not unexpected; when the effectiveness of dicobalt hexacarbonyl complexes **177** and **230**, featuring a methyl group and phenyl group respectively, is compared there is a significant reduction in yield as the bulk on the alkyne is increased. Concurrently, an equivalent decrease in efficiency was expected when moving to the even bulkier TES substituent.



Scheme 119

The failure of this substrate, and the low yield of the phenyl substituted compound, showed that substitution on the alkyne has a large effect on how well the cyclisation will proceed. Whilst a methyl group is tolerated as well as a proton, groups which are sterically larger than methyl result in a decreased effectiveness of the cyclisation.

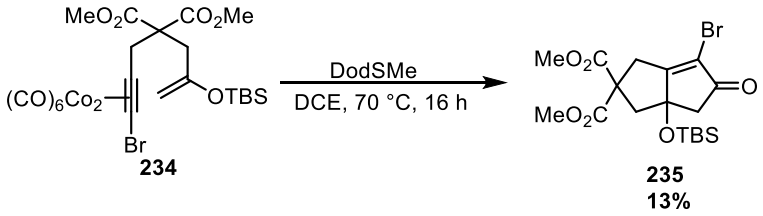
One further substrate was tested with this in mind. It was envisaged that a substrate with a halogen substituent on the alkyne would generate a useful product with a vinyl halide functionality that could be used for further reactions. The synthesis of this compound began with compound **164**, which was brominated directly using *N*-bromosuccinimide and silver carbonate to generate **232** in a good **69%** yield (**Scheme 120**). The silyl enol ether of this compound was prepared using the standard conditions and this worked well to give the product **233** in **71%** yield. Finally, complexation provided the dicobalt hexacarbonyl complex **234** in an excellent **97%** yield.



Scheme 120

Thus, with complex **234** in hand, the Pauson-Khand reaction could be attempted. Subjecting this complex to the standard conditions afforded the cyclopentenone product in a **13%** yield

(**Scheme 121**). It is suspected that there may be a considerable steric interference due to the size of the atomic radius of bromine (187 pm vs 70 pm for carbon). However, despite this low yield, this is a positive result and serves as proof of concept that utilising halogenated alkynes in the Pauson-Khand reaction is possible. This opens up the potential applications for the methodology further as it is now may be possible to append this bicyclic cyclopentenone motif to other molecules through various coupling or alkylation reactions using the vinyl bromide group.



Scheme 121

As shown with the above examples, substitution on the alkyne has a significant effect on the success of the Pauson-Khand reaction. A small substituent such as a methyl group is tolerated readily as shown in many examples, however, when larger groups are employed the yield of the reaction is negatively impacted. To further explore the tolerability of this methodology to bulky substituents which are adjacent to the alkyne rather than directly substituted, compounds **236** and **237**, were targeted (**Figure 17**); compound **236** features a large TBS ether substituent, while compound **237** features a much smaller methyoxymethylether (MOM) substituent. Both products represent interesting structures with an additional pendant oxygen atom present. Comparing the results from the Pauson-Khand reaction towards compounds **236** and **237** to the results of those substrates featuring substitution directly on the alkyne would provide insight into the sensitivity of the reaction to adjacent steric clashes.

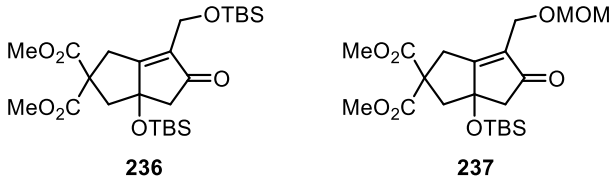
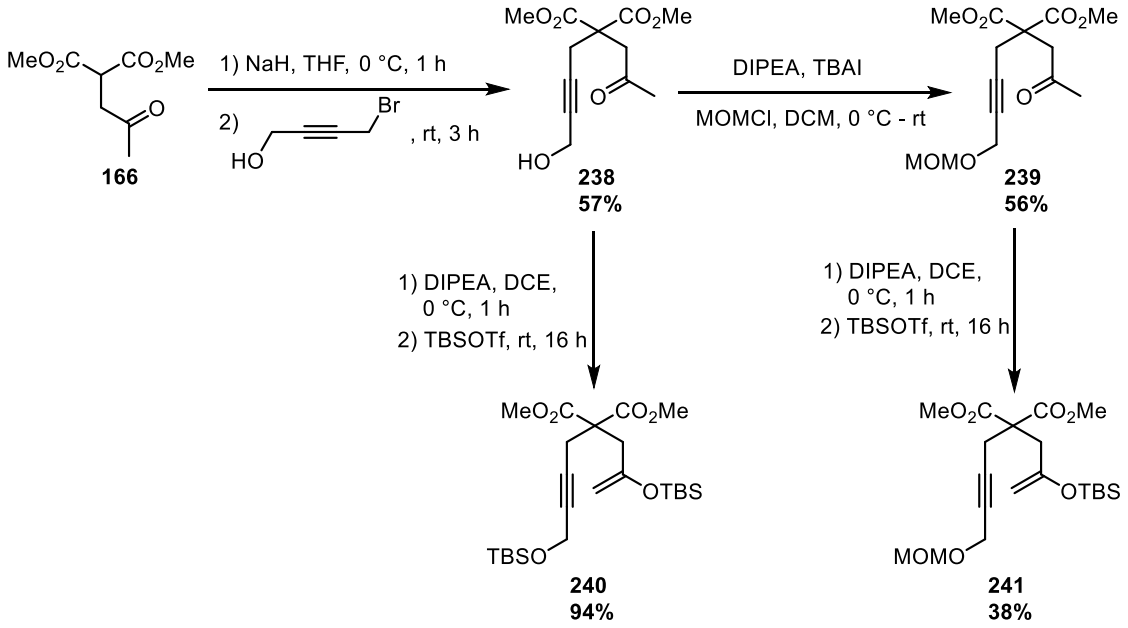


Figure 17

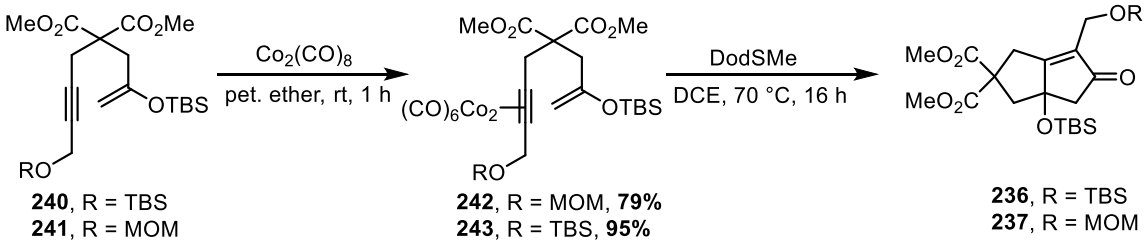
The synthesis of the newly targeted compounds began, again, with previously prepared intermediate **166**, derived from dimethyl malonate. **166** was alkylated using bromobutynol as

the electrophile and this delivered compound **238** in a good **57%** yield (**Scheme 122**). Reaction with MOMCl effectively protected the pendant alcohol functionality in a good yield of **56%** and, in turn, this was converted to the silyl enol ether derivative **241** in an uncharacteristically low yield of **38%**. Alternatively, the alcohol group present in **238** was protected as the silyl (TBS) ether, alongside the formation of the silyl enol ether to deliver desired compound **240** in an excellent **94%** yield.



Scheme 122

Both protected species were carried into the subsequent steps. The MOM protected species, compound **241**, formed the dicobalthexacarbonyl complex in **79%** (**Scheme 123**). The equivalent TBS protected species performed better in this reaction, affording the cobalt complex in **95%** yield. Complexes **242** and **243** were subsequently employed in the PKR and, to our delight, both compounds worked excellently (**Table 11**). MOM-protected compound **242** delivered the cyclopentenone in a pleasingly high **87%** on a small (0.2 mmol) scale. On a comparable scale, the TBS-protected compound fared similarly well affording **236** in **81%** yield, however, upon scaling up to almost 1 mmol, the product was obtained in slightly increased **88%** yield.



Scheme 123

Table 11

Entry	Scale (mmol of complex)	Yield (%)	Product
1	0.20	**87**	**237**
2	0.30	**81**	**236**
3	0.93	**88**	**236**

Pleasingly, the results above show that sterically-large substituents do not hinder the reaction if they are not directly attached to the alkyne. Indeed, the TBS-substituted substrate **243** performs as well as the MOM-substituted **242**. The efficient cyclisation of this substrate is a key finding for future work. The successful cyclisation toward this framework guided our research interests towards the natural product Xeromphalinone C (**Figure 18**). This natural product featured structural similarities to compound **244**, the globally-deprotected cyclopentenone. Building this natural product through our methodology would highlight its applicability within complex synthetic systems (*vide infra*).

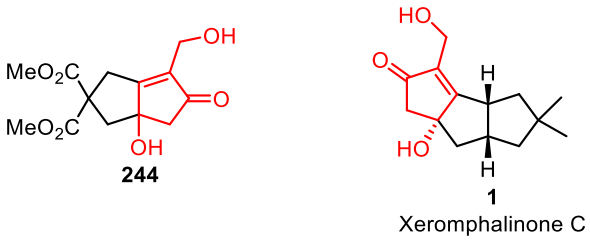
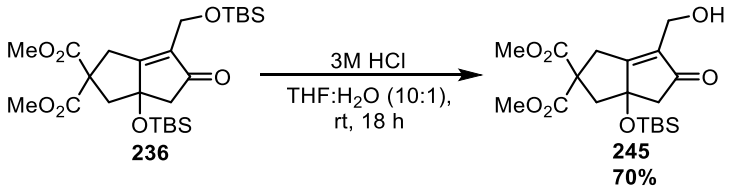


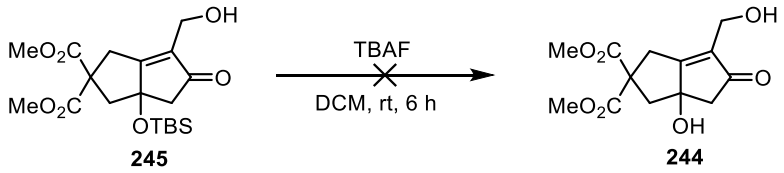
Figure 18

In order to reveal the free alcohol groups masked within **236**, the standard reaction with 3 M HCl was carried out (**Scheme 124**). This reaction was partially successful in that mono-deprotection of the primary silyl ether was achieved and product **245** was isolated in **70%** yield; it was somewhat disappointing that global deprotection was not realised.



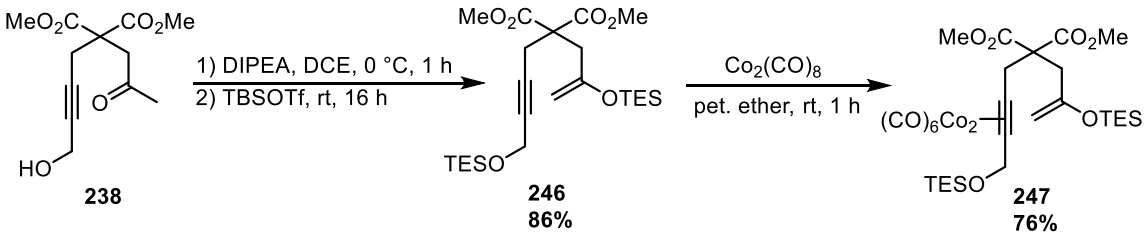
Scheme 124

Nevertheless, this was a positive result as one of the protecting groups was removed completely and this opened up the possibility of alternative conditions for the deprotection of the other centre. This was attempted using classical silyl ether deprotection conditions of *tetra*-butylammonium fluoride (TBAF), though this proved to be fruitless and only destroyed the starting material (**Scheme 125**).



Scheme 125

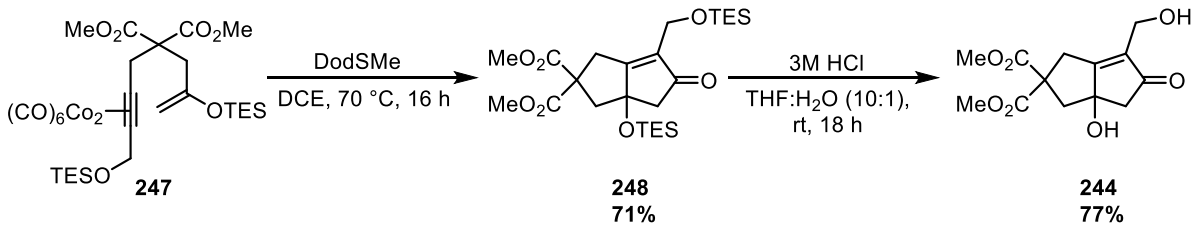
With the sensitivity of the substrate in mind, no further deprotection conditions were attempted on this compound and instead the idea of finding a protecting group which would be more acid-labile than the TBS group was conceived. As shown with many examples previously, the TES ethers perform admirably in the Pauson-Khand reaction and often are cleaved more readily at the end of the sequence. Therefore, substrate **246** was formed in one step from compound **238** in a similar fashion used previously with the TBS analogue **240**. An excellent **86%** yield of intermediate **246** was achieved and, subsequently, the cobalt complex was formed in a good yield of **76%** (**Scheme 126**).



Scheme 126

This compound was subjected to the Pauson-Khand reaction conditions and to our delight cyclised efficiently to afford the cyclopentenone **248** in **71%** (**Scheme 127**). Even more

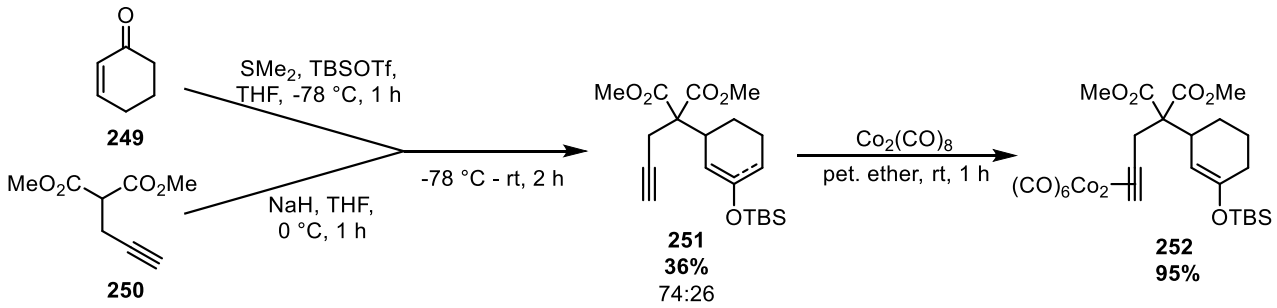
pleasingly, the silyl groups were removed from this compound effectively under mildly acidic conditions to afford the diol **244** in an excellent **77%** yield.



Scheme 127

1.3.8 Trisubstituted Silyl Enol Ethers

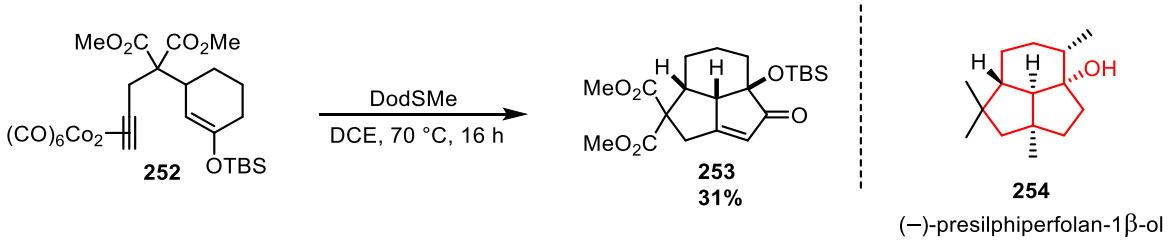
To this point, only disubstituted alkenes had been employed in the reaction. It is known that trisubstituted alkenes typically require high temperatures and long reaction times to perform in the Pauson-Khand reaction.[54] A substrate in which the alkene reactive partner is incorporated in a ring has the benefit of being synthetically tractable while aiding our investigation into steric limitations. To prepare a compound of this type, silyl enol ether **251** was prepared *via* alkylation of **250** in the presence of cyclohexanone, dimethyl sulfide and TBSOTf (**Scheme 128**). The active electrophile is formed *in situ* by conjugate addition of the dimethyl sulfide to the cyclohexanone which is thus trapped by the TBSOTf. This forms a species with a positively charged dimethyl sulfide group which can act as an effective leaving group for the addition of the nucleophile. It is in this way that compound **251** is formed with a favourable ratio of desired isomer, featuring the double bond as shown in **Scheme 128**, to undesired. Subsequently, the dicobalt hexacarbonyl complex **252** was obtained in a high yield of **95%**.



Scheme 128

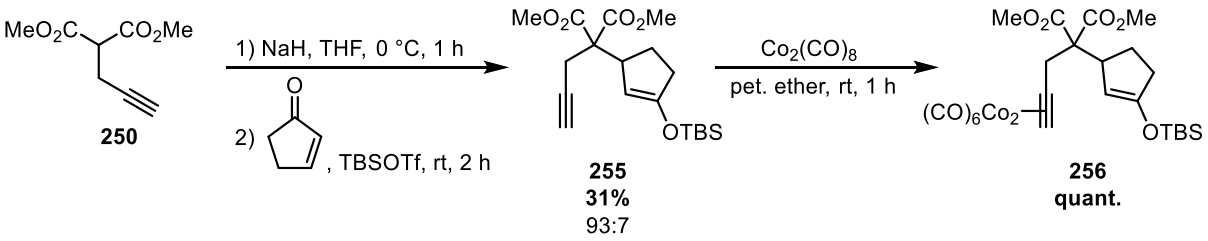
Following this, **252** was employed in the Pauson-Khand reaction and, pleasingly, the tricyclic product was delivered in a good yield of **31%**, and as a single diastereomer (**Scheme 129**). In

this example, there is impressive complexity built up in just one step, producing three contiguous chiral centres and a complex bowl-shaped tricyclic ring system. This is a very positive result for the methodology as this trisubstituted alkene performed admirably and did not require excessive reaction times or temperatures. In addition, this tricyclic-fused system is structurally similar to the tricyclic core of natural product (–)-presilphiperfolan-1b-ol.[166]



Scheme 129

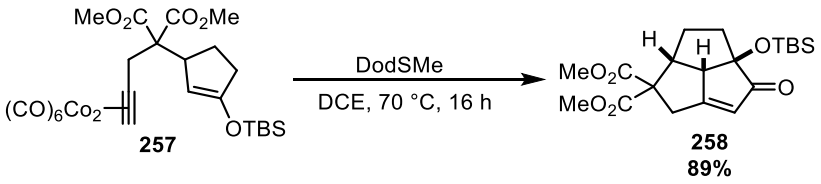
Thus, with the success of the 6-membered cyclic silyl enol ether there was a desire to attempt the 5-membered analogue. This would deliver a similarly complex 5,5,5-fused ring system featuring, again, three challenging and contiguous stereocentres. The synthesis of compound **255** was conducted in a similar fashion to the previous example. It began with compound **250**, as before, but with a direct conjugate addition to cyclopentenone and *in situ* trapping with TBSOTf (**Scheme 130**). This delivered the silyl enol ether in a good **31%** yield with an excellent ratio of isomers, 93:7 of the desired isomer. The dicobalt hexacarbonyl complex **256** was subsequently prepared in an excellent quantitative yield.



Scheme 130

With complex **256** in hand, the Pauson-Khand reaction could be conducted (**Scheme 131**). Pleasingly, when this complex was subjected to the standard reaction conditions the product could be isolated in an excellent **89%** yield, again, as a single diastereomer. The reasoning proposed for the difference in performance between the two superficially similar compounds **252** and **257** relates to the difference in strain between the 5-membered cyclic silyl enol ether

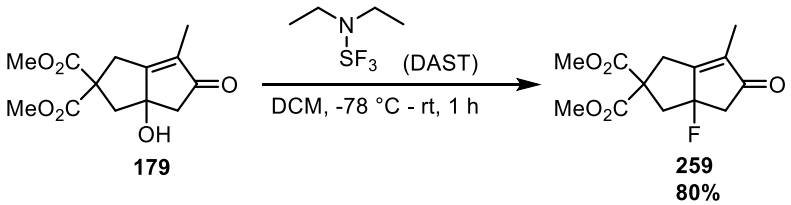
and the 6-membered. We believe that the larger strain for the 5-membered ring thus makes cyclisation more favourable to release the strain.[45]



Scheme 131

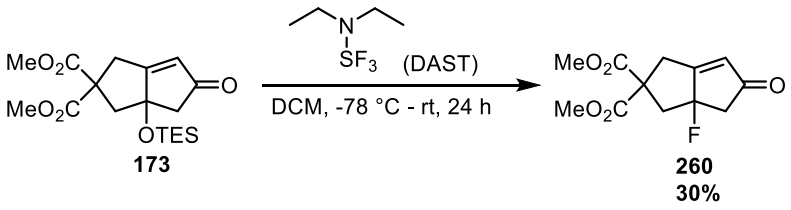
1.3.9 Derivatisation of Cyclopentenones

Buoyed by the overall success of the project, our focus was turned to attempting to derivatise the products in order to elevate the impact of the methodology. Clearly, the objective of synthesising oxygenated cyclopentenones was met but it is evident from the literature that fluorinated cyclopentenones are compounds of interest.[161,162] It is known that hydroxyl groups can be converted into fluorines by using electrophilic fluorination reagents such as diethylaminosulfur trifluoride (DAST).[167] It was proposed that our oxygenated cyclopentenone products may be converted to their fluorinated analogues in one step. To this end, compound **179** was reacted with DAST and, gratifyingly, this readily converted to the fluorinated product with an **80%** isolated yield after just one hour (**Scheme 132**).



Scheme 132

To push this further, it was theorised that the fluorinated products may be accessible directly from the silyl ether cyclopentenones, the direct products of the Pauson-Khand reaction. It is possible that the electrophilic fluorinating reagent could deprotect the silyl ether revealing the hydroxyl group *in situ* and thus react further to produce the fluorinated product. So, to investigate this possibility, compound **173** was reacted under the same conditions as in **Scheme 132** (shown below in **Scheme 133**), however, 24 h was required for complete conversion of **173**. This afforded the fluorinated product in a moderate yield of **30%** though this represented **81%** based on recovered starting material.



Scheme 133

It must be highlighted that this reaction was not optimised further and it may be possible that increasing the equivalents of the electrophilic fluorinating agent would provide access to greater yields of product. This is further evidence of the considerable versatility of the methodology and highlights that the products can be used to deliver varied, decorated bicyclic scaffolds.

1.4 Conclusions

In a continuation of the work within our laboratories to develop novel and flexible methodologies for the Pauson-Khand reaction, we successfully employed silyl enol ethers as alkene equivalents for this transformation. To determine the substrate applicability of this developing methodology, we established substrate scope. The first substrates to be explored were the 5,5-bicyclic molecules shown in **Figure 19**. The major structural variations which were explored were in the alkyl chain which linked the two reacting centres. The diester motif was used to good effect with both TBS and TES ethers delivering the cyclopentenones in **88%** and **77%**, respectively. This link was expanded to a tosyl-protected nitrogen atom which was similarly used to good effect with TBS and TES ethers. Internal alkynes were explored due to their tendency to cyclise less efficiently than their terminal counterparts. With four examples we have shown that methyl groups are tolerated with considerable ease by the methodology for the diester and nitrogen-linked examples. An oxygen linked example was also employed here and this cyclised well to give the product in **59%** yield.

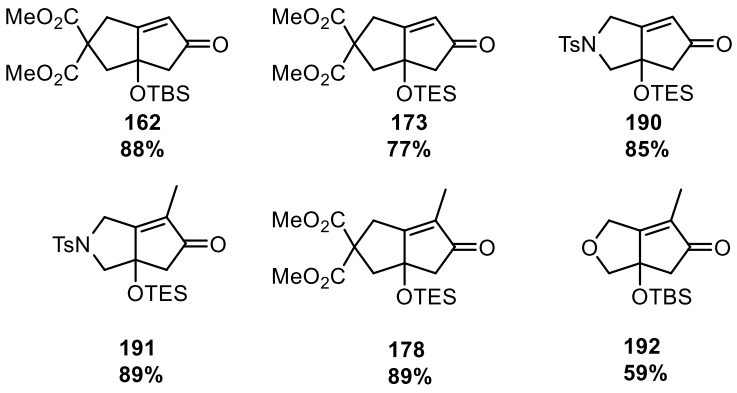


Figure 19

In addition to silyl enol ethers derived from ketones; we also cyclised four examples of silyl enol ethers derived from aldehydes (**Figure 20**). These substrates delivered cyclopentenones featuring α-substitution as a mixture of diastereomers. The common diester link was used for two examples which compared the TES and TBS ethers; both of which cyclised excellently. Additionally, a nitrogen linked example was shown to cyclise effectively to give **66%** of the

cyclopentenone product. Furthermore, a 6,5-fused example was synthesised through this methodology.

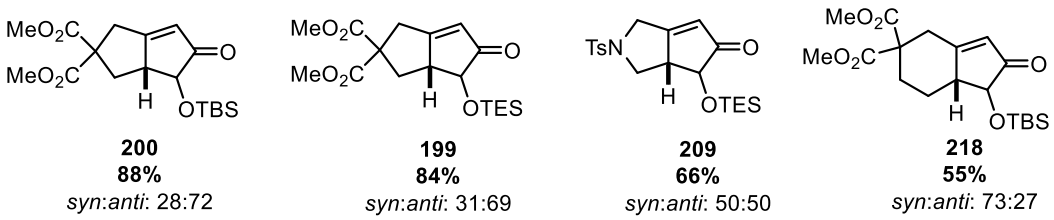


Figure 20

We were determined to find out the steric limitations at the alkyne by cyclising three substrates with large substituents in this position (**Figure 21**). The phenyl substituted example **228** cyclised and the product was isolated in a moderate yield of **24%**. This was a considerable decrease from the equivalent terminal alkyne substrate which cyclised efficiently to give the cyclopentenone in **88%** and the methylated alkyne substrate which delivered the cyclopentenone in **93%**. Subsequently when the bulk on the alkyne was increased to a triethylsilyl substituent, this proved to be too large for the cyclisation to proceed. However, a bromine-substituted alkyne substrate did cyclise to give **13**% of the desired product. In addition, three substrates which have similar structural features to natural product Xeromphalinone C were synthesised successfully.

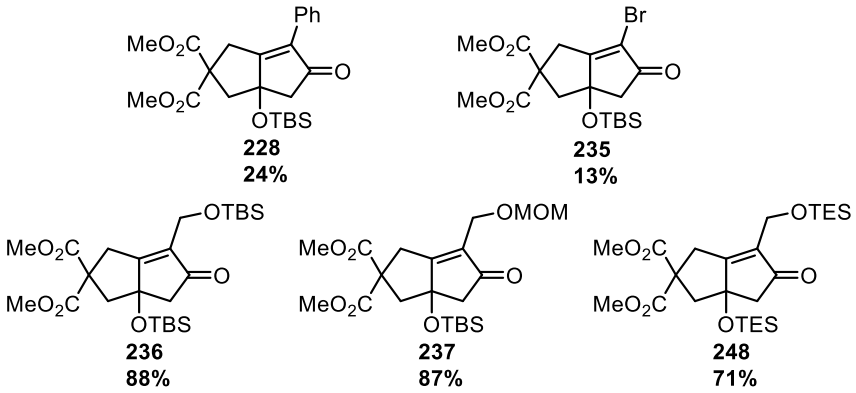


Figure 21

Also, the tolerance for further substitution on the alkene was investigated. A trisubstituted alkene was utilised to give tricyclic product **253** in **31%** yield as a single diastereomer. This

was followed by cyclisation of another trisubstituted alkene to give tricyclic product **258** in an impressive **89%** yield.

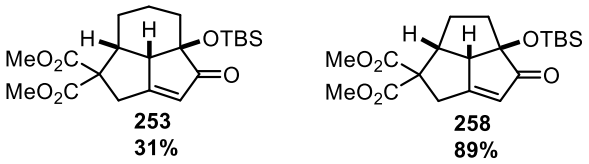


Figure 22

To showcase the versatility of the methodology, two oxygenated cyclopentenones were converted to fluorinated cyclopentenones (**Figure 23**). One compound was converted from the free alcohol to the fluorinated compound in an excellent **80%** while the other was transformed directly from the silyl ether in a good **30%** yield. This highlights the utility of the compounds as potential intermediates in a synthetic route.

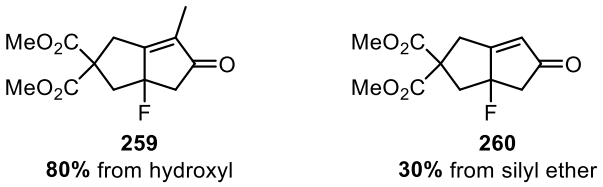


Figure 23

1.5 Experimental

1.5.1 General Experimental Considerations

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.[168]

Dry DCM, Et_2O, THF, and toluene 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.

Petroleum ether refers to petroleum ether in the boiling point (b.p.) range 40 - 60 °C unless otherwise stated.

DCE refers to 1,2,-dichloroethane unless otherwise stated, which was purified by distillation from calcium hydride and stored over 4 Å molecular sieves.

Instrumentation and data

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. Plates were analysed using a Mineralight UVGL-25, lamp or developed using a vanillin 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 $^{13}C\{1H\}$ 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 $^{3}J_{H\text{-}H}$ 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.

1.5.2 General Procedures

General Procedure A:

The dicobalthexacarbonyl complex and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The additive was added and the mixture heated to the set temperature for the allotted time. At this point, solvent was removed *in vacuo* to provide the crude material as a black gum. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure A****, data are reported as:* (a) amount of dicobalthexacarbonyl complex; (b) volume of solvent; (c) additive; (d) reaction temperature; (e) reaction time; (f) isolated yield; and (g) product appearance. Individual characterisation data for each cyclopentenone product is provided.

General Procedure B:

The carbonyl-containing substrate and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and DIPEA was added dropwise. The mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and the silylating agent was added dropwise. The reaction was stirred for 16 h at room temperature then quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase washed with a further quantity of Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure B****, data are reported as:* (a) carbonyl compound; (b) solvent volume; (c) DIPEA; (d) silylating agent; (e) isolated yield; and (f) compound appearance. Individual characterisation data for each silyl enol ether compound is provided.

General Procedure C:

The silyl enol ether substrate and pet. ether were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ was added and the mixture was stirred at room temperature for 1 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to provide the crude product as a red oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5) and concentrated *in vacuo* to provide the dicobalthexacarbonyl complex.

For experiments which were carried out according to ***General Procedure C****, data are reported as:* (a) silyl enol ether; (b) solvent volume; (c) $CO_2(CO)_8$; (d) isolated yield; and (e) product appearance. Individual characterisation data for each dicobalt hexacarbonyl compound is provided.

General Procedure D:

The cyclopentenone substrate and THF:H_2O (10:1) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. 3 M aqueous HCl was added to this solution and reaction mixture was stirred at the set temperature for the allotted time. At this point, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase washed with a further quantity of Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 50:50 – 30:70) and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure D****, data are reported as:* (a) amount of cyclopentenone substrate; (b) volume of THF:H_2O (10:1) mixture; (c) 3 M aqueous HCl solution; (d) reaction temperature; (e) reaction time; (f) isolated yield; and (g) product appearance. Individual characterisation data for each product is provided.

General Procedure E:

Tert-butyl tosylcarbamate and distilled DMF were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to 0 °C and NaH (60% dispersion in mineral oil) was added and the resulting mixture was stirred for 1 h. At this point, the reaction mixture was warmed to room temperature and chloroacetone was added rapidly. The

reaction mixture was stirred for a subsequent duration at room temperature prior to being quenched by the addition of brine. Following this, Et_2O was added to create a biphasic mixture, which was separated, and the aqueous layer was washed with a further quantity of Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 50:50) and concentrated *in vacuo* to provide *tert*-butyl (2-oxopropyl)(tosyl)carbamate as a colourless oil.

For experiments which were carried out according to ***General Procedure E****, data are reported as:* (a) amount of *tert*-butyltosylcarbamate; (b) volume of distilled DMF; (c) amount of NaH; (d) amount of chloroacetone; (e) time; (f) yield of *tert*-butyl (2-oxopropyl)(tosyl)carbamate; and (g) product appearance.

General Procedure F:

Substrate and pet. ether were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ was added and the mixture stirred at room temperature for 1 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to provide the crude product as a red oil. The crude material was dissolved in DCE and added to a flame-dried, round-bottom flask equipped with a stirrer bar. The additive was added and the mixture was heated to the set temperature for the allotted time. At this point, solvent was removed *in vacuo* to provide the crude material as a black gum. The crude material was purified by flash column chromatography and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure F****, data are reported as:* (a) amount of substrate; (b) volume of pet. ether; (c) amount of $Co_2(CO)_8$; (d) volume of DCE; (f) amount of DodSMe; (g) reaction temperature; (h) reaction time; (i) yield of product; and (j) product description

General Procedure G:

2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (*syn*:*anti*, 90:10) was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in DCE. DodSMe and $Co_2(CO)_8$ were added to the solution and the resulting mixture

was heated to 70 °C for 5 h. The reaction was cooled to room temperature and solvent was removed *in vacuo* to provide the crude material as a black gum. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one as a pale yellow oil.

For experiments which were carried out according to ***General Procedure G****, data are reported as:* (a) amount of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one; (b) volume of DCE; (c) amount of DodSMe; (d) amount of $Co_2(CO)_8$; (e) yield of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one; and (f) *syn*:*anti* ratio

General Procedure H:

NaH (60% dispersion in mineral oil) and the appropriate solvent were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethylmalonate was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, 2-(3-chloropropyl)-1,3-dioxolane was added dropwise followed by the additive and the reaction mixture heated to reflux. The reaction mixture was stirred for 24 h and then quenched by the addition of brine. Following this, EtOAc was added to create a biphasic mixture, which was separated and the aqueous layer was washed with a further quantity of EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 30:70) and concentrated *in vacuo* to provide dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate as a colourless oil.

For experiments which were carried out according to ***General Procedure H****, data are reported as:* (a) amount of NaH; (b) volume of solvent; (c) amount of dimethyl malonate; (d) amount of 2-(3-chloropropyl)-1,3-dioxolane; (e) amount of additive; (f) yield of dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate; and (g) product description.

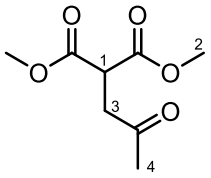
1.5.3 General Computational Details

A series of DFT techniques were employed to evaluate the free energies of relevant cobalt hexacarbonyl complexes and other distinct intermediates and transitions states through the mechanism of the Pauson-Khand reaction. All DFT calculations were performed with the Gaussian09 quantum chemistry package[169] employing the hybrid functional of Lee, Yang and

Parr with Becke's parameter exchange[170] – b3LYP – with associated 6-31G(d) basis set.[171] Structures corresponding to intermediates in all potential energy surfaces described herein were confirmed to be minima through vibrational frequency calculations and depicted no imaginary frequencies. Calculations were performed using a polarisable continuum model for THF or 1,2-DCE where appropriate.[172] A superfine integration grid and Grimme's original D3 damping function were applied to all calculations.[173] All relevant output files are provided in Appendix page 6 and page 17.

1.5.4 Experimental Procedures and Compound Analyses

Preparation of dimethyl 2-(2-oxopropyl)malonate.[174]



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Scheme 75

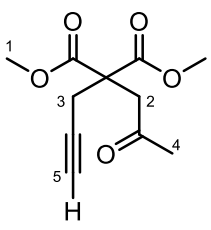
NaH (1.17 g, 31.9 mmol) and distilled DMF (30 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethylmalonate (3.05 mL, 26.6 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and chloroacetone (2.55 mL, 31.9 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then quenched by the addition of distilled water (30 mL). Following this, Et_2O (30 mL) was added to create a biphasic mixture, which was separated and the aqueous layer washed with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide dimethyl 2-(2-oxopropyl)malonate (2.52 g, 13.37 mmol, **50%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.91 (1H, t, *J* = 7.1 Hz, H_1), 3.77 (6H, s, H_2), 3.09 (2H, d, *J* = 7.2 Hz, H_3), 2.22 (3H, s, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.3, 168.7, 52.2, 46.0, 41.5, 29.1 ppm.

IR (ν_{max}/cm^{-1}): 2957, 1732, 1716, 1156.

Preparation of dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate.[158]



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Scheme 75

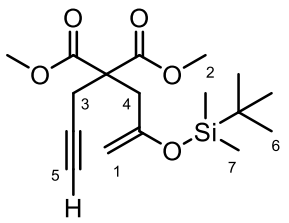
NaH (95% dispersion in mineral oil, 0.16 g, 6.12 mmol) and distilled DMF (20 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(2-oxopropyl)malonate (1.05 g , 5.57 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and propargyl bromide (0.75 mL, 6.68 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then quenched by the addition of 2 M HCl (20 mL). Following this, Et_2O (20 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as an orange oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (1.17 g, 5.16 mmol, **93%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.72 (6H, s, H_1), 3.33 (2H, s, H_2), 2.98 (2H, d, ^4J = 2.7 Hz, H_3), 2.17 (3H, s, H_4), 2.02 (1H, t, J = 2.7, H_5) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.9, 169.1, 79.2, 71.2, 53.8, 52.6, 44.9, 29.7, 22.8 ppm.

IR (ν_{max}/cm^{-1}): 3278, 2954, 1738, 1718, 1201.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate.[164]



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Scheme 75

Prepared according to **General Procedure B**:

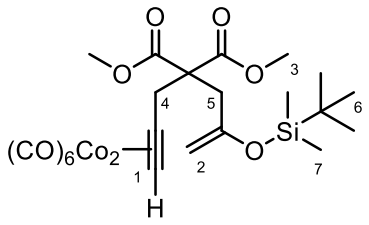
(a) Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.57 g, 2.52 mmol); (b) DCE (10 mL); (c) DIPEA (0.49 mL, 2.78 mmol); (d) TBSOTf (0.64 mL, 2.78 mmol); (e) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (0.62 g, 1.81 mmol, **72%**); and (f) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.18 (1H, d, ^2J = 1.0 Hz, H_1), 4.17 (1H, d, ^2J = 1.0 Hz, H_1), 3.75 (6 H, s, H_2), 2.95 (2H, d, ^4J = 2.7 Hz, H_3), 2.86 (2H, s, H_4), 2.01 (1H, t, ^4J = 2.7 Hz, H_5), 0.93 (9H, s, H_6), 0.17 (6H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 154.4, 93.8, 79.2, 70.9, 55.9, 52.3, 38.5, 25.4, 22.2, 17.8, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 3289, 2954, 1742, 1632, 1182.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.[164]



165

Scheme 75

Prepared according to **General Procedure C**:

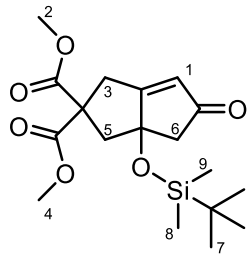
(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (1.98 g, 5.80 mmol); (b) pet. ether (58 mL); (c) $Co_2(CO)_8$ (2.08 g, 6.09 mmol); (d) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (3.45 g, 0.94 mmol, **95%**); and (e) red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.97 (1H, s, H_1), 4.18 (1H, d, ^2J = 1.3 Hz, H_2), 4.15 (1H, d, ^2J = 1.3 Hz, H_2), 3.76 (6H, s, H_3), 3.73 (2H, d, ^4J = 0.8 Hz, H_4), 2.86 (2H, s, H_5), 0.94 (9H, s, H_6), 0.19 (6H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.5, 170.1, 154.4, 93.5, 87.9, 73.3, 57.1, 52.3, 40.1, 37.6, 25.5, 17.9, -5.0 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2931, 2856, 2092, 2050, 2000, 1738, 1628.

Preparation of dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.[164]



162

Scheme 76

Prepared according to **General Procedure A**:

Table 5, entry 1: (a) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.96 g, 1.54 mmol); (b) DCE (15 mL); (c) $CyNH_2$ (0.62 mL, 5.39 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.01 g, 0.03 mmol, **2%**); and (g) white solid. To note, starting material (0.048 g, 0.08 mmol, 5%) and decomplexed starting material (0.121 g, 0.35 mmol, 23%) were also recovered.

Table 5, entry 2: (a) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.97 g, 1.55 mmol); (b) DCE (15 mL); (c) TMTU (0.97 g, 7.36 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.12 g, 0.32 mmol, **21%**); and (g) white solid. To note, decomplexed starting material (0.152 g, 0.45 mmol, 29%) was also recovered.

Table 5, entry 3: (a) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.10 g, 0.29 mmol); (b) DCE (15 mL); (c) no additive; (d) 70 °C; (e) 16 h; (f) dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.019 g, 0.05 mmol, **18%**); and (g) white solid.

Table 5, entry 4: (a) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.48 g, 0.76 mmol); (b) DCE (10 mL); (c) DodSMe (0.96 mL, 3.60 mmol); (d) 70 °C; (e) 2 h; (f) dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.23 g, 0.62 mmol, **81%**); and (g) white solid.

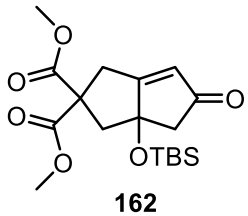
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.93 (1H, d, ^4J = 1.5 Hz, H_1), 3.80 (3H, s, $H_{3/4}$), 3.79 (1H, dd, ^2J = 18.0 Hz, ^4J = 2.0 Hz, H_2), 3.76 (3H, s, $H_{3/4}$), 3.07 (1H, d, ^2J = 18.0 Hz, H_2), 2.99 (1H, d, ^2J = 14.0 Hz, H_5), 2.62 (1H, d, ^2J = 18.2 Hz, H_6), 2.52 (1H, d, ^2J = 18.2 Hz, H_6), 2.32 (1H, d, ^2J = 14.0 Hz, H_5), 0.83 (9H, s, H_7), 0.05 (3H, s, $H_{8/9}$), 0.02 (3H, s, $H_{8/9}$) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.6, 181.8, 171.5, 170.4, 125.5, 85.0, 60.0, 52.8, 47.6, 46.4, 33.6, 25.0, 17.4, -3.6, -4.0 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2931, 2856, 1722, 1650, 1256, 1062.

Melting point: 78 – 80 °C.

Preparation of dimethyl 3*a*-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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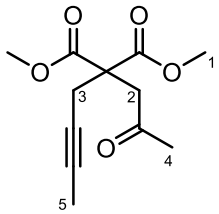
Scheme 77

Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (0.058 g, 0.170 mmol) and distilled DCE (1.7 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ (0.059 g, 0.172 mmol) was added and the solution was stirred for 1 h at room temperature. After this time, DodSMe (0.21 ml, 0.81 mmol) was added and the mixture was heated to the 70 °C for 16 h. At this point, the reaction mixture was filtered through celite and the solvent was removed *in vacuo* to provide the crude material. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide dimethyl 3-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate as a white solid (0.058 g, 0.157 mmol, **93%**).

Characterisation data for this compound found on page 116.

Preparation of dimethyl 2-(but-2-yn-1-yl)-2-(2-oxopropyl)malonate.[175]



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Scheme 78

NaH (60% dispersion in mineral oil) (0.29 g, 7.34 mmol) and distilled DMF (15 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(2-oxopropyl)malonate (1.26 g , 6.67 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and 1-bromobut-2-yne (0.7 mL, 8.00 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then quenched by the addition of 2 M HCl (20 mL). Following this, Et_2O (20 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as an orange oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide dimethyl 2-(but-2-yn-1-yl)-2-(2-oxopropyl)malonate (1.05 g, 4.35 mmol, **65%**) as a white solid.

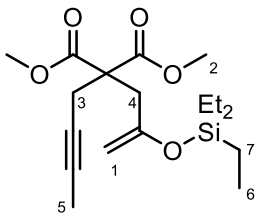
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.74 (6H, s, H_1), 3.34 (2H, s, H_2), 2.94 (2H, q, ^5J = 2.6 Hz, H_3), 2.20 (3H, s, H_4), 1.77 (3H, t, ^5J = 2.6 Hz, H_5) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.9, 169.4, 78.7, 73.1, 54.3, 52.6, 45.2, 29.8, 23.3, 3.0 ppm.

IR (ν_{max}/cm^{-1}): 3278, 2954, 1738, 1718, 1201.

Melting point: 67 - 69 °C.

Preparation of dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate.



176

Scheme 78

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(but-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.82 g, 3.40 mmol); (b) DCE (10 mL); (c) DIPEA (0.65 mL, 3.74 mmol); (d) TESOTf (0.65 mL, 3.74 mmol); (e) dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate (0.94 g, 2.65 mmol, **78%**); and (f) colourless oil.

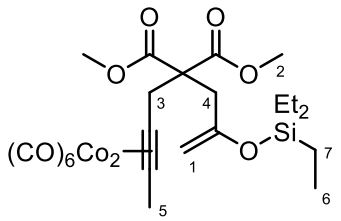
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.16 (2H, d, ^{2}J = 0.9 Hz, H_1), 4.14 (2H, d, ^{2}J = 0.9 Hz, H_1), 3.73 (6H, s, H_2), 2.86 (2H, q, ^{5}J = 2.5 Hz, H_3), 2.86 (2H, s, H_4), 1.77 (3H, t, ^{5}J = 2.5 Hz, H_5), 0.99 (9H, t, J = 7.9 Hz, H_6), 0.70 (6H, q, J = 7.9 Hz, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 154.3, 92.3, 78.1, 73.5, 55.7, 52.1, 38.7, 22.3, 6.1, 4.1, 3.0 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2916, 2879, 1742, 1629, 1182.

HRMS (ESI) m/z: $[M+H]^+$ Calc. for $C_{18}H_{31}O_5Si$: 355.1935; **found** 355.1936.

Preparation of dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate dicobalthexacarbonyl complex.



177

Scheme 79

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate (0.87 g, 2.46 mmol); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.93 g, 2.71 mmol); (d) dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate dicobalthexacarbonyl complex (1.33 g, 2.08 mmol, **84%**); (e) as a red oil.

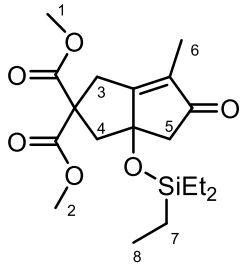
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.16 (1H, d, ^2J = 1.5 Hz, H_1), 4.13 (1H, d, ^2J = 1.5 Hz, H_1), 3.77 (6H, s, H_2), 3.75 (2H, s, H_3), 2.88 (2H, s, H_4), 2.71 (3H, s, H_5), 0.99 (9H, t, J = 7.9 Hz, H_6), 0.71 (6H, q, J = 8.0 Hz, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.4, 170.1, 154.1, 94.1, 92.1, 90.2, 56.7, 52.0, 40.0, 38.3, 21.5, 6.1, 4.1 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2877, 2087, 2043, 1998, 1738, 1626, 1202.

HRMS (NSI) m/z: [M+H]$^+$ Calc. for $C_{24}H_{31}Co_2O_{11}Si$: 641.0294; **found**: 641.0281.

Preparation of dimethyl 6-methyl-5-oxo-3*a*-((triethylsilyl)oxy)-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 79

Prepared according to **General Procedure A**:

(a) Dimethyl 2-(but-2-yn-1-yl)-2-(2-((triethylsilyl)oxy)allyl)malonate dicobalthexacarbonyl complex (1.33 g, 2.08 mmol); (b) DCE (20 mL); (c) DodSMe (2.61 mL, 9.88 mmol); (d) 70 °C; (e) 20 h; (f) dimethyl 6-methyl-5-oxo-3*a*-((triethylsilyl)oxy)-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.69 g, 1.81 mmol, **87%**); and (g) pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.76 (3H, s, $H_{1/2}$), 3.71 (3H, s, $H_{1/2}$), 3.69 (1H, dd, ^2J = 18.2 Hz, ^4J = 1.7 Hz, H_3), 2.97 (1H, d, ^2J = 13.4 Hz, H_4), 2.94 (1H, d, ^2J = 18.1 Hz, H_3), 2.58 (1H, d, ^2J = 18.1

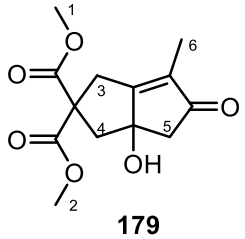
Hz, H_5), 2.45 (1H, d, ^2J = 18.2 Hz, H_5), 2.13 (1H, d, ^2J = 13.8 Hz, H_4), 1.69 (3H, d, ^5J = 1.32 Hz, H_6), 0.84 (9H, t, J = 7.9 Hz, H_7), 0.47 (6H, q, J = 7.8 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.5, 174.9, 171.6, 170.6, 132.9, 83.0, 60.2, 52.7, 52.4, 46.6, 46.5, 32.4, 7.9, 6.2, 5.4 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2877, 1738, 1718, 1683, 1255, 1074.

HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{19}H_{31}O_6Si$: 383.1884; **found**: 383.1886.

Preparation of dimethyl 3*a*-hydroxy-6-methyl-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 80

Prepared according to **General Procedure D**:

(a) Dimethyl 6-methyl-5-oxo-3*a*-((triethylsilyl)oxy)-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.61 g, 1.58 mmol); (b) THF:H_2O (10:1) (8 mL); (c) 3 M aqueous HCl (0.17 mL); (d) room temperature; (e) 18 h; (f) dimethyl 3*a*-hydroxy-6-methyl-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.37 g, 1.39 mmol, **89%**); and (g) colourless oil.

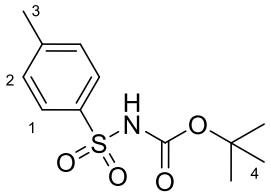
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.82 (3H, s, $H_{1/2}$), 3.76 (3H, s, $H_{1/2}$), 3.51 (1H, dd, ^2J = 18.4 Hz, ^4J = 1.6 Hz, H_3), 3.19 (1H, d, ^2J = 18.5 Hz, H_3), 2.97 (1H, d, ^2J = 14.2 Hz, H_4), 2.85 (1H, s, OH), 2.60 (1H, d, ^2J = 18.0 Hz, H_5), 2.51 (1H, d, ^2J = 18.0 Hz, H_5), 2.17 (1H, d, ^2J = 14.2 Hz, H_4), 1.72 (3H, d, ^5J = 1.0 Hz, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.8, 173.5, 172.5, 171.0, 133.6, 81.6, 60.1, 53.0, 52.8, 47.3, 44.6, 32.3, 8.0 ppm.

IR (ν_{max}/cm^{-1}): 3453, 2955, 1731, 1714, 1673, 1253, 1069.

HRMS (NSI) m/z: $[M+NH_4]^+$ Calc. for $C_{12}H_{18}O_6N$: 272.1129; **found** 272.1130.

Preparation of *tert*-butyl tosylcarbamate.[176]



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Scheme 82

p-Toluenesulfonamide (5 g, 29.2 mmol), Et_3N (4.5 mL, 32.1 mmol), DMAP (0.36 g, 2.92 mmol), and distilled DCM (25mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. Di-*tert*-butyl dicarbonate (7.5 mL, 32.1 mmol) was added to this solution and the resulting mixture was stirred at room temperature for 14 h. After this time, the mixture was concentrated *in vacuo* and the residue was dissolved in EtOAc (50 mL). 1 M HCl (50 mL) was added to create a biphasic mixture, which was separated and the organic phase was washed with distilled water (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a colourless oil. The crude was dissolved in a small amount of Et_2O and triturated with pet. ether to give *tert*-butyl tosylcarbamate as a white crystalline solid (7.35 g, 27.08 mmol, **93%**).

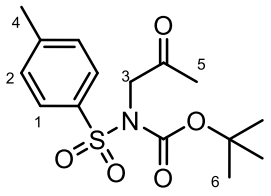
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.92 – 7.88 (2H, m, H_1), 7.36 – 7.31 (2H, m, H_2), 7.12 (1H, s, NH), 2.48 (3H, s, H_3), 1.41 (9H, s, H_4) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 148.6, 144.2, 135.5, 129.0, 127.7, 83.6, 27.4, 21.2.

IR (ν_{max}/cm^{-1}): 3212, 2979, 1750, 1436, 1152.

Melting point: 117 – 119 °C.

Preparation of *tert*-butyl (2-oxopropyl)(tosyl)carbamate.[177]



185

Scheme 82

Prepared according to **General Procedure E**:

Table 6, entry 1: (a) *tert*-butyltosylcarbamate (1.50 g, 5.53 mmol); (b) DMF (20 mL); (c) NaH (0.23 g, 5.81 mmol); (d) chloroacetone (0.48 mL, 6.08 mmol); (e) 16 h; (f) *tert*-butyl (2-oxopropyl)(tosyl)carbamate (0.80 g, 2.43 mmol, **44%**); and (g) colourless oil.

Table 6, entry 2: (a) *tert*-butyltosylcarbamate (1.40 g, 5.03 mmol); (b) DMF (10 mL) (c) NaH (0.22 g, 5.53 mmol); (d) chloroacetone (0.44 mL, 5.53 mmol); (e) 16 h; (f) *tert*-butyl (2-oxopropyl)(tosyl)carbamate (0.31 g, 0.94 mmol, **19%**); and (g) colourless oil.

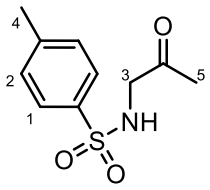
Table 6, entry 3: (a) *tert*-butyltosylcarbamate (7.12 g, 26.2 mmol); (b) DMF (35 mL); (c) NaH (1.10 g, 27.5 mmol); (d) chloroacetone (2.29 mL, 28.8 mmol); (e) 16 h; (f) *tert*-butyl (2-oxopropyl)(tosyl)carbamate (1.62 g, 4.95 mmol, **19%**); and (g) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.96 – 7.91 (2H, m, H_1), 7.36 – 7.31 (2H, m, H_2), 4.64 (2H, s, H_3), 2.46 (3H, s, H_4), 2.24 (3H, s, H_5), 1.32 (9H, s, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.0, 150.0, 144.0, 136.2, 128.7, 128.1, 84.4, 54.1, 27.3, 26.2, 21.2 ppm.

IR (ν_{max}/cm^{-1}): 3277, 1738, 1719, 1600, 1349, 1149.

Preparation of *N*-(2-oxopropyl)toluenesulfonamide.[178]



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Scheme 83

Tert-butyl (2-oxopropyl)(tosyl)carbamate (0.74 g, 2.25 mmol) and distilled DCM (10 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. Trifluoroacetic acid (0.52 mL, 6.75 mmol) was added to this solution and the resulting mixture was stirred at room temperature for 16 h. At this point, the solvent was removed *in vacuo* and toluene was added to the residue. This was concentrated *in vacuo* once more to give *N*-(2-oxopropyl)toluenesulfonamide (0.4 g, 1.76 mmol, **78%**) as a white powder.

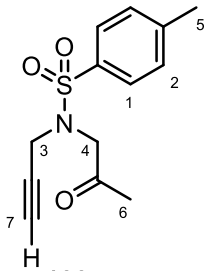
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.78 – 7.73 (2H, m, H_1), 7.35 – 7.31 (2H, m, H_2), 5.31 (1H, t, *J* = 4.4 Hz, NH), 3.87 (2H, d, *J* = 4.7 Hz, H_3), 2.44 (3H, s, H_4), 2.13 (3H, s, H_5) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 200.5, 143.3, 135.6, 129.3, 126.7, 51.6, 26.6, 21.0 ppm.

IR (ν_{max}/cm^{-1}): 3277, 1716, 1600, 1325, 1160.

Melting point: 94 – 96 °C. °C, **Literature value**: 96 – 98 °C.[179]

Preparation of *N*-(2-oxopropyl)-N-(prop-2-yn-1-yl)toluenesulfonamide.[180]



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Scheme 83

N-(2-oxopropyl)toluenesulfonamide (0.15 g, 0.66 mmol), K_2CO_3 (0.1 g, 0.73 mmol) and DMF (10 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The suspension was stirred at room temperature for 30 min. At this point, propargyl bromide (0.1 mL, 0.86 mmol) was added dropwise. The reaction mixture was stirred for 16 h at room temperature. At this point, a further 0.55 eq. of K_2CO_3 (0.05 g, 0.36 mmol) and 0.6 eq. propargyl bromide (0.05 mL, 0.43 mmol) were added. The reaction mixture was stirred for another 8 h and then filtered through celite and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 80:20 – 40:60) and concentrated *in vacuo* to provide *N*-(2-oxopropyl)-N-(prop-2-yn-1-yl)toluenesulfonamide (0.13 g, 0.51 mmol, **77%**) as a white solid.

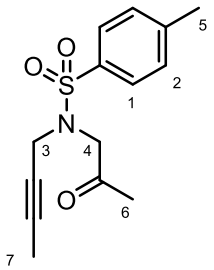
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.76 – 7.70 (2H, m, H_1), 7.36 – 7.31 (2H, m, H_2), 4.19 (2H, d, ^4J = 2.2 Hz, H_3), 4.06 (2H, s, H_4), 2.45 (3H, s, H_5), 2.25 (3H, s, H_6), 2.15 (1H, t, *J* = 2.5 Hz, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 202.7, 143.5, 135.0, 129.2, 127.1, 75.7, 74.1, 54.7, 37.4, 26.6, 21.1 ppm.

IR (ν_{max}/cm^{-1}): 3277, 3249, 1715, 1600, 1161.

Melting point: 60 – 62 °C, **Literature value**: 63 °C.

Preparation of *N*-(but-2-yn-1-yl)-*N*-(2-oxopropyl)toluenesulfonamide.[181]



183

Scheme 83

N-(2-oxopropyl)toluenesulfonamide (0.16 g, 0.70 mmol), K_2CO_3 (0.19 g, 1.4 mmol) and distilled DMF (6 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The suspension was stirred at room temperature for 30 min. At this point, 1-bromobutyne (0.08 mL, 0.91 mmol) was added dropwise. The reaction mixture was stirred for 5 h at room temperature. The reaction was quenched by the addition of distilled H_2O (15 mL). Following this, Et_2O (15 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase was washed with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and then concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 80:20 – 40:60) and concentrated *in vacuo* to provide *N*-(but-2-yn-1-yl)-*N*-(2-oxopropyl)toluenesulfonamide (0.16 g, 0.57 mmol, **82%**) as a white solid.

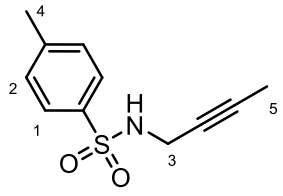
^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 7.75 – 7.71 (2H, m, H_1), 7.35 – 7.31 (2H, m, H_2), 4.09 (2H, q, ^5J = 2.3 Hz, H_3), 3.97 (2H, s, H_4), 2.44 (3H, s, H_5), 2.25 (3H, s, H_6), 1.62 (3H, t, ^5J = 2.4 Hz, H_7) ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 203.4, 143.3, 135.0, 129.1, 127.2, 82.1, 71.0, 55.1, 38.2, 26.6, 21.1, 2.8 ppm.

IR (ν_{max}/cm^{-1}): 2922, 1708, 1600, 1348, 1158.

Melting point: 59 - 61 °C, **Literature value**: 56 – 57 °C.

Preparation of *N*-(but-2-yn-1-yl)-toluenesulfonamide.[182]



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Scheme 84

K_2CO_3 (1.22 g, 6.72 mmol) and MeCN (20 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. *p*-Toluenesulfonamide (4.6 g, 26.9 mmol) and 1-bromobutyne (0.59 mL, 6.72 mmol) were added to this suspension. The resulting mixture was refluxed for 24 h. The reaction was quenched by the addition of distilled water (25 mL). Following this, Et_2O (25 mL) was added to create a biphasic mixture. The mixture was separated and the aqueous phase was extracted with Et_2O (2 × 25 mL). The combined organic extracts were extracted with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow solid. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 50:50) and concentrated *in vacuo* to provide *N*-(but-2-yn-1-yl)-toluenesulfonamide (0.95 g, 4.23 mmol, **63%**) as a white solid.

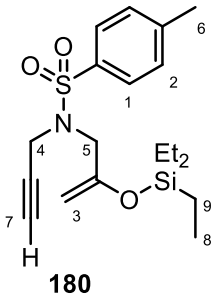
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.82 – 7.77 (2H, m, H_1), 7.35 – 7.30 (2H, m, H_2), 4.78 (1H, t, *J* = 5.7 Hz, NH), 3.80 – 3.74 (2H, m, H_3), 2.44 (3H, s, H_4), 1.60 (3H, t, ^5J = 2.4 Hz, H_5) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 143.1, 136.3, 129.1, 127.0, 80.6, 72.8, 32.9, 21.0, 2.8 ppm.

IR (ν_{max}/cm^{-1}): 3256, 2151, 1443, 1321, 1157.

Melting point: 62 – 64 °C, **Literature value**: 61 °C.

Preparation of *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide.



180

Scheme 85

Prepared according to **General Procedure B**:

(a) *N*-(2-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.45 g, 1.70 mmol); (b) DCE (15 mL); (c) DIPEA (0.33 mL, 1.87 mmol); (d) TESOTf (0.55 mL, 2.54 mmol); (e) *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.57 g, 1.51 mmol, **89%**); and (f) colourless oil. To note this reaction was conducted for 20 h.

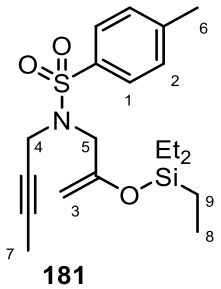
^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 7.78 – 7.74 (2H, m, H_1), 7.32 – 7.28 (2H, m, H_2), 4.34 (1H, d, ^{2}J = 1.5 Hz, H_3), 4.27 (1H, d, ^{2}J = 1.5 Hz, H_3), 4.18 (2H, d, ^{4}J = 2.4 Hz, H_4), 3.77 (2H, s, H_5), 2.43 (3H, s, H_6), 2.03 (1H, t, ^{4}J = 2.5 Hz, H_7), 0.99 (9H, t, J = 7.9 Hz, H_8), 0.71 (6H, q, J = 7.9 Hz, H_9) ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 152.3, 142.9, 136.0, 128.9, 127.3, 92.0, 76.3, 73.2, 49.6, 35.8, 21.0, 6.1, 4.3 ppm.

IR (ν_{max}/cm^{-1}): 3273, 2965, 2912, 2877, 1639, 1600, 1162.

HRMS (ESI) m/z: [M+H]$^+$ Calc. for $C_{19}H_{30}NO_3SSi$: 380.1710; **found** 380.1707.

Preparation of *N*-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide.



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Scheme 85

Prepared according to **General Procedure B**:

(a) *N*-(2-oxopropyl)-*N*-(but-2-yn-1-yl)toluenesulfonamide (0.87 g, 3.10 mmol); (b) DCE (15 mL); (c) DIPEA (0.59 mL, 3.41 mmol); (d) TESOTf (0.73 mL, 3.41 mmol); (e) *N*-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (1.09 g, 2.76 mmol, **89%**); and (f) colourless oil.

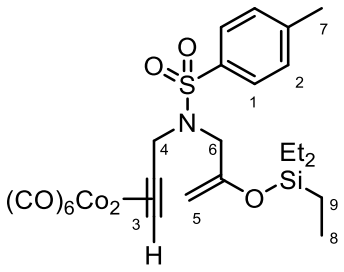
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.79 – 7.76 (2H, m, H_1), 7.33 – 7.27 (2H, m, H_2), 4.34 (1H, d, *J* = 1.3 Hz, H_3), 4.26 (1H, d, *J* = 1.3 Hz, H_3), 4.11 (2H, q, ^{5}J = 2.3 Hz, H_4), 3.73 (2H, s, H_5), 2.44 (3H, s, H_6), 1.56 (3H, t, ^{5}J = 2.4 Hz, H_7), 0.99 (9H, t, *J* = 7.9 Hz, H_8), 0.71 (6H, q, *J* = 7.8 Hz, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 152.6, 142.6, 136.1, 128.7, 127.3, 91.7, 81.0, 71.4, 49.6, 36.4, 21.0, 6.1, 4.3, 2.7 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2914, 2977, 1639, 1352, 1162.

HRMS (ESI) m/z: [M+H]$^+$ Calc. for $C_{20}H_{32}NO_3SSi$: 394.1867; **found** 394.1865.

Preparation of *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide dicobalthexacarbonyl complex.



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Scheme 86

Prepared according to **General Procedure C**:

(a) *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.50 g, 1.31 mmol); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.47 g, 1.37 mmol); (d) *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide dicobalthexacarbonyl complex (0.83 g, 1.24 mmol, **94%**; (e) red oil.

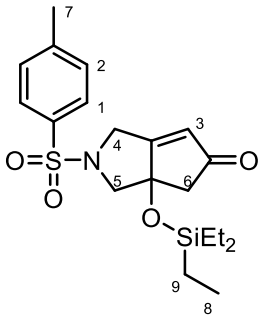
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.80 – 7.74 (2H, m, H_1), 7.33 – 7.26 (2H, m, H_2), 6.00 (1H, s, H_3), 4.67 (2H, s, H_4), 4.17 (2H, d, ^2J = 2.8 Hz, H_5), 3.98 (2H, s, H_6), 2.44 (3H, s, H_7), 0.93 (9H, t, *J* = 7.9 Hz, H_8), 0.63 (6H, q, *J* = 7.9 Hz, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 198.9, 152.6, 142.8, 137.6, 129.1, 127.1, 92.3, 88.7, 73.3, 50.3, 48.6, 21.1, 6.1, 4.2 ppm.

IR (ν_{max}/cm^{-1}): 3102, 2955, 2935, 2912, 2875, 2098, 2052, 2036, 2019, 2002, 1622, 1160.

HRMS (ESI) m/z: $[M+H]^+$ Calc. for $C_{25}H_{30}Co_2NO_9SSi$: 666.0069; **found** 666.0075.

Preparation of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one.



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Scheme 86

Prepared according to **General Procedure A**:

(a) *N*-(prop-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide dicobalthexacarbonyl complex (0.67 g, 1.01 mmol); (b) DCE (15 mL); (c) DodSMe (1.27 mL, 4.78 mmol); (d) 70 °C; (e) 24 h; (f) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.35 g, 0.86 mmol, **85%**); and (e) white oil.

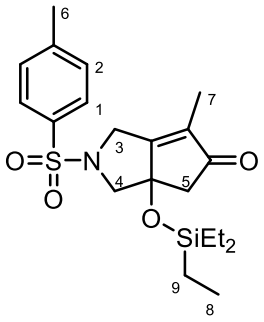
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.74 (2H, d, *J* = 8.2 Hz, H_1), 7.34 (2H, d, *J* = 8.2 Hz, H_2), 5.95 – 5.92 (1H, m, H_3), 4.33 (1H, dd, ^2J = 15.6 Hz, ^4J = 1.8 Hz, H_4), 4.17 (1H, d, ^2J = 15.6 Hz, H_4), 3.91 (1H, d, ^2J = 10.5 Hz, H_5), 3.05 (1H, d, ^2J = 10.5 Hz, H_5), 2.55 (1H, d, ^2J = 17.9 Hz, H_6), 2.44 (3H, s, H_7), 2.43 (1H, d, ^2J = 17.9 Hz, H_6), 0.87 (9H, t, *J* = 7.9 Hz, H_8), 0.59 – 0.42 (6H, m, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.1, 175.3, 143.5, 133.7, 129.4, 126.9, 125.6, 82.5, 58.7, 46.3, 45.7, 21.1, 6.3, 5.3 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2912, 2875, 1722, 1600, 1347, 1164.

HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{20}H_{30}NO_4SSi$: 408.1659; **found** 408.1656.

Preparation of 6-methyl-2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one.



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Scheme 87

N-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (1.11 g, 2.82 mmol) and pet. ether (15 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ (1.01 g, 2.96 mmol) was added and the mixture stirred at room temperature for 2 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to provide the crude product as a red oil. This material was dissolved in DCE (25 mL) and DodSMe (3.55 mL, 13.4 mmol) was added to the solution. The resulting mixture was heated to 70 °C for 5 h. At this point, the reaction mixture was concentrated *in vacuo*, DCM (20 mL) was added and this mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 60:40) and concentrated *in vacuo* to provide 6-methyl-2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (1.16 g, 2.74 mmol, **97%**) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.77 – 7.74 (2H, m, H_1), 7.35 – 7.32 (2H, m, H_2), 4.24 (1H, dd, ^2J = 15.1 Hz, ^5J = 1.2 Hz, H_3), 4.13 (1H, d, ^2J = 15.0 Hz, H_3), 3.89 (1H, d, ^2J = 10.4 Hz, H_4), 3.03 (1H, d, ^2J = 10.4 Hz, H_4), 2.58 (1H, d, ^2J = 18.0 Hz, H_5), 2.45 (3H, s, H_6), 2.43 (1H, d, ^2J = 18.0 Hz, H_5), 1.70 (3H, d, ^5J = 0.9 Hz, H_7), 0.85 (9H, t, J = 7.9 Hz, H_8), 0.55 – 0.39 (6H, m, H_9) ppm.

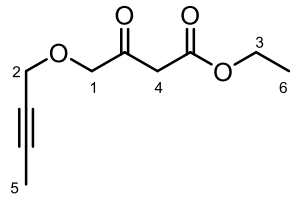
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.3, 167.9, 143.3, 134.1, 133.9, 129.3, 126.9, 80.8, 59.1, 46.0, 45.0, 21.0, 8.2, 6.3, 5.3 ppm.

IR (ν_{max}/cm^{-1}): 2956, 1727, 1696, 1349, 1167.

HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{21}H_{32}NO_4SSi$: 422.1816; **found** 422.1813.

Melting point: 60 – 62 °C.

Preparation of ethyl 4-(but-2-yn-1-yloxy)-3-oxobutanoate.[183]



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Scheme 89

NaH (60% dispersion in mineral oil) (1.22 g, 30.5 mmol) and dry THF (20 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The suspension was cooled to 0 °C and ethyl 4-chloro-3-oxobutanoate (3.1 mL, 23.0 mmol) was added dropwise over 3 h using a syringe pump. At this point, but-2-yn-1-ol (1.15 mL, 19.2 mmol) was added dropwise over 2 h using a syringe pump. The reaction mixture was left to stir for 14 h at room temperature and then quenched by the addition of 2 M HCl (15 mL). Following this, EtOAc (20 mL) was added to create a biphasic mixture, which was separated and the aqueous layer washed with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide dimethyl ethyl 4-(but-2-yn-1-yloxy)-3-oxobutanoate (3.12 g, 15.7 mmol, **82%**) as a pale yellow oil.

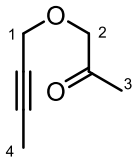
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.26 – 4.17 (6H, m, H_1, H_2, H_3), 3.56 (2H, s, H_4), 1.86 (3H, t, ^5J = 2.3 Hz, H_5), 1.29 (3H, t, J = 7.1 Hz, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.1, 166.5, 88.6, 83.6, 73.5, 60.9, 58.7, 45.6, 13.6, 3.0 ppm.

IR (ν_{max}/cm^{-1}): 2982, 1719, 1657, 1094.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{10}H_{15}O_4$: 199.0965; **found:** 199.0964.

Preparation of 1-(but-2-yn-1-yloxy)propan-2-one.



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Scheme 89

Dimethyl ethyl 4-(but-2-yn-1-yloxy)-3-oxobutanoate (1.10 g, 5.55 mmol), *p*-toluenesulfonic acid monohydrate (0.21 g, 1.11 mmol), ethanol (15 mL), and distilled water (11.2 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. This mixture was heated to reflux and stirred for 68 h before being quenched by the addition of sat. $NaHCO_3$ (15 mL). Following this, EtOAc (15 mL) was added to create a biphasic mixture, which was separated and the aqueous layer washed with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 1-(but-2-yn-1-yloxy)propan-2-one (0.65 g, 5.15 mmol, **93%**) as a pale yellow oil.

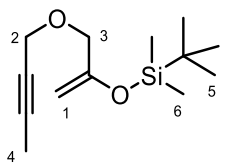
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.23 (2H, q, ^5J = 2.3 Hz, H_1), 4.14 (2H, s, H_2), 2.19 (3H, s, H_3), 1.87 (3H, t, ^5J = 2.3 Hz, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.9, 83.2, 74.0, 73.6, 58.5, 26.0, 3.0 ppm.

IR (ν_{max}/cm^{-1}): 2922, 2857, 1717, 1099.

HRMS (NSI) m/z: $[M+NH_4]^+$ Calc. for $C_7H_{14}NO_2$: 144.1019; **found**: 144.1016.

Preparation of ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane.



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Scheme 90

Prepared according to **General Procedure B**:

(a) 1-(but-2-yn-1-yloxy)propan-2-one (0.61 g, 4.86 mmol); (b) DCE (49 mL); (c) DIPEA (1.02 mL, 5.83 mmol); (d) TBSOTf (1.34 mL, 5.83 mmol); (e) ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane 0.89 g, 3.68 mmol, **76%**; and (f) colourless oil.

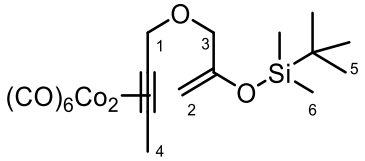
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.40 – 4.38 (1H, m, H_1), 4.28 (1H, apparent s, H_1), 4.16 (2H, q, ^{5}J = 2.3 Hz, H_2), 3.89 (2H, apparent s, H_3), 1.87 (3H, t, ^{5}J = 2.3 Hz, H_4), 0.95 (9H, s, H_5), 0.2 (6H, s, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 154.5, 91.4, 81.9, 74.5, 70.0, 57.5, 25.1, 17.6, 3.1, -5.2 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2928, 2857, 1638, 1250, 826.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{13}H_{24}O_2Si$: 241.1618**; found:** 241.1619.

Preparation of ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane dicobalthexacarbonyl complex.



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Scheme 91

Prepared according to **General Procedure C**:

(a) ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane (0.81 g, 3.38 mmol); (b) pet. ether (12 mL); (c) $Co_2(CO)_8$ (1.20 g, 3.55 mmol); (d) ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane dicobalthexacarbonyl complex (1.78 g, 3.38 mmol, **quant.**); and (e) red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.71 (2H, s, H_1), 4.44 – 4.42 (1H, m, H_2), 4.29 (1H, s, H_2), 3.98 (2H, s, H_3), 2.69 (3H, s, H_4), 0.96 (9H, s, H_5), 0.21 (6H, s, H_6) ppm.

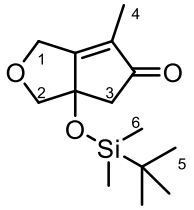
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.1, 154.6, 90.5, 71.4, 70.1, 40.9, 25.1, 22.1, 19.9, 18.1, -5.2. ppm.

IR (ν_{max}/cm^{-1}): 2955, 2930, 2859, 2089, 2046, 1992, 1632, 1250, 825.

HRMS (APCI/ion trap) m/z: $[M+H]^+$ calcd for $C_{19}H_{24}Co_2O_8SiH$: 526.9983; **found:** 526.9988.

LRMS (EI/ion trap) m/z: $[M-CO]^+$ calcd for $C_{19}H_{24}Co_2O_8Si$: 498.0, **found:** 498.0.

Preparation of 3*a*-((*tert*-butyldimethylsilyl)oxy)-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one.



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Scheme 91

Prepared according to **General Procedure A**:

(a) ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane dicobalthexacarbonyl complex (1.01 g, 1.92 mmol); (b) DCE (12 mL); (c) DodSMe (2.42 mL, 9.12 mmol); (d) 70 °C; (e) 16 h; (f) 3*a*-((*tert*-butyldimethylsilyl)oxy)-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one (0.31 g, 1.14 mmol, **59%**); and (e) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.68 (1H, dd, ^2J = 15.0 Hz, ^4J = 1.3 Hz, H_1), 4.53 (1H, d, ^2J = 15.0 Hz, H_1), 4.22 (1H, d, ^2J = 9.4 Hz, H_2), 3.50 (1H, d, ^2J = 9.4 Hz, H_2), 2.61 (1H, d, ^2J = 17.8 Hz, H_3), 2.50 (1H, d, ^2J = 17.8 Hz, H_3), 1.79 (3H, t, ^5J = 1.3 Hz, H_4), 0.88 (9H, s, H_5), 0.09 (3H, s, H_6), 0.06 (3H, s, H_6) ppm.

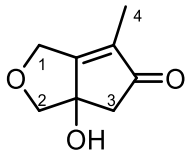
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.8, 172.4, 133.0, 82.0, 76.8, 63.4, 45.7, 25.0, 17.5, 8.5, -3.7, -3.8 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2926, 2855, 1713, 1682, 1082, 1001, 833.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{14}H_{24}O_3SiH$: 269.1573**; found:** 269.1580.

Melting point: 62 – 64 °C.

Preparation of 3*a*-hydroxy-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one.



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Scheme 92

Prepared according to **General Procedure D**:

Reaction at room temperature

(a) 3*a*-((*tert*-butyldimethylsilyl)oxy)-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one (0.24 g, 0.89 mmol); (b) THF:H_2O (10:1) (2.65 mL); (c) 3 M aqueous HCl (0.05 mL); (d) room temperature; (e) 100 h; (f) 3*a*-hydroxy-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one (0.07 g, 0.46 mmol, **52%**); and (g) pale yellow oil. To note, starting material (0.079 g, 0.294 mmol, 33%) was also recovered.

Reaction at 40 °C

(a) 3*a*-((*tert*-butyldimethylsilyl)oxy)-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one (0.213 g, 0.79 mmol); (b) THF:H_2O (10:1) (2.35 mL); (c) 3 M aqueous HCl (0.04 mL); (d) 40 °C; (e) 100 h; (f) 3*a*-hydroxy-6-methyl-3*a*,4-dihydro-1*H*-cyclopenta[c]furan-5(3*H*)-one (0.075 g, 0.49 mmol, **62%**); and (g) pale yellow oil.

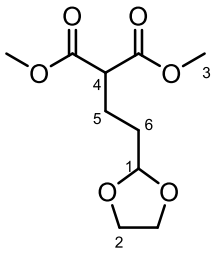
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.74 (1H, dd, ^2J = 15.7 Hz, ^4J = 1.5 Hz, H_1), 4.54 (1H, d, ^2J = 15.7 Hz, H_1), 4.21 (1H, d, ^2J = 9.6 Hz, H_2), 3.55 (1H, d, ^2J = 9.6 Hz, H_2), 3.04 (1H, s, OH), 2.65 (1H, d, ^2J = 17.3 Hz, H_3), 1.77 (3H, s, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.1, 171.9, 133.2, 80.4, 75.8, 75.8, 63.2, 44.6, 8.5 ppm.

IR (ν_{max}/cm^{-1}): 3387, 1707, 1686, 1030, 995.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_8H_{10}O_3$: 155.0708**; found:** 155.0707.

Preparation of dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)malonate.[184]



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Scheme 94

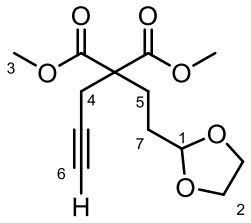
NaH (60% dispersion in mineral oil) (0.30 g, 7.54 mmol) and distilled THF (20 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. This solution was cooled to 0 °C and dimethylmalonate (0.82 mL, 7.18 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, TBAI (0.66 g, 1.79 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (0.76 mL, 6.46 mmol) were added dropwise, and the reaction mixture was heated to reflux and stirred for 17 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL). Following this, Et_2O (20 mL) was added to create a biphasic mixture, which was separated and the aqueous layer was washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 50:50) and concentrated *in vacuo* to provide dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)malonate (1.36 g, 5.85 mmol, **91%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.90 (1H, t, *J* = 4.5 Hz, H_1), 4.00 – 3.83 (4H, m, H_2), 3.75 (6H, s, H_3), 3.48 (1H, t, *J* = 7.6 Hz, H_4), 2.10 – 2.02 (2H, m, H_5), 1.76 – 1.69 (2H, m, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.2, 103.2, 64.4, 52.0, 50.8, 30.7, 22.6 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2890, 1731, 1438, 1141.

Preparation of dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(prop-2-yn-1-yl)malonate.[185]



204

Scheme 94

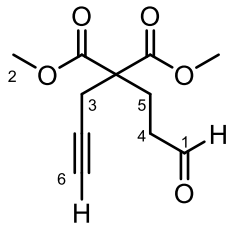
NaH (60% dispersion in mineral oil) (0.27 g, 6.65 mmol) and dry THF (15 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)malonate (1.40 g , 6.05 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and propargyl bromide (0.59 mL, 6.65 mmol) was added dropwise. The reaction mixture was stirred for 19 h and then quenched by the addition of distilled water (25 mL). Following this, Et_2O (25 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as an orange oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 30:70) and concentrated *in vacuo* to provide dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(prop-2-yn-1-yl)malonate (0.64 g, 2.35 mmol, **39%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.88 (1H, t, J = 4.5 Hz, H_1), 4.02 – 3.82 (4H, m, H_2), 3.74 (6H, s, H_3), 2.82 (2H, d, ^4J = 2.7 Hz, H_4), 2.22 – 2.15 (2H, m, H_5), 2.02 (1H, t, ^4J = 2.7 Hz, H_6), 1.63 – 1.55 (2H, m, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.0, 103.4, 78.0, 71.0, 64.4, 56.0, 52.3, 28.1, 26.0, 22.6 ppm.

IR (ν_{max}/cm^{-1}): 3286, 2955, 1732, 1438, 1201.

Preparation of dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate.[186]



203

Scheme 94

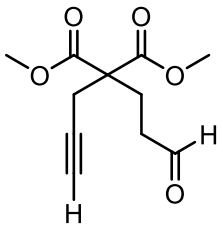
Dimethyl 2-(2-(1,3-dioxolan-2-yl)ethyl)-2-(prop-2-yn-1-yl)malonate (0.64 g, 2.35 mmol) and dry THF (10 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. 6M HCl (48 mL) and H_2O:AcOH (1:1) (32 mL) were added to the solution and the reaction mixture was stirred at room temperature for 16 h. This was quenched by the addition of solid K_2CO_3 (35 g) and then by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). Et_2O (25 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 50:50) and concentrated *in vacuo* to provide dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.44 g, 1.92 mmol, **82%**) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.77 (1H, t, *J* = 1.2 Hz, H_1), 3.77 (6H, s, H_2), 2.85 (2H, d, ^4J = 2.7 Hz, H_3), 2.58 – 2.51 (2H, m, H_4), 2.45 – 2.38 (2H, m, H_5), 2.06 (1H, t, ^4J = 2.7 Hz, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.9, 169.7, 77.7 71.5, 55.5, 52.5, 38.5, 24.4, 23.2 ppm.

IR (ν_{max}/cm^{-1}): 3282, 2956, 1437, 1202.

Telescoped preparation of dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate.[186]



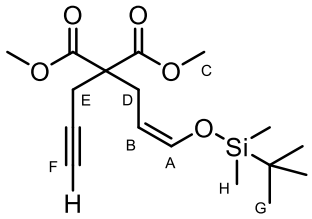
203

Scheme 94

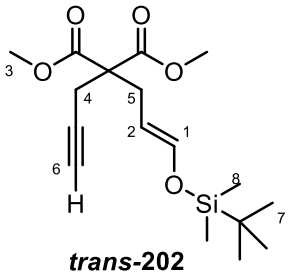
NaH (0.20 g, 5.02 mmol) and dry THF (10 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. This solution was cooled to 0 °C and dimethylmalonate (0.55 mL, 4.79 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, TBAI (0.44 g, 1.20 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (0.51 mL, 4.31 mmol) were added dropwise, and the reaction mixture was heated to reflux and stirred for 4 h. After this time, the reaction was quenched by the addition of saturated aqueous ammonium chloride solution (20 mL). Following this, Et_2O (20 mL) was added to create a biphasic mixture, which was separated and the aqueous layer was washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. NaH (0.16 g, 4.74 mmol) and dry THF (20 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and the crude material was added dropwise as a solution in THF (2 mL). The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and propargyl bromide (0.42 mL, 4.74 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then quenched by the addition of distilled water (25 mL). Following this, Et_2O (25 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as an orange oil. The crude product was dissolved in dry THF (15 mL) and added to a round-bottom flask equipped with a stirrer bar. 6M HCl (75 mL) and H_2O:AcOH (1:1) (50 mL) were added to the solution and the reaction mixture was stirred at room temperature for 16 h. This was quenched by the addition of solid K_2CO_3 (35 g) and then by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). Et_2O (25 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 50:50) and concentrated *in vacuo* to provide dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.593 g, 2.62 mmol, **61%**) as a pale yellow oil.

Characterisation data for this compound found on page 137.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate.



***cis*-202**



***trans*-202**

Scheme 95

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.48 g, 2.13 mmol; (b) DCE (15 mL); (c) DIPEA (0.45 mL, 2.56 mmol); (d) TBSOTf (0.59 mL, 2.56 mmol); (e) dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (0.52 g, 1.53 mmol, **72%**, *cis*:*trans*, 33:67); and (f) colourless oil.

***Trans* isomer**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.35 (1H, dt, J = 11.8 Hz, ^4J = 1.1 Hz, H_1), 4.77 (1H, dt, J = 11.8 Hz, J = 8.1 Hz, H_2), 3.75 (6H, s, H_3), 2.83 – 2.80 (2H, m, H_4), 2.68 (2H, dd, J = 8.1 Hz, ^4J = 1.1 Hz, H_5), 2.02 (1H, t, ^4J = 2.4 Hz, H_6), 0.93 (9H, s, H_7), 0.14 (6H, s, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 143.6, 103.0, 78.4, 70.8, 56.8, 52.2, 30.1, 25.1, 22.0, 17.8, -5.8 ppm.

***Cis* isomer**

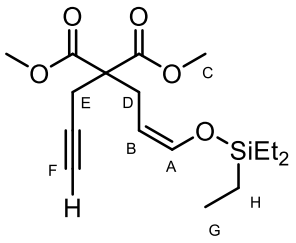
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.34 (1H, dt, J = 6.1 Hz, ^4J = 1.4 Hz, H_A), 4.23 (1H, td, J = 11.4 Hz, ^4J = 6.0 Hz, H_B), 3.75 (6H, s, H_C), 2.89 (2H, dd, J = 7.6 Hz, ^4J = 1.4 Hz, H_D), 2.83 – 2.80 (2H, m, H_E), 1.98 (1H, t, ^4J = 2.7 Hz, H_F), 0.94 (9H, s, H_G), 0.14 (6H, s, H_H) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 141.7, 101.8, 78.9, 70.4, 56.7, 52.2, 26.4, 25.1, 22.4, 17.7, -5.9 ppm.

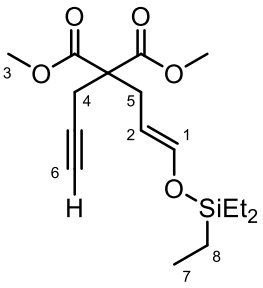
IR (ν_{max}/cm^{-1}): 3286, 2953, 2931, 1738, 1438, 1171.

HRMS (ESI) m/z: $[M+Na]^+$ Calc. for $C_{17}H_{28}O_5SiNa$: 363.1598; **found** 363.1598.

Preparation of dimethyl 2-(prop-2-yn-1-yl)-2-(3-((triethylsilyl)oxy)allyl)malonate.



cis-201



trans-201

Scheme 95

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(3-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.59 g, 2.60 mmol; (b) DCE (15 mL); (c) DIPEA (0.54 mL, 3.12 mmol); (d) TESOTf (0.67 mL, 3.12 mmol); (e) dimethyl 2-(prop-2-yn-1-yl)-2-(3-((triethylsilyl)oxy)allyl)malonate (0.55 g, 1.62 mmol, **62%,** *cis*:*trans*, 29:71); and (f) colourless oil.

***Trans* isomer**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.36 (1H, dt, J = 11.9 Hz, ^{4}J = 1.1 Hz, H_1), 4.77 (1H, dt, J = 11.8 Hz, J = 8.1 Hz, H_2), 3.75 (6H, s, H_3), 2.80 (2H, d, ^{4}J = 2.6 Hz, H_4), 2.68 (2H, dd, J = 8.1 Hz, ^{4}J = 1.1 Hz, H_5), 2.02 (1H, t, ^{4}J = 2.7 Hz, H_6), 0.98 (9H, t, J = 7.9 Hz, H_7), 0.67 (6H, q, J = 8.0 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 143.4, 102.9, 78.5, 70.8, 56.8, 52.2, 30.0, 21.9, 5.9, 3.9 ppm.

***Cis* isomer**

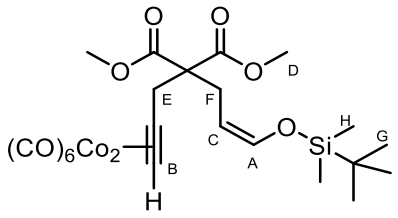
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.35 (1H, dt, J = 5.7 Hz, ^{4}J = 1.5 Hz, H_A), 4.22 (1H, dt, J = 7.6 Hz, J = 5.9 Hz, H_B), 3.74 (6H, s, H_C), 2.89 (2H, dd, J = 7.6 Hz, ^{4}J = 1.3 Hz, H_D), 2.80 (2H, d, ^{4}J = 2.1 Hz, H_E), 1.98 (1H, t, ^{4}J = 2.7 Hz, H_F), 0.99 (9H, t, J = 7.9 Hz, H_G), 0.67 (6H, q, J = 7.9 Hz, H_H) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 141.6, 101.7, 78.9, 70.4, 56.7, 52.1, 26.2, 22.3, 6.0, 3.9 ppm.

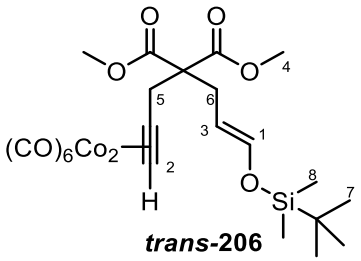
IR (ν_{max}/cm^{-1}): 3291, 2953, 2878, 1736, 1661, 1169.

HRMS (ESI) m/z: [M+Na]$^+$ Calc. for $C_{17}H_{28}O_5SiNa$: 363.1598; **found** 363.1597.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



***cis*-206**



***trans*-206**

Scheme 96

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (0.47 g, 1.37 mmol, *cis*:*trans*, 33:67) ; (b) pet. ether (10 mL); (c) $Co_2(CO)_8$ (0.49 g, 1.43 mmol); (d) ((3-(but-2-yn-1-yloxy)prop-1-en-2-yl)oxy)(*tert*-butyl)dimethylsilane dicobalthexacarbonyl complex (0.77 g, 1.23 mmol, **90%,** *cis*:*trans*, 33:67); and (e) red oil. To note this reaction was conducted for 3 h.

***Trans* isomer**

^{1}H NMR ($CDCl_3$, 400MHz): δ_H 6.32 (1H, s, H_1), 5.96 (1H, s, H_2), 4.88 – 4.80 (1H, m, H_3), 3.75 (6H, s, H_4), 3.64 (2H, s, H_5), 2.65 – 2.60 (2H, m, H_6), 0.92 (9H, s, H_7), 0.14 (6H, s, H_8) ppm.

***Cis* isomer**

^{1}H NMR ($CDCl_3$, 400MHz): δ_H 6.30 (1H, s, H_A), 6.04 (1H, s, H_B), 4.33 – 4.27 (1H, m, H_C), 3.75 (6H, s, H_D), 3.64 (2H, s, H_E), 2.90 – 2.83 (2H, m, H_F), 0.96 (9H, s, H_G), 0.16 (6H, s, H_H) ppm.

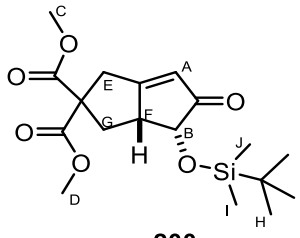
The following data refers to the mixture of isomers.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.1, 170.4, 170.1, 103.1, 101.9, 87.8, 87.4, 73.2, 72.7, 58.7, 57.8, 52.1, 37.6, 37.2, 30.7, 27.1, 25.1, 17.8, -5.8, -5.9 ppm.

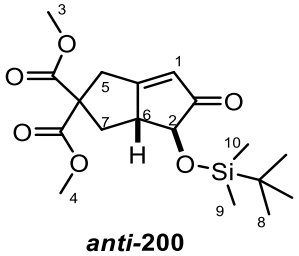
IR (ν_{max}/cm^{-1}): 2956, 2093, 2052, 2002, 1991, 1727, 1666, 1171.

HRMS (NSI) m/z: [M+H]$^+$ Calc. for $C_{23}H_{29}Co_2O_{11}Si$: 627.0138; **found** 627.0131.

Preparation of dimethyl 4-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



***syn*-200**



***anti*-200**

Scheme 96

Prepared according to **General Procedure A**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complexes (0.98 g, 1.4 mmol, *cis*:*trans*,

33:67); (b) DCE (10 mL); (c) DodSMe (1.53 mL, 5.79 mmol); (d) 70 °C; (e) 5 h; (f) dimethyl 4-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.32 g, 0.87 mmol, **71%**, *syn*:*anti*, 32:68); and (g) white oil.

***Syn* isomer**

^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 5.89 – 5.86 (1H, m, H_A), 4.16 (1H, d, *J* = 5.9 Hz, H_B), 3.80 (3H, s, $H_{C/D}$), 3.76 (3H, s, $H_{C/D}$), 3.32 – 3.30 (2H, m, H_E), 3.17 – 3.08 (1H, m, H_F), 2.47 (1H, dd, *J* = 13.1 Hz, *J* = 8.0 Hz, H_G), 2.24 (1H, t, *J* = 12.8 Hz, H_G), 0.89 (9H, s, H_H), 0.16 (3H, s, $H_{I/J}$), 0.13 (6H, s, $H_{I/J}$) ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 207.1, 183.4, 171.7, 170.7, 122.3, 72.4, 59.7 52.7, 52.6, 49.3, 35.4, 31.9, 25.2, 17.9, -5.0, -5.7 ppm.

***Anti* isomer**

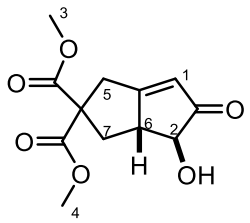
^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 5.95 (1H, dd, ^4J = 2.0 Hz, ^4J = 1.7 Hz, H_1), 4.00 (1H, d, *J* = 3.5 Hz, H_2), 3.81 (3H, s, $H_{3/4}$), 3.77 (3H, s, $H_{3/4}$), 3.36 (1H, dt, ^2J = 19.1 Hz, ^4J = 2.0 Hz, H_5), 3.21 (1H, d, ^2J = 19.1 Hz, H_5), 3.08 – 3.00 (1H, m, H_6), 2.87 (1H, dd, ^2J = 13.0 Hz, *J* = 8.1 Hz, H_7), 1.94 (1H, d, ^2J = 13.0 Hz, H_7), 0.93 (9H, s, H_8), 0.17 (3H, s, $H_{9/10}$), 0.14 (3H, s, $H_{9/10}$) ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 206.5, 178.0, 171.1, 170.7, 123.0, 81.4, 59.8, 52.8, 52.7, 52.5, 37.4, 25.3, 35.2, 17.9, -5.0, -5.6 ppm.

IR (ν_{max}/cm^{-1}): 2953, 1731, 1637, 1438, 1159.

HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{18}H_{29}O_6Si$: 369.1728; **found** 369.1730

Preparation of dimethyl 4-hydroxy-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



***anti*-207**

Scheme 97

Prepared according to **General Procedure D**:

(a) Dimethyl 4-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.24 g, 0.64 mmol, *syn*:*anti*, 32:68); (b) THF:H_2O (10:1) (3.75 mL); (c) 3 M aqueous HCl (0.07 mL); (d) room temperature; (e) 18 h; (f) dimethyl 4-hydroxy-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.06g, 0.22 mmol, **34%**); and (g) white solid. To note, starting material (0.059 g, 0.16 mmol, 25%) we also recovered.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.00 (1H, dd, ^4J = 4.0 Hz, 1.8 Hz, H_1), 4.00 (1H, d, J = 3.2 Hz, H_2), 3.79 (3H, s, $H_{3/4}$), 3.76 (3H, s, $H_{3/4}$), 3.41 (1H, d, ^2J = 19.3 Hz, H_5), 3.21 (1H, d, ^2J = 19.3 Hz, H_5), 3.10 – 3.01 (1H, m, H_6), 2.96 (1H, s, OH), 2.94 (1H, dd, ^2J = 12.8 Hz, J = 8.0 Hz, H_7), 1.98 (1H, dd, ^2J = 13.0 Hz, J = 11.8 Hz, H_7) ppm.

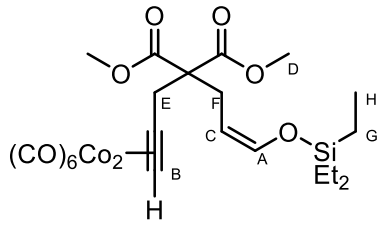
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.8, 180.6, 171.0, 170.6, 122.0, 80.4, 60.0, 52.9, 52.7, 52.0, 37.0, 35.2 ppm.

IR (ν_{max}/cm^{-1}): 3516, 2957, 1710, 1635, 1252.

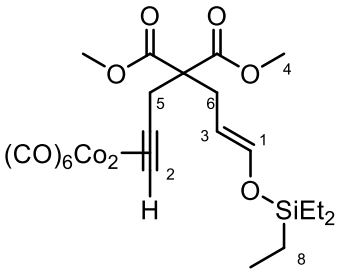
HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{12}H_{15}O_6$: 255.0869; **found** 255.0863.

Melting point: 108 – 110 °C.

Preparation of dimethyl 2-(3-((triethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



***cis*-208**



***trans*-208**

Scheme 98

Prepared according to **General Procedure C**:

(a) Dimethyl-2-(3-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate (0.29 g, 0.84 mmol, *cis*:*trans*, 29:71); (b) pet. ether (8.4 mL); (c) $Co_2(CO)_8$ (0.3 g, 0.88 mmol); (d) dicobalthexacarbonyl complex, (0.38 g, 0.61 mmol, **72%**, *cis*:*trans*, 29:71); and (e) red oil.

cis

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.40 – 6.37 (1H, m, H_A), 6.10 (1H, s, H_B), 4.34 (1H, dt, *J* = 6.9 Hz, *J* = 7.2 Hz, H_C), 3.80 (6H, s, H_D), 3.69 (2H, s, H_E), 2.91 (2H, d, *J* = 7.2 Hz, H_F), 1.05 (9H, t, *J* = 7.9 Hz, H_G), 0.74 (6H, q, *J* = 7.8 Hz, H_H).

trans

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.38 – 6.34 (1H, m, H_1), 6.00 (1H, s, H_2), 4.89 (1H, dt, *J* = 11.8 Hz, *J* = 8.0 Hz, H_3), 3.80 (6H, s, H_4), 3.67 (2H, s, H_5), 2.66 (2H, d, *J* = 8.1 Hz, H_6), 1.02 (9H, t, *J* = 7.9 Hz, H_7), 0.71 (6H, q, *J* = 7.8 Hz, H_8).

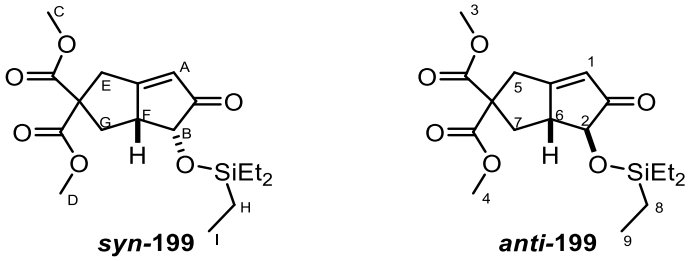
The following data refers to the mixture of isomers.

^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 199.6, 170.9, 170.6,143.7, 141.7, 103.5, 102.4, 88.4, 87.9, 73.7, 73.2, 59.2, 58.3, 52, 38.0, 37.6, 31.3, 29.7, 27.6, 25.6, 6.5, 6.4, 4.42, 4.40.

IR (ν_{max}/cm^{-1}): 2955, 2879, 2099, 2053, 2015, 1732, 1438, 1174.

HRMS (NSI) m/z: $[M+NH_4]^+$ Calc. for $C_{23}H_{32}Co_2NO_{11}Si$: 644.0403; **found** 644.0401.

Preparation of dimethyl 4-((triethylsilyl)oxy)-5-oxo-3,3*a*,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



Scheme 98

Prepared according to **General Procedure D**:

(a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.24 g, 0.64 mmol, *syn*:*anti*, 30:70); (b) THF:H_2O (10:1) (5 mL); (c) 3 M aqueous HCl (0.81 mL); (d) room temperature; (e) 5 h; (f) 4-hydroxy-2-tosyl-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.05 g, 0.17 mmol, **20%**); and (g) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.79 – 7.74 (2H, m, H_1), 7.41 – 7.65 (2H, m, H_2), 6.09 (1H, dd, ^4J = 3.6 Hz, ^4J = 1.9 Hz, H_3), 4.35 (1H, dt, ^2J = 17.3 Hz, ^4J = 1.8 Hz, H_4), 4.18 (1H, dd, ^2J = 9.5 Hz, J = 8.6 Hz, H_5), 4.09 (1H, d, ^2J = 17.2 Hz, H_4), 3.95 (1H, apparent d, ^4J = 3.6 Hz, H_6), 3.15 – 3.06 (1H, m, H_7), 2.92 (1H, s, OH), 2.86 (1H, dd, J = 10.6 Hz, ^2J = 9.5 Hz, H_5), 2.47 (3H, s, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.5, 174.8, 144.3, 133.3, 130.0, 127.4, 122.6, 78.9, 51.13, 51.10, 47.7 21.5 ppm.

IR (ν_{max}/cm^{-1}): 3445, 3063, 2916, 1711, 1659, 1344, 1159.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}NO_4SH$: 294.0795**; found:** 294.0791

Melting point: decomposes over 153 – 158 °C.

Prepared according to **General Procedure A**:

(a) Dimethyl-2-(3-((triethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.375 g, 0.599 mmol; *cis:trans*, 29:71); (b) DCE (6 mL); (c) DodSMe, (0.75 mL, 2.84 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 4-((triethylsilyl)oxy)-5-oxo-3,3*a*,4,5-

tetrahydropentalene-2,2(1*H*)-dicarboxylate, (0.19 g, 0.52 mmol, **86%**, *syn*:*anti*, 30:70); and (g) pale yellow oil.

***syn*-197**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.90 (1H, dd, ^4J = 3.4 Hz, ^4J = 2.0 Hz, H_1) 4.17 (1H, d, J = 3.4 Hz, H_2), 3.81 (3H, s, H_3), 3.78 (3H, s, H_4), 3.37 (1H, d, ^2J = 19.1 Hz, H_5), 3.22 (1H, d, ^2J = 19.1 Hz, H_5), 3.09 – 3.00 (1H, m, H_6), 2.89 (1H, dd, ^2J = 12.9 Hz, J = 8.0 Hz, H_7), 1.95 (1H, dd, ^2J = 12.9 Hz, J = 11.7 Hz, H_7), 1.00 (9H, t, J = 8.0 Hz, H_9), 0.73 – 0.65 (6H, m, H_8) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 206.2, 178.0, 171.0, 170.7, 123.1, 80.9, 59.8, 52.8, 52.7, 52.6, 37.3, 35.2, 6.2, 4.2 ppm.

***anti*-197**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.97 – 5.94 (1H, m, H_A), 3.99 (1H, d, J = 5.9 Hz, H_B), 3.81 (3H, s, H_C), 3.78 (3H, s, H_D), 3.33 (2H, dt, ^2J = 5.9 Hz, ^4J = 1.6 Hz, H_E), 3.18 – 3.08 (1H, m, H_F), 2.48 (1H, dd, ^2J = 13.1 Hz, J = 8.1 Hz, H_G), 2.26 (1H, dd, ^2J = 13.1 Hz, J = 12.7 Hz, H_G), 0.98 (9H, t, J = 8.0 Hz, H_I), 0.72 – 0.65 (6H, m, H_H) ppm.

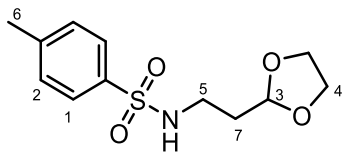
^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 207.1, 183.4, 171.8, 170.7, 122.3, 72.2, 59.7, 52.8, 52.6, 49.4, 35.4, 31.7, 6.2, 4.3 ppm.

The following data refers to the mixture of isomers.

IR (ν_{max}/cm^{-1}): 2931, 2856, 1733, 1637, 1438, 1251.

HRMS (NSI) m/z: $[M+H]^+$ Calc. for $C_{18}H_{29}O_6Si$: 369.1728; **found**: 369.1730.

Preparation of *N*-(2-(1,3-dioxolan-2-yl)ethyl)-toluenesulfonamide.[187]



213

Scheme 100

2-(2-bromoethyl)-1,3-dioxolane (1.3 mL, 11.06) and MeCN (25 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. *p*-Toluenesulfonamide (3.79 g, 22.12

mmol) and K_2CO_3 (3.06 g, 22.12 mmol) were added to this solution and the reaction mixture heated to reflux for 3 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 30:70) and concentrated *in vacuo* to provide *N*-(2-(1,3-dioxolan-2-yl)ethyl)-toluenesulfonamide (2.40g, 8.85 mmol, **80%**) as a white solid.

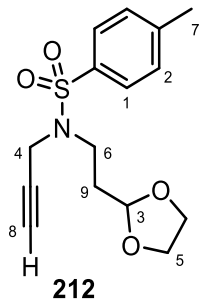
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.78 – 7.72 (2H, m, H_1), 7.34 – 7.29 (2H, m, H_2), 5.24 (1H, t, *J* = 5.7 Hz, NH), 4.84 (1H, t, *J* = 4.1 Hz, H_3), 3.94 – 3.75 (4H, m, H_4), 3.14 – 3.06 (2H, m, H_5), 2.43 (3H, s, H_6), 1.86 – 1.80 (2H, m, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 142.8 136.5, 129.2, 126.6, 102.8, 64.4, 37.9, 31.6, 21.0 ppm.

IR (ν_{max}/cm^{-1}): 3257, 2961, 2895, 1595.

Melting point: 59 – 61 °C, **Literature value**: 63 °C.

Preparation of *N*-(2-(1,3-dioxolan-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide.[188]



212

Scheme 100

N-(2-(1,3-dioxolan-2-yl)ethyl)-toluenesulfonamide (0.30 g, 1.1 mmol) was added to a flame-dried, round-bottom flask and dissolved in DMF (20 mL). NaH (60% dispersion in mineral oil) (0.06 g, 1.43 mmol) was added to this solution and the reaction mixture was stirred at room temperature for 30 min. At this point, propargyl bromide (0.20 mL, 1.81 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. This was quenched by the addition of distilled water (20 mL). Et_2O (20 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash

column chromatography (pet. ether:Et_2O, 10:90) and concentrated *in vacuo* to provide *N*-(2-(1,3-dioxolan-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.28 g, 0.9 mmol, **82%**) as a white solid.

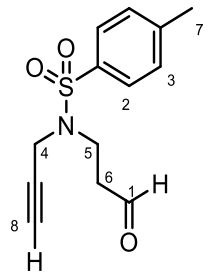
^{1}H NMR ($CDCl_3$, 400MHz): δ_H 7.78 – 7.73 (2H, m, H_1), 7.33 – 7.29 (2H, m, H_2), 4.94 (1H, t, *J* = 4.6 Hz, H_3), 4.18 (2H, d, ^4J = 2.5 Hz, H_4), 4.01 – 3.84 (4H, m, H_5), 3.40 – 3.33 (2H, m, H_6), 2.44 (3H, s, H_7), 2.05 (1H, t, ^4J = 2.5 Hz, H_8), 2.02 – 1.96 (2H, m, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 143.0, 135.4, 129.0, 127.3, 101.8, 76.2, 73.2, 64.5, 41.5, 36.2, 31.8, 21.0 ppm.

IR (ν_{max}/cm^{-1}): 3269, 2952, 2886, 1597.

Melting point: 60 – 62 °C.

Preparation of *N*-(3-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide.



211

Scheme 100

N-(2-(1,3-dioxolan-2-yl)ethyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.92 g, 2.96 mmol) and dry THF (15 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. 6M HCl (60 mL) and H_2O:AcOH (1:1) (40 mL) were added to the solution and the reaction mixture was stirred at room temperature for 16 h. This was quenched by the addition of solid K_2CO_3 (40 g) and then by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). Et_2O (25 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 80:20)

and concentrated *in vacuo* to provide *N*-(3-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.69 g, 2.62 mmol, **88%**) as a pale yellow oil.

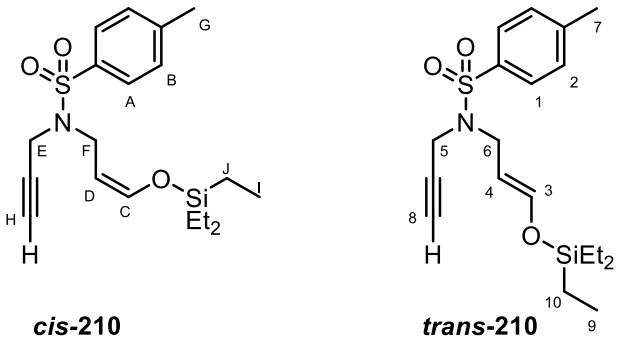
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.82 (1H, t, *J* = 1.1, H_1), 7.78 – 7.73 (2H, m, H_2), 7.36 – 7.31 (2H, m, H_3), 4.16 (2H, d, ^4J = 2.5 Hz, H_4), 3.54 (2H, t, *J* = 6.9 Hz, H_5), 2.89 (2H, td, *J* = 6.9 Hz, *J* = 1.1 Hz, H_6), 2.45 (3H, s, H_7), 2.09 (1H, t, *J* = 2.5 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.5, 143.4, 134.8, 129.2, 127.3, 76.2, 73.5, 42.6, 40.1, 37.2, 21.1 ppm.

IR (ν_{max}/cm^{-1}): 3279, 1721, 1597, 1493.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{13}H_{15}NO_3SH$: 266.0845; **found:** 266.0844.

Preparation of *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide.



***cis*-210** ***trans*-210**

Scheme 101

The following experiments were performed using **General Procedure B** with the exception that each experiment was carried out over differing reaction times.

Results are reported as: (a) carbonyl compound; (b) solvent volume; (c) DIPEA; (d) silylating agent; (e) reaction time; (f) isolated yield; and (g) compound appearance.

Table 7, entry 1: (a) *N*-(3-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.63 g, 2.38 mmol); (b) DCE (10 mL); (c) DIPEA (0.46 mL, 2.62 mmol); (d) TESOTf (0.56 mL, 2.62 mmol); (e) 16 h; (f) *N*-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.65 g, 1.71 mmol, **72%**, *cis*:*trans,* 29:71); and (g) colourless oil.

Table 7, entry 2: (a) *N*-(3-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (0.79 g, 2.97 mmol); (b) DCE (10 mL); (c) DIPEA (0.57 mL, 3.26 mmol); (d) TESOTf (0.7 mL, 3.26 mmol); (e) 6 h; (f) *N*-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.88 g, 2.33 mmol, **78%**, *cis*:*trans,* 45:55); and (g) colourless oil.

Table 7, entry 3: (a) *N*-(3-oxopropyl)-*N*-(prop-2-yn-1-yl)toluenesulfonamide (1.86 g, 7.01 mmol); (b) DCE (15 mL); (c) DIPEA (1.35 mL, 7.71 mmol); (d) TESOTf (1.66 mL, 7.71 mmol); (e) 8 h; (f) *N*-(but-2-yn-1-yl)-*N*-(2-((triethylsilyl)oxy)allyl)toluenesulfonamide (1.81 g, 4.77 mmol, **68%**, *cis*:*trans,* 48:52); and (g) colourless oil.

***Trans* isomer**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.71 – 7.74 (2H, m, H_1), 7.32 – 7.28 (2H, m, H_2), 6.44 (1H, dt, *J* = 12.0 Hz, ^4J = 1.0 Hz, H_3), 4.85 (1H, dt, *J* = 12.0 Hz, *J* = 7.8 Hz, H_4), 4.09 (2H, d, ^4J = 2.5 Hz, H_5), 3.74 (2H, dd, *J* = 7.8 Hz, ^4J = 0.8 Hz, H_6), 2.42 (3H, s, H_7), 2.01 (1H, t, ^4J = 2.5 Hz, H_8), 0.96 (9H, t, *J* = 7.9 Hz, H_9), 0.65 (6H, q, *J* = 7.9 Hz, H_{10}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 145.6, 143.4, 136.0, 129.0, 127.2, 103.1, 76.1, 73.1, 44.1, 34.5, 21.0, 5.9, 3.9 ppm.

***Cis* isomer**

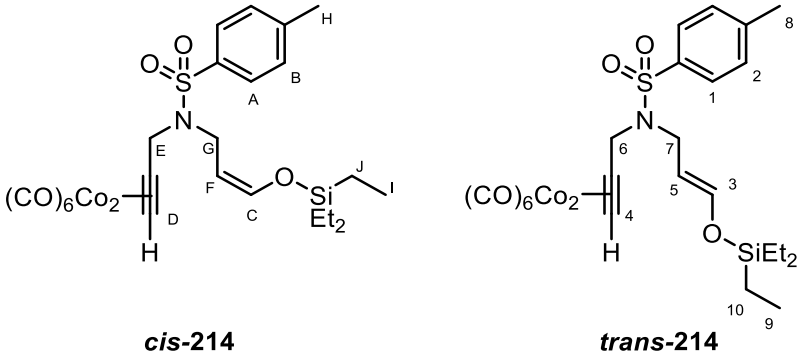
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.77 – 7.74 (2H, m, H_A), 7.30 – 7.27 (2H, m, H_B), 6.40 (1H, dt, *J* = 5.8 Hz, ^4J = 1.2 Hz, H_C), 4.43 (2H, td, *J* = 7.3 Hz, *J* = 5.8 Hz, H_D), 4.07 (2H, d, ^4J = 2.4 Hz, H_E), 3.97 (2H, dd, *J* = 7.3 Hz, *J* = 1.1 Hz, H_F), 2.42 (3H, s, H_G), 1.99 (1H, t, ^4J = 2.4 Hz, H_H), 0.96 (9H, t, *J* = 7.9 Hz, H_I), 0.65 (6H, q, *J* = 7.9 Hz, H_J) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 143.1, 143.3, 136.5, 129.3, 127.6, 103.2, 77.3 72.7, 40.3, 35.6, 21.0, 5.9, 3.9 ppm.

IR (ν_{max}/cm^{-1}): 3271, 2955, 2911, 2876, 1659.

HRMS (NSI/ion trap) m/z: $[M+NH_4]^+$ calcd for $C_{19}H_{29}NO_3SSiNH_4$: 397.1976; **found:** 397.1977; **$[M+Na]^+$ calcd for $C_{19}H_{29}NO_3SSiNa$:** 402.1530 **found:** 402.1529.

Preparation of *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide dicobalthexacarbonyl complex.



***cis*-214** ***trans*-214**

Scheme 102

Prepared according to **General Procedure C**:

(a) *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.41 g, 1.07 mmol, *cis*:*trans*, 29:71); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.40 g, 1.12 mmol); (d) dicobalthexacarbonyl complexes (0.59 g, 0.88 mmol, **83%**, *cis*:*trans*, 30:70); and (e) red oil.

***Cis* isomer**

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.78 – 7.75 (2H, m, H_A), 7.36 – 7.31 (2H, m, H_B), 6.34 (1H, dt, *J* = 5.5 Hz, ^4J = 1.6 Hz, H_C), 6.11 (1H, t, ^4J = 1.0 Hz, H_D), 4.47 (2H, s, H_E), 4.27 – 4.21 (1H, m, H_F), 4.11 (2H, d, *J* = 7.4 Hz, H_G), 2.45 (3H, s, H_H), 0.97 (9H, t, *J* = 7.9 Hz, H_I), 0.67 (6H, q, *J* = 8.0 Hz, H_J) ppm.

***Trans* isomer**

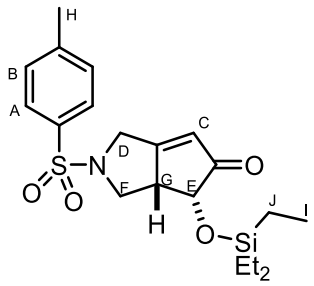
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.76 – 7.73 (2H, m, H_1), 7.35 – 7.31 (2H, m, H_2), 6.36 (1H, dt, *J* = 11.9 Hz, ^4J = 0.9 Hz, H_3), 6.05 (1H, t, ^4J = 0.9 Hz, H_4), 4.64 (1H, dt, *J* = 12.0 Hz, *J* = 7.8 Hz, H_5), 4.49 (2H, s, H_6), 3.90 (2H, d, *J* = 7.6 Hz, H_7), 2.45 (3H, s, H_8), 0.94 (9H, t, *J* = 7.9 Hz, H_9), 0.61 (6H, q, *J* = 7.9 Hz, H_{10}) ppm.

The following data refers to the mixture of isomers.

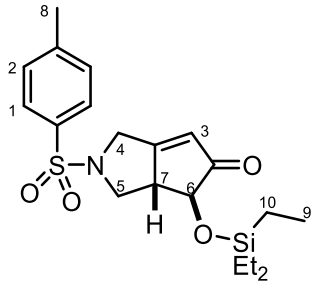
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 198.7, 145.0, 142.9, 142.4, 137.3, 129.3, 129.2, 126.8, 126.7, 103.1, 102.6, 89.8, 72.9, 48.3, 47.0, 45.1, 41.1, 21.0, 5.9, 5.8, 3.8, 3.8.

IR (ν_{max}/cm^{-1}): 2957, 2913, 2878, 2083, 2052, 2012, 2000.

Preparation of 2-tosyl-4-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one.



***syn*-209**



***anti*-209**

Scheme 102

Prepared according to **General procedure A**:

(a) *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide dicobalthexacarbonyl complex (0.41 g, 0.62 mmol), (0.98 g, 1.4 mmol, *cis*:*trans*, 30:70); (b) DCE (10 mL); (c) DodSMe (0.79 mL, 2.95 mmol); (d) 70 °C; (e) 3 h; (f) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.17 g, 0.41 mmol, **66%**, *syn*:*anti*, 50:50); (g) white solid.

Scheme 103

Prepared according to **General Procedure F**:

Table 8, entry 1: (a) *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.60 g, 1.59 mmol, *cis*:*trans*, 45:55); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.60 g, 1.74 mmol); (d) DCE (12 mL); (e) DodSMe (2 mL, 7.55 mmol); (f) 70 °C; (g) 3 h; (h) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.37 g, 0.92 mmol, **58%**, *syn*:*anti*, 70:30); and (i) white solid.

Table 8, entry 2: (a) *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.61 g, 1.60 mmol, *cis*:*trans*, 48:52); (b) pet. ether (12 mL); (c) $Co_2(CO)_8$ (0.58 g, 1.69 mmol); (d) DCE (12 mL); (e) DodSMe (2.01 mL, 7.6 mmol); (f) 70 °C; (g) 1.5 h; (h) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.34 g, 0.82 mmol, **52%**, *syn*:*anti*, 41:59); and (i) white solid.

Table 8, entry 3: (a) *N*-(prop-2-yn-1-yl)-*N*-(3-((triethylsilyl)oxy)allyl)toluenesulfonamide (0.44 g, 1.15 mmol, *cis*:*trans*, 48:52); (b) pet. ether (12 mL); (c) $Co_2(CO)_8$ (0.41 g, 1.21 mmol); (d) DCE (12 mL); (e) DodSMe (1.45 mL, 5.47 mmol); (f) 55 °C; (g) 8 h; (h) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.28 g, 0.69 mmol, **60%**, *syn*:*anti*, 48:52); and (i) white solid.

***Syn* isomer**

^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 7.73 – 7.66 (2H, m, H_A), 7.35 – 7.29 (2H, m, H_B), 5.88 – 5.86 (1H, m, H_C), 4.26 (1H, dt, ^2J = 17.1 Hz, ^4J = 2.0 Hz, H_D), 4.12 (1H, d, J = 5.4 Hz, H_E), 4.04 (1H, d, ^2J = 17.0 Hz, H_D) 3.70 (1H, apparent t, ^2J = 8.0 Hz, J = 8.0 Hz, H_F) 3.20 – 3.11 (1H, m, H_G), 3.08 (1H, dd, ^2J = 10.6 Hz, J = 8.3 Hz, H_F), 2.46 (3H, s, H_H), 0.88 (9H, t, J = 7.9 Hz, H_I), 0.65 – 0.54 (6H, m, H_J). ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 206.1, 177.6, 144.2, 133.3, 130.0, 127.5, 123.2, 71.8, 48.6, 48.4, 46.5, 21.5, 6.6, 4.7 ppm.

***Anti* isomer**

^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 7.73 – 7.66 (2H, m, H_1), 7.35 – 7.29 (2H, m, H_2), 5.97 (1H, dd, ^4J = 3.7 Hz, ^4J = 1.8 Hz, H_3), 4.29 (1H, dt, ^2J = 11.4 Hz, ^4J = 1.8 Hz, H_4), 4.06 (1H, dd, ^2J = 9.5 Hz, J = 8.5 Hz, H_5), 4.00 (1H, dt, ^2J = 17.0 Hz, ^4J = 1.4 Hz, H_4), 3.88 (1H, d, J = 3.6 Hz, H_6), 3.05 – 2.95 (1H, m, H_7), 2.78 (1H, dd, J = 10.6 Hz, ^2J = 9.5 Hz, H_5), 2.40 (3H, s, H_8), 0.94 (9H, t, J = 7.9 Hz, H_9), 0.65 – 0.54 (6H, m, H_{10}). ppm.

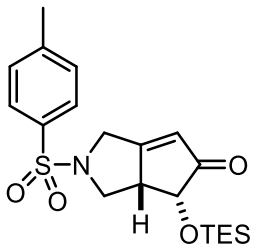
^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 205.0, 172.5, 144.3, 133.5, 130.0, 127.4, 123.6, 79.3, 51.9, 51.4, 47.8, 21.6, 6.6, 4.7 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2937, 2911, 2877, 1715, 1645.

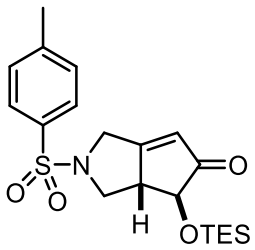
HRMS (NSI/ion trap) m/z: [M+H]$^+$ calcd for $C_{20}H_{30}NO_4SSi$: 408.1659; **found:** 408.1659.

Melting point: Decomposes over 60 – 68 °C.

Attempts to epimerise 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one.



***syn*-209**



***anti*-209**

Scheme 104

2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.386 g, 0.95 mmol, *syn*:*anti*, 70:30) was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in DCE (12 mL). DodSMe (1.2 mL, 4.5 mmol) and black cobalt residues (0.187 g) were added to the solution and the resulting mixture was heated to 70 °C for 5 h. The reaction was cooled to room temperature and solvent was removed *in vacuo* to provide the crude material as a black gum. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to provide 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.336 g, 0.82 mmol, *syn*:*anti*, 32:68) as a pale yellow oil.

Scheme 105

According to ***General Procedure G***:

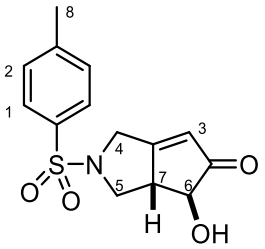
Table 9, **Entry 1**: (a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.082 g, 0.201 mmol); (b) DCE (20 mL); (c) N/A; (d) N/A; (e) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.082 g, 0.201 mmol, **quant**.); and (f) *syn*:*anti* 90:10

Table 9, **Entry 2**: (a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.044 g, 0.11 mmol); (b) DCE (10 mL); (c) DodSMe (0.135 mL, 0.51 mmol); (d) N/A; (e) yield of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.039 g, 0.096 mmol, **87%**); and (f) *syn*:*anti* 90:10.

Table 9, **Entry 3**: (a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.114 g, 0.28 mmol); (b) DCE (28 mL); (c) N/A (d) $Co_2(CO)_8$ (0.096 g, 0.28 mmol); (e) yield of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.069 g, 0.17 mmol, **61%**); and (f) *syn*:*anti* 80:20.

Table 9, **Entry 4**: (a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.092 g, 0.23 mmol); (b) DCE (23 mL); (c) DodSMe (0.28 mL, 1.07 mmol); (d) $Co_2(CO)_8$ (0.08 g, 0.23 mmol); (e) yield of 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.062 g, 0.152 mmol, **67%**); and (f) *syn*:*anti* 90:10.

Preparation of 4-hydroxy-2-tosyl-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one.



***anti*-215**

Scheme 106

Prepared according to **General Procedure D**:

(a) 2-tosyl-3*a*-((triethylsilyl)oxy)-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.24 g, 0.64 mmol, *syn*:*anti*, 30:70); (b) THF:H_2O (10:1) (5 mL); (c) 3 M aqueous HCl (0.81 mL); (d) room temperature; (e) 5 h; (f) 4-hydroxy-2-tosyl-2,3,3*a*,4-tetrahydrocyclopenta[c]pyrrol-5(1*H*)-one (0.05 g, 0.17 mmol, **20%**); and (g) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.79 – 7.74 (2H, m, H_1), 7.41 – 7.65 (2H, m, H_2), 6.09 (1H, dd, ^4J = 3.6 Hz, ^4J = 1.9 Hz, H_3), 4.35 (1H, dt, ^2J = 17.3 Hz, ^4J = 1.8 Hz, H_4), 4.18 (1H, dd, ^2J = 9.5 Hz, J = 8.6 Hz, H_5), 4.09 (1H, d, ^2J = 17.2 Hz, H_4), 3.95 (1H, apparent d, ^4J = 3.6 Hz, H_6), 3.15 – 3.06 (1H, m, H_7), 2.92 (1H, s, OH), 2.86 (1H, dd, J = 10.6 Hz, ^2J = 9.5 Hz, H_5), 2.47 (3H, s, H_8) ppm.

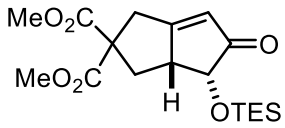
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.5, 174.8, 144.3, 133.3, 130.0, 127.4, 122.6, 78.9, 51.13, 51.10, 47.7 21.5 ppm.

IR (ν_{max}/cm^{-1}): 3445, 3063, 2916, 1711, 1659, 1344, 1159.

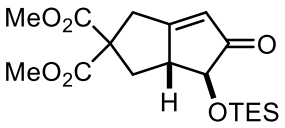
HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{14}H_{15}NO_4SH$: 294.0795**; found:** 294.0791

Melting point: decomposes over 153 – 158 °C.

Attempts to epimerise dimethyl 5-oxo-4-((triethylsilyl)oxy)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



***syn*-199**

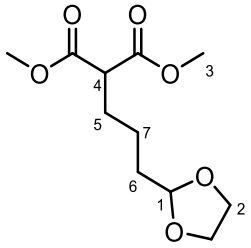


***anti*-199**

Scheme 107

Dimethyl 5-oxo-4-((triethylsilyl)oxy)-3,3a,4,5-tetrahydropentalene-2,2(1H)-dicarboxylate (0.095 g, 0.258 mmol, *syn*:*anti*, 69:31) was added to a flame-dried, round-bottom flask and dissolved in dry THF (5.2 mL) and the solution was cooled to 0 °C. DBU (0.005 mL, 0.032 mmol) was added to the solution and the resulting mixture was warmed to room temperature and stirred for 16 h. After this time, TLC analysis showed a complex mixture of products and so the reaction was quenched and discarded.

Preparation of dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate.[189]



222

Scheme 110

Prepared according to **General Procedure H**:

Table 10, Entry 1: (a) NaH (0.13 g, 3.35 mmol); (b) THF (15 mL); (c) dimethyl malonate (0.35 mL, 3.05 mmol); (d) 2-(3-chloropropyl)-1,3-dioxolane (0.44 mL, 3.35 mmol); (e) no additive; (f) no reaction; and (g) N/A.

Table 10, Entry 2: (a) NaH (0.13 g, 3.35 mmol) (b) THF (15 mL) (c) dimethyl malonate (0.35 mL, 3.05 mmol); (d) 2-(3-chloropropyl)-1,3-dioxolane (0.44 mL, 3.35 mmol); (e) NaI (0.09 g, 0.61 mmol); (f) dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate (0.04 g, 0.18 mmol, **6%**); and (g) colourless oil.

Table 10, Entry 3: (a) NaH (0.15 g, 3.80 mmol) (b) THF (15 mL); (c) dimethyl malonate (0.4 mL, 3.45 mmol); (d) 2-(3-chloropropyl)-1,3-dioxolane (0.5 mL, 3.80 mmol); (e) TBAI (0.32 g, 0.86 mmol); (f) dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate (0.26 g, 1.04 mmol, **30%**); and (g) colourless oil.

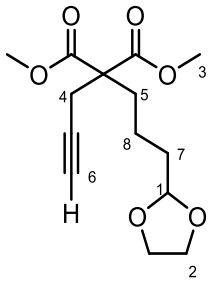
Table 10, Entry 4: (a) NaH (0.12 g, 2.97 mmol); (b) THF:NMP (3:1), (12 mL); (c) dimethyl malonate (0.31 mL, 2.70 mmol); (d) 2-(3-chloropropyl)-1,3-dioxolane (0.32 mL, 2.43 mmol); (e) TBAI (0.25 g, 0.68 mmol); (f) dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate (0.38 g, 1.56 mmol, **64%**); and (g) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.86 (1H, t, *J* = 4.7 Hz, H_1), 4.00 – 3.82 (4H, m, H_2), 3.75 (6H, s, H_3), 3.39 (1H, t, *J* = 7.5 Hz, H_4), 2.02 – 1.93 (2H, m, H_5), 1.74 – 1.66 (2H, m, H_6), 1.53 – 1.42 (2H, m, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.3, 103.6, 64.4, 52.0, 51.2, 32.9, 28.2, 21.4 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2878, 1749, 1732, 1435, 1142.

Preparation of dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)-2-(prop-2-yn-1-yl)malonate.[189]



221

Scheme 111

NaH (60% dispersion in mineral oil) (0.12 g, 2.94 mmol) and dry THF (12 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)malonate (0.60 g, 2.45 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, propargyl bromide (0.33 mL, 3.67 mmol) was added dropwise and reaction mixture warmed to rt. The reaction mixture was stirred for 3 h and then quenched by the addition of NH_4Cl (20 mL). Following

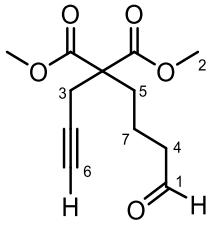
this, EtOAc (20 mL) was added to create a biphasic mixture, which was separated, and the aqueous layer was washed with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flushed through a plug of silica gel and concentrated *in vacuo* to provide dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)-2-(prop-2-yn-1-yl)malonate (0.68g, 2.40 mmol, **98%**) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.86 (1H, t, *J* = 4.6 Hz, H_1), 3.99 – 3.83 (4H, m, H_2), 3.75 (6H, s, H_3), 2.84 (2H, d, ^4J = 4.6 Hz, H_4), 2.15 – 2.07 (2H, m, H_5), 2.01 (1H, t, ^4J = 2.7 Hz, H_6), 1.74 – 1.66 (2H, m, H_7), 1.39 – 1.28 (2H, m, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.1, 103.5, 78.3, 70.8, 64.4, 56.5, 52.3, 33.4, 31.5, 22.3, 18.1 ppm.

IR (ν_{max}/cm^{-1}): 3281, 2955, 2880, 1730, 1435, 1200

Preparation of dimethyl 2-(4-oxobutyl)-2-(prop-2-yn-1-yl)malonate.[186]



220

Scheme 111

Dimethyl 2-(3-(1,3-dioxolan-2-yl)propyl)-2-(prop-2-yn-1-yl)malonate (0.64 g, 2.23 mmol) and dry THF (10 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. 6M HCl (40 mL) and H_2O:AcOH (1:1) (25 mL) were added to the solution and the reaction mixture was stirred at room temperature for 24 h. This was quenched by the addition of solid K_2CO_3 (25 g) and then by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). Et_2O (25 mL) was added, the organic phase separated, and the aqueous phase was washed with Et_2O (3 × 25 mL). The combined organic extracts were washed with brine (15 mL), dried over

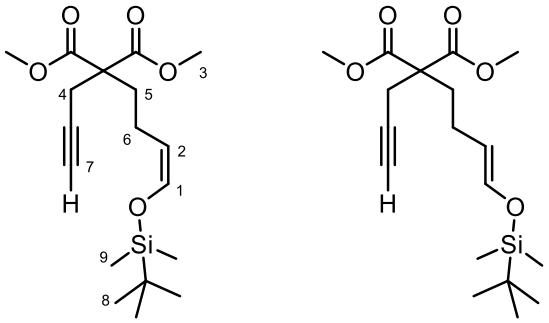
Na_2SO_4, filtered, and concentrated *in vacuo* to provide dimethyl 2-(4-oxobutyl)-2-(prop-2-yn-1-yl)malonate (0.45 g, 1.87 mmol, **84%**) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.78 (1H, t, *J* = 1.4 Hz H_1), 3.77 (6H, s, H_2), 2.88 (2H, d, ^4J = 2.7 Hz, H_3), 2.50 (2H, td, *J* = 10.9 Hz, *J* = 1.4 Hz, H_4), 2.13 – 2.06 (2H, m, H_5), 2.03 (1H, t, ^4J = 2.7 Hz, H_6), 1.62 – 1.54 (2H, m, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.0, 169.9, 78.1, 71.1, 56.3, 52.4, 43.2, 31.1, 22.4, 16.4 ppm.

IR (ν_{max}/cm^{-1}): 3281, 2955, 1726, 1200, 1179.

Preparation of dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate.



***cis*-219** ***trans*-219**

Scheme 112

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(4-oxobutyl)-2-(prop-2-yn-1-yl)malonate (0.45 g, 1.87 mmol); (b) DCE (12 mL); (c) DIPEA (0.36 mL, 2.06 mmol); (d) TBSOTf (0.46 mL, 2.06 mmol); (e) dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.58 g, 1.63 mmol, **84%**, *cis*:*trans*, 92:8); and (f) as a colourless oil. To note this reaction was conducted for 2 h.

***Cis* isomer**

^{1}H NMR ($CDCl_3$, 400MHz): δ_H 6.20 (1H, dt, *J* = 5.8 Hz, ^4J = 1.4 Hz, H_1), 4.42 (1H, td, *J* = 10.5 Hz, *J* = 5.9 Hz, H_2), 3.75 (6H, s, H_3), 2.89 (2H, d, ^4J = 2.7 Hz, H_4), 2.18 – 2.11 (2H, m, H_5), 2.06 – 1.99 (2H, m, H_6), 2.01 (1H, t, ^4J = 2.7 Hz, H_7), 0.94 (9H, s, H_8), 0.14 (6H, s, H_9) ppm.

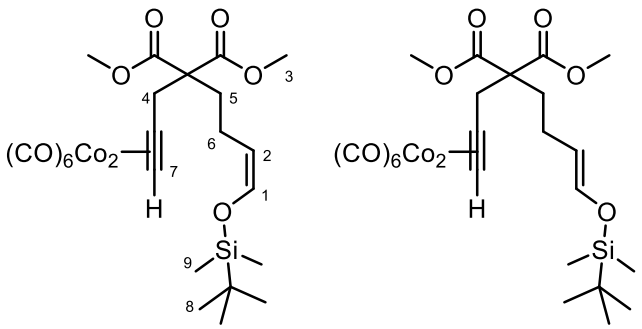
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 170.5, 138.8, 108.1, 78.5, 70.7, 56.4, 52.2, 31.3, 25.2, 22.2, 18.0, 17.8, - 5.8 ppm.

Note: ^{1}H and ^{13}C NMR chemical shift signals relating to the *trans* isomer were not sufficiently strong to fully assign.

IR (ν_{max}/cm^{-1}): 3292, 2953, 2930, 2857, 1736, 1655.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{18}H_{31}O_5Si$: 355.1935**; found:** 355.1940.

Preparation of dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



***cis*-223** ***trans*-223**

Scheme 113

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.41 g, 1.07 mmol, *cis*:*trans*, 92:8); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.54 g, 1.58 mmol); (d) Dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate complex (0.97 g, 1.51 mmol, **quant.**, *cis*:*trans*, 92:8); and (e) red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.22 (1H, d, J = 5.7 Hz, H_1), 6.03 (1H, s, H_2), 4.45 – 4.36 (1H, m, H_3), 3.76 (6H, s, H_4), 3.71 (2H, s, H_5), 2.06 (2H, s, H_6), 2.05 (2H, s, H_7), 0.95 (9H, s, H_8), 0.16 (6H, s, H_9) ppm.

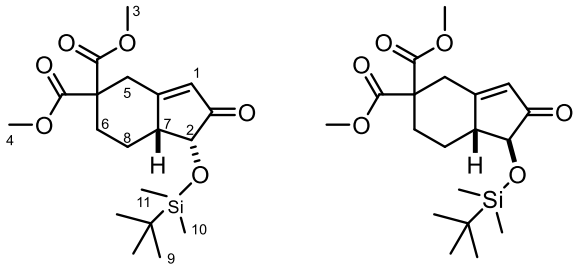
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.2, 170.4, 139.0, 107.5, 72.9, 57.7, 52.1, 37.1, 31.9, 25.1, 18.3, 17.8, - 5.9 ppm.

Signals for the *trans*-isomer were not strong enough to fully assign.

IR (ν_{max}/cm^{-1}): 2951, 2091, 2050, 1998, 1971, 1736, 1657.

HRMS for this compound could not be obtained.

Preparation of dimethyl 1-((*tert*-butyldimethylsilyl)oxy)-2-oxo-1,2,4,6,7,7a-hexahydro-5*H*-indene-5,5-dicarboxylate.



***syn*-218** ***anti*-218**

Scheme 113

Prepared according to **General Procedure A**:

(a) Dimethyl 2-(4-((*tert*-butyldimethylsilyl)oxy)but-3-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.94 g, 1.47 mmol, *cis*:*trans*, 92:8); (b) DCE (15 mL); (c) DodSMe (1.85 mL, 6.97 mmol); (d) 70 °C; (e) 24 h; (f) dimethyl 1-((*tert*-butyldimethylsilyl)oxy)-2-oxo-1,2,4,6,7,7*a*-hexahydro-5*H*-indene-5,5-dicarboxylate (0.31 g, 0.81 mmol, **55%**, *syn*:*anti*, 73:27); and (g) white solid.

***syn*-215**

^{1}H NMR ($CDCl_3$, 400 MHz): 5.97 (1H, t, ^4J = 1.8 Hz, H_1), 3.81 (1H, d, J = 2.9 Hz, H_2), 3.79 (3H, s, $H_{3/4}$), 3.75 (3H, s, $H_{3/4}$), 3.47 (1H, dd, ^2J = 14.6 Hz, ^4J = 1.8 Hz, H_5), 2.65 (1H, d, ^2J = 14.7 Hz, H_5), 2.61 – 2.51 (1H, m, $H_{6)}$ 2.60 – 2.52 (1H, m, H_7), 2.34 – 2.25 (1H, m, H_8), 1.99 (1H, td, J = 13.7 Hz, J = 3.4 Hz, H_7), 1.39 – 1.26 (1H, m, H_8), 0.93 (9H, s, H_9), 0.18 (3H, s, H_{10}). 0.14 (3H, s, H_{10}). ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.0, 172.5, 170.7, 169.7, 126.8, 79.2, 55.2, 52.6, 52.4, 48.2, 34.9, 29.8, 27.2, 25.3, 17.8, -4.8, -5.6 ppm.

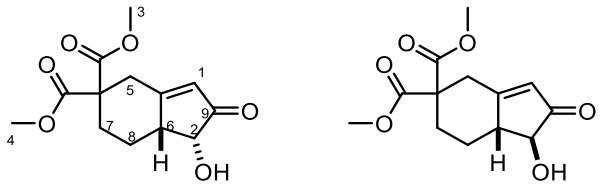
Signals for the *anti*-isomer were not strong enough to fully assign.

IR (ν_{max}/cm^{-1}): 2928, 2855, 1722, 1705, 1618.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{19}H_{31}O_6Si$: 383.1884**; found:** 383.1885.

Melting point: 122 – 124 °C.

Preparation of dimethyl 1-hydroxy-2-oxo-1,2,4,6,7,7*a*-hexahydro-5*H*-indene-5,5-dicarboxylate.



***syn*-224** ***anti*-224**

Scheme 114

Prepared according to **General Procedure D**:

(a) Dimethyl 1-((*tert*-butyldimethylsilyl)oxy)-2-oxo-1,2,4,6,7,7*a*-hexahydro-5*H*-indene-5,5-dicarboxylate (0.275 g, 0.72 mmol, *syn*:*anti*, 73:27); (b) THF:H_2O (10:1) (4.25 mL); (c) 3 M aqueous HCl (0.08 mL); (d) room temperature; (e) 18 h; (f) dimethyl 1-hydroxy-2-oxo-1,2,4,6,7,7*a*-hexahydro-5*H*-indene-5,5-dicarboxylate (0.17g, 0.62 mmol, **86%**, *syn*:*anti*, 79:21); and (g) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.02 (1H, dd, ^4J = 1.5 Hz, ^4J = 1.5 Hz, H_1), 4.21 (1H, dd, J = 6.6 Hz, J = 2.2 Hz, H_2), 3.77 (3H, s, $H_{3/4}$), 3.72 (3H, s, $H_{3/4}$), 3.53 (1H, dd, J = 13.4 Hz, J = 2.2 Hz, H_5), 2.89 – 2.81 (1H, m, H_6), 2.72 – 2.67 (1H, m, H_5), 2.60 (1H, dq, J = 14.1 Hz, J = 2.9 Hz, H_7), 2.21 (1H, m, H_8), 1.94 (1H, td, J = 20.8 Hz, J = 3.8 Hz, H_7), 1.72 (1H, s, OH), 1.33 (1H, qd, J = 22.1 Hz, J = 3.4 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.4, 178.8, 171.3, 169.8, 126.1, 72.6, 57.7, 53.4, 53.0, 45.4, 36.2, 30.5, 25.9 ppm.

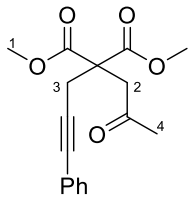
Signals for the *anti*-isomer were not strong enough to fully assign.

IR (ν_{max}/cm^{-1}): 3368, 3350, 2957, 1724, 1686, 1618, 1435, 1251, 1047.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{13}H_{17}O_6$: 269.1025**; found:** 269.1019.

Melting point: 122 – 124 °C.

Preparation of Preparation of dimethyl 2-(2-oxopropyl)-2-(3-phenylprop-2-yn-1-yl)malonate.



225

Scheme 115

NaH (60% dispersion in mineral oil) (0.22 g, 5.5 mmol) and distilled THF (17 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(2-oxopropyl)malonate (0.94 g, 5 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was warmed to room temperature and (3-bromoprop-1-yn-1-yl)benzene (1.17 g, 6 mmol) was added dropwise. The reaction mixture was stirred for 16 h and then quenched by the addition of 2 M HCl (20 mL). Following this, Et_2O (20 mL) was added to create a biphasic mixture. The organic phase was separated and the aqueous phase washed with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as an orange oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 50:50) and concentrated *in vacuo* to provide the desired product (1.27 g, 4.2 mmol, **84%**) as a colourless oil.

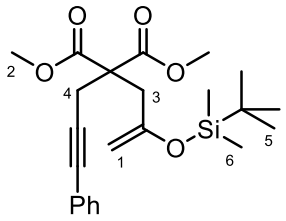
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.41 – 7.26 (5H, m, ArH), 3.78 (6H, s, H_1), 3.43 (2H, s, H_2), 3.24 (2H, s, H_3) 2.22 (3H, s, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.9, 169.2, 131.1, 127.8, 127.6, 122.5, 83.9, 83.3, 54.2, 52.6, 41.1, 29.7, 23.8 ppm.

IR (ν_{max}/cm^{-1}): 2953, 1736, 1717.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{17}H_{19}O_5$: 303.1233**; found** 303.1230.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate.



226

Scheme 115

Prepared according to **General Procedure B**.

(a) Dimethyl 2-(2-oxopropyl)-2-(3-phenylprop-2-yn-1-yl)malonate (1.26 g, 4.17 mmol); (b) DCE (15 mL); (c) DIPEA (0.88 mL, 6 mmol); (d) TBSOTf (1.15 mL, 5.01 mmol); (e) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate (1.58 g, 3.8 mmol, **91%**); and (f) colourless oil.

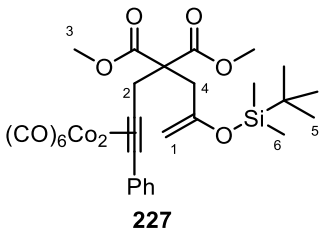
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.40 – 7.27 (5H, m, ArH), 4.21 (1H, d, ^2J = 0.98 Hz H_1), 4.18 (1H, d, ^2J = 0.98 Hz H_1), 3.77 (6H, s, H_2), 3.18 (2H, s, H_3), 2.92 (2H, s, H_4), 0.95 (9H, s, H_5), 0.19 (6H, s, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 154.3, 131.1, 127.7, 127.3, 123.0, 93.5, 84.5, 83.0, 56.3, 52.3, 38.7, 25.3, 23.1, 17.8, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 1738, 1628.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{23}H_{33}O_5Si$: 417.2097**; found** 417.2098.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



227

Scheme 115

Prepared according to **General Procedure C**.

(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate (1.53 g, 3.67 mmol); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (1.32 g, 3.86 mmol); (d) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (2.57 g, 3.66 mmol, **quant**.); and (e) red oil.

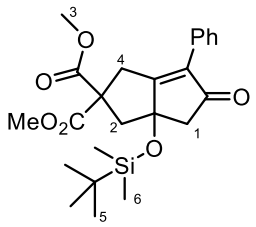
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.50 – 7.21 (5H, m, ArH), 4.13 (1H, s, H_1), 4.04 (1H, s, H_1), 3.87 (2H, s, H_2), 3.54 (6H, s ,H_3), 2.90 (2H, s, H_4), 0.94 (9H, s, H_5), 0.18 (6H, s, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.5, 170.5, 154.8, 138.5, 129.0, 128.7, 127.5, 94.8, 93.7, 91.4, 57.7, 52.3, 41.9, 38.5, 25.9, 18.3, -4.6 ppm.

IR (ν_{max}/cm^{-1}): 2089, 2047, 1994, 1734, 1626.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{29}H_{33}Co_2O_{11}Si$: 703.0456**; found** 703.0460.

Preparation of dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-5-oxo-6-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



228

Scheme 116

Prepared according to **General Procedure A**.

(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.98 g, 1.4 mmol); (b) DodSMe (1.76 mL, 6.65 mmol); (c) DCE (15 mL); (d) 70 °C; (e) 16 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-5-oxo-6-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate 0.145 g, 0.33 mmol, **24%**; and (g) colourless oil. To note, starting material (0.128 g, 0.18 mmol, 13%) and decomplexed starting material (0.07 g, 0.17 mmol, 12%) were also recovered.

Scheme 118

(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(3-phenylprop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.98 g, 1.4 mmol); (b) DodSMe (1.76 mL, 6.65 mmol); (c) DCE

(15 mL); (d) reflux; (e) 16 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-5-oxo-6-phenyl-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate 0.04 g, 0.09 mmol, **6%**; and (g) colourless oil.

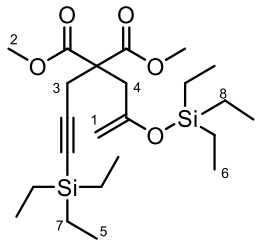
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.40 – 7.22 (5H, m, ArH), 4.09 (1H, d, ^2J = 18.8 Hz, H_1), 3.82 (3H, s, H_3), 3.70 (3H, s, H_3), 3.10 (1H, d, ^2J = 18.8 Hz, H_1), 3.07 (1H, d, ^2J = 14.2 Hz, H_2), 2.80 (1H, d, ^2J = 18.2 Hz H_5), 2.71 (1H, d, ^2J = 18.2 Hz H_5), 2.36 (1H, d, ^2J = 14.2 Hz, H_2), 0.85 (9H, s, H_6), 0.05 (3H, s, H_7), 0.02 (3H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.8, 174.8, 171.4, 170.5, 135.1, 129.7, 128.4, 128.3, 128.1, 83.3, 60.7, 52.8, 52.7, 48.4, 46.4, 34.3, 25.1, 17.4, -3.5, -3.8 ppm.

IR (ν_{max}/cm^{-1}): 2951, 2928, 2855, 1734, 1713.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{24}H_{33}O_6Si$: 445.2038**; found** 445.2041.

Preparation of dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate.



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Scheme 118

Di*iso*propylamine (0.74 mL, 5.3 mmol) was added to a flame-dried Schlenk flask equipped with a stirrer bar, dissolved in dry THF (8 mL), and the mixture was cooled to 0 °C. 2.5 M ^{n}butyllithium in hexane (2.12 mL, 5.3 mmol) was added dropwise and the mixture was stirred for 30 minutes then cooled to -78 °C using a dry ice/acetone bath. At this point, the dimethyl 2-(2-oxopropyl)-2-(3-phenylprop-2-yn-1-yl)malonate (0.54 g, 2.4 mmol) was added dropwise as a solution in THF (4.5 mL) followed by TESCl (0.89 mL, 5.3 mmol) in one portion. After 4 h, the mixture was allowed to warm to room temperature and saturated aqueous $NaHCO_3$ solution and EtOAc were added to create a biphasic mixture, which was separated, and the aqueous layer was washed with EtOAc. The combined organic extracts were washed with

brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5 – 70:30) and concentrated *in vacuo* to provide the desired product (0.38 g, 0.83 mmol, **35%**) as a colourless oil.

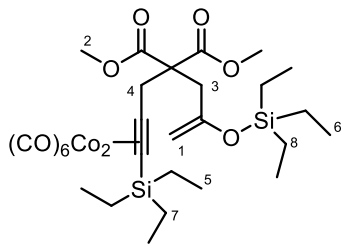
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.17 (1H, d, ^2J = 0.98 Hz, H_1), 4.14 (1H, d, ^2J = 0.98 Hz, H_1), 3.73 (6H, s, H_2), 2.97 (2H, s, H_3), 2.88 (2H, s, H_4), 0.99 (9H, t, J = 8.0 Hz, H_5), 0.98 (9H, t, J = 8.0 Hz, H_6), 0.70 (6H, q,J = 8.0 Hz, H_7), 0.58 (6H, q, J = 8.0 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 154.2, 102.5, 92.4, 84.5, 55.6, 52.0, 38.6, 23.4, 6.9, 6.1, 4.1, 3.9 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2913, 2876, 1742.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{23}H_{43}O_5Si_2$: 455.2644; **found**: 455.2648.

Preparation of dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



230

Scheme 118

Prepared according to **General Procedure C**.

(a) Dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate (0.58 g, 1.27 mmol); (b) pet. ether (10 mL); (c) $Co_2(CO)_8$ (0.46 g, 1.33 mmol); (d) dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.91 g, 1.22 mmol, **96%**); and (e) red oil.

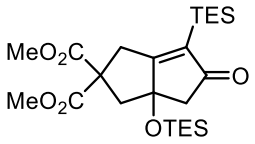
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.15 (2H, m, H_1), 3.76 (6H, s, H_2), 3.68 (2H, s, H_3), 2.97 (2H, s, H_4), 1.10 (9H, t, J = 8.0 Hz, H_5), 0.98 (9H, t, J = 8.0 Hz, H_6), 0.87 (6H, q, J = 8.0 Hz, H_7), 0.71 (6H, q, J = 8.0 Hz, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 200.2, 170.5, 154.7, 104.2, 92.7, 81.3, 56.8, 52.5, 40.6, 37.6, 7.8, 6.7, 5.8, 4.6 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2913, 2878, 2087, 2043, 2008, 1742.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{29}H_{43}O_{11}Co_2Si_2$: 741.1002; **found**: 741.0998.

Preparation of dimethyl 5-oxo-6-(triethylsilyl)-3a-((triethylsilyl)oxy)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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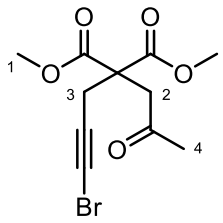
Scheme 119

Prepared according to **General Procedure A**.

(a) Dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(3-(triethylsilyl)prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.44 g, 0.59 mmol); (b) DCE (6 mL); (c) DodSMe (0.75 mL, 2.82 mmol); (d) 70 °C; (e) 16 h; (f) 0%; and (g) N/A.

Preparation of dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-oxopropyl)malonate.



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Scheme 120

Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.57 g, 2.50 mmol) was added to a flame-dried, round-bottom flask, and dissolved in distilled acetone (6 mL). *N*-bromosuccinimide (0.49 g, 2.75 mmol) and $AgCO_3$ (0.042 g, 0.25 mmol) were added sequentially and the reaction mixture was stirred at room temperature for 1 h. After this time, the reaction was quenched by addition of H_2O (10 mL) and Et_2O (10 mL) to create a biphasic mixture which was separated, and the aqueous layer washed with Et_2O (3 × 10 mL). The

combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5 – 70:30) and concentrated *in vacuo* to provide the dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.53 g, 1.72 mmol, **69%**) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.75 (6H, s, H_1), 3.33 (2H, s, H_2), 3.05 (2H, s, H_3), 2.20 (3H, s, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.6, 168.9, 74.7, 53.8, 52.6, 45.0, 41.3, 29.6, 24.0 ppm.

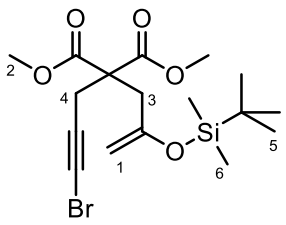
IR (ν_{max}/cm^{-1}): 2961, 1758, 1728, 1717.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{11}H_{14}{}^{79}BrO_5$: 305.0025; **found**: 305.0018.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{11}H_{14}{}^{81}BrO_5$: 307.0005; **found**: 306.9999.

Melting point: 55 – 57 °C.

Preparation of dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate.



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Scheme 120

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.26 g, 0.86 mmol); (b) DCE (8.6 mL); (c) DIPEA (0.18 mL, 1.03 mmol); (d) TBSOTf (0.24 mL, 1.03 mmol); (e) dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate (0.26 g, 0.61 mmol, **71%**); and (f) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.20 – 4.14 (2H, m, H_1), 3.76 (6H, s, H_2), 2.99 (2H, s, H_3), 2.85 (2H, s, H_4), 0.95 (9H, s, H_5), 0.19 (6H, s, H_6) ppm.

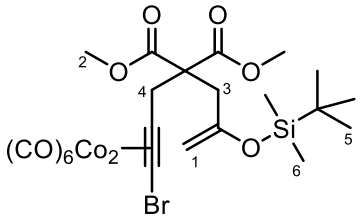
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.5, 154.1, 93.6, 75.1, 55.9, 52.3, 40.7, 38.7, 25.3, 23.5, 17.8, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 1740.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{17}H_{28}{}^{79}BrO_5Si$: 419.0889; **found**: 419.0886

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{17}H_{28}{}^{81}BrO_5Si$: 421.0871; **found**: 421.0866.

Preparation of dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate dicobalthexacarbonyl complex.



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Scheme 120

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate (0.247 g, 0.59 mmol); (b) pet. ether (15 mL); (c) $Co_2(CO)_8$ (0.211 g, 0.62 mmol); (d) dicobalthexacarbonyl complex (0.403 g, 0.57 mmol, **quant.**); and (e) red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.25 (1H, s, H_1), 4.21 (1H, s, H_1), 3.81 (6H, s, H_2), 3.81 (2H, s, H_3), 2.97 (2H, s, H_4), 0.98 (9H, s, H_5), 0.22 (6H, s, H_6) ppm.

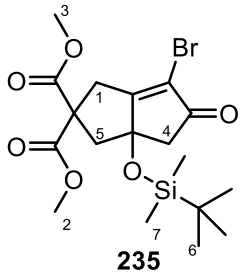
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 197.3, 169.9, 154.2, 93.4, 91.2, 85.3, 56.6, 52.1, 40.7, 36.4, 25.4, 17.9, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 2955, 2932, 2859, 2099, 2058, 2023, 1740.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{23}H_{28}{}^{79}BrO_{11}Co_2Si$: 704.9248; **found**: 704.9253.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{23}H_{28}{}^{81}BrO_{11}Co_2Si$: 706.9232; **found**: 706.9236.

Preparation of dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate.



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Scheme 121

Prepared according to **General Procedure A**.

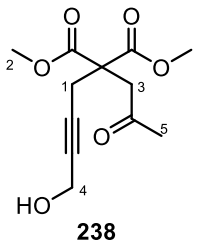
(a) dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate dicobalthexacarbonyl complex (0.403 g, 0.57 mmol); (b) DCE (6 mL); (c) DodSMe (0.72 mL, 2.71 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 2-(3-bromoprop-2-yn-1-yl)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)malonate (0.032 g, 0.072 mmol, **13%**); and (g) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.89 (1H, d, ^2J = 19.0 Hz, H_1), 3.81 (3H, s, H_2), 3.77 (3H, s, H_3), 3.28 (1H, d, ^2J = 18.8 Hz, H_1), 3.02 (1H, d, ^2J = 14.1 Hz, H_4), 2.70 (1H, d, ^2J = 18.1 Hz, H_5), 2.63 (1H, d, ^2J = 18.6 Hz, H_5), 2.43 (1H, d, ^2J = 13.6 Hz, H_4), 0.84 (9H, s, H_6), 0.05 (3H, s, H_7), 0.03 (3H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 203.5, 180.0, 171.4, 170.4, 126.6, 83.7, 600, 52.7, 52.6, 47.4, 46.4, 34.6, 25.0, 17.4, -3.5, -4.1 ppm.

HRMS (NSI/ion trap) m/z: $[2M-2Br]^+$ calcd for $C_{36}H_{54}O_{12}Si_2$: 735.3227; **found:** 735.3222.

Preparation of dimethyl 2-(4-hydroxybut-2-yn-1-yl)-2-(2-oxopropyl)malonate.



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Scheme 122

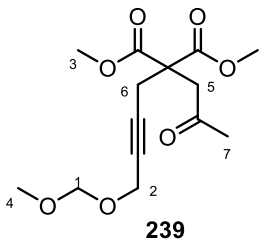
NaH (0.31 g, 7.85 mmol) and dry THF (20 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C, dimethyl 2-(2-oxopropyl)malonate (1.34 g, 7.14 mmol) was added dropwise as a solution in THF (7 mL), and the resulting mixture was stirred at 0 °C for 1 h. At this point, 4-bromobut-2-yn-1-ol (1.28 g, 8.57 mmol) was added dropwise as a solution in THF (2 mL) and the reaction mixture was warmed to rt. The reaction mixture was stirred for 3 h then quenched by the addition of NH_4Cl (20 mL) and EtOAc (20 mL) to create a biphasic mixture. This mixture was separated and the aqueous layer washed with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (15 mL) dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether 40 – 60:EtOAc, 70:30 – 30:70) and concentrated *in vacuo* to provide the desired product (1.04 g, 4.07 mmol, **57%**) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.23 (2H, t, ^5J = 2.2 Hz, H_1), 3.75 (6H, s, H_2), 3.34 (2H, s, H_3), 3.05 (2H, t, ^5J = 2.2 Hz, H_4), 2.21 (3H, s, H_5), 1.90 (1H, s, OH) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.8, 169.2, 81.4, 80.3, 53.9, 52.6, 50.6, 45.0, 29.7, 23.2 ppm.

IR (ν_{max}/cm^{-1}): 3449, 2955, 1736, 1717.

Preparation of dimethyl 2-(4-(methoxymethoxy)but-2-yn-1-yl)-2-(2-oxopropyl)malonate.



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Scheme 122

Dimethyl 2-(4-hydroxybut-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.331 g, 1.29 mmol) and dry DCM (5 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar, and cooled to 0 °C. TBAI (0.12 g, 0.32 mmol) and DIPEA (0.34 mL, 1.94 mmol) were added to this solution followed by MOMCl, and the reaction was subsequently warmed to room temperature and stirred for 16 h. The reaction was quenched by the addition of saturated

aqueous $NaHCO_3$ (5 mL), and EtOAc (15 mL) was added to create a biphasic mixture. This mixture was separated and the aqueous layer washed with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL) dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether 40 – 60:EtOAc, 70:30 – 50:50) and concentrated *in vacuo* to provide the desired product (0.22 g, 0.73 mmol, **56%**) as a colourless oil.

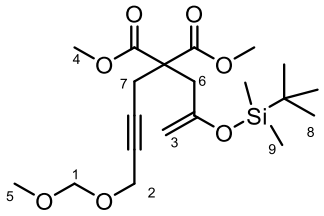
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.69 (2H, s, H_1), 4.19 (2H, t, ^5J = 2.1 Hz, H_2), 3.75 (6H, s, H_3), 3.38 (3H, s, H_4), 3.37 (2H, s, H_5), 3.07 (2H, t, ^5J = 2.2 Hz, H_6), 2.21 (3H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.8, 169.1, 94.0, 80.8, 78.5, 55.0, 53.9, 53.8, 52.6, 45.0, 29.7, 23.2 ppm.

IR (ν_{max}/cm^{-1}): 2953, 1740, 1719.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{14}H_{21}O_7$: 301.1287**; found** 301.1287

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate.



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Scheme 122

Prepared according to **General Procedure B**.

(a) Dimethyl 2-(4-(methoxymethoxy)but-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.21 g, 0.71 mmol); (b) DCE (3 mL); (c) DIPEA (0.14 mL, 0.78 mmol); (d) TBSOTf (0.18 mL, 0.78 mmol); (e) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate (0.111 g, 0.28 mmol, **38%**); and (f) as a colourless oil.

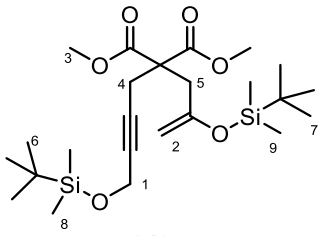
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.69 (2H, s, H_1), 4.19 (2H, t, ^5J = 2.1 Hz, H_2), 4.17 – 4.14 (2H, m, H_3), 3.74 (6H, s, H_4), 3.38 (3H, s, H_5), 2.99 (2H, t, ^4J = 2.1 Hz, H_6), 2.84 (2H, s, H_7), 0.93 (9H, s, H_8), 0.18 (6H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.7, 154.2, 149.5, 93.9, 93.5, 81.2, 78.1, 55.9, 55.0, 53.9, 52.2, 38.6, 25.3, 22.8, -3.5, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 1742, 1630.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{20}H_{35}O_7Si$: 415.2152**; found** 415.2146.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate.



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Scheme 122

Prepared according to **General Procedure B**

(a) Dimethyl 2-(4-hydroxybut-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.43 g, 1.42 mmol); (b) DCE (14.2 mL); (c) DIPEA (0.54 mL, 3.11 mmol); (d) TBSOTf (0.72 mL, 3.11 mmol); (e) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate (0.65 g, 1.33 mmol, **94%**); and (f) colourless oil.

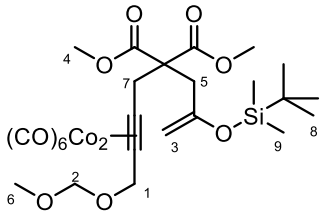
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.28 (2H, t, ^5J = 2.1 Hz, H_1), 4.17 (1H, d, ^2J = 1.0 Hz, H_2), 4.15 (1H, d, ^2J = 1.0 Hz, H_2), 3.73 (6H, s, H_3), 2.98 (2H, t, ^5J = 2.1 Hz, H_4), 2.84 (2H, s, H_5), 0.93 (9H, s, H_6), 0.91 (9H, s, H_7), 0.17 (6H, s, H_8), 0.11 (6H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.7 154.2, 93.5, 81.3, 79.5, 76.8, 76.5, 76.2, 55.8, 52.1, 51.2, 38.6, 25.4, 22.5, 17.8, -3.4, -5.1, -5.7 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2859, 1744.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{24}H_{44}O_6Si_2$: 485.2749; **found** 485.2735.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



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Scheme 123

Prepared according to **General Procedure C**.

(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate (0.11 g, 0.25 mmol); (b) pet. ether (2.5 mL); (c) $Co_2(CO)_8$ (0.09 g, 0.27 mmol); (d) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.14 g, 0.20 mmol, **79%**); and (e) red oil.

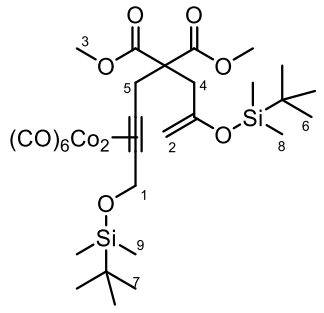
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.80 (2H, s, H_1), 4.68 (2H, s, H_2), 4.18 (1H, s, H_3), 4.14 (1H, s, H_3), 3.77 (6H, s, H_4), 3.76 (2H, s, H_5), 3.44 (3H, s, H_6), 2.84 (2H, s, H_7), 0.95 (9H, s, H_8), 0.19 (6H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.2, 170.0, 154.1, 95.7, 94.3, 93.2, 87.9, 67.3, 57.1, 54.8, 52.1, 40.5, 38.4, 25.4, 17.9, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2932, 2089, 2047, 2012, 1740.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{26}H_{35}Co_2O_{13}Si$: 701.0511**; found** 701.0505.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



243

Scheme 123

Prepared according to **General Procedure C**.

(a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate (0.62 g, 1.29 mmol); (b) pet. ether (13 mL); (c) $Co_2(CO)_8$ (0.46 g, 1.35 mmol); (d) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.95 g, 1.23 mmol, **95%**); and (e) red oil.

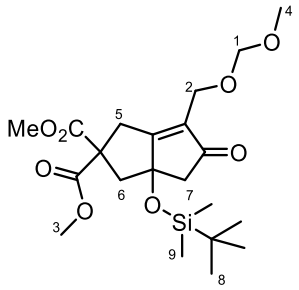
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.76 (2H, s, H_1), 4.17 (1H, d, ^2J = 1.4 Hz, H_2), 4.14 (1H, d, ^2J = 1.4 Hz, H_2), 3.76 (6H, s, H_3), 3.74 (2H, s, H_4), 2.84 (2H, s, H_5), 0.96 (9H, s, H_6), 0.95 (9H, s, H_7), 0.19 (6H, s, H_8), 0.14 (6H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.7, 170.0, 154.2, 99.0, 93.2, 87.2, 63.2, 57.1, 52.1, 40.3, 38.3, 25.4, 18.0, 17.9, -5.1, -6.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2859, 2089, 2045, 2010, 1740.

LRMS m/z (Electrospray) Calc. for $C_{28}H_{44}Co_2O_{10}Si_2$ (M-2CO): 714.1; **found:** 714.1.

Preparation of dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-((methoxymethoxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 123

Prepared according to **General Procedure A**.

Table 11, **entry 1**: (a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-(methoxymethoxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.13 g, 0.19 mmol); (b) DCE (2.3 mL); (c) DodSMe (0.29 mL, 1.11 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-((methoxymethoxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.073 g, 0.165 mmol, **87%**); and (g) colourless oil.

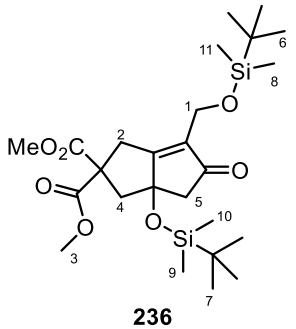
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.65 (2H, s, H_1), 4.31 (1H, d, ^2J = 13.2 Hz, ^5J = 0.9 Hz, H_2), 4.26 (1H, d, ^2J = 13.2 Hz, ^5J = 1.7 Hz, H_2), 3.80 (3H, s, H_3), 3.78 (1H, d, ^2J = 18.4 Hz, H_5), 3.74 (3H, s, H_3), 3.38 (3H, s, H_4), 3.25 (1H, d, ^2J = 18.4 Hz, H_5), 3.00 (1H, d, ^2J = 13.8 Hz, H_6), 2.64 (2H, d, ^2J = 18.5 Hz, H_7), 2.53 (2H, d, ^2J = 18.5 Hz, H_7), 2.29 (1H, d, ^2J = 14.0 Hz, H_6), 0.82 (9H, s, H_8), 0.02 (3H, s, H_9), 0.00 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.2, 177.0, 171.6, 170.5, 133.4, 95.7, 83.7, 60.3, 59.5, 54.8, 52.8, 52.6, 47.4, 46.3, 33.0, 25.0, 17.4, -3.5, -3.9 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2857, 1738, 1717, 1682.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{21}H_{35}O_8Si$: 443.2101**; found** 443.2099.

Preparation of dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 123

Prepared according to **General Procedure A**.

Table 11, entry 2: (a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.23 g, 0.3 mmol); (b) DCE (3 mL); (c) DodSMe (0.38 mL, 1.43 mmol); (d) 70 °c; (e) 16 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.125 g, 0.24 mmol, **81%**); and (g) colourless oil.

Table 11, **entry 3**: (a) Dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(4-((*tert*-butyldimethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.72 g, 0.93 mmol); (b) DCE (9.3 mL); (c) DodSMe (1.17 mL, 4.41 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 3a-

((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.42 g, 0.82 mmol, **88%**); and (g) colourless oil.

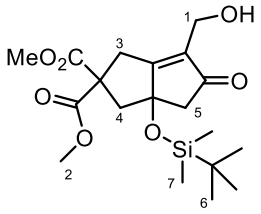
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.43 (2H, m, H_1), 3.79 (1H, dt, ^2J = 18.4 Hz, ^5J = 2.2 Hz, H_2), 3.79 (3H, s, H_3), 3.74 (3H, s, H_3), 3.33 (1H, d, ^2J = 18.7 Hz, H_2), 2.95 (1H, d, ^2J = 13.9 Hz, H_4), 2.61 (1H, d, ^2J = 18.2 Hz, H_5), 2.51 (1H, d, ^2J = 18.2 Hz, H_5), 2.30 (1H, d, ^2J = 13.9 Hz, H_4), 0.92 (9H, s, H_6), 0.82 (9H, s, H_7), 0.11 (3H, s, H_8), 0.10 (3H, s, H_9), 0.01 (3H, s, H_{10}), 0.00 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.4, 175.7, 171.7, 170.6, 136.1, 83.9, 60.5, 57.1, 52.8, 52.6, 47.5, 46.3, 33.2, 25.4, 25.0, 17.8, 17.4, -3.5, -3.8, -6.0, -6.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2857, 1738, 1717, 1682.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{25}H_{45}O_7Si$: 513.2684**; found** 513.2698.

Preparation of dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



245

Scheme 124

Prepared according to **General Procedure D**:

(a) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.325 g, 0.63 mmol); (b) THF:H_2O (10:1) (3.70 mL); (c) 3 M aqueous HCl (0.07 mL); (d) room temperature; (e) 18 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.175 g, 0.44 mmol, **70%**); and (g) colourless oil.

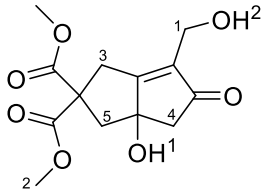
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.41 (2H, dd, J = 6.0 Hz, ^5J = 1.3 Hz, H_1), 3.80 (3H, s, H_2), 3.76 (3H, s, H_2), 3.73 (1H, d, ^2J = 18.3 Hz, H_3), 3.20 (1H, d, ^2J = 18.2 Hz, H_3), 3.02 (1H, d, ^2J = 14.0 Hz, H_4), 2.66 (1H, d, ^2J = 18.3 Hz, H_5), 2.55 (1H, d, ^2J = 18.3 Hz, H_5), 2.30 (3H, t, J = 6.1 Hz, OH), 2.28 (1H, d, ^2J = 14.0 Hz, H_4), 0.82 (9H, s, H_6), 0.04 (3H, s, H_7), 0.01 (3H, s, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.7, 175.7, 171.6, 170.3, 135.0, 83.6, 60.3, 56.0, 52.9, 52.7, 47.5, 46.3, 32.5, 25.0, 17.4, -3.5, -3.8 ppm.

IR (ν_{max}/cm^{-1}): 3449, 2953, 2930, 2857, 1736, 1715, 1676.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{19}H_{31}O_7Si$: 399.1834; **found**: 399.1826.

Preparation of dimethyl 3a-hydroxy-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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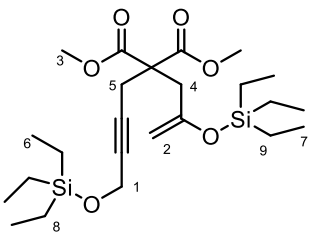
Scheme 125

Dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.045g, 0.11 mmol) was added to a flame-dried, round-bottom flask and dissolved in dry DCM (0.037 mL). A 1 M solution of TBAF in toluene (0.11 mL, 0.11 mmol) was added dropwise and the resulting mixture was allowed to stir at room temperature for 6 h. After this time, TLC analysis showed a complex mixture of products, and, as such, the reaction was abandoned.

Preparation of dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(4-((triethylsilyl)oxy)but-2-yn-1-yl)malonate.



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Scheme 126

Prepared according to **General Procedure B**:

(a) Dimethyl 2-(4-hydroxybut-2-yn-1-yl)-2-(2-oxopropyl)malonate (0.585 g, 2.28 mmol); (b) DCE (23 mL); (c) DIPEA (0.87 mL, 5.02 mmol); (d) TESOTf (1.13 mL, 5.02 mmol); (e) 0.466 g, 0.96 mmol, **86%**; and (f) colourless oil.

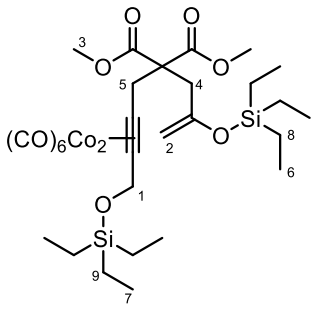
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.29 (2H, s, H_1), 4.18 (1H, s, H_2), 4.15 (1H, s, H_2), 3.74 (6H, s, H_3), 2.97 (2H, s, H_4), 2.87 (2H, s, H_5), 1.06 – 0.93 (18H, m, H_6, H_7), 0.76 – 0.59 (12H, m, H_8, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.8, 154.1, 92.4, 81.1, 79.5, 55.4, 52.0, 50.9, 38.7, 22.3, 6.1, 6.0, 4.1, 4.0 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2913, 2876, 1742.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{24}H_{45}O_6Si_2$: 485.2755; **found**: 485.2757.

Preparation of dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(4-((triethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



247

Scheme 126

Prepared according to **General Procedure C**.

(a) Dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(4-((triethylsilyl)oxy)but-2-yn-1-yl)malonate (0.466 g, 0.96 mmol); (b) pet. ether (9.6 mL); (c) $Co_2(CO)_8$ (0.345 g, 1.01 mmol); (d) dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(4-((triethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.561 g, 0.73 mmol, **76%**); and (e) red oil.

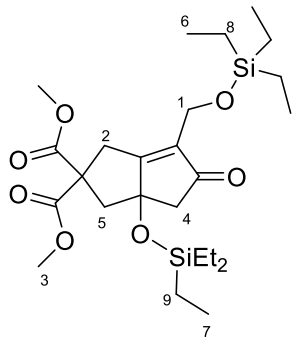
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.77 (2H, s, H_1), 4.18 – 4.12 (2H, m, H_2), 3.76 (6H, s, H_3), 3.74 (2H, s, H_4), 2.87 (2H, s, H_5), 1.02 (9H, t, J = 7.9 Hz, H_6), 1.00 (9H, t, J = 7.9 Hz, H_7), 0.72 (6H, q, J = 8.2 Hz, H_8), 0.70 (6H, q, J = 8.1 Hz, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.3, 170.0, 154.2, 99.1, 92.1, 87.2, 62.7, 56.8, 51.9, 39.8, 37.9, 6.1, 6.0, 4.1, 3.8 ppm.

IR (ν_{max}/cm^{-1}): 2954, 2878, 2089, 2045, 2010, 1740, 1624.

HRMS (NSI/ion trap) m/z: [M-Co(CO)$_6$+H]$^+$ calcd for $C_{24}H_{45}O_6Si_2$: 485.2755; **found**: 485.2753.

Preparation of dimethyl 5-oxo-3a-((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 127

Prepared according to **General Procedure A**:

(a) dimethyl 2-(2-((triethylsilyl)oxy)allyl)-2-(4-((triethylsilyl)oxy)but-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.528 g, 0.69 mmol); (b) DCE (6.9 mL); (c) DodSMe (0.87 mL, 3.28 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 5-oxo-3a-((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.25 g, 0.49 mmol, **71%**); and (g) colourless oil.

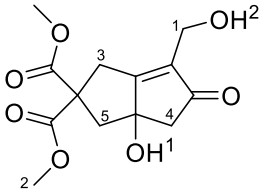
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.50 – 4.39 (2H, m, H_1), 3.83 (1H, dt, ^2J = 18.4 Hz, ^5J = 2.4 Hz, H_2), 3.81 (3H, s, H_3), 3.74 (3H, s, H_3), 3.35 (1H, d, ^2J = 18.8 Hz, H_2), 2.98 (1H, d, ^2J = 13.7 Hz, H_4), 2.63 (1H, d, ^2J = 18.1 Hz, H_5), 2.51 (1H, d, ^2J = 18.2 Hz, H_5), 2.24 (1H, d, ^2J = 13.7 Hz, H_4), 0.98 (9H, t, J = 7.9 Hz, H_6), 0.90 (9H, t, J = 7.9 Hz, H_7), 0.65 (6H, q, J = 7.9 Hz, H_8), 0.54 (6H, q, J = 7.9 Hz, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.2, 176.3, 171.7, 170.7, 135.6, 83.6, 60.7, 56.9, 52.6, 52.4, 46.9, 46.2, 33.0, 6.2, 6.2, 5.4, 3.8 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2876, 1738, 1715, 1682.

HRMS (NSI/ion trap) m/z: $[M+H]^+$ calcd for $C_{25}H_{45}O_7Si_2$: 513.2704; **found**: 513.2705.

Preparation of dimethyl 3a-hydroxy-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



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Scheme 127

Prepared according to **General Procedure D**:

(a) dimethyl 3a-((triethylsilyl)oxy)-6-(((triethylsilyl)oxy)methyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.230 g, 0.45 mmol); (b) THF:H_2O (10:1) (2.65 mL); (c) 3 M aqueous HCl (0.05 mL); (d) room temperature; (e) 18 h; (f) dimethyl 3a-hydroxy-6-(hydroxymethyl)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.098 g, 0.34 mmol, **77%**); and (g) white solid.

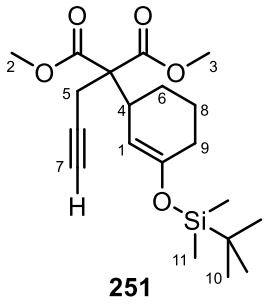
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.45 – 4.30 (2H, s, H_1), 3.84 (3H, s, H_2), 3.78 (3H, s, H_2), 3.63 (1H, d, ^2J = 19.0 Hz, H_3), 3.37 (1H, d, ^2J = 19.0 Hz, H_3), 3.22 (1H, s, OH^1), 2.99 (1H, d, ^2J = 14.2 Hz, H_4), 2.71 (1H, s, OH^2), 2.63 (1H, d, ^2J = 18.1 Hz, H_5), 2.56 (1H, d, ^2J = 18.1 Hz, H_5), 2.23 (1H, d, ^2J = 14.2 Hz, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 206.9, 175.5, 172.3, 170.8, 135.3, 82.0, 60.5, 55.7, 53.1, 52.8, 47.6, 44.1, 32.5 ppm.

IR (ν_{max}/cm^{-1}): 3262, 3086, 1734, 1715, 1684.

HRMS (NSI/ion trap) m/z: $[M-H_2O]^+$ calcd for $C_{13}H_{12}O_4$: 267.0869; **found**: 267.0871.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate.



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Scheme 128

In a flame-dried, round-bottom flask NaH (0.18 g, 4.4 mmol) was suspended in dry THF (20 mL) and cooled to 0 °C then dimethyl 2-(prop-2-yn-1-yl)malonate (0.68 g, 4 mmol) was added and the mixture was stirred for 1 h at 0 °C. In a separate flame-dried, round-bottom flask 2-Cyclohexen-1-one (0.39 mL, 4 mmol) was dissolved in dry THF (20 mL), and cooled to -78 °C. TBSOTf (1.1 mL, 4.8 mmol) and dimethyl sulfide (0.89 mL, 12 mmol) were added sequentially and the reaction was stirred at -78 °C for 1 h. After this time, the dimethyl 2-(prop-2-yn-1-yl)malonate/NaH mixture was transferred to the 2-cyclohexen-1-one/TBSOTf/dimethyl sulfide solution slowly and stirred at -78 °C for 2 h before being warmed to room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added to create a biphasic mixture, which was separated, and the aqueous layer was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide the dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.551 g, 1.45 mmol, **36%**) as a pale yellow oil.

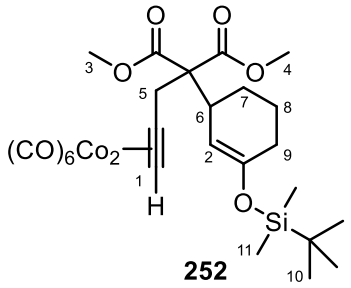
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.90 – 4.87 (1H, m, H_1), 3.76 (3H, s, H_2, 3.74 (3H, s, H_3), 3.23 – 3.15 (1H, m, H_4) 2.90 – 2.79 (2H, m, H_5), 2.09 – 2.89 (2H, m, H_6), 2.01 (1H, t, ^4J = 2.7 Hz, H_7), 1.88 – 1.76 (2H, m, H_8), 1.66 – 1.53 (1H, m, H_9), 1.36 – 1.25 (1H, m, H_9), 0.92 (9H, s, H_{10}), 0.15 (3H, s, H_{11}). 0.13 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.73, 169.68, 152.3, 103.8, 79.3, 70.5, 60.2, 51.97, 51.93, 38.5, 29.1, 25.2, 23.7, 22.0, 21.8, 17.5, -4.8, -5.1 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2857, 1732, 1672.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{20}H_{33}O_5Si$: 381.2092; **found:** 381.2092.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



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Scheme 128

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.216 g, 0.57 mmol); (b) pet. ether (5.7 mL); (c) $Co_2(CO)_8$ (0.205 g, 0.6 mmol); (d) dicobalthexacarbonyl complex (0.35 g, 0.53 mmol, **93%**); and (e) red oil.

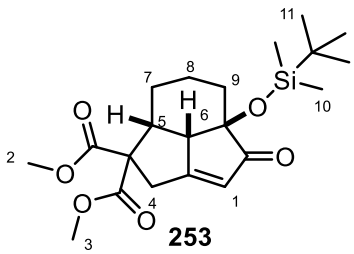
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.93 (1H, s, H_1), 4.92 (1H, s, H_2), 3.76 (3H, s, $H_{3/4}$), 3.73 (3H, s, $H_{3/4}$), 3.65 (2H, s, H_5), 3.06 – 2.97 (1H, m, H_6), 2.08 – 1.76 (4H, m, $H_{7/8/9}$), 1.38 – 1.22 (2H, s, $H_{7/8/9}$), 0.92 (9H, s, H_{10}), 0.15 (3H, s, H_{11}), 0.12 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.6, 170.3, 170.2, 152.8, 104.2, 88.5, 73.6, 62.6, 52.3, 52.2, 39.9, 38.6, 29.6, 25.6, 24.5, 22.1, 17.9, -4.3, -4.7 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2093, 2048, 1730.2, 1672.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{26}H_{33}Co_2O_{11}Si$: 667.0451; **found:** 667.0446.

Preparation of dimethyl 4a-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2,2a^1,4,4a,5,6,7,7a-octahydro-1*H*-cyclopenta[*cd*]indene-1,1-dicarboxylate.



253

Scheme 129

Prepared according to **General Procedure A**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.33 g, 0.5 mmol); (b) DCE (5 mL); (c) DodSMe, (0.63 mL, 2.4 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 4*a*-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2,2*a*1,4,4*a*,5,6,7,7*a*-octahydro-1*H*-cyclopenta[cd]indene-1,1-dicarboxylate (0.07 g, 0.16 mmol, **31%**); and (g) colourless oil.

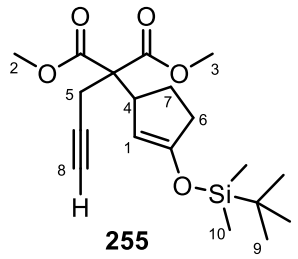
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.90 (1H, m, H_1), 3.79 (3H, s, $H_{2/3}$), 3.78 (3H, s, $H_{2/3}$), 3.60 (1H, ddd, ^2J = 20.7 Hz, ^4J = 1.9 Hz, ^4J = 1.9 Hz, H_4), 3.38 (1H, d, J = 7.4 Hz, H_5), 3.14 (1H, dd, ^2J = 20.7 Hz, ^4J = 2.2 Hz, H_4), 3.10 – 3.01 (1H, m, H_6), 1.80 (1H, d, ^2J = 14.4 Hz, H_7), 1.62 – 1.43 (4H, m, H_8, H_9), 1.32 (1H, td, ^2J = 14.0 Hz, J = 3.4 Hz, H_7), 0.93 (9H, s, H_{11}), 0.17 (3H, s, H_{10}), 0.07 (3H, s, H_{10}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 209.9, 177.7, 171.2, 168.8, 121.6, 82.0, 64.9, 56.6, 52.6, 40.1, 34.0, 25.3, 22.9, 19.8, 17.8, -3.5, -4.0 ppm.

IR (ν_{max}/cm^{-1}): 2951, 2928, 2857, 2012, 1732, 1719, 1632.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{21}H_{33}O_6Si$: 409.2041; **found:** 409.2047.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate.



255

Scheme 130

NaH (0.13 g, 3.3 mmol) and dry THF (15 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and dimethyl 2-(prop-2-yn-1-yl)malonate (0.51 g, 3 mmol) was added dropwise as a solution in THF (5 mL). The resulting mixture was stirred at 0 °C for 1 h. At this point, cyclopentene-1-one (0.24 mL, 3 mmol) and TBSOTf (0.76 mL, 3.3 mmol) were added, and the reaction mixture was warmed to rt and

stirred for 2 h. The reaction was quenched by pouring into a saturated aqueous solution of KH_2PO_4 and this was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5 – 90:10) and concentrated *in vacuo* to provide the dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.336 g, 0.92 mmol, **31%**) as a pale yellow oil.

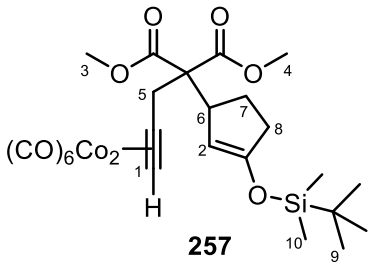
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.66 (1H, dt, *J* = 1.9 Hz, ^4J = 1.9 Hz, H_1), 3.75 (3H, s, $H_{2/3}$), 3.73 (3H, s, $H_{2/3}$), 3.64 – 3.57 (1H, m, H_4), 2.83 (1H, ^2J = 17.1 Hz, ^4J = 2.7 Hz, H_5), 2.77 (1H, ^2J = 17.1 Hz, ^4J = 2.7 Hz, H_5), 2.33 – 2.19 (2H, m, H_6), 2.14 – 2.03 (1H, m, H_7), 2.00 (1H, t, ^4J = 2.7 Hz, H_8), 1.90 – 1.79 (1H, m, H_7) 0.92 (9H, s, H_9), 0.17 (3H, s, H_{10}) 0.16 (3H, s, H_{10}).

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 169.9, 156.7, 101.9 79.1, 70.4, 60.2, 51.9, 45.2, 32.3, 25.1, 23.0, 22.1, 17.5, -5.1, -5.3.

IR (ν_{max}/cm^{-1}): 2953, 2930, 2857, 1757, 1732, 1643.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{19}H_{31}O_5Si$: 367.1941; **found:** 367.1933.

Preparation of dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclohex-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex.



257

Scheme 130

Prepared according to **General Procedure C**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate (0.279 g, 0.76 mmol); (b) pet. ether (7.5 mL); (c) $Co_2(CO)_8$ (0.274 g, 0.8 mmol); (d) dicobalthexacarbonyl complex (0.494 g, 0.76 mmol, **quant.**); and (e) red oil.

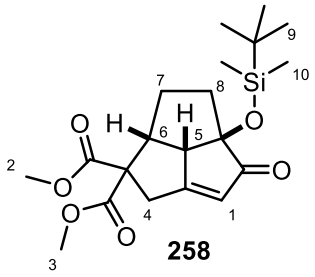
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.96 (1H, t, ^4J = 0.8 Hz, H_1), 4.67 (1H, dt, J = 1.7 Hz, ^4J = 1.7 Hz, H_2), 3.76 (3H, s, H_3), 3.75 (3H, s, H_4), 3.67 (1H, dd, ^2J = 16.7 Hz, ^4J = 0.9 Hz, H_5), 3.60 (1H, dd, ^2J = 16.7 Hz, ^4J = 0.9 Hz, H_5), 3.49 –3.43 (1H, m, H_6) 2.33 – 2.17 (2H, m, H_7), 2.14 – 2.03 (1H, m, H_8), 1.90 – 1.79 (1H, m, H_8) 0.93 (9H, s, H_9), 0.18 (3H, s, H_{10}) 0.17 (3H, s, H_{10}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.1, 170.12, 170.09, 156.8, 101.6, 87.9, 73.0, 61.9. 51.82, 51.76, 45.7, 38.2, 32.3, 25.1, 23.3, 17.6, -5.2, -5.4 ppm.

IR (ν_{max}/cm^{-1}): 2953, 2932, 2897, 2857, 2091, 2048, 2002, 1730, 1643.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{25}H_{31}Co_2O_{11}Si$: 653.0300; **found:** 653.0298.

Preparation of dimethyl 4*a*-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2*a*^{1},4,4*a*,5,6,6*a*-hexahydrocyclopenta[*cd*]pentalene-1,1(2*H*)-dicarboxylate.



258

Scheme 131

Prepared according to **General Procedure A**:

(a) Dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)-2-(prop-2-yn-1-yl)malonate dicobalthexacarbonyl complex (0.35 g, 0.53 mmol); (b) DCE (5 mL); (c) DodSMe, (0.67 mL, 2.53 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 4*a*-((*tert*-butyldimethylsilyl)oxy)-4-oxo-2,2*a*^{1},4,4*a*,5,6,7,7*a*-octahydro-1*H*-cyclopenta[*cd*]indene-1,1-dicarboxylate (0.18 g, 0.47 mmol, **89%**); and (g) white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.08 (1H, t, ^4J = 1.9 Hz, H_1), 3.81 (3H, s, $H_{2/3}$), 3.75 (3H, s, $H_{2/3}$), 3.63 (1H, d, ^2J = 18.0 Hz, H_4), 3.41 (1H, d, J = 7.3 Hz, H_5) 3.32 (1H, dt, J = 11.1 Hz, J = 7.3 Hz, H_6), 2.93 (1H, ddd, ^2J = 18.0 Hz, ^4J = 1.9 Hz, ^4J = 1.9 Hz, H_4), 2.11 (1H, dd J = 7.4 Hz, J = 6.8 Hz, H_7),

1.96 – 1.85 (1H, m, H_7), 1.74 (1H, dt, ^2J = 12.9 Hz, J = 7.4 Hz, H_8), 0.98 – 0.92 (1H, m, H_8), 0.90 (9H, s, H_9), 0.18 (3H, s, H_{10}), 0.08 (3H, s, H_{10}) ppm.

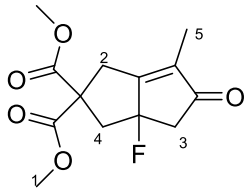
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.6, 178.7, 171.6, 169.2, 127.3, 89.4, 63.4, 62.0, 52.7, 52.2, 44.7, 39.9, 34.6, 25.7, 25.3, 17.7, -3.7, -4.0 ppm.

IR (ν_{max}/cm^{-1}) 2955, 2936, 2859, 1755, 1730, 1711, 1628.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{20}H_{31}O_6Si$: 395.1890; **found:** 395.1888.

Melting point: 79 – 81 °C.

Preparation of dimethyl 3a-fluoro-6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.



259

Scheme 132

Diethylaminosulfur trifluoride (0.034 mL, 0.259 mmol) was added to a flame-dried, round-bottom flask, dissolved in dry DCM (0.26 mL) and the solution was cooled to -78 °C. Dimethyl 3a-hydroxy-6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.063 g, 0.23 mmol) was added as a solution in dry DCM (0.26 mL), and the resulting mixture was allowed to warm to room temperature and stirred for 1 h. After this time, the reaction was quenched by the addition of H_2O (1 mL) and DCM (1 mL) to create a biphasic mixture, which was separated, and the aqueous phase was washed with DCM (3 × 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude material as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 50:50) and concentrated *in vacuo* to provide the dimethyl 3a-fluoro-6-methyl-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.050 g, 0.184 mmol, **80%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.69 (3H, s, H_1), 3.69 (3H, s, H_1), 3.75 – 3.66 (1H, m, H_2), 3.18 (1H, apparent t, J = 15.2 Hz, H_3), 3.08 (1H, dd, ^2J = 18.6 Hz, ^4J = 4.4 Hz, H_2), 2.79 (1H, apparent

t, *J* = 18.0 Hz, H_4), 2.54 (1H, apparent t, *J* = 16.8 Hz, H_3), 2.43 (1H, dd, $^3J_{H\text{-}F}$ = 38.1 Hz, ^2J = 15.0 Hz, H_4), 1.82 – 1.77 (3H, m, H_5) ppm.

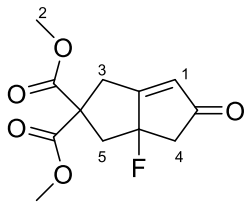
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.5, 170.8, 170.2, 168.1 (d, $^2J_{C\text{-}F}$ = 13.9 Hz), 136.9 (d, $^3J_{C\text{-}F}$ = 6.1 Hz), 102.4 (d, $^1J_{C\text{-}F}$ = 176.7 Hz), 60.2, 52.9, 43.6 (d, $^2J_{C\text{-}F}$ = 26.8 Hz), 42.6 (d, $^2J_{C\text{-}F}$ = 27.3 Hz), 32.3, 8.1 ppm.

^{19}F NMR ($CDCl_3$, 94.1 MHz): δ_F -136.4 – (-137.9) (m) ppm.

IR (ν_{max}/cm^{-1}): 2983, 2955, 2924, 1686.

HRMS m/z (NSI/ion trap) m/z $[M+H]^+$ Calc. for $C_{13}H_{16}O_5F$: 271.09763; **found:** 271.09600.

Preparation of dimethyl 3a-fluoro-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate.[161]



260

Scheme 133

Diethylaminosulfur trifluoride (0.034 mL, 0.259 mmol) was added to a flame-dried, round-bottom flask, dissolved in dry DCM (0.26 mL) and the solution cooled to -78 °C. Dimethyl 5-oxo-3a-((triethylsilyl)oxy)-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.083 g, 0.259 mmol) was added as a solution in dry DCM (0.26 mL), and the resulting mixture was allowed to warm to room temperature and stirred for 24 h. After this time, the reaction was quenched by the addition of H_2O (1 mL) and DCM (1 mL) to create a biphasic mixture, which was separated, and the aqueous phase was washed with DCM (3 × 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude material as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 60:40 – 50:50) and concentrated *in vacuo* to provide the dimethyl 3a-fluoro-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.02 g, 0.078 mmol, **30%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.09 – 6.04 (1H, m, H_1), 3.83 (3H, s, H_2), 3.82 – 3.78 (1H, m, H_3), 3.78 (3H, s, H_2), 3.18 (1H, apparent t, J = 15.7 Hz, H_4), 3.18 (1H, dd, ^{2}J = 18.8 Hz, ^{4}J = 4.0 Hz, H_3), 2.77 (1H, apparent t, J = 18.4 Hz, H_5), 2.55 (1H, apparent t, J = 17.9 Hz, H_5), 2.50 (1H, dd, $^{3}J_{H\text{-}F}$ = 38.5 Hz, ^{2}J = 15.2 Hz, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.4, 175.3 (d, $^{2}J_{C\text{-}F}$ = 13.5 Hz), 170.7, 170.0, 128.3 (d, $^{3}J_{C\text{-}F}$ = 4.9 Hz), 103.8 (d, $^{1}J_{C\text{-}F}$ = 178.5 Hz), 60.1, 53.0, 44.0 (d, $^{2}J_{C\text{-}F}$ = 26.5 Hz), 42.2 (d, $^{2}J_{C\text{-}F}$ = 26.6 Hz), 33.3 ppm.

^{19}F NMR ($CDCl_3$, 94.1 MHz): δ_F -137.7 – (-138.2) (m) ppm.

IR (ν_{max}/cm^{-1}): 2984, 2957, 2901, 1721, 1686, 1435.

Melting point: 95 – 97 °C. **Literature value**: 98 – 100 °C.

Chapter 2

The Total Synthesis of Xeromphalinone C

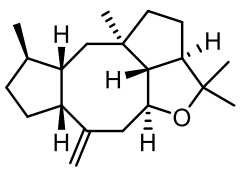
2.1 Introduction

2.1.1 Applications of the Pauson-Khand Reaction in Total Synthesis

The total synthesis of natural products is a broad area of interest for synthetic organic chemists. The target molecules are often structurally complex and may have medicinally-important bioactivities, which make these molecules attractive for total synthesis. Another common motivator for undertaking a natural product synthesis is that it provides a platform where chemists can highlight the applicability of developing synthetic methodologies in the arena of complex molecule synthesis.

A reaction which finds common application in the total synthesis of natural products is the Pauson-Khand reaction.[18] This is due to its tremendous potential for generating structural complexity from accessible starting materials and to the ubiquity of cyclopentenone motifs in natural products. Furthermore, the reaction has a key advantage of forming three carbon-carbon bonds in a single step which is of significant value when building complex molecules. This introductory section will discuss the use of the Pauson-Khand reaction in total synthesis through the elaboration of some selected examples.

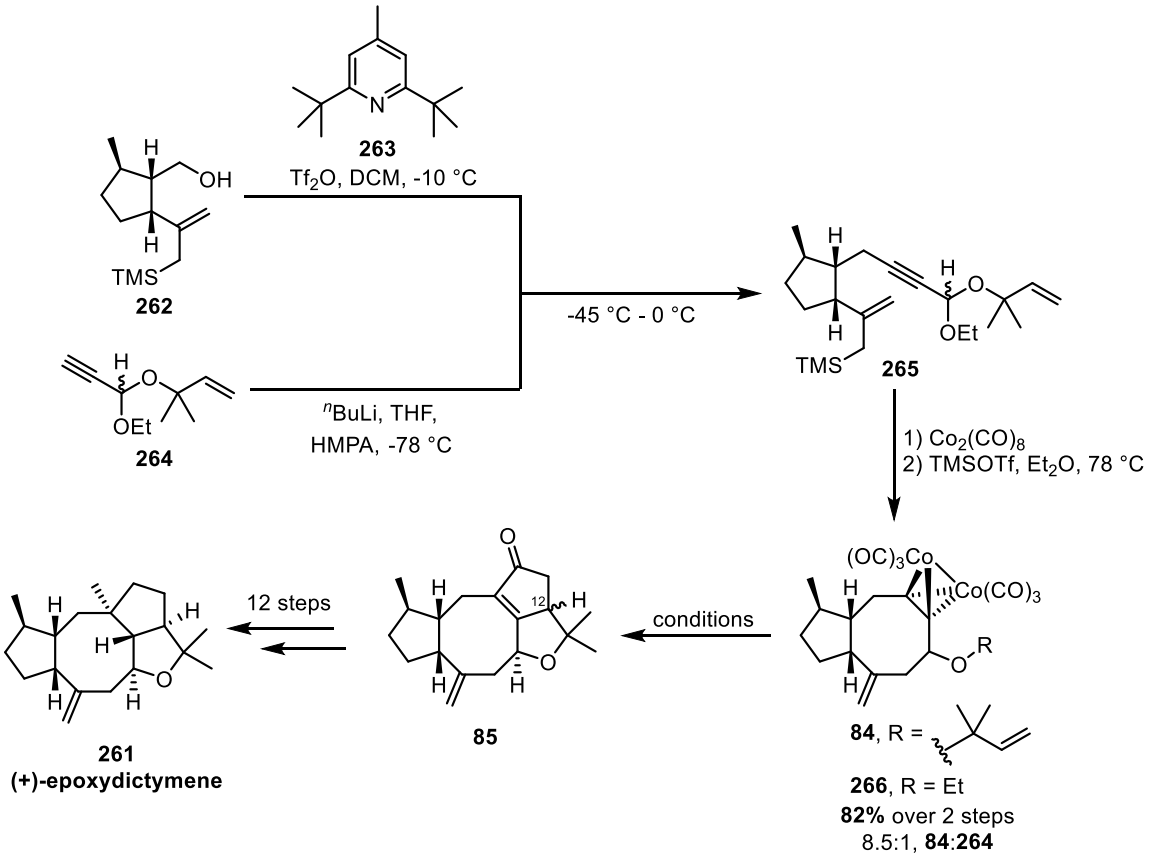
A celebrated example of the Pauson-Khand reaction in total synthesis was Schreiber and co-worker's synthesis of epoxydictymene.[88,92,94] Epoxydictymene **261** (**Figure 24**) is a tetracyclic diterpene natural product which was isolated from the brown alga *Dictyota dichotoma*[190] and contains an 8-membered ring and and *trans*-fused 5,5-ring system. It is this 5,5-fused ring system which makes the Pauson-Khand reaction an attractive strategy to realise this total synthesis.



261
(+)-epoxydictymene

Figure 24

As part of the development of an *N*-oxide-promoted Pauson-Khand reaction protocol, Schreiber and co-workers utilised an elegant synthetic sequence of a Nicholas reaction followed by a Pauson-Khand reaction (**Scheme 134**). The authors coupled two fragments, **262** and **264**, to deliver Nicholas precursor **265**. From compound **265**, the researchers prepared the dicobalt hexacarbonyl-alkyne complex and subsequently performed an intramolecular Nicholas reaction using the allyl silane portion of the molecule as the nucleophile. This worked to good effect forming the 8-membered ring in an excellent yield of **82%** over 2 steps, whilst also providing the desired Pauson-Khand precursor **84** in high selectivity. The authors employed three varied sets of promotion methods to facilitate the Pauson-Khand cyclisation: thermal, *N*-oxide, and ultrasound (**Table 12**). Whilst each set of conditions provided the desired cyclopentenone product in good yields, the oxidative approach (**Table 12**, **Entry 2**), which had been developed by the same authors,[92] provided the optimal diastereoselectivity at the C12 position. This is an excellent example of the power that the Pauson-Khand reaction has in generating complexity; here, the tetracyclic core of epoxydictymene is furnished from a bicyclic starting material in just one step.



Scheme 134

Table 12

Entry	Conditions	Yield	d.r. (*α*:*β*)
1	MeCN, air, reflux, 15 min	**85%**	5:1
2	NMO, DCM, 12 h	**70%**	11:1
3	))), MeCN	**40%**	3:1

Another example of a total synthesis programme where the Pauson-Khand reaction was used to engender a complex ring system came from our own laboratories in the formal synthesis of (±)-*α*- and (±)-*β*-cedrene.[97,191] *α*- and *β*-Cedrene are two isomeric forms of a synthetically-challenging [5.3.1.0] all-carbon tricyclic sesquiterpene (**Scheme 135**). *α*-Cedrene features an endocyclic, trisubstituted, double bond, where *β*-cedrene has an exocyclic, 1,1-disubstituted, double bond. Both molecules share an all-carbon tricyclic skeleton, featuring a tantalising 7,5-fused ring system in which the 7-membered ring contains a one-carbon bridge. *α*- and *β*-Cedrene had been the subject of several completed total synthesis programmes prior to the embarkation of the work in our own laboratories.[192–194] However, none of these reported syntheses had exploited the competence of the Pauson-Khand reaction in synthesising 5,5,6-fused ring systems.

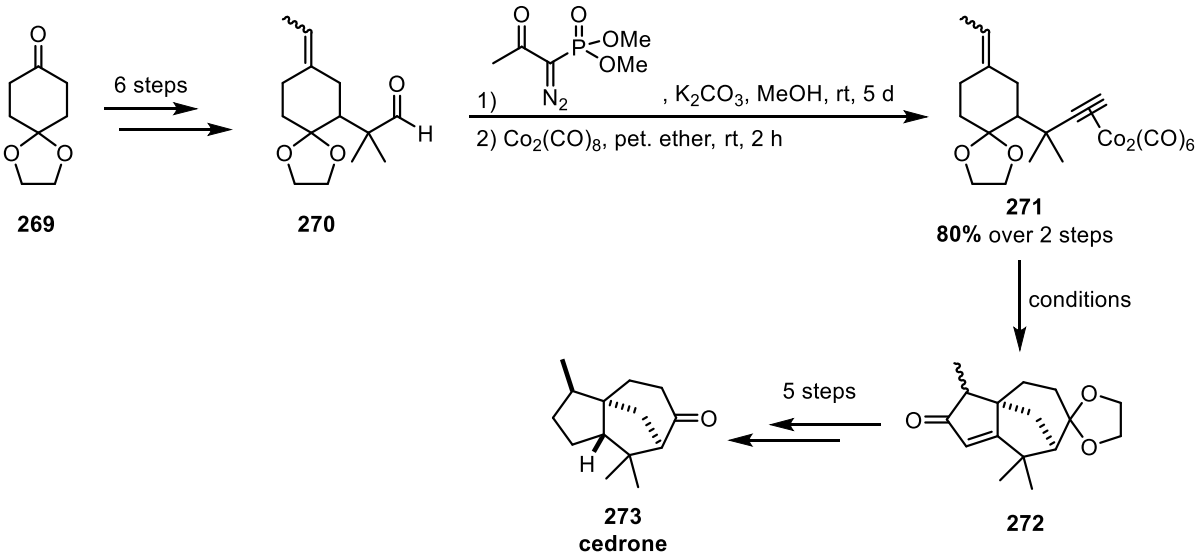
267
α–cedrene

268
β-cedrene

Scheme 135

The key alkynyl component within Pauson-Khand precursor **271** was accessed from prepared aldehyde **270** through a Seyferth-Gilbert homologation using the Ohira-Bestmann reagent, and subsequent cobalt complexation provided the desired intermediate in a very good yield over the two steps (**Scheme 136**). Various cyclisation conditions were tested, all of which proved very effective in facilitating the desired transformation (**Table 13**). The most effective conditions involved the use of TMANO.2H_2O delivering the cyclopentenone in an outstanding **91%** yield (**Table 13**, **Entry 1**). In our laboratories, our efforts are focused on continually

enhancing the practicality of the Pauson-Khand reaction in general. Concurrently with the formal synthesis of *α*- and *β*-cedrene we were developing novel reaction conditions for the Pauson-Khand reaction which involved the use of a polymer-supported sulfide.[108] We were able to test these developing conditions within the context of total synthesis in the formation of **272** (**Table 13**, **Entry 4**). These conditions resulted in a vast increase in reaction rate, and the product was isolated in an excellent **80%** after only 30 minutes. The use of the polymer support greatly simplifies the purification of the resulting cyclopentenone as it sequesters the unwanted cobalt residues which can be removed *via* simple filtration. Most importantly, it avoids the hazards associated with the lachrymatory ^{n}BuSMe and provides a comparable yield in the same cyclisation. The Pauson-Khand product **272** could be converted into cedrone in just 5 further steps, thus completing the formal total syntheses of *α*- and *β*-cedrene.

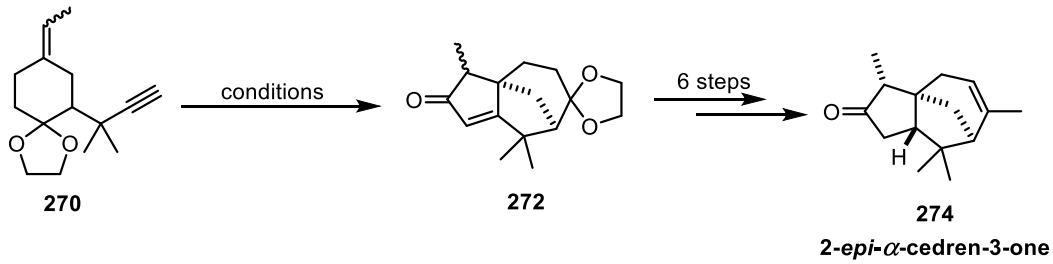


Scheme 136

Table 13

Entry	Conditions	Yield
1	TMANO.$2H_2O$ (9 eq.), acetone, rt, 16 h	**91%**
2	NMO.H_2O (8 eq.), DCM, rt, 16 h	**84%**
3	^{n}BuSMe (4.3 eq.), DCE, 83 °C, 30 min	**83%**
4	Polymer-supported sulfide, DCE, 83 °C, 30 min	**80%**

Recently, we returned to this productive vein of chemistry with the total synthesis of 2-*epi*-α-cedren-3-one.[195] The synthetic route to the Pauson-Khand precursor was identical to the route for the formal total synthesis of cedrene described above, though a *Z*-selective olefination protocol was developed to provide the desired alkene geometry. As with the formal synthesis of cedrene, various Pauson-Khand methodologies were employed in the total synthesis of 2-*epi*-α-cedren-3-one to determine the optimal cyclisation conditions (**Scheme 136**, **Table 14**). The first attempted cyclisation was conducted using sulfide promotion with the pre-formed dicobalt hexacarbonyl-alkyne complex, and the product was accessed in an excellent **83%** yield (**Table 14**, **Entry 1**). The focus of this research was to establish an efficient catalytic cyclisation protocol which could be employed to construct the tricyclic core of 2-*epi*-α-cedren-3-one. To this end, a series of attempts using substoichiometric amounts of $Co_2(CO)_8$ were conducted. The most successful of these operated under microwave irradiation, with addition of the promotor cyclohexylamine (*vide supra*), and the desired product was isolated in **69%** after only 10 minutes (**Table 14**, **Entry 2**). The annulation method was further enhanced by exploiting ^{n}BuSMe as an additive (**Table 14**, **Entries 2 and 3**). When conducted in DCE, the cyclopentenone was obtained in a very good **65%**, and further improvements were provided by utilising toluene as solvent whereby the product was isolated in **85%** yield; an impressive result with regards to the catalytic variant of the Pauson-Khand reaction. From **272**, the synthesis of 2-*epi*-α-cedren-3-one was completed in 6 steps and thus the first total synthesis of this molecule was realised in an overall 17 step sequence.

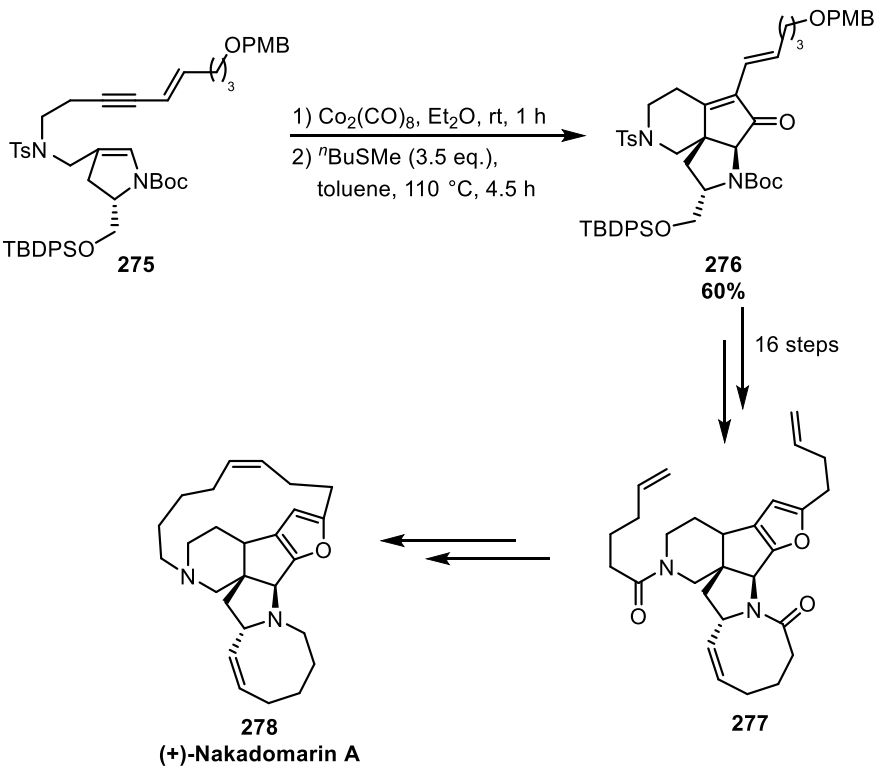


Scheme 137

Table 14

Entry	Conditions	Yield
1	1) $Co_2(CO)_8$, pet. ether, 2 h 2) ^{n}BuSMe, DCE, 83 °C, 40 min	**83%**
2	$Co_2(CO)_8$ (20 mol%), $CyNH_2$, toluene, MW, 100 °C, 10 min	**69%**
3	$Co_2(CO)_8$ (20 mol%), ^{n}BuSMe, DCE, MW, 100 °C, 10 min	**65%**
4	$Co_2(CO)_8$ (20 mol%), ^{n}BuSMe, toluene, MW, 100 °C, 10 min	**85%**

In 2010, researchers in Japan employed an interesting Pauson-Khand reaction in their formal total synthesis of Nakadomarin A (**Scheme 138**).[196] In this study, the authors utilised an enamine as the alkene reacting partner, an elegant, and indeed rare, example of the use of a functionalised reacting partner in the Pauson-Khand reaction. The synthetic sequence the researchers utilised was a one-pot alkyne-complexation and Pauson-Khand reaction, promoted by ^{n}BuSMe. This process converted the monocyclic enyne **275** into the tricyclic **276** containing three stereogenic centres. The reaction generated a complex pyrrolidine-cyclopentenone fused ring system through the use of an enamine as a functionalised alkene partner for the Pauson-Khand reaction. The use of the enamine demonstrated the great potential applications that the use of varied functionalised alkene components could have in the Pauson-Khand reaction for generating diverse structural motifs. The authors completed their formal total synthesis in a further 16 steps from this cyclopentenone to compound **277**, which was an intermediate in the total synthesis conducted by Nishida and co-workers[197] and a later total synthesis disclosed by Kerr *et al*.[198]



Scheme 138

2.1.2 A Novel Class of Natural Products

In 2010, six novel linear triquinane sesquiterpenes, Xeromphalinones A – F, and the related sesquiterpene, Pleurocybellone A, were isolated from three basidiomycetes (**Figure 25**, **top**).[5] Linear triquinanes are categorised by their core ABC-ring structure, with capnellenes and hirsutanes being the most common (**Figure 25**, **bottom**).

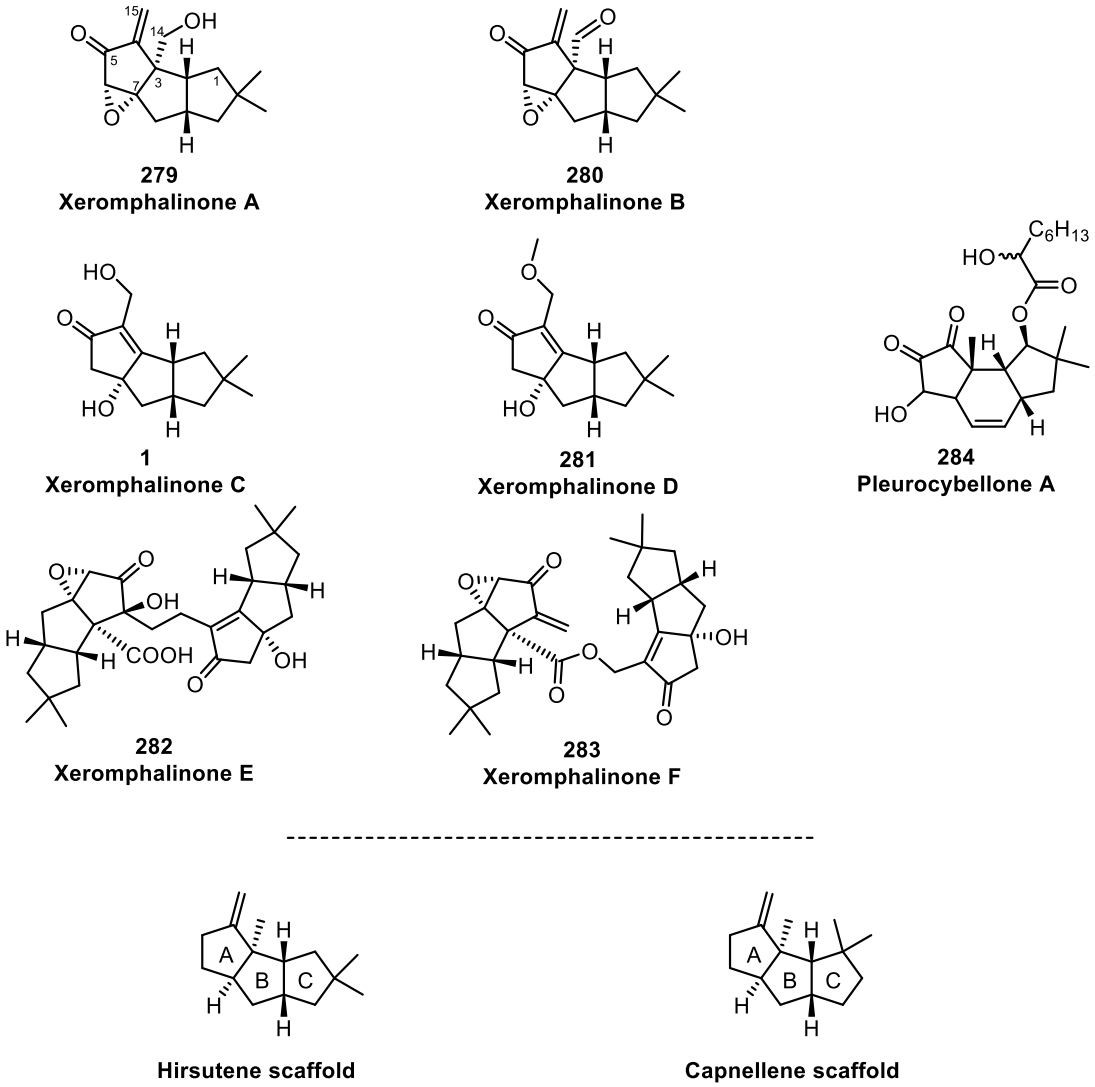
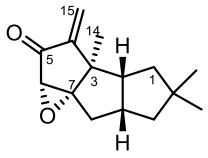


Figure 25

Xeromphalinones A and B are identical carbon frameworks at different oxidation levels, the A-ring features an exocyclic methylene and an epoxide motif. The stereochemistry of this epoxide is determined by analogy to the structurally-related 1-desoxyhypnophilin (**Figure 26**),[199] the relative configuration of which was confirmed by a racemic total synthesis in 2001.[200] Routine modifications of the hirsutane and capnellene scaffolds are oxidation and unsaturation, though Xeromphalinones A and B are the first known molecules with oxidation at the C14 carbon. Rings B and C of Xeromphalinones C and D are identical to Xeromphalinones A and B though ring A features structural modifications. Specifically, Xeromphalinones C and D do not feature an exocyclic methylene, but instead feature an endocyclic double bond with a hydroxymethyl substituent. These molecules do not feature a C14 carbon, thus making Xeromphalinone C a norhirsutene; a type of sesquiterpene with only

14 carbon atoms. Xeromphalinone D, the methyl ether of Xeromphalinone C, was only observed by the authors when methanol was used in the purification of Xeromphalinone C and was not identified in the culture fluid by HPLC/MS. This indicates that the molecule may be a derivative formed on isolation rather than a natural product made by the fungi. Xeromphalinones E and F comprise the most complex of the natural products which were isolated here. Both molecules consist of two substructures which are structurally related to the other discrete Xeromphalinones. The left-most substructure of Xeromphalinone E is similar to Xeromphalinone A, with C14 having the oxidation state of a carboxylic acid and additional hydroxyl at C4, and the right-most is similar to Xeromphalinone C, without the hydroxyl on C15. These two fragments are joined by an ethylene group. The substructures of Xeromphalinone F are also very closely related to Xeromphalinones A and C. Indeed, this molecule seems to be a heterodimer where the two fragments are joined by the formation of an ester from the carbonyl on C14 of Xeromphalinone A and the alcohol of Xeromphalinone C.



285
1-Desoxyhypnophilin

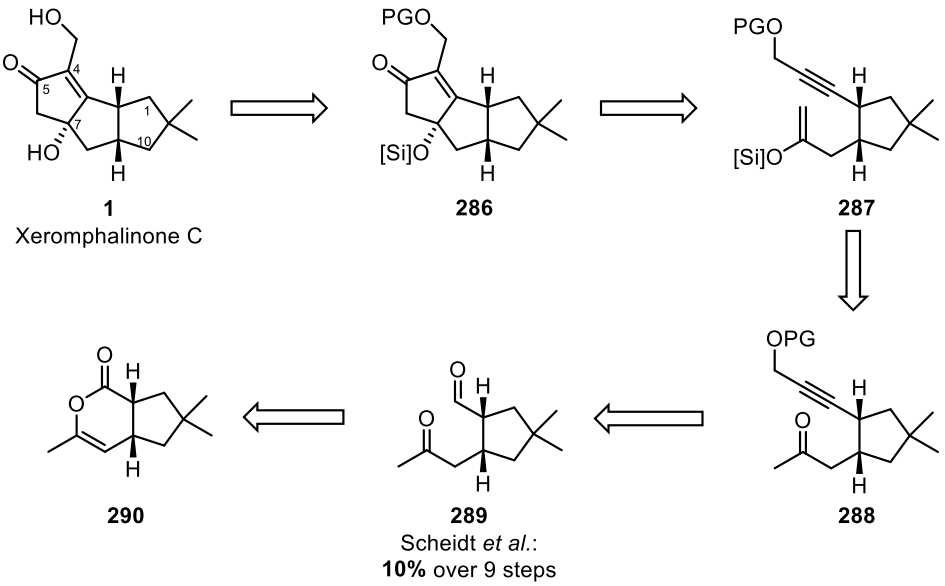
Figure 26

Evaluation of the biological significance of these compounds found that Xeromphalinones A, B and F (and Pleurocybellone A) had significantly high cytotoxicity (IC_{50}) in the range of 1 – 5 µg/mL, where Xeromphalinones C and D were much less active, exceeding 100 µg/mL. The common structural motif between the bioactive Xeromphalinones is the exocyclic double bond. Clearly, this would make these molecules much more ready Michael acceptors compared with those that feature the endocyclic double bond, Xeromphalinones C and D. A synthetic route to Xeromphalinones A – F may provide a viable method for the generation of sufficient quantities of these compounds for further biological testing. A structural commonality between all the novel Xeromphalinones is the cyclopentenone moiety with oxidation at the C7 position. Whilst the most direct method for the synthesis of standard cyclopentenones is the Pauson-Khand reaction, any subsequent installation of the required

C7 oxidation would be difficult. Thus, our developing silyl enol ether Pauson-Khand methodology is an ideal methodology to implement in a total synthesis of this class of molecules. The most synthetically tractable structure would appear to be Xeromphalinone C, though from this molecule, the other Xeromphalinones in this class could be accessed, making the synthesis of this molecule a keystone through which the whole family of natural products could potentially be delivered.

2.2 Previous and Proposed Work

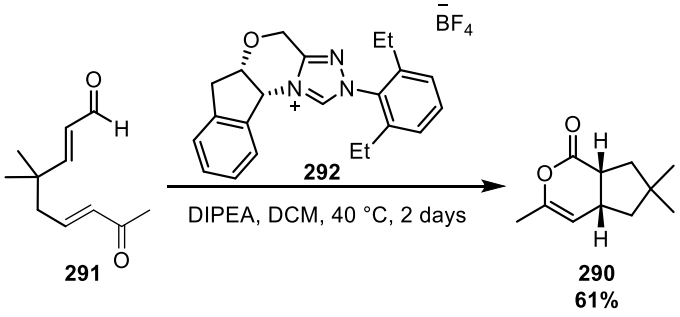
The total synthesis of Xeromphalinone C would provide a platform with which we can effectively exhibit the capabilities of the silyl enol ether Pauson-Khand reaction in synthesising functionalised cyclopentenones. Furthermore, Xeromphalinone C could be seen as a potential intermediate in the synthesis of Xeromphalinones A-D, and as a fragment for the synthesis of Xeromphalinones E and F. A retrosynthetic analysis of Xeromphalinone C is described in **Scheme 139**, and highlights key compound **289**, which is known in the scientific literature.[201] The final stage of the synthetic programme was expected to be a global deprotection of cyclopentenone **286**, which would be prepared utilising our methodology for the Pauson-Khand reaction as described in the previous chapter. The silyl enol ether cyclisation precursor **287** could be synthesised directly from the keto-alkyne **288**, which, itself, could be formed through a Ramirez-Corey-Fuchs homologation of the known keto-aldehyde, **289**, which is ultimately derived from chiral lactone **290**.



Scheme 139

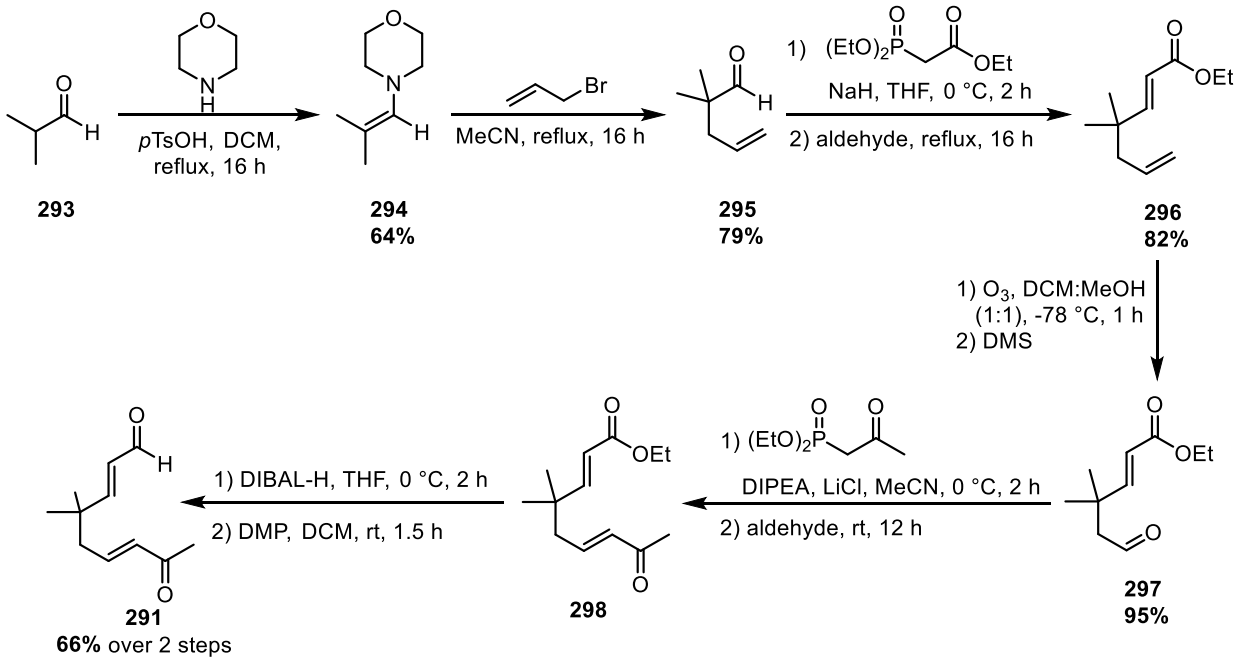
Keto-aldehyde **289** has been synthesised by Scheidt and co-workers in **10%** over 9 steps in their efforts towards the synthesis of another natural product, in this synthesis they utilised a chiral lactonisation procedure (**Scheme 140**).[201] The chiral lactonisation methodology had been disclosed by the same authors in an earlier body of work.[202] This strategy utilised a triazole *N*-heterocyclic carbene (NHC) as an organocatalyst to effect an intramolecular Stetter reaction. This would be an important step in our synthetic route as it would result in the

formation of the first cyclopentane ring with the geminal dimethyl substituents in place and the desired *syn* stereochemistry of the protons at the ring junction.



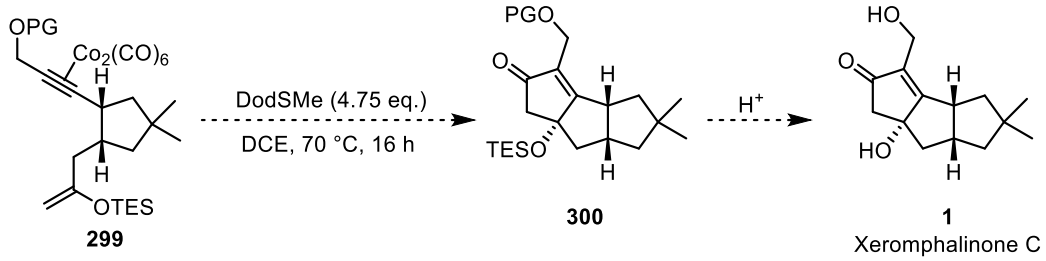
Scheme 140

The authors synthesised the unsaturated ketoaldehyde cyclisation precursor **291** in **18%** over 7 steps (**Scheme 141**). The starting material for this synthesis was *iso*-butyraldehyde as it is readily available in large quantities for a low cost. The first step involved enamine formation using morpholine, followed by alkylation with allyl bromide. Subsequently, the authors employed a Horner-Wadsworth-Emmons reaction to access the required carbonyl functionality, and ozonolysis was conducted on the terminal olefin to deliver an aldehyde with which the enone could be installed through a further Horner-Wadsworth-Emmons reaction. A reduction and oxidation protocol successfully completed the synthesis of compound **291**, the cyclisation precursor.



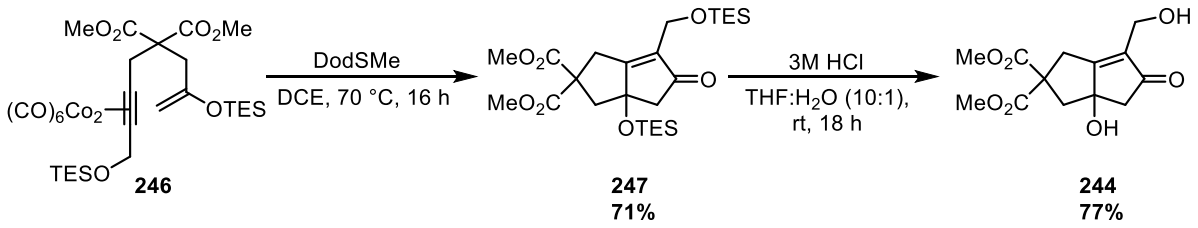
Scheme 141

Due to the complexity of the core structure of Xeromphalinone C, the silyl enol ether Pauson-Khand reaction will be the key step in this total synthesis (**Scheme 142**). This will deliver the tricyclic core of the natural product by forming the full 5,5,5-fused framework, importantly, with the installation of the necessary oxygen functionality at the ring junction. From compound **300** the total synthesis could be completed by a global deprotection of the silyl ether and the removal of the alcohol protecting group. The most efficient method for doing this would be to employ a protecting group which can be removed under the same conditions as the silyl ether. A silyl protecting group would be the most convenient as this can also be installed in the same step, under the same conditions, as the silyl enol ether.



Scheme 142

It is at these final stages of the proposed route that prior work conducted in our lab, and indeed disclosed in this thesis, becomes pertinent. During the development of our methodology, we employed dicobalthexacarbonyl complex **246**, to good effect, in our protocol (**Scheme 143**). The Pauson-Khand cyclisation was affected in a very good **71%** yield and the subsequent silyl deprotection of both silyl ethers occurred in **77%** yield. Complex **246** contains structural similarities around the reacting centres as the proposed Pauson-Khand reaction we are targeting in our synthesis of Xeromphalinone C (**Scheme 143**). The successful cyclisation, and subsequent global deprotection, of this substrate supports our hypothesis that the key Pauson-Khand reaction in the synthesis of Xeromphalinone C would provide us with the requisite cyclopentenone motif.



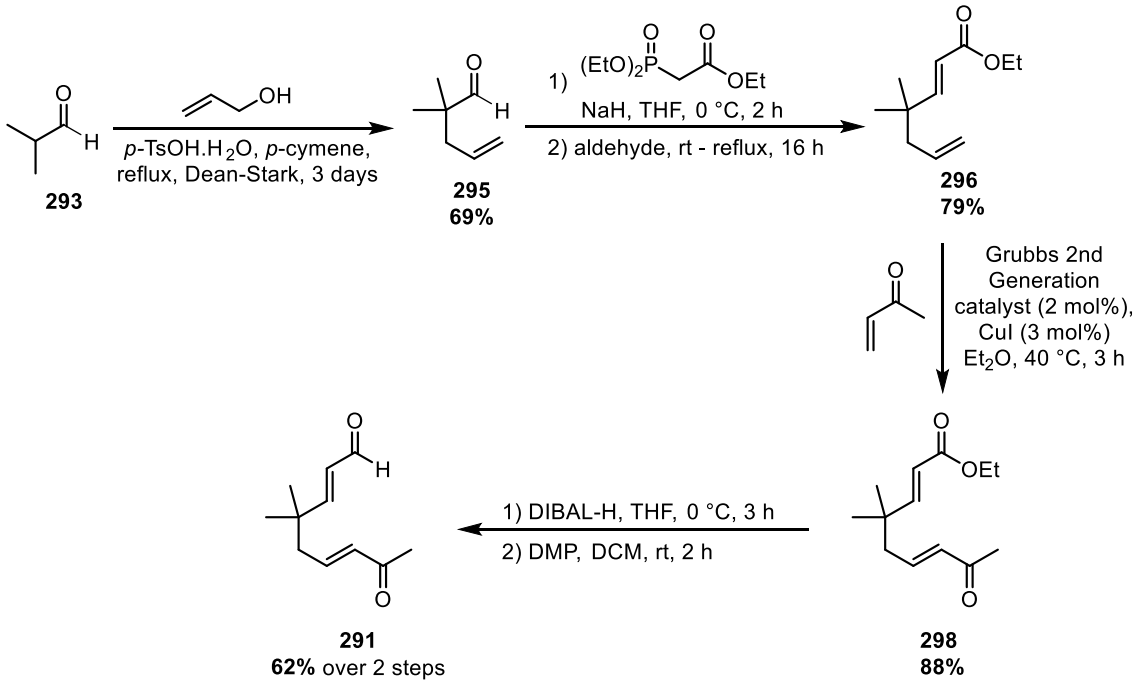
Scheme 143

The first requirement of the project would be to prepare significant quantities of chiral lactone **290**, which will allow exploration of the synthesis of the key silyl enol ether Pauson-Khand precursor, and its application in the cobalt-mediated transformation.

2.3 Results and Discussion

2.3.1 Synthesis of Aldehyde 291

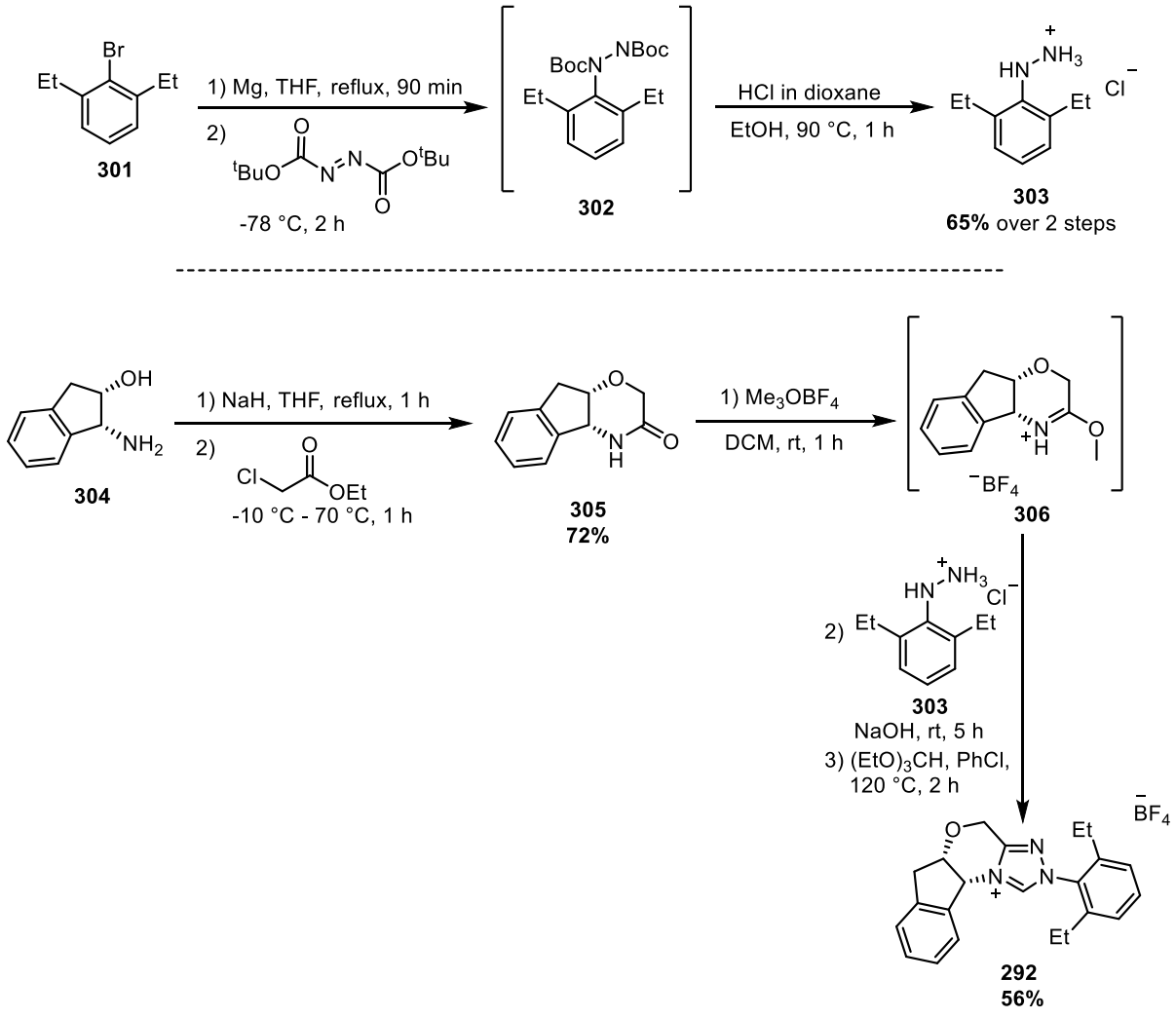
Exploiting the work conducted by Scheidt *et al*.,[201] the total synthesis of Xeromphalinone C similarly began with *iso*butyraldehyde **293**. Having said this, adjustments were made to the published synthetic route in an attempt to improve its efficiency (**Scheme 144**). The first improvement was made by avoiding the unnecessary formation of the enamine and subsequent alkylation as these steps were deemed costly (*c.f.* **Scheme 141**). Alternatively, compound **295** was accessed in one step *via* a Claisen rearrangement in **69%** yield after a fractional distillation of the volatile product.[203] The next step was the successful Horner-Wadsworth-Emmons reaction, which delivered **296** in a good **79%** yield. Further improvements to the route could be realised by subsequently implementing a cross metathesis using Grubbs 2nd generation catalyst with the addition of CuI. This allowed access to the ketoester compound **298** in an excellent **88%** yield over one step, where the previous authors had employed a two-step process (ozonolysis followed by a Horner-Wadsworth-Emmons reaction) which had the potential to prove tricky to conduct on a large scale. To complete this portion of the synthesis, a global reduction with DIBAL-H followed by oxidation with DMP provided the keto-aldehyde **291** in a good **62**% yield over 2 steps.



Scheme 144

2.3.2 Preparation of Chiral Lactone 290

In order to perform the chiral cyclisation to deliver key chiral lactone **290**, it was necessary to first synthesise triazolium NHC **292**. The synthesis of this compound was performed in a modular fashion, where aryl hydrazinium salt **303** and chiral morpholinone **305** are the building blocks.[202] Synthesis of aryl hydrazinium salt started from the requisite aryl bromide **301** (**Scheme 145, top**). From this compound, the corresponding Grignard reagent was formed and this was reacted with di-*tert*-butyl azodicarboxylate to afford Boc-protected hydrazine **302**, which was directly reacted with HCl in dioxane without isolation to deliver chloro- hydrazinium salt **303** in a very good yield of **65**% over the two steps.

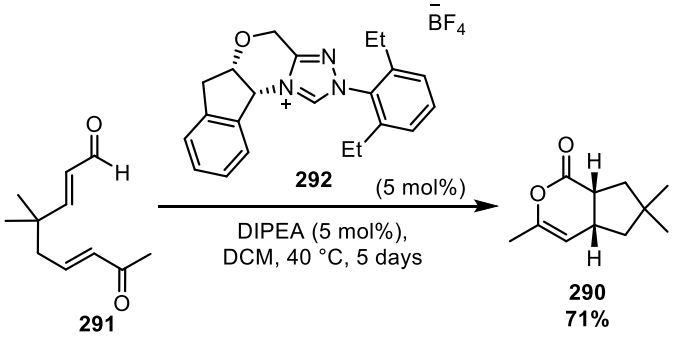


Scheme 145

The morpholinone building block, which provides the chiral component to the NHC, was made from commercially available amino-alcohol **304** (**Scheme 145**, **bottom**). This compound was

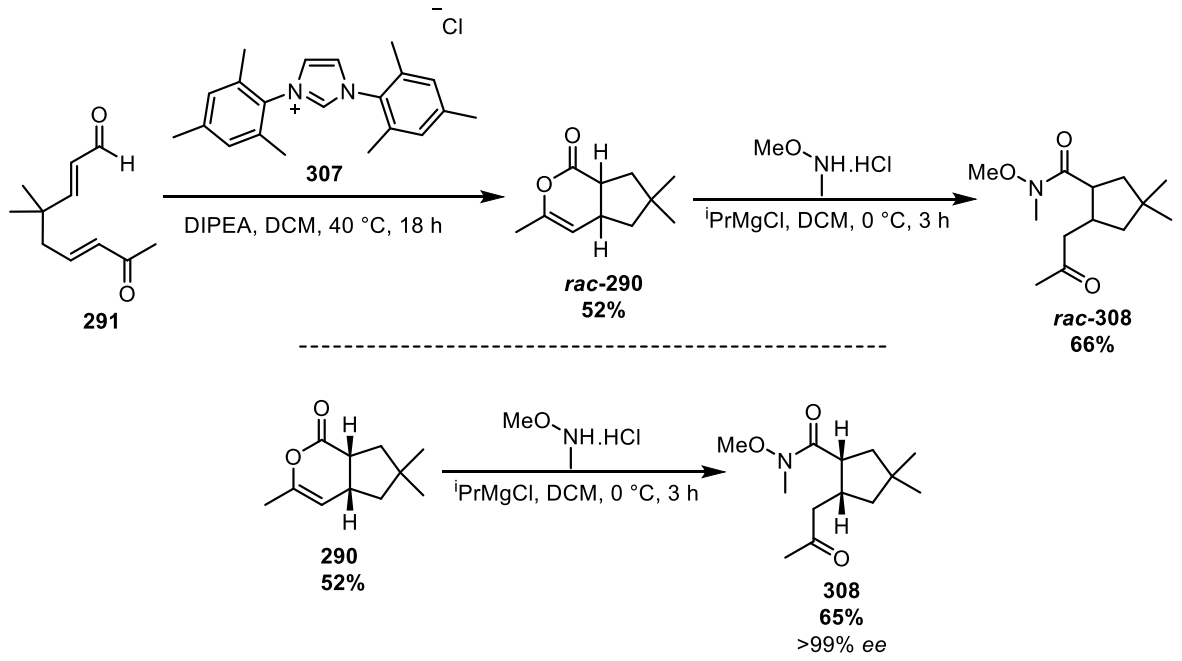
reacted with ethylchloroacetate to access morpholinone **305** in a pleasing **72%**. The formation of the triazolium NHC was completed in one step from the previously prepared **303** and **305**. The first phase involved methylation of the morpholinone using trimethyloxonium tetrafluoroborate, which also provided the tetrafluoroborate counterion required for the NHC salt. Then, the aryl hydrazine, which had been accessed from salt **303** through reaction with NaOH, was reacted with **306** *in situ* to combine the two building blocks to form the hydrazonamide which was further reacted with triethylorthoformate to deliver NHC **292** in a pleasing **56%** yield.

With the chiral NHC in hand, the lactonisation of compound **291** could be realised. This involved reacting **291** with 5 mol% of the prepared NHC and DIPEA at an elevated temperature, and over a period of 5 days, to achieve a yield of **71%** (**Scheme 146**). Indeed, this was an improvement of **10%** on the yield reported in the literature.[201]



Scheme 146

Determination of the enantiomeric excess achieved in the chiral cyclisation was an important endeavour. This had been explored by Scheidt *et al*. through formation of the corresponding Weinreb amide directly from the chiral lactone **290** who reported that the *ee* of the transformation was >99%. In order to properly determine the *ee* in our hands, an achiral sample of the same compound was deemed necessary, and this was synthesised using the same cyclisation method as described above, though with an achiral organocatalyst, specifically mesitylimidazolium chloride, as a stoichiometric reactant (**Scheme 147**, **top**). The racemic lactone ***rac*-290** was isolated in a good yield of **52%**. Converting this compound to the Weinreb amide was facile and was achieved by reacting the achiral lactone ***rac*-290** with dimethylhydroxylamine in the presence of *iso*-propylmagnesium bromide as base giving the desired compound in a good **66%** yield.

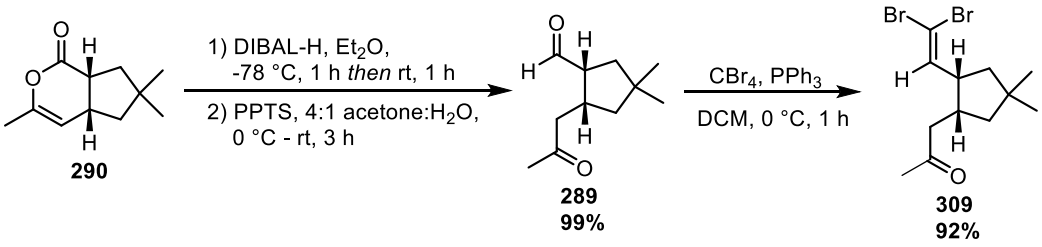


Scheme 147

This method was subsequently used to form the Weinreb amide of the chiral variant, which performed equally well providing the enantiomeric Weinreb amide **308** in **65**% yield (**Scheme 147**, **bottom**). Pleasingly, upon analysis by chiral-HPLC, the chiral material was determined to have an enantiomeric excess >99%.

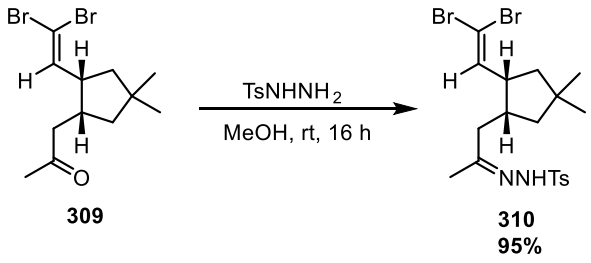
2.3.3 Synthesis of the Keto-Alkyne Pauson-Khand Reaction Precursor.

With lactone **290** in hand, and its chirality determined, the route could be continued towards the key Pauson-Khand reaction precursor. The next step in the route was a ring-opening of the chiral lactone using DIBAL-H and PPTS in sequence (**Scheme 148**). This afforded keto-aldehyde **289** in a delightful **98%** yield; indeed, this reaction had been conducted by Scheidt and co-workers and was the final compound in their synthesis which was relevant to our own. To this point, our synthetic route comprised of 7 steps and compound **289** could be accessed in a **21%** overall yield. By comparison, the route of Scheidt and co-workers was 9 steps with a **9%** overall yield. Pleased with our optimised reaction pathway, we embarked on the next stage of the total synthesis, which continued with the formation of dibromoolefin **309**. This was achieved efficiently in a **92%** yield using carbon tetrabromide and triphenylphosphine.



Scheme 148

Confident in the high enantiomeric excess of this compound, based on the comparison of the Weinreb amide samples, it was now important to confirm that it was, indeed, the desired enantiomer, with respect to Xeromphalinone C. Scheidt *et al*. had illustrated that the most thermodynamically stable diastereomer of keto-aldehyde **289** was in fact the *anti* diastereomer,[201] where the protons are on opposite faces of the cyclopentane ring. This is formed due to the epimerisable chiral centre adjacent to the aldehyde. Thus, it was imperative to determine that we had the isolated the desired enantiomer of **289** and that no epimerisation to the more stable *anti* diastereomer had occurred after the formation of **309**. Dibromoolefin **309** was a viscous oil, however, it could be readily converted to the crystalline tosylhydrazone **310** in an excellent **95%** yield (**Scheme 149**).



Scheme 149

Pleasingly, a single crystal of this compound could be grown efficiently for X-ray diffraction (**Figure 27**). It is clear from this image that the two chiral centres have the desired *syn* relationship and that the compound has the same stereochemistry as the proposed structure of Xeromphalinone C. With this crystal data, combined with the enantiomeric excess we had previously determined, we were confident that we had a single enantiomer with the correct stereochemistry to continue the total synthesis of Xeromphalinone C.

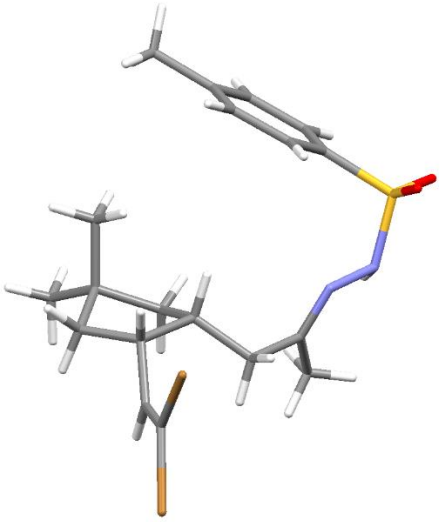
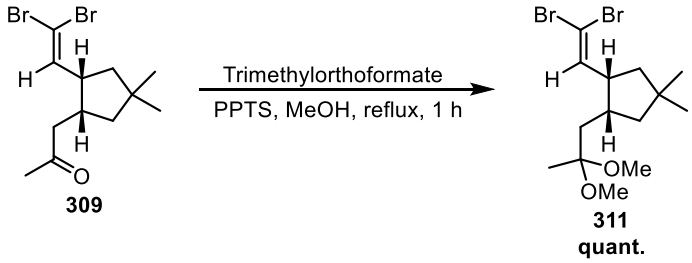


Figure 27

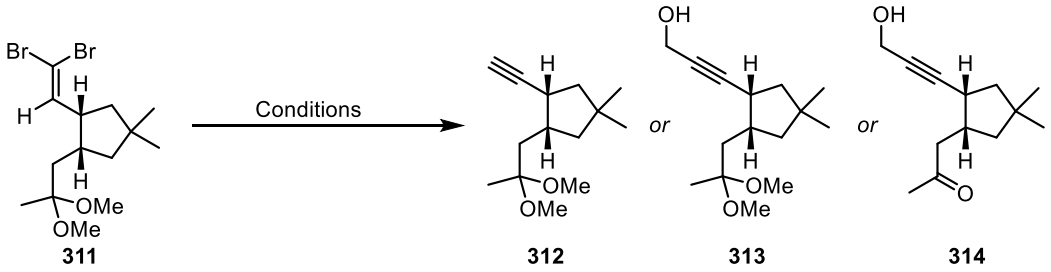
The next synthetic transformation was the application of a Ramirez-Corey-Fuchs sequence to install the requisite alkyne component, which required reacting dibromoolefin **309** with ^{n}BuLi. It was expected that the ketone functionality would be an obstacle to the efficacy of this reaction, therefore, a simple protecting group strategy was employed. It was important that this protecting group be easy to install and readily-cleavable so it did not have a significant impact on the efficiency of the synthetic route. With this in mind, dimethyl acetal was chosen, and the formation of compound **311** was facile (**Scheme 150**). The product was isolated in quantitative yield using trimethylorthoformate and PPTS in methanol.



Scheme 150

Thus, with compound **311** in hand, the Ramirez-Corey-Fuchs homologation could be realised. It was envisaged that the Ramirez-Corey-Fuchs reaction followed by *in situ* alkylation of the newly formed alkyne could be performed *via* a one-pot procedure (**Scheme 151**, **Table 15**). The first attempt (**Table 15**, **Entry 1**) used 2.2 equivalents of ^{n}butyllithium followed by 1.1 equivalents of paraformaldehyde. In this case, it was pleasing to see the success of the Ramirez-Corey-Fuchs reaction, however, the subsequent alkylation did not proceed at all, and

instead an **85%** yield of the terminal alkyne **312** was isolated. It was hypothesised that there may have been two reasons for this: insufficient deprotonation of the alkyne or inadequate solubility of the electrophile, or, indeed, both reasons may have contributed. Thus, when the reaction was repeated (**Table 15**, **Entry 2**), the equivalents of ^{n}butyllithium and paraformaldehyde were increased to 3.3 eq. and 5 eq., respectively. This had the desired effect and we were delighted to isolate compound **313** in an excellent **93%** yield. In order to keep this sequence concise, and to minimise loss of product on isolation and purification, a further attempt was performed (**Table 15**, **Entry 3**), which used identical homologation and alkylation conditions to **Entry 2** with an added deprotection step. It was discovered that this deprotection could be realised by washing the organic phase with 6M HCl in the aqueous work-up; this worked to good effect, delivering the keto-alcohol product **314** in an excellent **78%** yield from compound **311**, which had undergone three significant chemical transformations.



311 **312** **313** **314**

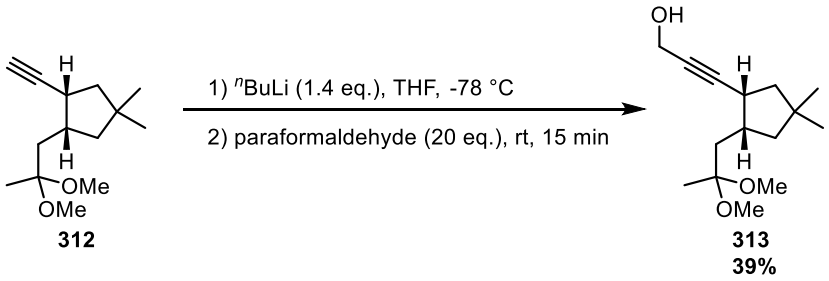
Scheme 151

Table 15

Entry	Conditions	312	313	314
1	1) ^{n}BuLi (2.2 eq.), THF, -78 °C, 30 min 2) Paraformaldehyde (1.1 eq.), rt, 15 min	**85%**	-	-
2	1) ^{n}BuLi (3.3 eq.), THF, -78 °C, 30 min 2) Paraformaldehyde (5 eq.), rt, 15 min	-	**93%**	-
3	1) ^{n}BuLi (3.3 eq.), THF, -78 °C, 30 min 2) Paraformaldehyde (5 eq.), rt, 15 min 3) 6M HCl (work-up)	-	-	**78%**

In addition to the above, alkylation of terminal alkyne **312** using ^{n}BuLi and paraformaldehyde also provided access to compound **313** (**Scheme 152**). However, this reaction afforded only

39% yield of the protected ketone, a substantial decrease in efficiency when compared to the one-pot procedure described above.



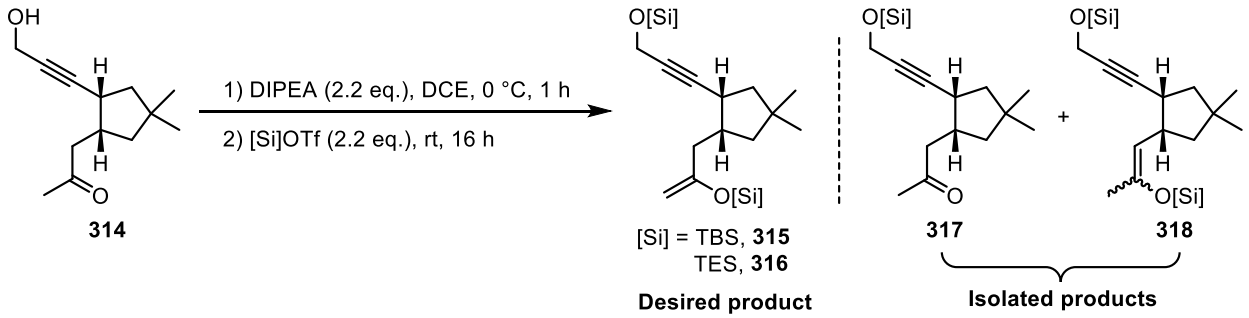
Scheme 152

Satisfied with the achievement of a concise and efficient synthesis to the keto-alcohol **314**, our attention turned to the ensuing silyl enol ether formation, cobalt complexation, and Pauson-Khand reaction. This next phase encapsulates the methodology which was developed in our laboratories and discussed *Chapter 1*. Indeed, our use of silyl enol ether moieties as alkene counterparts in the Pauson-Khand reaction for the first time was the key motivator for targeting the total synthesis of Xeromphalinone C, the preparation of which would showcase our developing protocol within complex molecule synthesis and, further highlight its importance as a valuable synthetic step for generating functionalised cyclopentenones.

2.3.4 Silyl Enol Ether Formation and Pauson-Khand Reaction

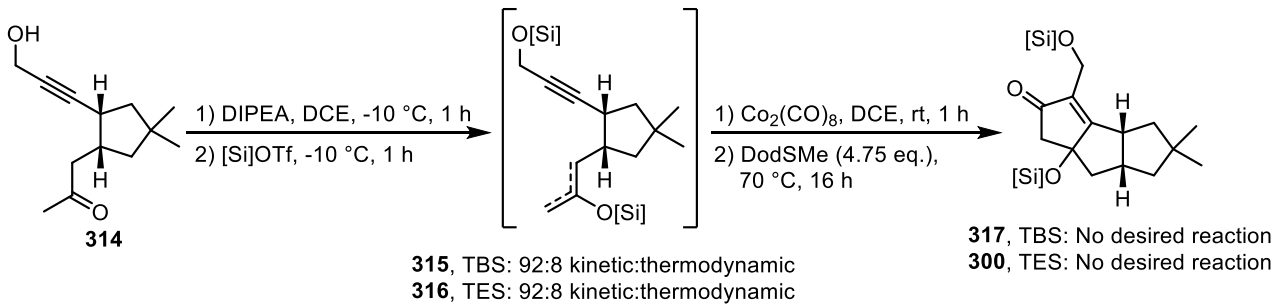
Due to the greater acidity of the alcohol proton relative to those adjacent to the ketone moiety, protection of the hydroxyl group within **314** was considered before the formation of the silyl enol ether. Having said this, it is important to note that Pauson-Khand reactions have indeed been conducted in the presence of a hydroxymethyl substituent on the alkyne and therefore protecting this group is not a necessity for the reaction to proceed.[40] Nonetheless, the initial strategy was to protect the alcohol as the silyl ether, whilst also forming the required silyl enol ether within the same step, which would mean that, downstream, i.e. post Pauson-Khand cyclisation, a global deprotection could directly provide the natural target. Disappointingly, when invoking the silyl enol ether formation conditions from Chapter 1, attempts to form either the TBS (**315**) or TES (**316**) silyl enol ethers proved fruitless, and the desired compounds were not isolated (**Scheme 153**). Instead, a complex mixture of various compounds was isolated, among which the hydrolysis product of the silyl enol ether and *cis* and *trans* isomers of the thermodynamic silyl enol ether were identified. Indeed, this mixture

was observed for both the TES and the more thermodynamically stable TBS silyl enol ether variants.



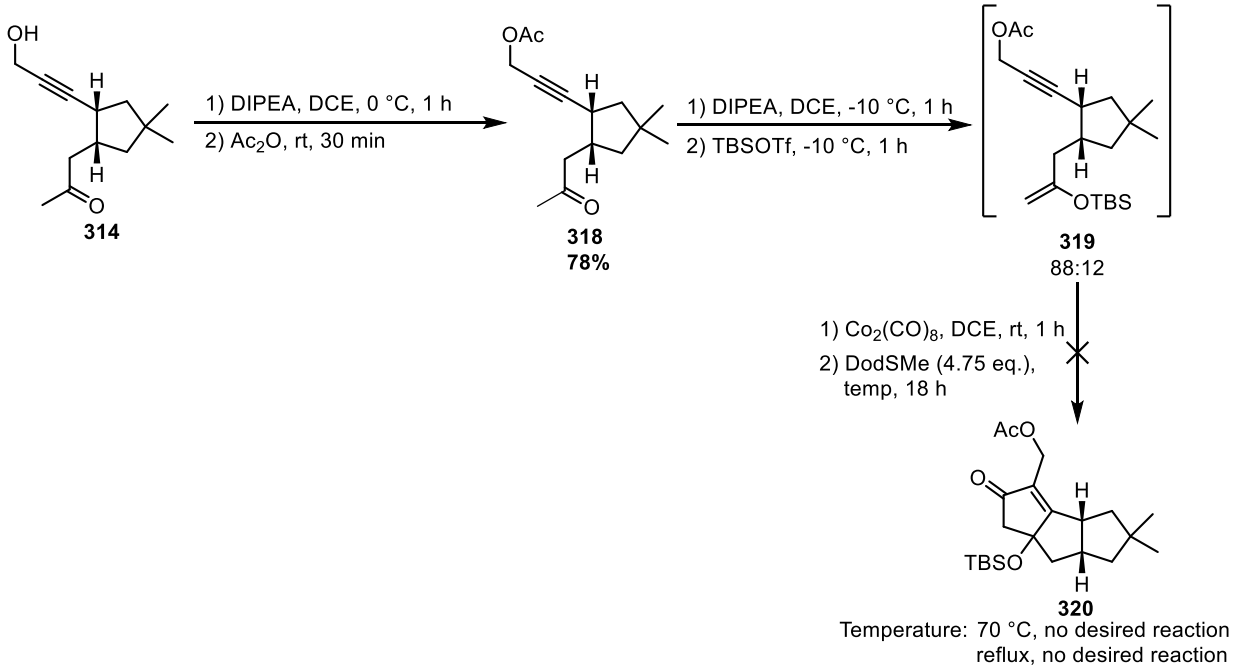
Scheme 153

The reasoning for the observation of such a mixture was attributed to the acidity of the silica gel used in the column chromatography. NMR analysis of the crude material determined that the desired product was indeed being formed in the reaction but hydrolysis/isomerisation occurred on purification. To avoid this complication, the silyl enol ethers were not isolated, and, instead, a telescoped process was conducted where the crude material from the silyl enol ether formation was subjected to alkyne complexation and Pauson-Khand reaction without isolation of any intermediates (**Scheme 154**). It was found that when the formation of the silyl enol ether was conducted at -10 °C, the ratio of kinetic:thermodynamic isomers was optimal at 92:8; conducting the reaction at -20 °C did not improve this observed ratio. An aqueous work-up was performed after the formation of the silyl enol ether as interference from unreacted silyl triflate was expected to hinder the Pauson-Khand reaction. It was observed from TLC analysis that subsequent formation of the dicobalt hexacarbonyl complexes proceeded efficiently in both cases, but, unfortunately, the Pauson-Khand reaction delivered no desired product under the standard conditions for either TES or TBS enol ethers.



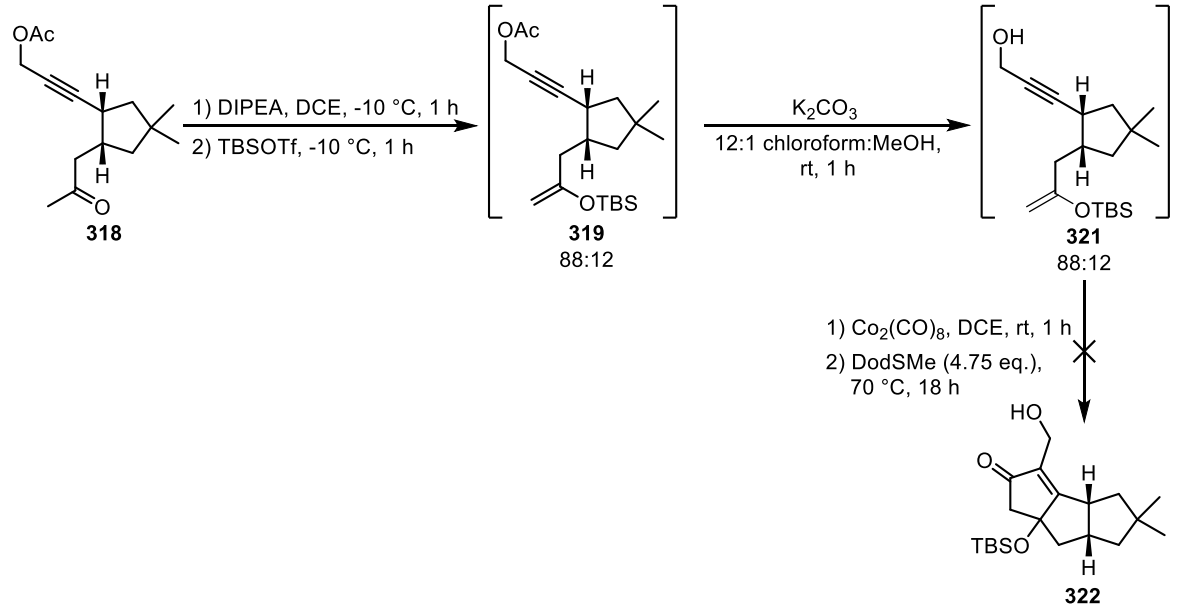
Scheme 154

Based on observations from Chapter 1, whereby the Pauson-Khand cyclisations of similar substrates had shown sensitivity when sterically-encumbering substituents were featured on the alkyne (*c.f.* **Scheme 119**), it was expected that the result above was caused by the large silyl-protected alcohol group within **315** and **316**. To counteract this, a smaller alcohol protecting group was selected, which would provide insight into whether sterics was a determining factor in the efficacy of the reaction. In this regard, an acetyl group was chosen as a suitable alternative, representing as a group with smaller steric impact than TES though maintaining robustness. As such, acetate **318** was formed from its corresponding alcohol using DIPEA and acetic anhydride, delivering the acetyl-protected product in **78**% yield (**Scheme 155**). As before, **317** was employed *via* a telescoped process where the silyl enol ether, which was an 88:12 ratio of kinetic:thermodynamic isomers, was not isolated but subjected, after aqueous work-up, to the now-standard alkyne complexation-Pauson-Khand reaction conditions. Disappointingly, this afforded none of the desired product and only considerable amount of degradation of the starting material was observed to the point that no unreacted material could be recovered. It was theorised that the reaction required more energy to proceed than was available in the system at 70 °C, therefore, the reaction was also performed at refluxing temperatures. Unfortunately, the same result was obtained.



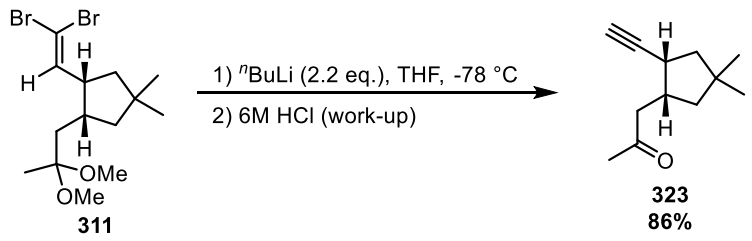
Scheme 155

At this stage, it was considered a possibility that the acetyl group was still too large and inflexible to achieve efficient cyclisation. Therefore, to decrease the size of this group even further, the silyl enol ether of **318** was formed once again, and this crude material was subjected to saponification conditions to return the free alcohol **321** (**Scheme 156**). This compound was subjected to the one-pot alkyne complexation-Pauson-Khand reaction under the standard conditions, but, unfortunately, no cyclised product was observed.



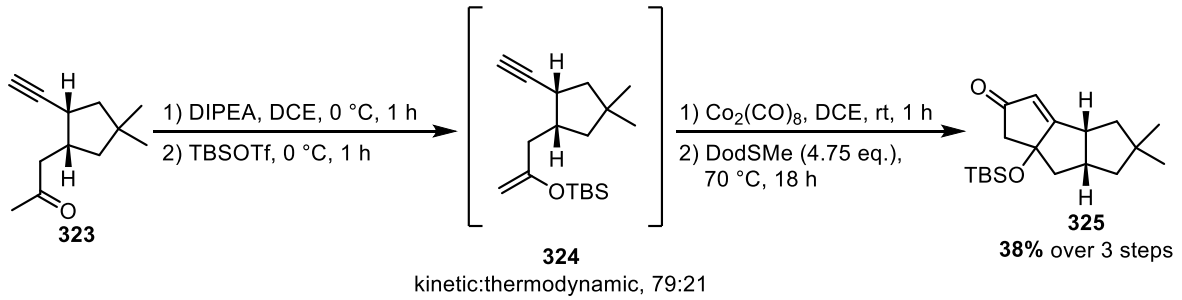
Scheme 156

To this point, the various silyl enol ether substrates tested had failed to provide any of the desired cyclopentenone product. It was maintained that this failure to react was due, largely, to the steric encumbrance of the alkyne substituent. Therefore, it was now deemed appropriate to remove the substituent entirely, in order to investigate the efficiency of a terminal alkyne variant within this programme of work. As such, the synthesis of **323** proceeded in the same fashion as compound **314**, whereby a Ramirez-Corey-Fuchs homologation was conducted on the dibromoolefin compound **311** (**Scheme 157**). Indeed, in this case, there was no need for electrophilic trapping with paraformaldehyde. Subsequent deprotection of the dimethyl acetal was conducted on work-up, in a similar fashion to the protocol employed previously, which delivered the keto-alkyne compound **323** in an excellent **86%** yield.



Scheme 157

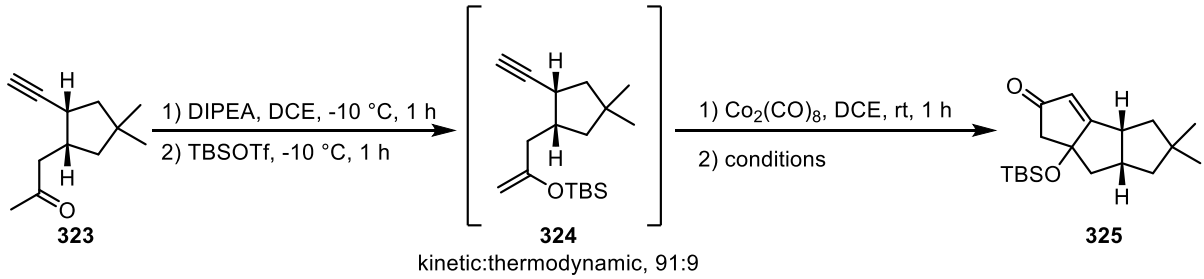
Subsequently, compound **323** was subjected to the previously described telescoped protocol for cyclopentenone formation, which was initially attempted with the TBS enol ether due to its perceived greater stability (**Scheme 158**). During this first attempt, the silyl enol ether formation was conducted at 0 °C and a ratio of 79:21 of the kinetic:thermodynamic product was obtained. This was subjected to the one-pot alkyne complexation-Pauson-Khand reaction conditions and, pleasantly, **38%** of this product was isolated. This amounts to an average of roughly **73%** for each step and, indeed, when considered from the point of view that only **79%** of the silyl enol ether could possibly cyclise, this is a very profitable outcome. At this point, the stereochemistry of the newly formed silyl ether centre remained ambiguous and could not be determined through NMR analysis.



Scheme 158

Elated with this result, efforts to improve this yield by alteration of the Pauson-Khand reaction conditions commenced (**Scheme 159**, **Table 16**). The silyl enol ether was formed at -10 °C as this had proven to be previously effective at delivering a favourable ratio of isomers; indeed, a ratio of 91:9 of kinetic:thermodynamic isomers was achieved as a result. It was observed, *via* NMR analysis and TLC analysis respectively, that preparation of the silyl enol ether formation and dicobalt hexacarbonyl complex were proceeding effectively, and so improvements to Pauson-Khand reaction step were the focus of this study. Initially, using the standard conditions with the improved ratio of isomers, cyclopentenone **325** was delivered

in an excellent **43%** yield over 3 steps (**Table 16**, **Entry 1**); a positive enhancement in the overall yield. Extending the reaction time for the Pauson-Khand reaction also proved to be agreeable as this provided access to the product in **56%** yield over 3 steps after a 64 h reaction time (**Table 16**, **Entry 2**). A further attempt was made where the reaction was conducted at a higher concentration, to, hopefully, invoke a faster reaction rate. However, in this case, the yield obtained was only **17%** over 3 steps (**Table 16**, **Entry 3**). It is important to point out that, whilst it was not possible to identify which diastereomer was being formed throughout each reaction entry, in each case, the same single product was isolated.



Scheme 159

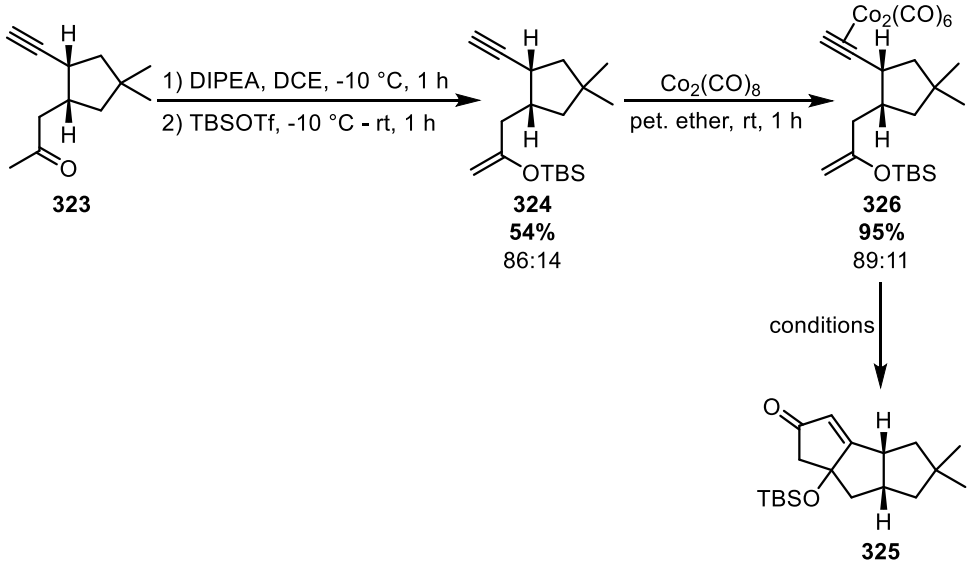
Table 16

Entry	Conditions	Yield of 317 over 3 steps
1	DodSMe (4.75 eq.), 70 °C, 16 h	**43%**
2	DodSMe (4.75 eq.), 70 °C, 64 h	**56%**
3*	DodSMe (4.75 eq.), 70 °C, 18 h	**17%**

*conducted at 1 M concentration

It was discovered that the silyl enol ether and the cobalt complex intermediates could, in fact, be isolated by making a simple change to the purification procedure; namely, by using basic or neutral alumina instead of silica gel as the stationary phase in the flash chromatography procedure. As a result of this change, silyl enol ether **324** could be isolated in **54%** with a kinetic:thermodynamic ratio of regioisomers of 86:14. The analogous dicobalt hexacarbonyl complex **326** was isolated in **95%** with a ratio of regioisomers of 89:11, the isolation of this complex allowed the use of pure cobalt complex within the ensuing cyclisation (**Scheme 160**). Initially, complex **326** was subjected to the optimal Pauson-Khand reaction conditions, namely DodSMe promotion at 70 °C in DCE, and, the cyclopentenone was isolated in a **44%** yield (**Table 17**, **Entry 1**). This corresponds to a yield of **24%** over 3 steps which represents a

decrease from the optimal yield over 3 steps achieved using the telescoped process. Following this, a further cyclisation was attempted where the amount of DodSMe was doubled to 9.5 eq. (**Table 17**, **Entry 2**). This resulted in a slight increase in the yield of the Pauson-Khand reaction to **53%**, which corresponds to **29%** yield over 3 steps. Disappointingly, this overall yield is still a decrease on the overall yield achieved using the telescoped process. As with the telescoped process, in each case, only one diastereomer of **325** was observed.



323 **324** **54%** 86:14 **326** **95%** 89:11 **325**

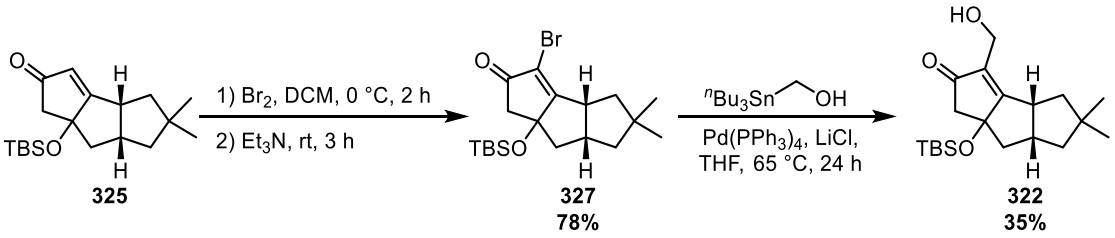
Scheme 160

Table 17

Entry	Conditions	Yield
1	DodSMe (4.75 eq.), DCE, 70 °C, 16 h	**44%**
2	DodSMe (9.5 eq.), DCE, 70 °C, 16 h	**53%**

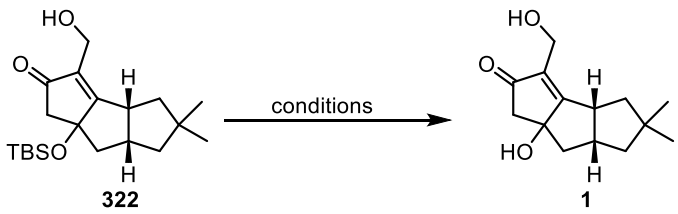
Thus, with compound **325** in hand the next step was to attempt the installation of the hydroxymethyl substituent at the vinylic position. This was attempted prior to deprotection of the silyl ether group as any free alcohol present was expected to interfere with the method of alkylation. At this stage, it was decided that the vinylic position must be activated before the alkylation can be enabled, therefore, the vinylic proton was converted to the more synthetically useful vinyl bromide **327** (**Scheme 161**). This proved to be a facile process and simple bromination of the double bond followed by elimination delivered the desired

cyclopentenone with an excellent **78%** yield. Following this, a Stille coupling was conducted using (tributylstannyl)methanol and this delivered the desired product in a good **35%** yield.



Scheme 161

At this stage, we were incredibly pleased to have all of the required bonds formed with respect to our natural target. From compound **322**, deprotection of the silyl ether motif, and confirmation the stereochemistry of this centre, would complete the synthesis of Xeromphalinone C (**Scheme 162**). The optimal deprotection conditions from *Chapter 1* were naturally considered first, however, due to the small reaction scale, it was not possible to use a 10:1 THF:H_2O solvent mixture, and instead the water which would have been added in this solvent mixture was incorporated into the aqueous HCl making this 0.59 M HCl rather than the typical 3 M HCl used in *Chapter 1* (**Table 18**, **Entry 1**). Unfortunately, this did not afford the product and, in fact, only **58%** of the starting material could be reisolated. Alternative conditions were employed that used AcOH as the acid source, and the temperature was increased to 50 °C as it was expected that this may help the reaction reach completion (**Table 18**, **Entry 2**). However, again, no desired reactivity was observed though **82%** of the starting material could be reisolated in this case. Subsequently, efforts were focused away from acidic media, as this was proving to be fruitless, and it was decided that a mild fluoride source in KF may facilitate the deprotection (**Table 18**, **Entry 3**). Utilising 5 eq. of this reactant however still did not afford the product and **80%** of the starting material was reisolated. At this stage, it was evident that **322** required significantly harsher conditions in order to react in the desired fashion, and, as a last attempt, it was decided to employ TBAF as the fluoride source (**Table 18**, **Entry 4**). Frustratingly, this only afforded decomposition of the starting material in its entirety.

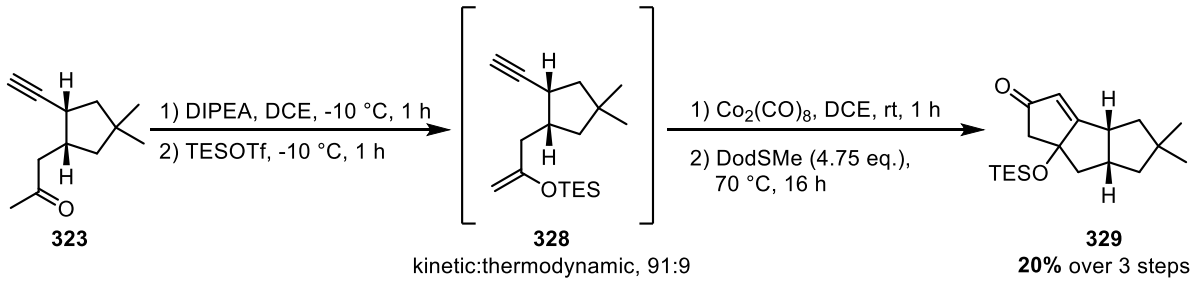


Scheme 162

Table 18

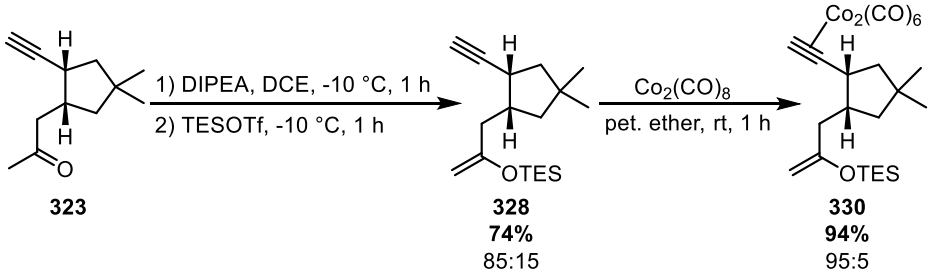
Entry	Conditions	Yield
1	0.59 M HCl, THF, rt, 18 h	-
2	AcOH:THF:H_2O (3:1:1), 50 °C, 16 h	-
3	KF (5 eq.), DMF:H_2O (1:1), rt, 5 h	-
4	TBAF, DCM, rt, 1 h	-

The results above were disappointing as it became clear that it was not possible to achieve the deprotection desired under mild conditions, and that harsh conditions only destroyed the material. Therefore, our focus turned to utilising the TES enol ether in the Pauson-Khand reaction in the hope that this would be a much more labile silyl ether. Initially, terminal alkyne **323** was employed in the telescoped process as this has proven to be the most efficient method of cyclisation to date (**Scheme 163**). As before, the silyl enol ether was formed at -10 °C and an aqueous work-up was performed to remove or quench unreacted reagents from this transformation. The crude material was subjected to a one-pot alkyne complexation and cyclisation, which delivered the cyclopentenone in a good yield of **20%** over 3 steps. This was a significant decrease in efficiency when compared to the analogous TBS enol ether, which was attributed to the greater hydrolytic stability of the TBS enol ether versus the TES enol ether.



Scheme 163

To investigate this reaction in more detail, the silyl enol ether and cobalt complex were isolated in turn, using basic alumina as discussed previously (**Scheme 164**). The silyl enol ether was isolated in a **74%** yield, much improved from the TBS analogue, with a kinetic:thermodynamic ratio of 85:15. The analogous dicobalt hexacarbonyl complex was isolated in an excellent **94%** yield with an improved kinetic:thermodynamic ratio of 95:5 after purification.

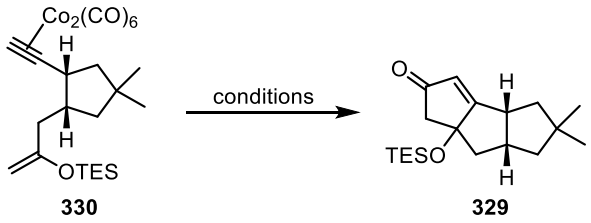


323 **328** **74%** 85:15 **330** **94%** 95:5

Scheme 164

With compound **330** in hand a fuller exploration of the seemingly capricious Pauson-Khand reaction itself was carried out in order to determine the most optimal set of conditions for our overall synthetic pathway (**Scheme 165**). Initially, the isolated cobalt complex **322** was applied to the standard conditions with 4.75 eq. of the promoter DodSMe and this delivered a yield of **22%** (**Table 19**, **Entry 1**). This yield corresponds to **15%** over 3 steps, which is lower than the telescoped process where **20%** was achieved over the same 3 steps. It was considered that the harsh reaction conditions may be resulting in degradation of the product, and, thus, the lower chemical yield. Subsequently, identical reaction conditions were employed using complex **330** but the reaction was halted after 8 h (**Table 19**, **Entry 2**). Unfortunately, the isolated yield did not agree with the hypothesis stated above as only **14%** of the product could be observed. Starting material could not be reobtained from the reaction mixture due to the stability issues of the silyl enol ether which have been previously discussed. In addition to the compound's sensitivity, separation becomes practically challenging due to its coelution with the significant excess of DodSMe using column chromatography. Therefore, considering that an increase in the amount of the promoter resulted in an improvement in the cyclisation with TBS analogue, the amount of DodSMe was doubled to 9.5 eq (**Table 19**, **Entry 3**). Pleasingly, this provided a significant increase in yield to **38%** after 16 h. To further explore this, the amount of promoter was increased again to 20 eq., however, while this delivered the product with an increased yield of **44%** this was not deemed a significant

enough improvement to warrant the use of such excess sulfide (**Table 19**, **Entry 4**). Utilising these conditions again, though extending the reaction period to 24 h, resulted in a yield enhancement to **51%** (**Table 19**, **Entry 5**). Finally, and more so for completeness at this stage, the reaction was attempted in the absence of the sulfide to ascertain if it was possible to cyclise without the aid of this reagent. Interestingly, the product was isolated in a **24%** yield showing that whilst thermal promotion did perform the cyclisation, significant quantities of DodSMe was necessary to achieve valuable amounts of product.



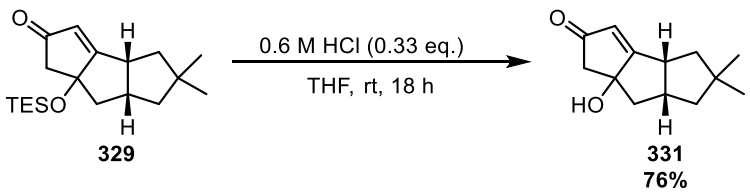
330 **329**

Scheme 165

Table 19

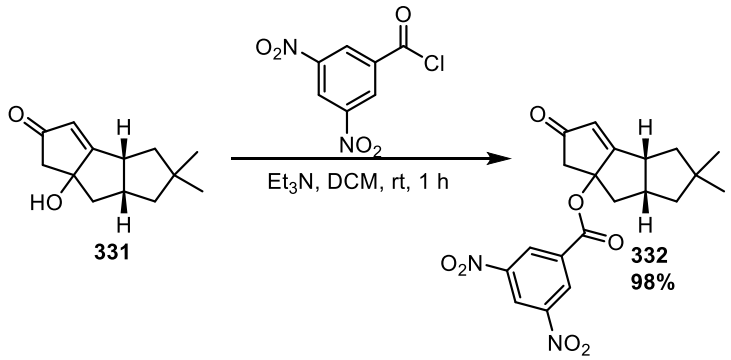
Entry	Conditions	Yield
1	DodSMe (4.75 eq.), DCE, 70 °C, 16 h	**22%**
2	DodSMe (4.75 eq.), DCE, 70 °C, 8 h	**14%**
3	DodSMe (9.5 eq.), DCE, 70 °C, 16 h	**38%**
4	DodSMe (20 eq.), DCE, 70 °C, 16 h	**44%**
5	DodSMe (9.5 eq.), DCE, 70 °C, 24 h	**51%**
6	DCE, 70 °C, 16 h	**24%**

With an appreciable quantity of cyclised **329** in hand, it was decided to check if the removal of the silyl ether protecting group was viable. Indeed, this was attempted prior to alkylation of the vinylic position as it was vital that this hydroxyl could be revealed for any synthesis of the natural target. To achieve this end, cyclopentenone **329** was reacted under our standard small-scale reaction conditions for silyl ether deprotection, and, to our delight, this worked excellently to afford the alcohol in **76%** yield (**Scheme 166**).



Scheme 166

The silyl ether formed in the Pauson-Khand reaction represents the third and final stereocentre which requires elucidation and, to this point, it was ambiguous. For the synthesis of Xeromphalinone C, this stereocentre must have a *anti* relationship to the protons at the ring junction *i.e*. it must be on the opposite face. This relationship could not be identified *via* NMR analysis, though structural determination through X-ray analysis of a single crystal would be an ideal method for identifying the relationship of these stereocentres. While compound **331** was not crystallisable itself, there was scope for derivatisation of this compound through the useful alcohol functionality, which could readily lead to a crystallisable compound. In this vein, **331** was swiftly converted to the dinitrophenylester in one step, and in a near-quantitative yield of **98%** (**Scheme 167**).



Scheme 167

Pleasingly, a single crystal, adequate for X-ray diffraction analysis, was grown to provide a clear picture of the new stereocentre. However, and extremely unfortunately, this compound was found to have the undesired stereochemistry at this site; the relationship between the protons and the ester group was *syn* (**Figure 28**).

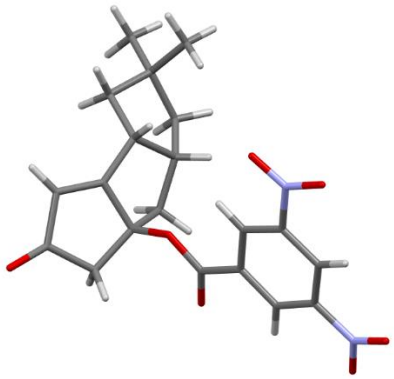


Figure 28

This was a considerably disappointing result as it showed that the key Pauson-Khand reaction provided the undesired stereochemistry required for our natural target. Indeed, it was completely diastereoselective for the undesired diastereomer. Additionally, inverting this stereocentre would be a challenging endeavour as it is a tertiary alcohol centre and any nucleophilic attack would need to occur from the bottom face of the bowl-shape structure and be subjected to potentially significant steric clashes.

2.3.5 Stereoselectivity of the Pauson-Khand Reaction

The proposed reasoning for this inherent diastereoselectivity comes from a consideration of the reaction mechanism. As described in the introduction to *Chapter 1*, dicobalt hexacarbonyl-alkyne complexes of an unsymmetrical alkyne can be considered as prochiral molecules due to the nature of the C_2Co_2 central structure (*c.f.* **Figure 4**). Therefore, when a chiral unsymmetrical alkyne such as compound **323** is converted to its dicobalt hexacarbonyl complex, each cobalt centre in the molecule becomes diastereotopic (**Figure 29**).

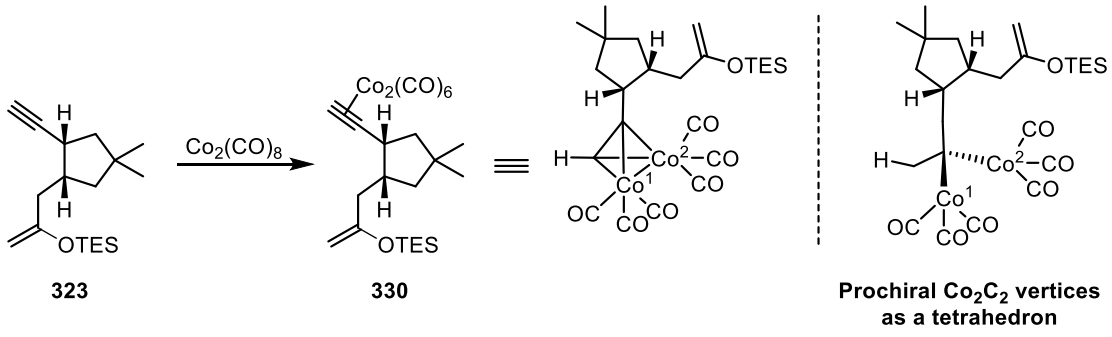


Figure 29

It is well accepted that the first step in any Pauson-Khand reaction is dissociation of a carbonyl ligand and this can occur from either cobalt atom. Therefore, if we consider dicobalt

hexacarbonyl complex **330**, where each cobalt atom is inequivalent due to their diastereotopicity, dissociation is likely to occur from one cobalt preferentially. As part of this overall programme of work, DFT calculations were performed on this complex to explore the possibility of selective carbonyl dissociation (**Figure 30**). It was found that dissociation from **Co^2** (cobalt atoms were named 1 and 2 arbitrarily) was preferred by 1.9 kcal/mol. This is a significant difference between these two intermediates and it is possible there would be complete selectivity for the lower energy intermediate. For these calculations, it was assumed that the sulfide promoter would act as a stabilisation agent for the coordinatively unsaturated intermediates downstream and therefore would have no effect on the energy of this particular CO loss step.

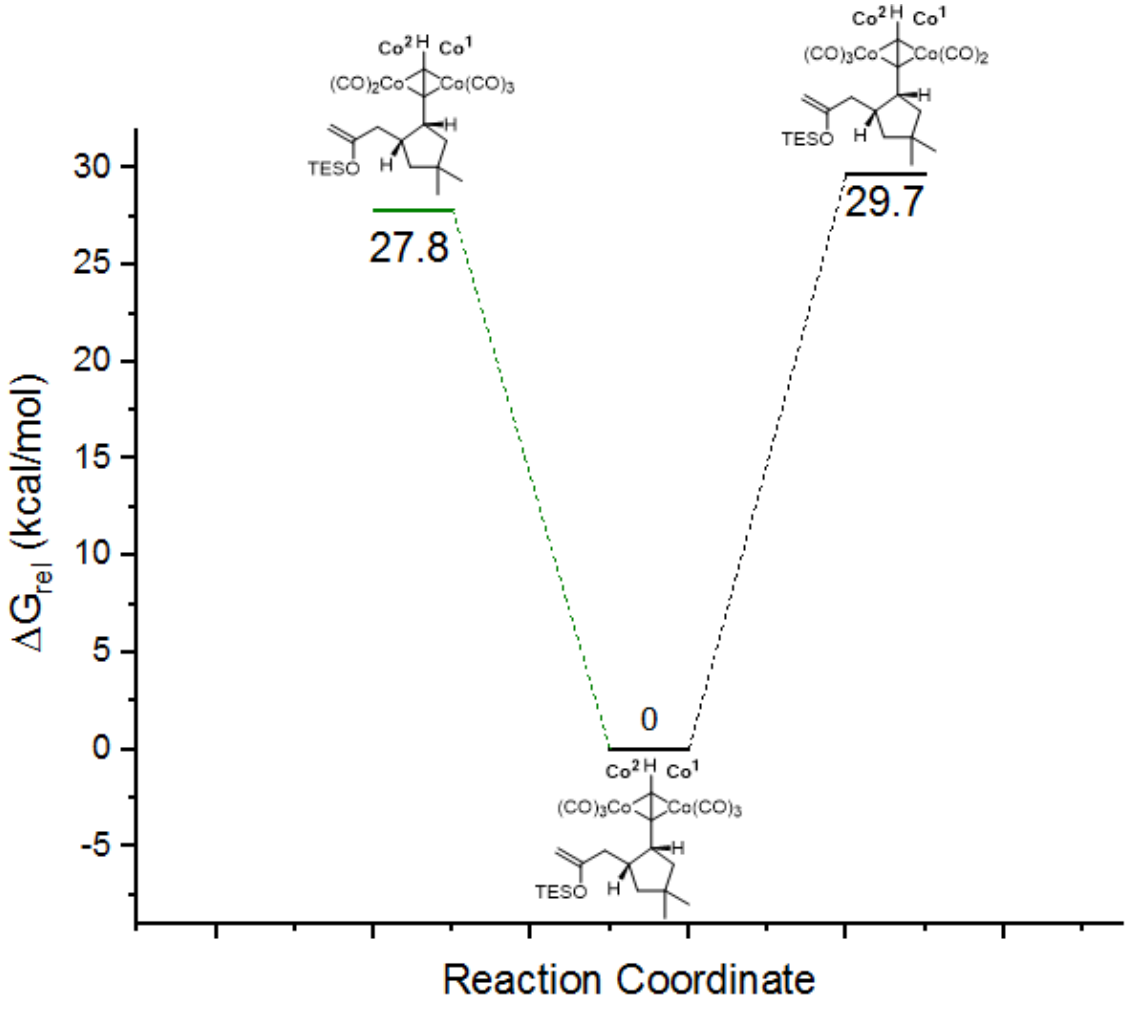


Figure 30

Further DFT calculations were conducted on the rest of the reaction pathway to determine if this proposed selectivity would correspond to the observed diastereomer. In this regard, the

next step of the reaction involves coordination of the alkene component, i.e. the TES enol ether. It is during this step that the stereocentre would be effectively set, though this is a reversible process and according to the Curtin-Hammett principle the product will be determined by the cyclisation mode, *syn* or *anti*, which has the lower energy barrier.

To establish which cyclisation mode is more energetically favoured we must first consider cyclisation through **Co^2**, the cobalt atom through which CO dissociation is more energetically favoured. In **Figure 31**, where the zero-point is the dicobalt hexacarbonyl complex starting material and coordinatively unsaturated $Co_2(CO)_5$-alkyne complex is 27.8 kcal/mol higher in energy, we can see that the *syn* (**Figure 31**, **right**) mode of alkene coordination is more energetically favoured than the *anti* (**Figure 31**, **left**) for this cobalt atom by 4.5 kcal/mol. Subsequently, the transition state barrier for cyclisation is lower for the *syn* coordination mode by 3.8 kcal/mol when compared with the transition state barrier for the *anti* coordination mode (28.8 kcal/mol *versus* 32.6 kcal/mol). After this point, the pathway is energetically downhill and therefore this indicates that cyclisation through **Co^2** would deliver the *syn* product which corroborates the experimental observations.

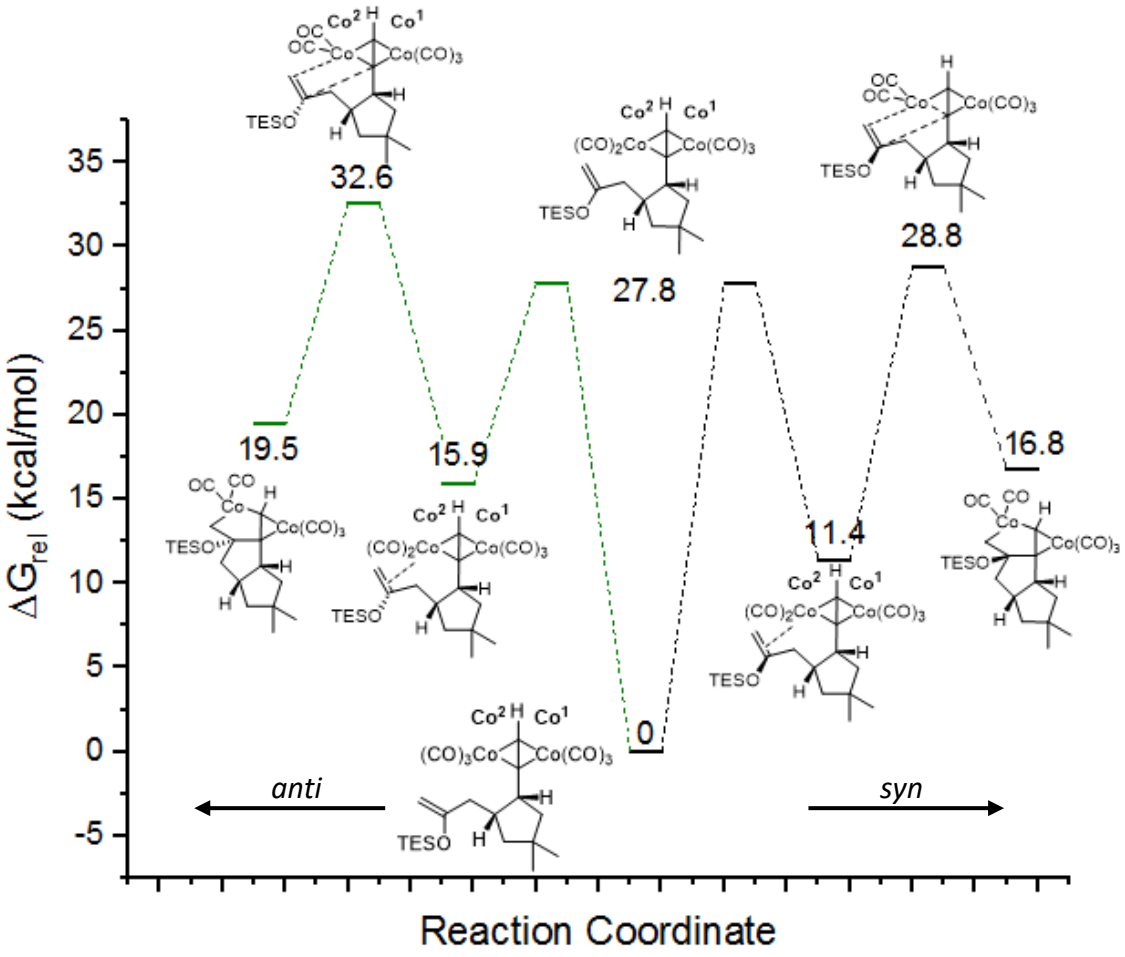


Figure 31

To complete the picture of this cyclisation, the cyclisation through **Co^1** was also studied computationally (**Figure 32**). Once more, the zero-point is fully saturated $Co_2(CO)_6$-alkyne complex and the energy for CO dissociation here is 29.7 kcal/mol Through this cobalt atom, CO dissociation is less energetically favourable, and indeed the *syn* coordination mode is, once again, more thermodynamically favoured than the *anti* coordination mode. However, the energy barrier to C-C bond formation for the *anti* coordination mode is much lower than the *syn* coordination mode, specifically 5.2 kcal/mol, which is a considerable difference. This study has indicated the C-C bond formation event is higher in energy than the CO dissociation, therefore, making this the rate-determining step. This is contrary to what is generally accepted as the rate-determining step. This disparity could be due to the strain which is incurred in our system to form the 5,5,5-tricyclic core or, indeed, because it is a doubly-substituted double bond, where one substituent is sterically large, and therefore increased steric clashes can occur during the C-C bond formation event. However, it must also be noted

that this discrepancy could be due to the way in which DFT calculations estimate the energy for CO dissociation. This estimation is done by direct comparison of the energies of the saturated and unsaturated complexes rather than the energy of the dissociation event. Indeed, the dissociation energy values obtained here may not be absolute, though the comparison between the dissociation for **Co^1** and **Co^2** is still valid as both have been calculated using the same method.

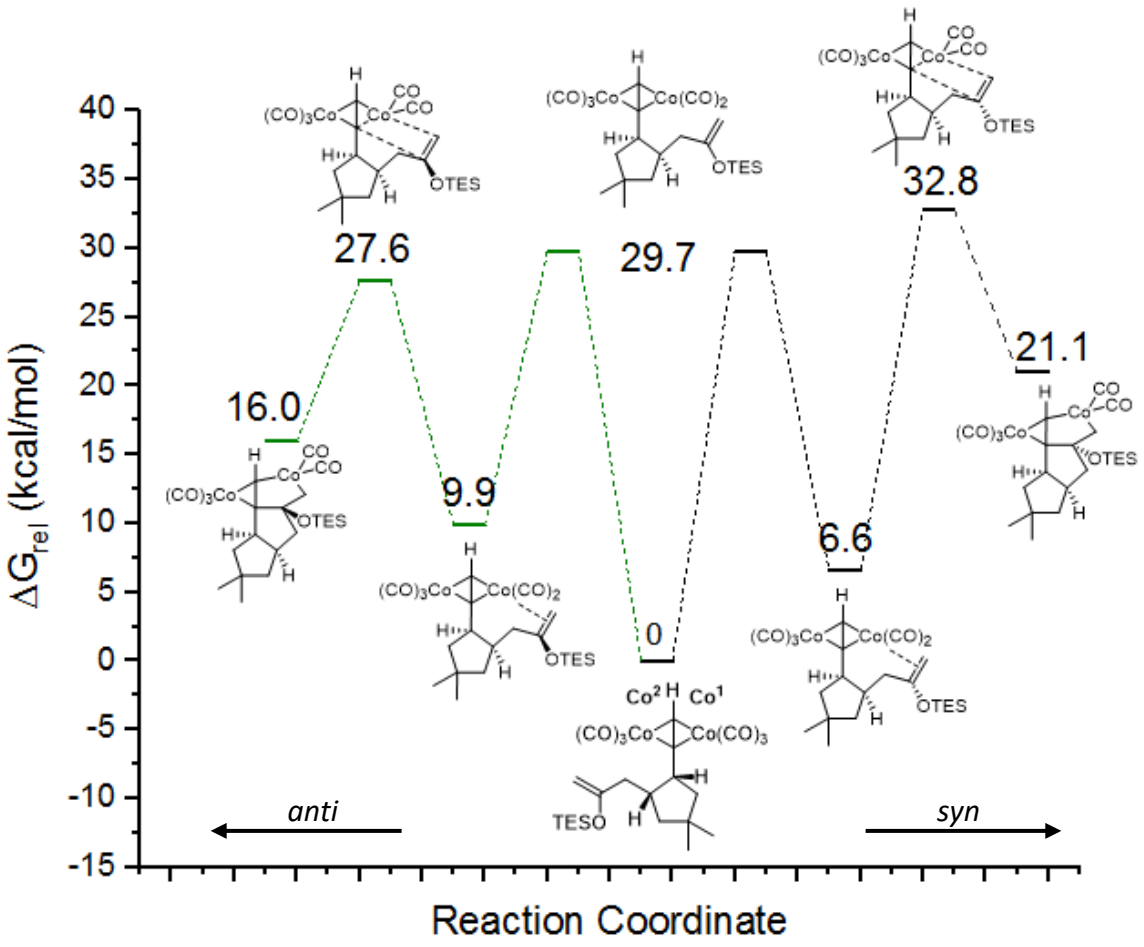


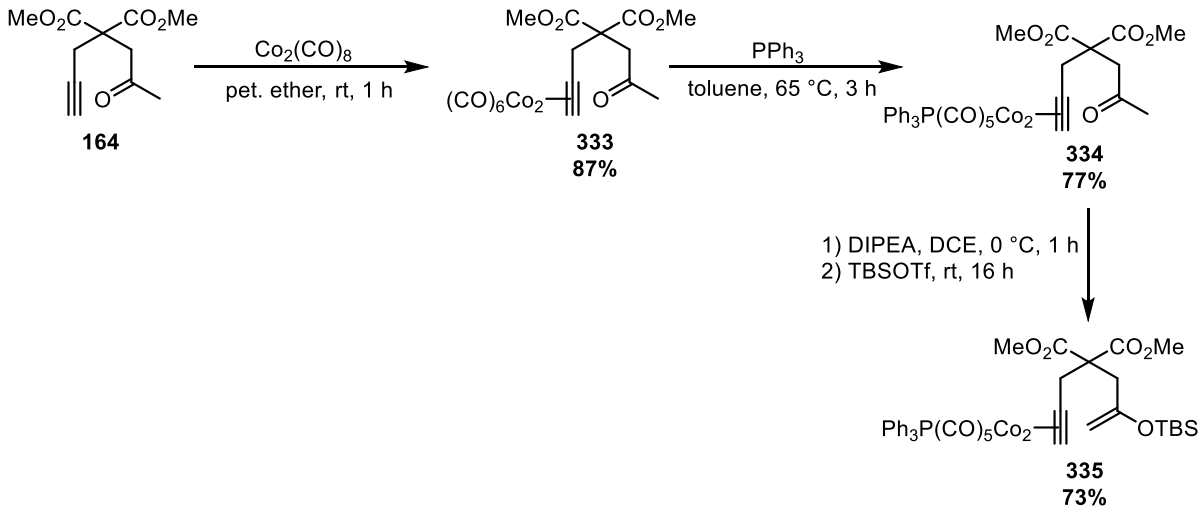
Figure 32

These experiments indicate that carbonyl dissociation from **Co^2** is energetically more favoured. Though, the overall rate-determining step is the C-C bond formation towards the *syn* product when cyclisation occurs through **Co^2**. Clearly, if the cyclisation event could occur at **Co^1** then the desired product would be favoured. Consideration of the literature on the chiral variations of the Pauson-Khand reaction clarifies that the addition of a phosphine has been known to facilitate dissociation of a carbonyl ligand from the distal cobalt *i.e*. the phosphine will only permit carbonyl dissociation from the cobalt to which it is not directly

attached.[98,139] This arises from the poorer π-acceptor qualities of the phosphine when compared with the carbonyl it has substituted. Therefore, these carbonyls receive more backdonation from the metal and, thus, are more tightly bound. In fact, the carbonyls on the other cobalt will also feel this effect but markedly less as they are further away. Based on this phenomenon, we considered that if carbonyl dissociation occurs favourably from **Co^2**, which delivers the *syn* product, then addition of a phosphine should trap the unsaturated **Co^2** and then a subsequent dissociation event would occur from **Co^1**, which, upon Pauson-Khand reaction, would deliver the desired *anti* product.

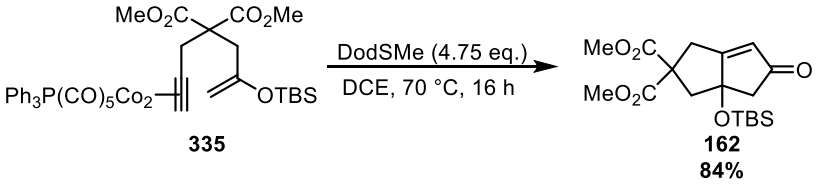
2.3.6 Pauson-Khand Reaction with a $Co_2(CO)_5PPh_3$ Alkyne Complex

As explained above, the addition of a phosphine to the ligand sphere of a dicobalt hexacarbonyl complex strengthens the metal-carbonyl bonds throughout the complex. Indeed, this means that the resulting complexes are much more stable than the hexacarbonyl analogues, and, as a result, react less readily. Prudence dictated that it was worthwhile to test the reactivity of a phosphine-substituted complex using a substrate which is known to cyclise successfully with the dicobalt hexacarbonyl analogue. Therefore, complex **333** was synthesised from keto-alkyne **164** in an excellent yield of **87%**, and this was converted directly to the triphenylphosphine-substituted analogue by heating the reacting components in toluene (**Scheme 168**). The phosphine-substituted complex was isolated in a very good yield of **77%** and this was transformed into the corresponding silyl enol ether using the standard conditions to afford **335** in a good **73%** yield.



Scheme 168

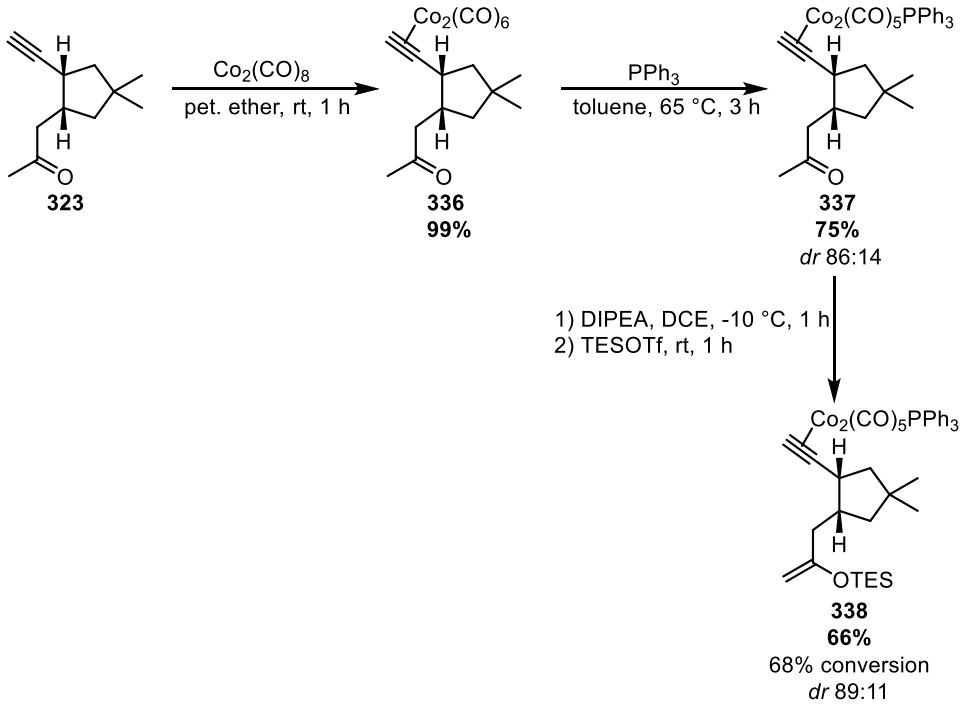
With this compound in hand, the Pauson-Khand reaction could be attempted using our standard conditions (**Scheme 169**). Pleasingly, this afforded the cyclopentenone product in an excellent yield of **84%**, which is comparable to the previously obtained yield of **88%** when the dicobalt hexacarbonyl complex was used (*c.f. Chapter 1*, **Scheme 70**).



Scheme 169

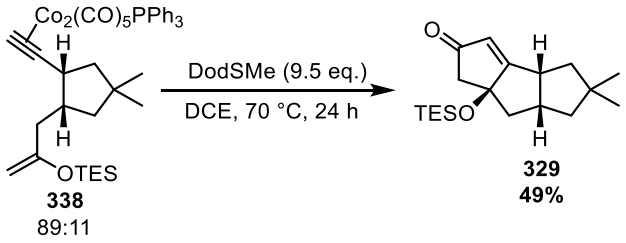
With evidence that the phosphine-pentacarbonyl cobalt complex performs well in the Pauson-Khand reaction of silyl enol ethers, we embarked on the synthesis of the phosphine analogue of dicobalt hexacarbonyl complex **330**. This began with the synthesis of the dicobalt hexacarbonyl complex of the keto-alkyne **323**, which was successfully prepared in an excellent **99%** yield (**Scheme 170**). Phosphination performed well to deliver the phosphine-substituted complex **337** in a **75%** yield, and in an 86:14 ratio of diastereomers. It should be outlined again that the cobalt centres in this complex are diastereotopic, and so alternating the ligand substitution on one cobalt makes them inequivalent and, therefore, there is the potential to form two diastereomeric complexes in this phosphination step. It was assumed that the major product featured the phosphine substituted on **Co^2** (**337-Co^2**) and that subsequent cyclisation

of this complex would deliver the *anti* product by reaction through **Co[1]**, as predicted by the theoretical calculations. The requisite silyl enol ether was formed as standard, however, only **68%** conversion was achieved and **66%** yield with a small change in the diastereomeric ratio to 89:11, however, this was isolated as a single kinetic regioisomer with no thermodynamic isomer present.



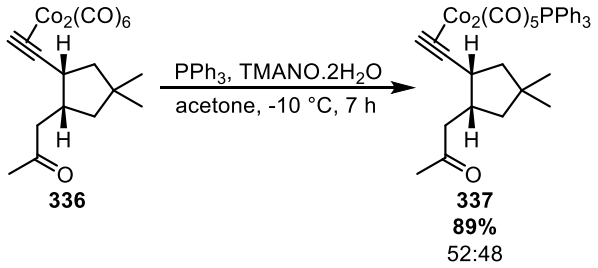
Scheme 170

This provided us with the material required to test our hypothesis, and when complex **338** was subjected to the Pauson-Khand reaction conditions, the product was obtained in a good **49%** yield after 24 h (**Scheme 171**). The addition of the phosphine to the ligand sphere did not inhibit the reaction and the yield of product was comparable to the analogous dicobalt hexacarbonyl reaction. In fact, this appreciable chemical yield was obtained over a much shorter reaction period, highlighting an improvement in reaction efficiency. However, and disappointingly, characterisation data of the cyclopentenone product obtained from this reaction was identical to the characterisation data obtained from the dicobalt hexacarbonyl complex reaction, i.e. the wrong (*syn*) isomer.



Scheme 171

It was theorised that the isolation of this single diastereomer arises from the mixture of two diastereomeric complexes which had been isolated, one featuring the phosphine on **Co^1** and the other featuring the phosphine on **Co^2**. It had been assumed on first isolation that the major isomer of this mixture featured the phosphine on **Co^2**, the desired isomer which was predicted by the computational experiments, however, the formation of only *syn*-**329** may indicate that, in fact, this was the minor isomer. Investigations next involved the synthesis of the phosphine-pentacarbonyl complexes at lower temperatures. This was driven by the expectation that complex **337-Co^1** is the kinetic product which forms first and then converts to the more thermodynamically stable **337-Co^2**. As such, the phosphination of compound **336** was conducted at -10 °C using TMANO.2H$_2$O to facilitate the dissociation of a carbonyl to allow the phosphine to bind (**Scheme 172**). This delivered the product in an excellent yield of **89%** with a more favourable ratio of isomers, this time 52:48.



Scheme 172

Rather than immediately react this compound in the Pauson-Khand reaction, a variable temperature NMR experiment was conducted on a small sample. As both diastereomeric complexes are visible in the NMR, this would determine whether they can interchange and at what temperature this begins. The NMR was conducted in d^8-toluene and a single acquisition was collected at room temperature before the solution was heated to 70 °C for two acquisitions then cooled to room temperature for a further acquisition. A partial spectrum is shown **Figure 33** featuring the signal for the alkyne proton; the first acquisition is shown at

the bottom in blue where the mixture has a ratio of 52:48 in favour of the thermodynamic diastereomer. Over time the ratio changes drastically from almost 1:1 to show a clear favourability for one diastereomer over the other. This diastereomer produces the undesired stereochemistry in the cyclopentenone product of the Pauson-Khand reaction and so can be identified as **337-Co^1**. This experiment shows that the mixture can isomerise readily at the reaction temperature, this is likely to occur *via* exchange of a phosphine on **Co^2** with a carbonyl on **Co^1** and driven by the greater thermodynamic stability of the product of that exchange.

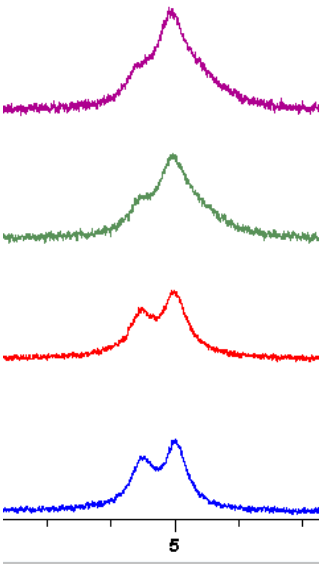
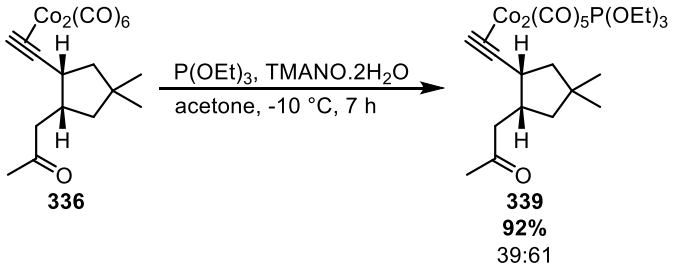


Figure 33

We considered the possibility that this exchange occurs rapidly because the large size of the substituents on the phosphine cause undesired steric clashes resulting in a greater energetic discrepancy between the two diastereomers. So, we endeavoured to synthesise a phosphine-pentacarbonyl dicobalt complex which had a less sterically large substituent. To this end, we chose a phosphite, $P(OEt)_3$. This has a considerably smaller Tolman cone angle than PPh_3 (145 ° for PPh_3 vs 109 °C for $P(OEt)_3$)[204] and so if the steric component of the phosphine had an effect on the rate of isomerisation then this should be limited by the smaller phosphite. The dicobalt pentacarbonyl-phosphite complex was formed using the low temperature conditions, which functioned well for PPh_3 analogue, and this delivered the product in an excellent **92%** yield (**Scheme 173**). In this case, the product was isolated in a less favourable ratio of diastereomers of 39:61.



Scheme 173

This isomerisation of this mixture of complexes was tested with the variable temperature NMR in a similar fashion to the study on the PPh_3 variant (**Figure 34**). Unfortunately, this exhibited the same propensity for isomerisation, in fact, the phosphite derivative **339** isomerised much more rapidly, as can be seen in the transition from the blue partial spectrum of data acquisition at room temperature, to the red spectrum, which was the first data acquisition at 70 °C.

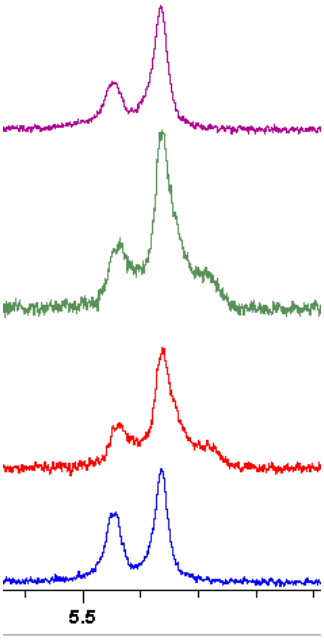
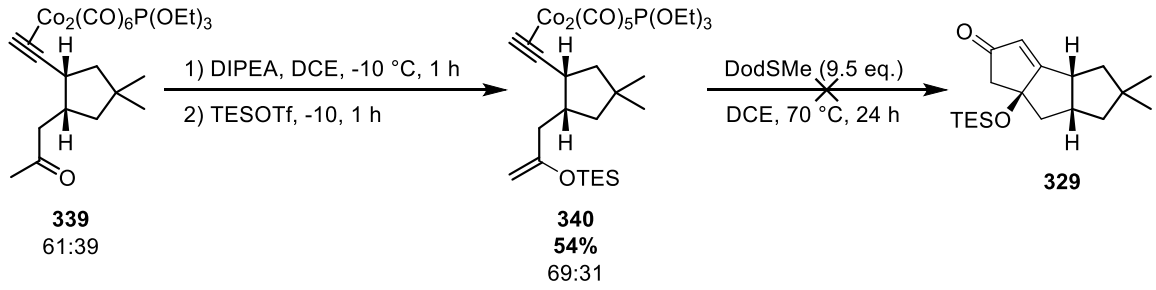


Figure 34

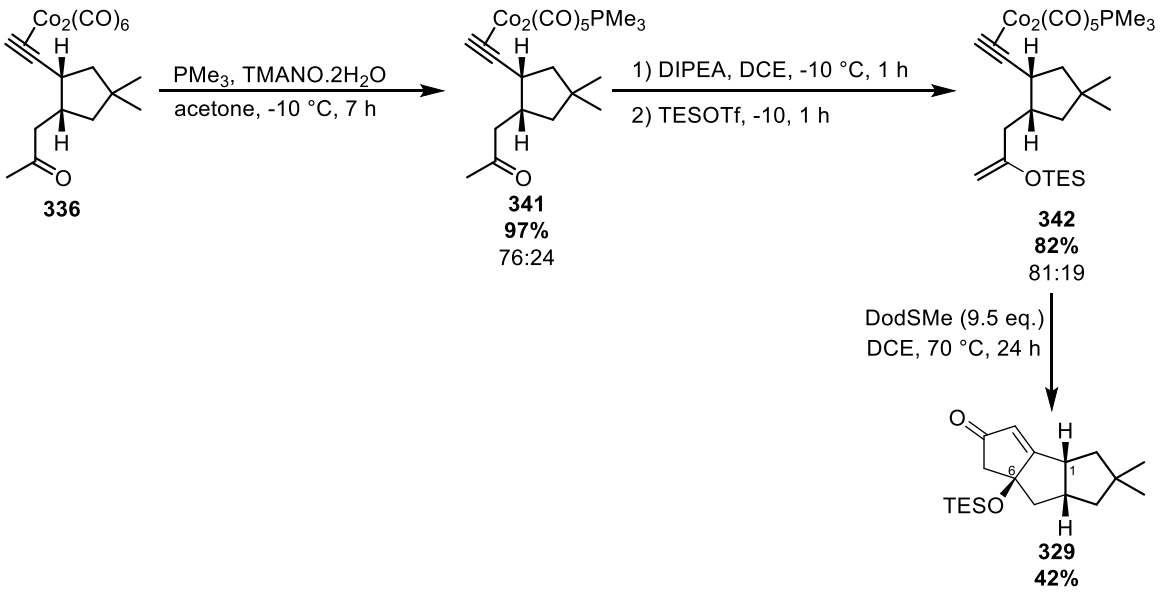
Nevertheless, the silyl enol ether of the phosphite derivative **339** was formed (in a good 54% yield) and this was applied to the Pauson-Khand reaction conditions (**Scheme 174**).To note, it was not clear from ^1H NMR analysis what the ratio of kinetic:thermodynamic silyl enol ethers were but it was assumed to be the same as had been observed previously in ketone **332**. Unexpectedly, when $Co_2(CO)_5P(OEt)_3$ complex **340** was subjected to the Pauson-Khand

reaction conditions, no product was formed and, instead, only decomposition of the starting material was observed.



Scheme 174

It had been expected that the phosphite-substituted complex would perform in a similar fashion to the PPh_3-substituted complex and so the result described above was a disappointment. Consideration of the Tolman Electronic Parameter (TEP) for the ligands showed that $P(OEt)_3$ is less electron-rich than PPh_3 (2076 cm^{-1} for $P(OEt)_3$ and 2069 cm^{-1} for PPh_3). It was theorised that perhaps the more electron-rich the phosphine ligand the more amicable behaviour it would exhibit through the course of the reaction. As explained before, the more electron-rich the phosphine, the more stable the overall cobalt complex, and reaction intermediates, due to the greater backdonation afforded to the other ligands. It was suggested that the improvement in reaction efficiency could be due to the greater stability of the intermediates in the reaction. To test this theory, the PMe_3-substituted complex was synthesised (**Scheme 175**); this phosphine is more electron-rich than PPh_3 (2064 cm^{-1} vs 2069 cm^{-1})[204] and is significantly smaller (118 °C vs 145 °),[204] and so it was expected this derivative would exhibit improved stability while having a limited steric impact, all whilst presenting some bias between the possible diastereomers of the product. The synthesis of the PMe_3 compound **341** was conducted under conditions described previously, providing the PMe_3-substituted complex in an excellent yield of **97%**. Though the ratio of isomers was 76:24 formation of the silyl enol ether worked well in **82%** but the ratio of isomers was changed further to favour the undesired isomer now in 81:19. However, pleasingly, the Pauson-Khand reaction for this complex performed well and the cyclopentenone was delivered in **42%** yield as a single diastereomer. Unfortunately, this was, once again, the cyclopentenone product with the undesired stereochemistry at the 6-position.



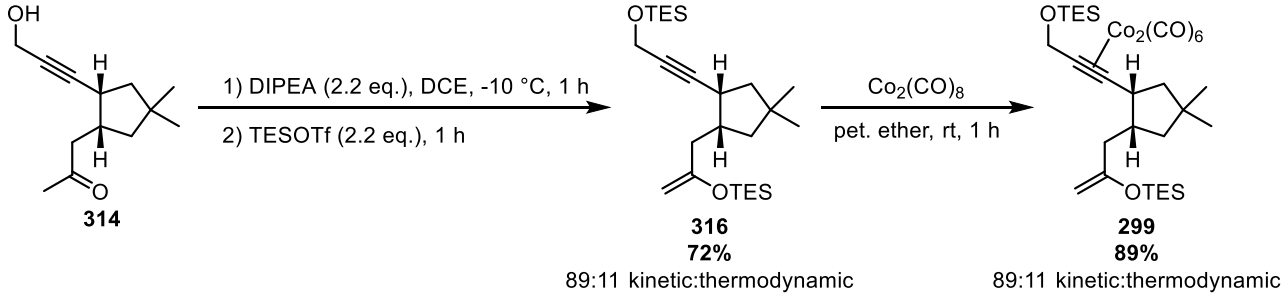
Scheme 175

While this overall stereoselectivity study had not yielded the desired outcome, which was a change in stereoselectivity of the Pauson-Khand reaction to deliver the targeted *anti* compound, it had neatly shown us the ability of a phosphine-substituted pentacarbonyl cobalt complex to improve the Pauson-Khand reaction when using silyl enol ethers. The improvement here is manifested in a shorter reaction time, although the overall isolated yield had not been improved. Indeed, a far from full optimisation was conducted at this stage with the more pressing goal of the synthesis of the natural product at the forefront of the research. Undoubtedly, more evidence is required in order to make a complete statement on the electronic and steric requirements of the phosphine ligand within such systems, though it seems that sterics, within reason, do not inhibit the reaction significantly and electronics may play the more important role.

2.3.7 Pauson-Khand Reaction Towards Xeromphalinone C.

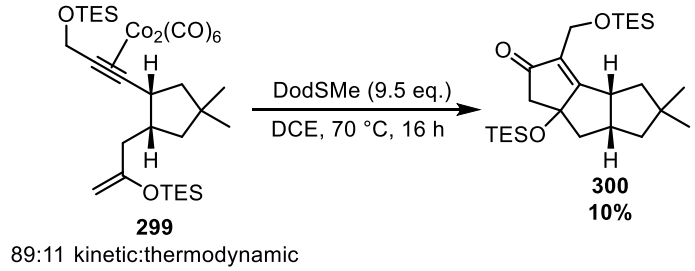
To this point, the Pauson-Khand cyclisations that were successful towards forming the core of the natural target provided the undesired stereochemistry, and cyclisations with an internal alkyne variant had provided no cyclopentenone product at all. However, until this stage, the reaction with an internal alkyne had not been conducted with the isolated dicobalt hexacarbonyl complex, and reactions had only been attempted in a telescoped fashion. Whilst it was assumed that the stereoselectivity for such an internal alkyne substrate would be identical to that observed for the terminal alkyne substrate **316**, we were still keen to

explore this transformation, which would further showcase the methodology as a useful synthetic technique for accessing complex cyclopentenone products. Additionally, it would provide the first total synthesis of non-natural compound 6-*epi*-Xeromphalinone C. To this end, the silyl enol ether **316** was formed, and, to our delight, the desired bis-silyl product was isolated in a **72%** yield with a ratio of 89:11 kinetic:thermodynamic silyl enol ethers (**Scheme 176**). The TES group was chosen as it had been shown that this group could be readily cleaved post-cyclisation. The formation of the dicobalt hexacarbonyl complex **299** was similarly fruitful, delivering this compound in an **89%** yield with an identical ratio of regioisomers.



Scheme 176

The first set of conditions attempted with cobalt complex **299** were the conditions that had been previously optimal with the isolated complexes, namely 9.5 eq. of DodSMe at 70 °C in DCE (**Scheme 177**). When this protocol was applied, to our amazement, the cyclopentenone product was isolated in **10%** yield, with the newly-formed stereocentre remaining ambiguous.

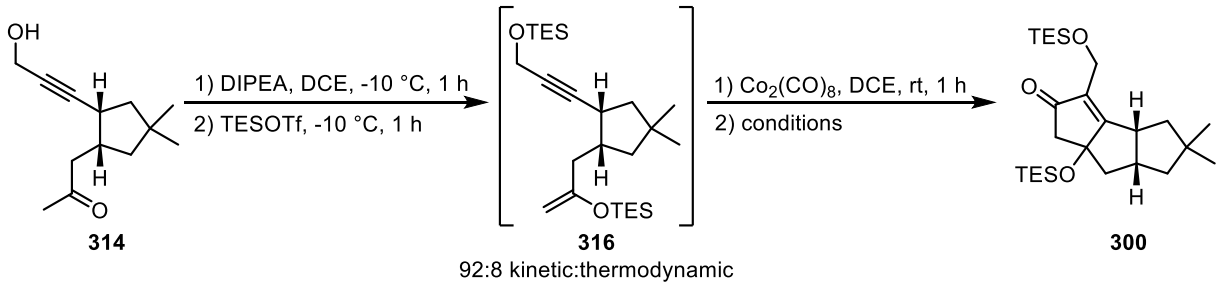


Scheme 177

With this evidence, it was clear that the use of a Pauson-Khand cyclisation that embedded the requisite internal alkyne was a viable method for accessing the full cyclopentenone framework present within the natural target. As such, efforts were immediately focused towards improving the overall efficiency of this particular transformation (**Scheme 178**, **Table 20**). The telescoped process has proven to be a synthetically useful protocol for the Pauson-

Khand reaction of silyl enol ethers. It had been attempted with substrate **316** *via* **299**, though using the original conditions of 4.75 eq. of DodSMe and had yet to be attempted with the seemingly more optimal 9.5 eq. of DodSMe method. When the telescoped process was employed with terminal substrates **326** and **330** it proved to be a more effective method when compared to the stepwise process of isolation of each intermediate, producing a greater yield of the cyclopentenone over 3 steps. This telescoped approach was subsequently employed once more, using 9.5 eq. of DodSMe in the Pauson-Khand reaction step, and this afforded cyclopentenone **300** in an increased yield of **10%** over 3 steps from **314** after 16 h, with no starting material remained (**Table 20**, **Entry 1**). Clearly, the efficacy of the Pauson-Khand reactions described in this chapter are influenced by the amount of kinetic silyl enol ether present in the reaction system and isomerisation to the internal double bond would result in a decrease in efficiency. It was hypothesised that the telescoped process afforded a basic reaction medium as a result of leftover DIPEA from the formation of the silyl enol ether, which helped to prevent any *in situ* isomerisation of the terminal double bond. To ensure the reaction mixture was basic throughout the reaction, 1 eq. of DIPEA was added along with 9.5 eq. of DodSMe. Whilst this amended protocol required a prolonged reaction time of 40 h, the product was delivered in an incredible **25%** yield over 3 steps (**Table 20**, **Entry 2**). This corresponded to an average yield of **63%** for each individual step, which is an extremely impressive result for this very challenging reaction sequence. This overall transformation produces the tricyclic core of the natural product with all the required functional groups in place. The vast improvement in this process was attributed to the basic reaction medium, which likely permitted greater stability of the kinetic silyl enol ether *in situ*, allowing more of this compound to react. It was also considered that the inclusion of molecular sieves may help this process even further. Molecular sieves have been shown to be effective in trapping CO to aid the Pauson-Khand reaction,[205] though, for our process, we anticipated that it may have a dual effect by also trapping any water that had been incorporated into the system over the long reaction period. Whilst each component of the reaction had been distilled, and the crude reactant had been dried with Na_2SO_4, it is possible that small amounts of water may still be present in the system which could result in partial hydrolysis of the silyl enol ether or unwanted isomerisation of this compound. With this in mind, the conditions from **Entry 2** were replicated, however, this time, oven-dried 4 Å molecular sieves were added (**Table 20**, **Entry 3**). The reaction required an even longer reaction time of 68 h, and delivered the

cyclopentenone product in **15%** yield over 3 steps. Disappointingly, this inclusion of molecular sieves did not have the desired effect and, in fact, this represented a decrease in the isolated yield of **300**.



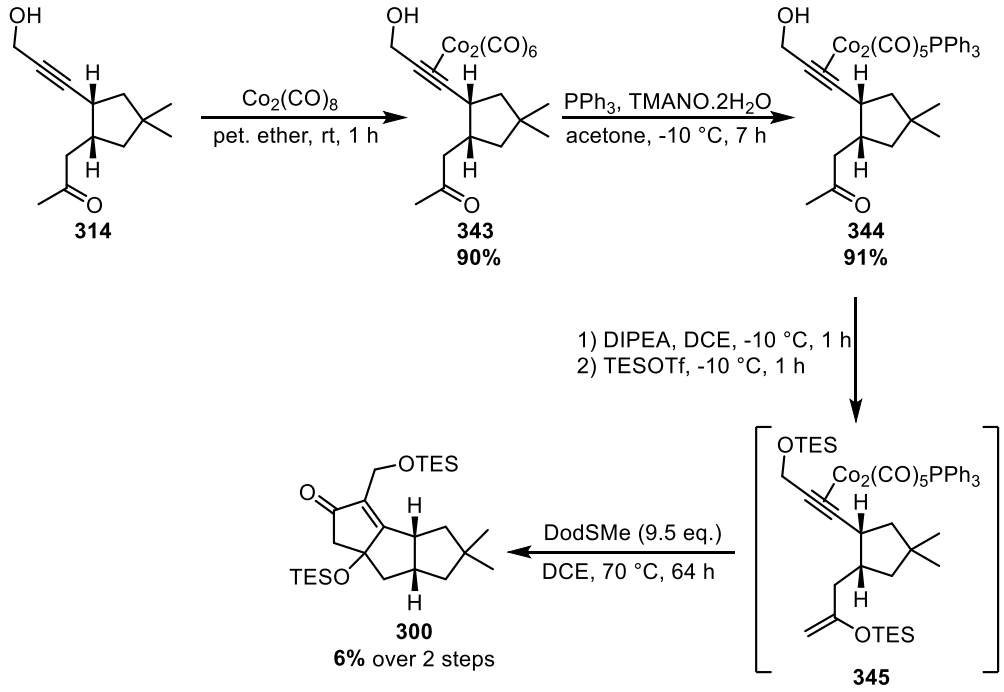
Scheme 178

Table 20

Entry	Conditions	Yield over 3 steps
1	DodSMe (9.5 eq.), 70 °C, 16 h	**10%**
2	DodSMe (9.5 eq.), DIPEA (1 eq.), 70 °C, 40 h	**25%**
3	DodSMe (9.5 eq.), DIPEA (1 eq.), 4 Å MS, 70 °C, 68 h	**15%**

As had been shown in the previous section, the use of a $Co_2(CO)_5PR_3$-alkyne complex can improve the efficacy of the Pauson-Khand reaction. Thus, it was prudent to attempt the above Pauson-Khand reaction with a phosphine-substituted complex. Indeed, complex **343** was easily synthesised from keto-alcohol **314** *via* dicobalt hexacarbonyl complexation and subsequent phosphination (**Scheme 179**). The $Co_2(CO)_6$-complexation worked well to give **343** in **90%** yield, then phosphination with triphenyl phosphine and $TMANO.2H_2O$ delivered the phosphine-pentacarbonyl dicobalt complex in **91%** as a mixture of diastereomers. It was not possible to identify the ratio of the mixture as the ^1H NMR spectrum was poorly resolved and the individual peak for the alkyne proton could not be separated. From here, the formation of the silyl enol ether intermediate **345** proceeded, however, the same isolation techniques that had proven to be so advantageous in the past, seemingly, did not purify this compound effectively. Whilst an amount of material corresponding to **53%** yield was isolated, the ^1H NMR spectrum was poorly resolved and it was not possible to determine the ratio of diastereomers or the ratio of kinetic vs thermodynamic silyl enol ether compounds. Despite this, the material was subjected to the Pauson-Khand reaction conditions without further

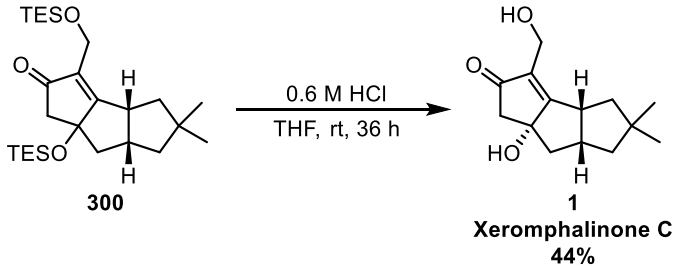
purification. Disappointingly, this did not result in much of an improvement in the yield compared with the analogous hexacarbonyl complex, with the product being isolated in only **6%** yield over the 2 steps from **344**. Additionally, substrate **345** required a long reaction time to deliver this amount of product and so the improvement in efficiency which had been observed in the previous examples did not exhibit itself here.



Scheme 179

Pleased with the vast improvements made to the Pauson-Khand reaction, we turned our attention to the final stage of the total synthesis programme; the global deprotection of the silyl ether moieties. We were confident that the deprotection of both TES ethers would work as well as it had for compound **329** (*c.f.* **Scheme 167**). Promptly, compound **300** was subjected to the optimal deprotection conditions (**Scheme 180**), which, pleasingly, provided access to the deprotected compound **1** in a good **44%** yield. Whilst, this compound was a white crystalline solid, the several attempts made to perform X-Ray diffraction studies in order to elucidate the crystal structure were unsuccessful. Having said this, with respect to stereoselectivity, and to our amazement, this compound was, in fact, the desired natural product Xeromphalinone C, which was confirmed upon comparison with the ^{13}C NMR

characterisation data from the literature (**Table 21**).[5] The ^{13}C NMR data of the synthetic sample clearly matches the isolated sample.

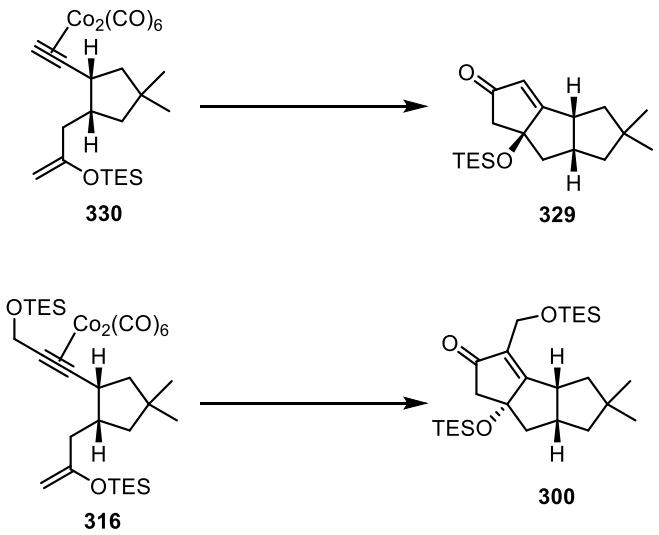


Scheme 180

Table 21

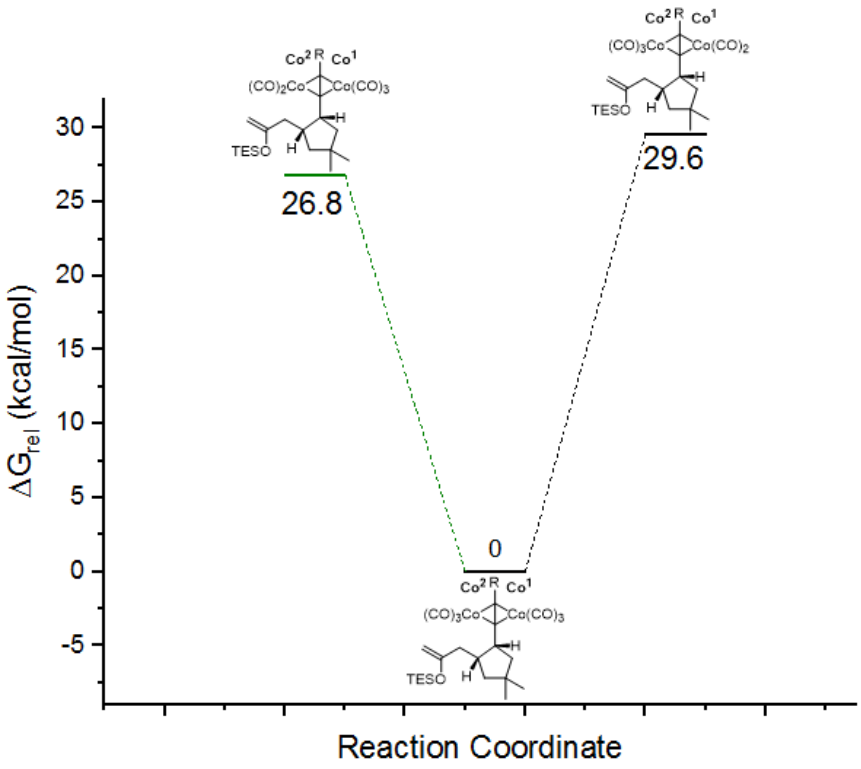
Synthetic	Isolated	Δ
209.0	209.0	0
183.9	183.8	-0.1
135.9	135.9	0
85.3	85.3	0
55.8	55.7	-0.1
51.3	51.3	0
49.2	49.2	0
47.2	47.2	0
46.6	46.5	+0.1
43.5	43.5	0
43.3	43.3	0
42.1	42.1	0
28.7	28.7	0
26.7	26.6	+0.1

Evidently, there is a clear distinction in the stereoselectivity between the cyclisation of terminal alkyne substrate **330** and internal substrate **316** (**Scheme 181**). Indeed, the Pauson-Khand annulation of **330** produced the tricyclic structure featuring all *syn* stereocentres, whereas reaction of **316** delivered the tertiary alcohol centre represented as *anti* to the protons at the ring junction.



Scheme 181

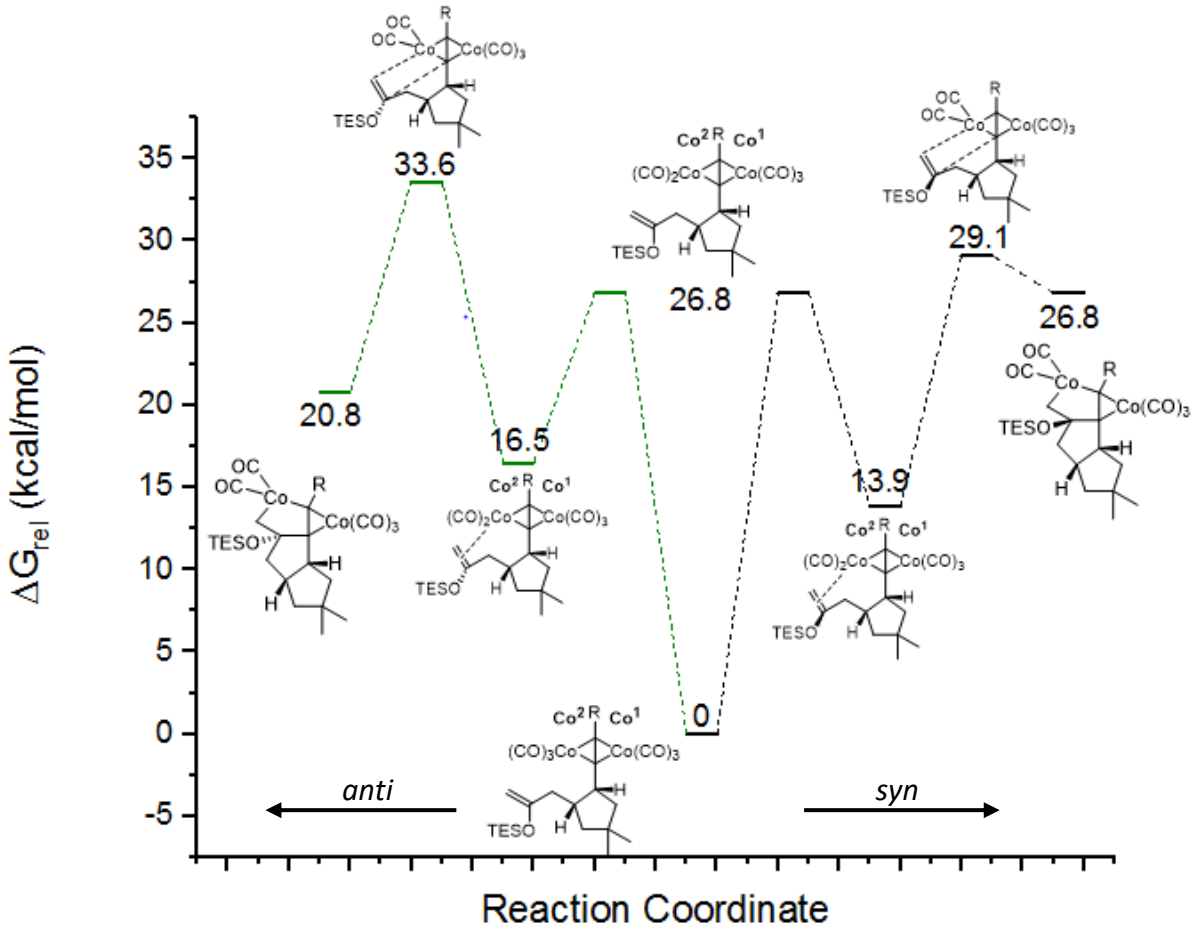
At this stage, the disparity in stereoselectivity between these Pauson-Khand reactions was unclear and, in an effort to probe further, theoretical calculations on the cyclisation mechanism for compound **316** were undertaken. These studies were conducted in the same manner as the theoretical calculations presented previously (*c.f*. **Figure 30**), and, as previously, there was a difference in the energies of CO dissociation between each cobalt atom; once more, dissociation from **Co^2** was more energetically favourable (**Figure 35**).



R = CH_2OTES

Figure 35

The continuation of the mechanistic pathway through this particular metal atom is shown in **Figure 36**. *Syn* coordination shows an energetic favourability of 2.6 kcal/mol over *anti* coordination. Strikingly, the energy barrier to the transition state of the C-C bond formation event is lower for the *syn*-coordinated complex than the *anti*. This is in direct contradiction to the experimental observations if the reaction is kinetically favoured. It was expected that the calculated energy barrier for the *anti*-coordinated complex would have been lower to reflect the exclusive formation of **300**. The pathway after the C-C bond formation event is energetically downhill, and thus irreversible after this point, so the calculations, once again, predict the C-C bond formation event to be the rate-determining step and the *syn* cyclisation mode to be the most energetically favoured.



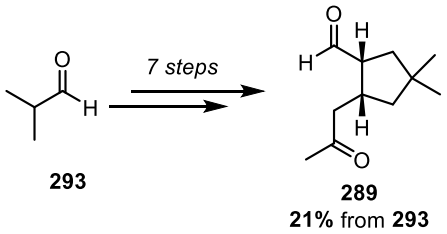
R = CH_2OTES

Figure 36

As yet, the reasoning for this misalignment between experimental and theoretical studies is unclear. It could be due to an inadequate level of theory for the calculations or that the action of the sulfide promoter is not being accounted for effectively. Furthermore, the reasoning for the switch in stereoselectivity in the Pauson-Khand reaction between the terminal alkyne and the internal alkyne is not obvious. It could be due an increased steric clash afforded to the complex when the alkyne substituent is in place.

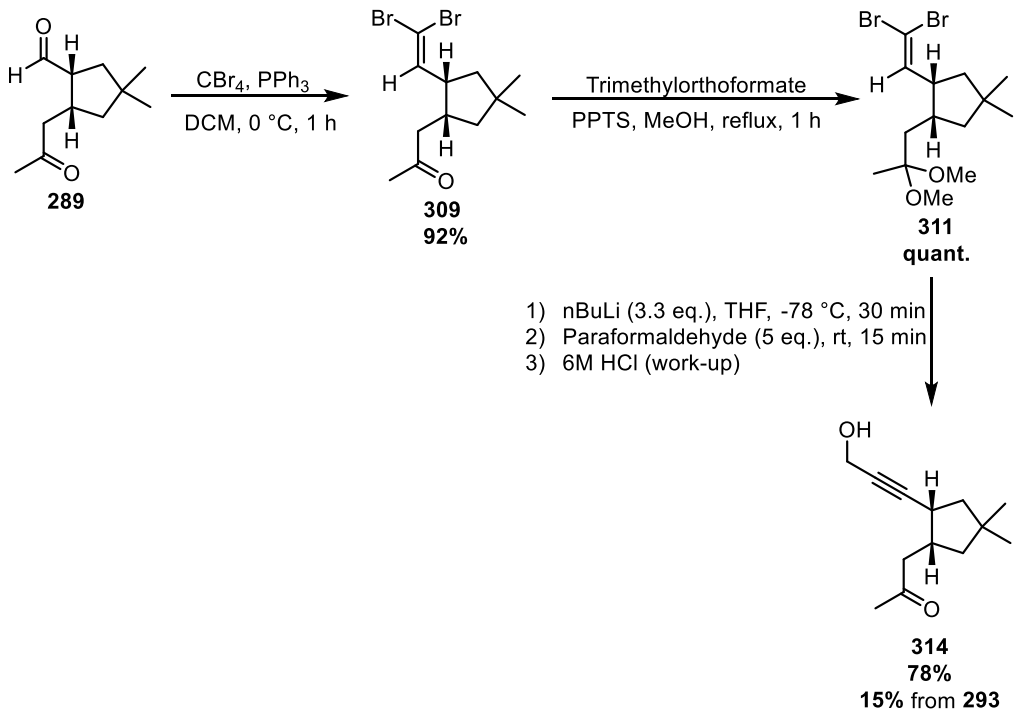
2.4 Conclusions

Following a very successful piece of research which developed the use of silyl enol ethers as alkene components in the Pauson-Khand reaction, the applicability of the methodology was extended into the natural product synthesis arena. Specifically, Xeromphalinone C was targeted due to its oxygenated cyclopentenone motif. The total synthesis of this molecule provided a platform to exhibit the utility of our methodology in the synthesis of a complex molecule. The synthesis began with the preparation of keto-aldehyde **289**, which contained two of the three stereocentres within the final target. Whilst this material was known in the literature, modification of the synthetic pathway towards this key material was performed, providing the desired compound in a more readily accessible and efficient manner. Gram quantities of **289** were isolated in **21%** yield over 7 steps (**Scheme 182**).



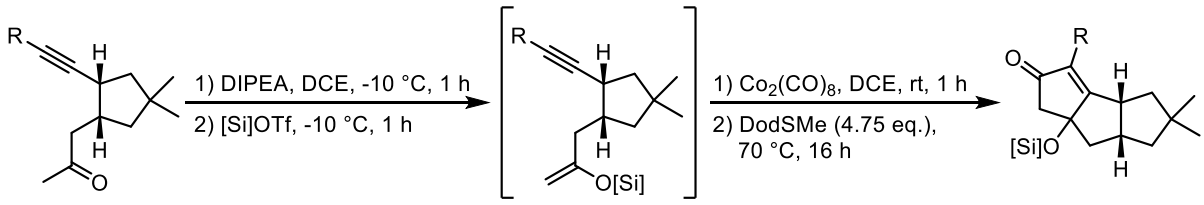
Scheme 182

In order to access the required keto-alcohol from **289**, the alkyne had to be installed through a Ramirez-Corey-Fuchs sequence which began with the formation of the dibromoolefin **309** (**Scheme 183**). This was followed by protection of the ketone using dimethyl acetal as a labile protecting group which can be removed with ease later in the synthesis. Completion of the Ramirez-Corey-Fuchs was conducted in conjugation with alkylation of the newly-formed alkyne to install the hydroxymethyl alkyne substituent, and subsequent facile deprotection of the acetal delivered the requisite keto-alcohol **314** in **15%** overall yield from starting material *iso*-butyraldehyde **293**.



Scheme 183

Investigations into the key Pauson-Khand reaction involved the preparation and application of a range of substrates. In particular, the most efficacious method was to perform the silyl enol ether formation, alkyne complexation, and Pauson-Khand reaction through a telescoped process. Initial attempts using conditions which had been optimised in *Chapter 1* did not furnish the fully functionalised cyclopentenone, however, the main framework of the natural target could be isolated when the alkyne was terminal (**Scheme 184**, **Table 22**). Attempts were made using various alkyne substituents whose steric impact was incrementally lowered but only when the substituent was removed entirely was any product obtained.

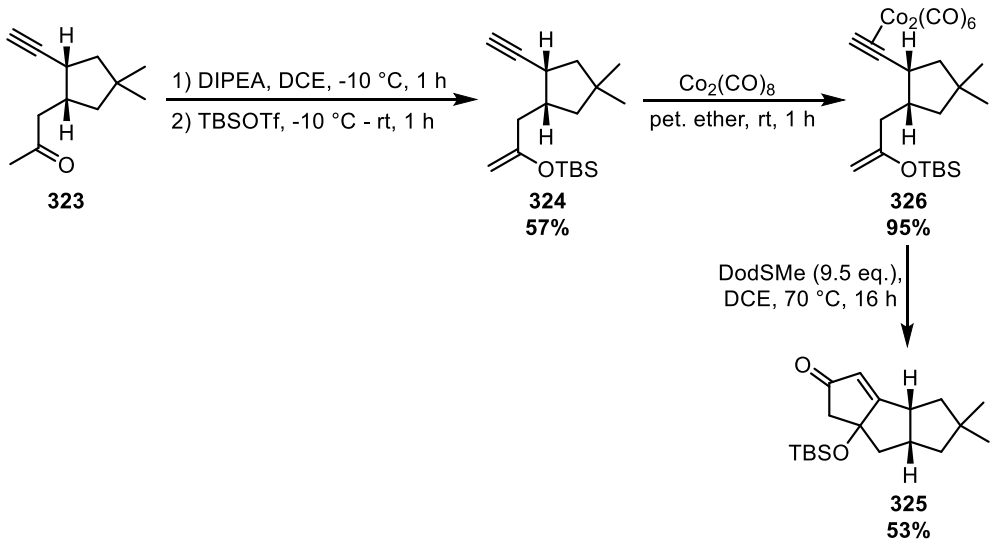


Scheme 184

Table 22

Entry	R	Yield
1	CH_2O[Si] (**315**/**316**)	N/A
2	CH_2OAc (**319**)	N/A
3	CH_2OH (**321**)	N/A
4	H (**326**)	**56%** over 3 steps

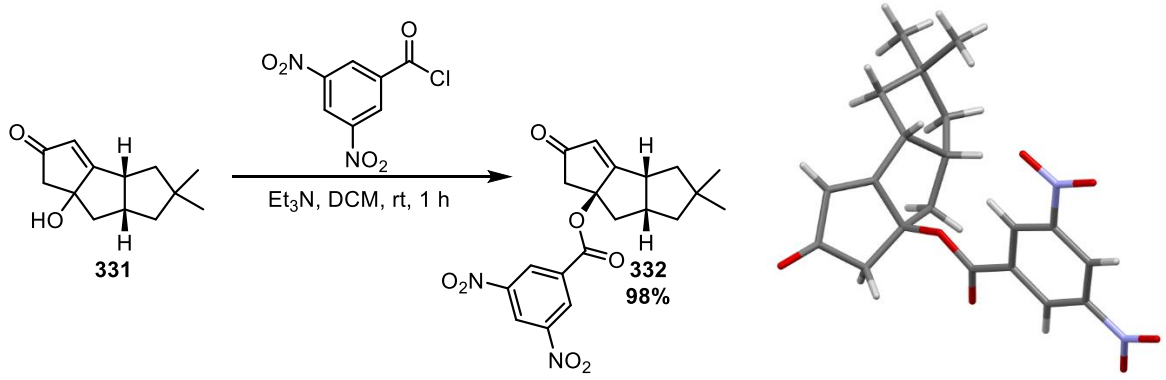
After further exploration with regards to the purification methods agreeable with our silyl enol ether substrates, it was noted that the silyl enol ether compounds could in fact be isolated when basic or neutral alumina was used as the stationary phase in the column chromatography (**Scheme 185**). To achieve the optimal yield for the stepwise process an increase in the amount of additive, from 4.75 eq. to 9.5 eq., was required. This allowed us to establish these conditions as the most optimal for this particular step-wise protocol and the product could be accessed in **29%** over 3 steps.



Scheme 185

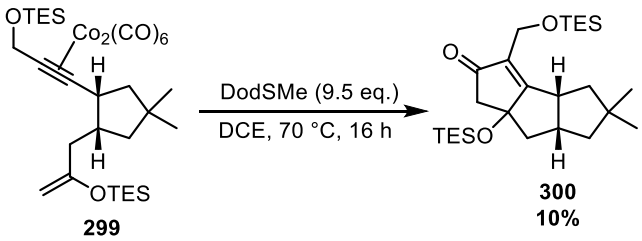
Following deprotection, the stereochemically-ambiguous oxygenated cyclopentenone **331** was reacted to form the dinitrophenyl hydrazine and a crystal structure was elucidated (**Scheme 186**). This revealed that the Pauson-Khand reaction with the terminal alkyne had afforded the undesired diastereomer, where all the chiral centres had a *syn* relationship. Based on this result, we expected that the Pauson-Khand reaction towards this tricyclic core

was inherently selective for the undesired diastereomer and so efforts were focused on synthesising 7-*epi*-Xeromphalinone C.



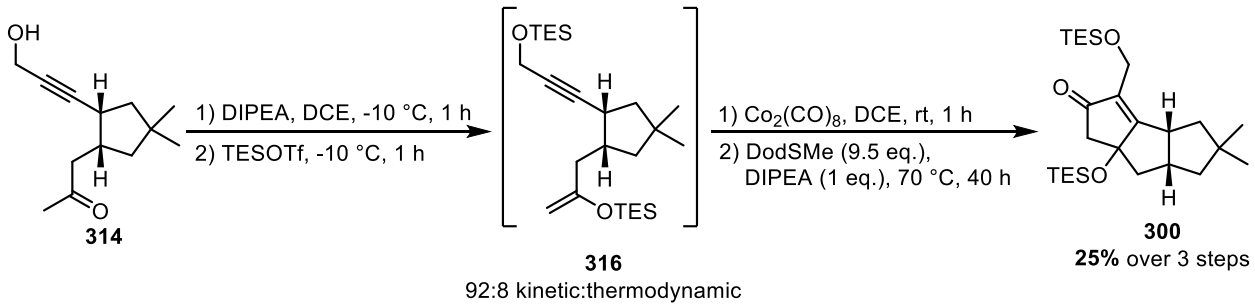
Scheme 186

When the optimised conditions of 9.5 eq. of DodSMe were applied to compound **299** a small amount of the desired product could be isolated (**Scheme 187**). This reaction represents the first successful silyl enol ether Pauson-Khand reaction used to synthesise a linear tricyclic molecule from an internal alkyne.



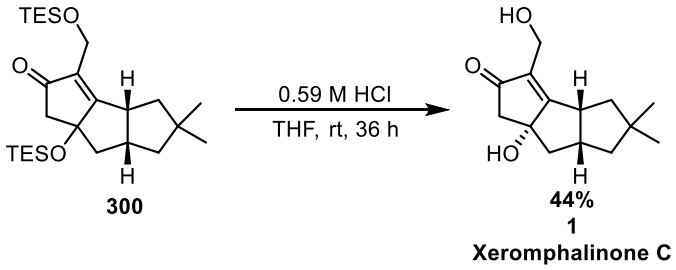
Scheme 187

This yield was improved upon further when the telescoped process was revisited. Importantly, a further modification that included the addition of 1 eq. of base to prevent isomerisation of the reactant *in situ* afforded the best yield of **25%** over 3 steps (**Scheme 188**). This yield corresponds to an average of **63%** for each individual step.



Scheme 188

The final deprotection proceeded well to reveal the oxygenated cyclopentenone, and astoundingly the analytical data for the synthesised sample was identical to that of the isolated Xeromphalinone C (**Scheme 189**). This reaction completed the total synthesis programme and the target molecule had been synthesised in 16 steps with an overall yield of **1.6%**. This natural product synthesis represented the first total synthesis of Xeromphalinone C and the first total synthesis to use the silyl enol ether Pauson-Khand reaction as a step to form an oxygenated cyclopentenone.



Scheme 189

2.5 Future Work

Xeromphalinone C was isolated along with 5 analogous triquinane sesquiterpenes (**Figure 37**). Clearly, Xeromphalinone C is the most synthetically tractable of these molecules. However, all feature an oxygen atom attached to carbon 7, therefore, represent prime examples of oxygenated cyclopentenone units that could be synthesised through our methodology. Moreover, a closer inspection of the Xeromphalinones shows that it may be possible to access them through Xeromphalinone C itself as a late-stage intermediate.

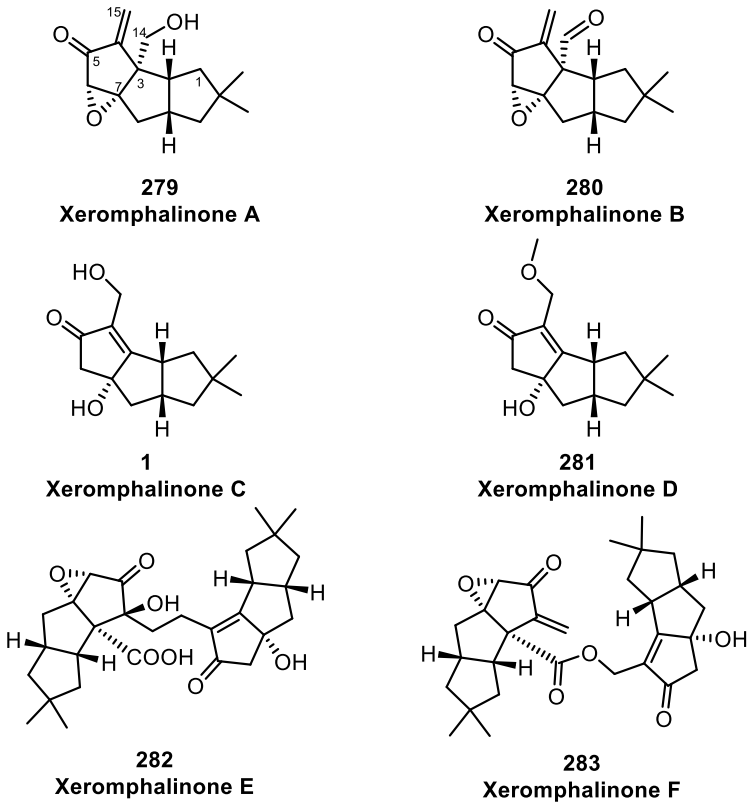
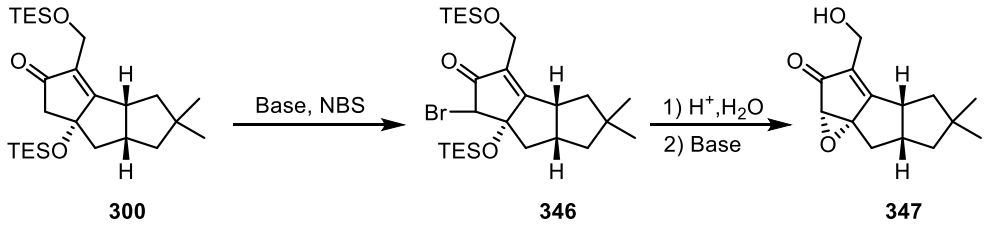


Figure 37

The compound which seems most obviously synthetically linked to Xeromphalinone C is Xeromphalinone D, which would likely be synthesised *via* a simple methylation reaction. However, Xeromphalinone D was only observed when methanol was used in purification and could not be detected by HPLC/MS analysis of the extraction broth and so this compound may be a by-product of purification rather than a naturally occurring molecule.

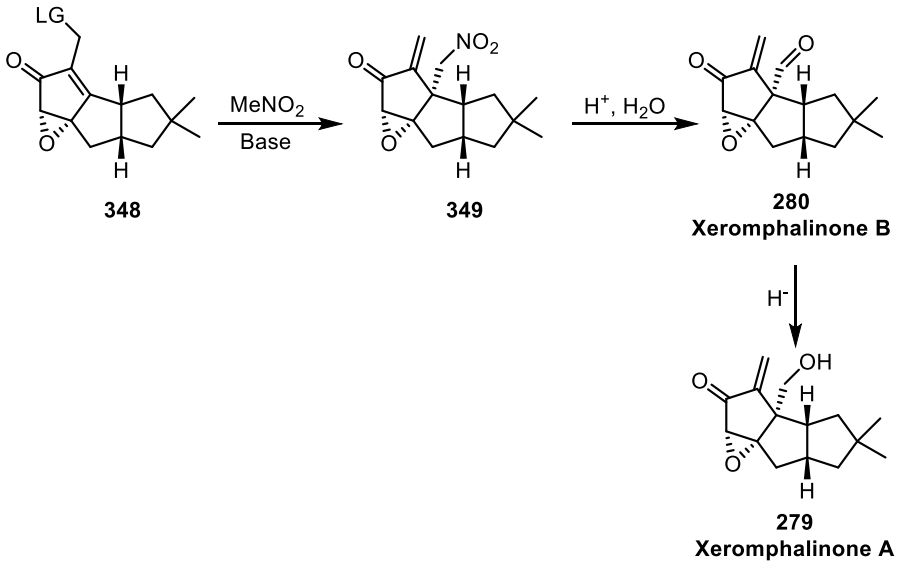
Xeromphalinones A and B may be the next-most accessible from Xeromphalinone C. Both molecules feature the carbon 7 oxygen as an epoxide and both possess exocyclic double bonds. In addition, they have an extra carbon, carbon 14, which is oxygenated, as a hydroxyl or aldehyde, and thus are the same compound at different oxidation levels. The formation of the epoxide may be realised through an α-keto-halogenation then nucleophilic displacement (**Scheme 190**). The halogenation process would have to be conducted on the protected cyclopentenone **300** to avoid any unwanted interference from free alcohol functionality.



300 **346** **347**

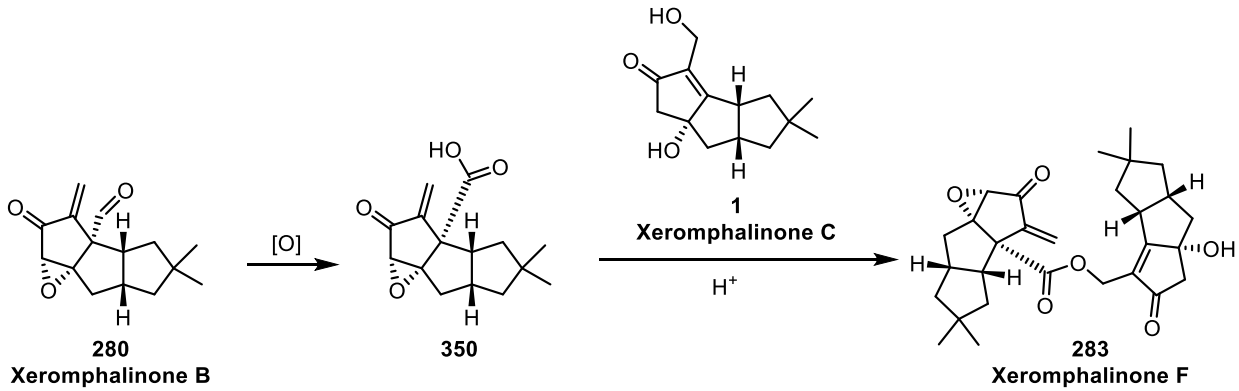
Scheme 190

From here, the installation of the hydroxymethyl substituent could be achieved through a Michael addition of nitromethane and concurrent elimination of the terminal hydroxyl to form the exocyclic double bond (**Scheme 191**). This could be followed by a Nef reaction, which is the acidic hydrolysis of a nitro group to a carbonyl group. The Michael addition would provide the stereochemistry at carbon 3 and there seems to be no reason to expect this reaction to stereoselective. Though, after the Nef reaction this centre becomes epimerisable, which could provide the correct diastereomer and thus Xeromphalinone B. After this, a simple reduction of the aldehyde to the alcohol would provide Xeromphalinone A.



Scheme 191

Furthermore, a Jones oxidation of Xeromphalinone B would convert the aldehyde into the carboxylic acid, compound **350** (**Scheme 192**). Formation of an ester between this compound and Xeromphalinone C would provide Xeromphalinone F.



Scheme 192

Xeromphalinones A, B and Fare of significant interest due to their high cytotoxic activities.[206,207] It is clear from the biological evaluation of this class of natural products that the exocyclic double bond is imperative for useful IC_{50} values. Shown here, Xeromphalinone C can be seen as an intermediate in the synthesis of these biologically relevant molecules with only a few common organic transformations required to access these.

2.6 Experimental

2.6.1 General Experimental Considerations

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.[168]

Dry DCM, Et_2O, THF, and toluene 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, and over calcium hydride, was performed prior to use.

Petroleum ether refers to petroleum ether with the boiling point (b.p.) range 40 - 60 °C, unless otherwise stated.

DCE refers to 1,2,-dichloroethane which was purified by distillation under argon over calcium hydride and stored over 4 Å molecular sieves.

*n*BuLi was obtained as a 2.5 M solution in hexanes, and standardised using diphenyl acetic acid in THF.[208]

Instrumentation and data

Thin layer chromatography was carried out using Camlab silica plates coated with fluorescent indicator UV254. Plates were analysed using a Mineralight UVGL-25 lamp or developed using a vanillin solution. Flash column chromatography was carried out using Prolabo silica gel (230-400 mesh) or using .

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 $^{13}C\{1H\}$ 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 $^{3}J_{H\text{-}H}$ 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.

2.6.2 General Procedures

General Procedure A:

Carbonyl-containing substrate and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and DIPEA was added dropwise. The mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and the silylating agent was added dropwise. The reaction was stirred for 16 h at room temperature then quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure A****, data are reported as:* (a) carbonyl compound; (b) volume of DCE; (c) DIPEA; (d) silylating agent; (e) isolated yield; and (f) compound appearance. Individual characterisation data for each silyl enol ether compound is provided.

General Procedure B:

Carbonyl-containing substrate and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and DIPEA was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the silylating agent was added dropwise and the reaction was stirred at -10 °C for 1 h, then quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude silyl enol ether and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ was added and the solution was stirred for 1 h at room temperature. After this time, DodSMe was added and the mixture was heated to the required temperature for the allotted time. At this point, the reaction mixture was filtered through

celite and the solvent was removed *in vacuo* to provide the crude material. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure B****, data are reported as:* (a) carbonyl compound; (b) volume of DCE; (c) DIPEA; (d) silylating agent; (e) kinetic:thermodynamic ratio of crude silyl enol ether; (f) volume of DCE; (g) amount of $Co_2(CO)_8$; (h) amount of DodSMe; (i) reaction temperature; (j) reaction time; (k) yield; and (l) product appearance. Individual characterisation data for each cyclopentenone compound is provided.

General Procedure C:

Carbonyl-containing substrate and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to -10 °C and DIPEA was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and the silylating agent was added dropwise. The reaction was stirred for at -10 °C for 1 h then quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 100:0 – 95:5) using basic alumina as the stationary phase and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure C****, data are reported as:* (a) carbonyl compound; (b) volume of DCE; (c) DIPEA; (d) silylating agent; (e) isolated yield; (f) kinetic:thermodynamic isomer ratio; and (g) compound appearance. Individual characterisation data for the major isomer of each silyl enol ether compound is provided.

General Procedure D:

The alkyne substrate and pet. ether were added to a flame-dried, round-bottom flask equipped with a stirrer bar. $Co_2(CO)_8$ was added and the mixture was stirred at room temperature for 1 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to provide the crude product as a red oil. The crude material was

purified by flash column chromatography using basic alumina as the stationary phase and concentrated *in vacuo* to provide the dicobalt hexacarbonyl complex.

For experiments which were carried out according to ***General Procedure D****, data are reported as:* (a) alkyne substrate; (b) volume of pet. ether; (c) $CO_2(CO)_8$; (d) isolated yield; (e) kinetic:thermodynamic isomer ratio; and (f) product appearance. Individual characterisation data for the major isomer of each dicobalt hexacarbonyl compound is provided.

General Procedure E:

The dicobalt hexacarbonyl complex and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The additive was added and the mixture was heated to the set temperature for the allotted time. At this point, solvent was removed *in vacuo* to provide the crude material as a black gum. The crude material was purified by flash column chromatography and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General procedure E****, data are reported as:* (a) amount of dicobalt hexacarbonyl complex; (b) volume of DCE ; (c) additive; (d) reaction temperature; (e) reaction time; (f) isolated yield; and (g) product appearance. Individual characterisation data for each cyclopentenone product is provided.

General Procedure F:

The cyclopentenone substrate and THF were added to a flame-dried, round-bottom flask equipped with a stirrer bar. 0.6M HCl was added to this solution and reaction mixture stirred at the set temperature for the allotted time. At this point, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure F****, data are reported as:* (a) amount of cyclopentenone substrate; (b) volume of THF; (c) aqueous HCl solution; (d) reaction temperature; (e) reaction time; (f) isolated yield; and (g) product appearance. Individual characterisation data for each alcohol product is provided.

General Procedure G:

Dicobalt pentacarbonylphosphine-alkyne complex and DCE were added to a flame-dried, round-bottom flask equipped with a stirrer bar. The solution was cooled to -10 °C and DIPEA was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and the silylating agent was added dropwise. The reaction was stirred for at -10 °C for 1 h then quenched by the addition of saturated aqueous $NaHCO_3$ solution. Et_2O was added, the organic phase separated, and the aqueous phase was washed with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 100:0 – 95:5) using basic alumina as the stationary phase and concentrated *in vacuo* to provide the title compound.

For experiments which were carried out according to ***General Procedure G****, data are reported as:* (a) carbonyl compound; (b) volume of DCE; (c) DIPEA; (d) silylating agent; (e) isolated yield; (f) diastereomeric ratio; (g) kinetic:thermodynamic isomer ratio; and (h) compound appearance. Individual characterisation data for the major isomer of each silyl enol ether compound is provided.

General Procedure H:

The dicobalt hexacarbonyl complex and acetone were added to a flame-dried, round-bottom flask equipped with a stirrer bar, and the reaction mixture was set to the required temperature. The phosphine was added in one portion followed by TMANO.$2H_2O$ in one portion, and the resulting mixture was stirred for the allotted time. After this time, the reaction mixture was concentrated *in vacuo* to give the crude product as a red oil. The crude material was purified by flash column chromatography and concentrated *in vacuo* to provide the title compound.

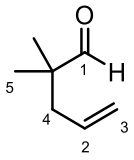
For experiments which were carried out according to ***General Procedure H****, data are reported as:* (a) amount of dicobalt hexacarbonyl complex; (b) volume of acetone; (c) reaction temperature; (d) amount of phosphine; (e) amount of TMANO.$2H_2O$; (f) reaction time; (g) yield; (h) product appearance; and (i) ratio of diastereomers. Individual characterisation data for each dicobalt pentacarbonylphosphine product is provided.

2.6.3 General Computational Details

A series of DFT techniques were employed to evaluate the free energies of relevant cobalt hexacarbonyl complexes and other distinct intermediates and transitions states through the mechanism of the Pauson-Khand reaction. All DFT calculations were performed with the Gaussian09 quantum chemistry package[169] employing the hybrid functional of Lee, Yang and Parr with Becke's parameter exchange[170] – b3LYP – with associated 6-31G(d) basis set for light atoms, and LANL2DZ effective core potentials and associated basis set for cobalt.[171] Structures corresponding to intermediates in all potential energy surfaces described herein were confirmed to be minima through vibrational frequency calculations and depicted no imaginary frequencies. Transition states were located employing the Synchronous Transit-Guided Quasi-Newton method[209] – QST3 – with inclusion of relevant guesses for transition state geometry, or by using the built-in Berny transition state optimisation, and confirmed by vibrational frequency calculation, which featured a unique imaginary frequency. In the calculation of carbonyl dissociation energies, the sum of electronic and zero-point vibrational energies was used.[210] A superfine integration grid and Grimme's original D3 damping function were used for all calculations.[173] Unless otherwise stated, all calculations were performed using a polarisable continuum model for 1,2-DCE.[172] All relevant output files are provided in the *Appendix*, page 52 onwards.

2.6.4 Experimental Procedures and Compound Analyses

Preparation of 2,2-dimethylpent-4-enal.[203]



295

Scheme 144

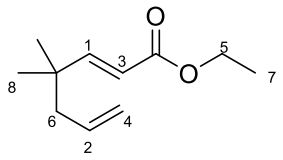
Isobutyraldehyde (18.03 g, 250 mmol) was added to a flame-dried round-bottom flask and dissolved in *p*-cymene (50 ml), prior to the sequential addition of allyl alcohol (11.60 g, 200 mmol) and *p*-toluenesulfonic acid monohydrate (0.076 g, 0.4 mmol). The reaction flask was fitted with a 30 cm Vigreux column and a 10 mL Dean-Stark tap equipped with a reflux condenser on top of the trap. The reaction was heated to 150 °C for 3 days, after which time the Dean-Stark trap was emptied repeatedly until no more condensate was collected. The reaction was then cooled to 40 °C, and the Dean-Stark trap and reflux condenser were replaced with a distillation head. The mixture was then fractionally distilled under high vacuum (12 mbar) at 60 °C, with the receiving flask cooled using liquid nitrogen, to yield 2,2-dimethylpent-4-enal (15.41 g, 137.5 mmol, **69%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.49 (1H, s, H_1), 5.72 (1H, ddt, *J* = 16.5 Hz, *J* = 10.6 Hz, *J* = 7.4 Hz, H_2), 5.13 – 5.04 (2H, m, H_3), 2.23 (2H, dt, *J* = 7.4 Hz, ^4J = 1.0 Hz, H_4), 1.07 (6H, s, H_5) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 205.4, 132.6, 117.9, 45.2, 40.9, 20.7 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2967, 2930, 2872, 2803, 2700, 1725, 1641, 1468.

Preparation of ethyl (*E*)-4,4-dimethylhepta-2,6-dienoate.[201]



296

Scheme 144

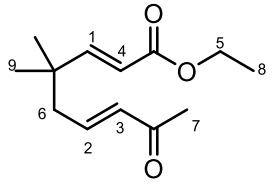
A flame-dried, round-bottom flask equipped with a stirrer bar was charged with NaH (2.60 g, 65 mmol) and dry hexane (200 mL), and the suspension was stirred for 30 min at room temperature before the solids were allowed to settle and the hexane was removed *via* cannula. Dry THF (25 mL) was added and the suspension was cooled to 0 °C. Triethyl phosphonoacetate was added dropwise as a solution in dry THF (24 mL) over 2 h, then the reaction mixture was allowed to stir at 0 °C for 1 h. 2,2-dimethylpent-4-enal was added dropwise as a solution in dry THF (50 mL) over 3 h then the cooling bath was removed and the reaction was stirred at room temperature for 1 h. After this time, the reaction mixture was heated to reflux for 16 h then cooled to room temperature and quenched by the slow addition of H_2O (40 mL). The quenched reaction mixture was poured into a separating funnel, and the resulting bilayer was separated. The aqueous layer was extracted with Et_2O (3 x 50 mL). The organic extracts were combined, and subsequently washed with saturated aqueous sodium bicarbonate (2 x 20 mL), and brine (20 mL), then dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 99:1 – 90:10) and concentrated *in vacuo* to yield ethyl (*E*)-4,4-dimethylhepta-2,6-dienoate (7.177 g, 39.37 mmol, **79%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.96 (1H, d, *J* = 16.0 Hz, H_1), 5.79-5.65 (1H, m, H_2), 5.74 (1H, d, *J* = 16.0 Hz, H_3), 5.10 – 5.00 (2H, m, H_4), 4.21 (2H, q, *J* = 7.1 Hz, H_5), 2.13 (2H, dt, *J* = 7.4 Hz, ^4J = 1.0 Hz, H_6, 1.31 (3H, t, *J* = 7.1 Hz, H_7), 1.07 (6H, s, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 166.6, 157.1, 133.8, 117.5, 117.3, 59.7, 45.9, 36.2, 25.6, 13.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2963, 1717, 1649, 1466.

Preparation of ethyl (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienoate.[201]



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Scheme 144

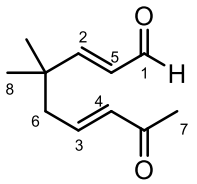
Ethyl (*E*)-4,4-dimethylhepta-2,6-dienoate (6.29 g, 34.5 mmol) and dry Et_2O (345 mL) were added to a flame-dried round-bottom flask under argon and methyl vinyl ketone (8.63 mL, 103.5 mmol) was added. The solution was then degassed by five cycles of freeze-pump-thaw. A stirrer bar, Grubbs' 2nd generation catalyst (0.586 g, 0.69 mmol), and CuI (0.197 g, 1.04 mmol) were added sequentially to the flask, and the reaction mixture was heated to 40 °C for 3 h before being cooled to room temperature and concentrated *in vacuo* to afford the crude mixture as a brown oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30 – 60:40) and concentrated *in vacuo* to provide ethyl (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienoate (6.844 g, 30.5 mmol, **88%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.90 (1H, d, *J* = 15.9 Hz, H_1), 6.64 (1H, dt, *J* = 15.7 Hz, *J* = 7.7 Hz, H_2), 6.05 (1H, dt, *J* = 15.9 Hz, ^4J = 1.2 Hz, H_3), 5.73 (1H, d, *J* = 15.9 Hz, H_4), 4.17 (2H, q, *J* = 7.2 Hz, H_5), 2.26 (2H, dd, *J* = 7.6 Hz, ^4J =1.1 Hz, H_6), 2.21 (3H, s, H_7), 1.27 (3H, t, *J* = 7.1 Hz, H_8), 1.08 (6H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 197.5, 166.2, 155.7, 142.9, 133.3, 118.2, 59.8, 44.3, 36.5, 26.6, 25.9, 13.7 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2965, 1715, 1699, 1672, 1649, 1628.

Preparation of (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal.[201]



291

Scheme 144

Ethyl (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienoate (6.536 g, 29.14 mmol) and dry THF (291 mL) were added to a flame-dried, round-bottom flask equipped with a stirrer bar, and the solution was cooled to 0 °C. DIBAL-H (118 mL, 145.7 mmol) was added dropwise over 2 h and then reaction was allowed to stir at 0 °C for 3 h. After this time, the reaction was quenched by the slow addition of a saturated aqueous solution of Rochelle's salt (300 mL) and stirred at room temperature for 2 h to form a biphasic mixture. The biphasic mixture was separated

and the aqueous layer was extracted with EtOAc (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude diol product as a colourless oil.

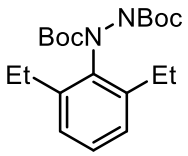
The crude diol was added to a flame-dried, round-bottom flask and dissolved in dry DCM (493 mL). DMP (62.77 g, 148 mmol) was added in 5 x 12.6 g portions over 30 min. After the final portion was added, the reaction was allowed to stir at room temperature for 2 h and then quenched by slow addition of sat. aq. $NaHCO_3$ (175 mL) and sat. aq. $Na_2S_2O_3$ (175 mL) simultaneously. The layers were separated and the aqueous layer was washed with DCM (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a pale yellow oil. The crude material was purified by flash column chromatography (hexane:EtOAc, 80:20 – 70:30) and concentrated *in vacuo* to give (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal (3.267 g, 18.12 mmol, **62%** over 2 steps) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.56 (1H, d, *J* = 7.6 Hz, H_1), 6.78 (1H, d, *J* = 15.9 Hz, H_2), 6.69 (1H, dt, *J* = 15.7 Hz, *J* = 7.7 Hz, H_3), 6.13 (1H, dt, *J* = 15.7 Hz, ^4J = 1.2 Hz, H_4), 6.09 (1H, dd, *J* = 15.9 Hz, *J* = 7.6 Hz, H_5), 2.36 (2H, dd, *J* = 7.6 Hz, ^4J = 1.3 Hz, H_6), 2.25 (3H, s, H_7), 1.20 (6H, s, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 197.3, 193.4, 164.8, 142.0, 133.6, 129.5, 44.1, 37.2, 26.8, 25.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2965, 1686, 1670, 1630, 1466.

Preparation of di-*tert*-butyl 1-(2,6-diethylphenyl)-2λ^2-2-diazane-1,2-dicarboxylate.



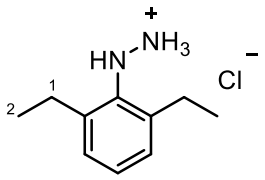
302

Scheme 145

Magnesium turnings (2.49 g, 102.5 mmol) were added to a flame-dried, three-necked, round-bottom flask equipped with a stirrer bar and immersed in dry THF (2 mL). One granule of I_2 was added followed by the dropwise addition of a solution of 2-bromo-1,3-diethylbenzene (2.18 g, 10.25 mmol) in dry THF (50 mL). After complete addition, the resulting mixture was heated to reflux for 1.5 h then cooled to room temperature. In a separate flame-dried, round-

bottom flask, di-*tert*-butyl (*Z*)-diazene-1,2-dicarboxylate (2.36 g, 10.25 mmol) was dissolved in dry THF (20 mL) and the resulting mixture was cooled to -78 °C. The preformed Grignard reagent was added to this reaction slowly using a syringe and the resulting mixture was allowed to stir for 2 h at -78 °C. After this time, the reaction was quenched by the addition of AcOH (0.64 mL) and warmed to room temperature. H_2O (25 mL) and Et_2O (30 mL) were added to create a biphasic mixture. The layers were separated and the aqueous layer was washed with DCM (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a pale yellow oil. The crude material was carried into the next reaction without further purification.

Preparation of 2-(2,6-diethylphenyl)hydrazin-1-ium chloride.[211]



303

Scheme 145

The crude di-*tert*-butyl 1-(2,6-diethylphenyl)-2λ^2-2-diazane-1,2-dicarboxylate was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in EtOH (25.6 mL). 4 M HCl in dioxane (25.6 mL, 102.5 mmol) was added to this solution and the resulting mixture was heated to 90 °C for 1 h. After this time, the mixture was cooled to room temperature and concentrated *in vacuo*. Et_2O (100 mL) was added to the residue and the suspension was stirred at room temperature for 1 h then filtered and the solid was washed with Et_2O (30 mL). The resulting solution was concentrated *in vacuo* to give 2-(2,6-diethylphenyl)hydrazin-1-ium chloride (1.33 g, 6.63 mmol, **65%** over 2 steps).

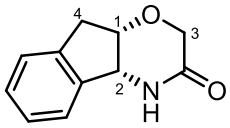
^{1}H NMR (DMSO-*d*6, 400 MHz): δ_H 9.69 (3H, s, NH_3), 7.24 – 7.19 (1H, m, ArH), 7.15 – 7.10 (2H, m, ArH), 2.78 (4H, q, *J* = 7.5 Hz, H_1), 1.18 (6H, t, *J* = 7.5 Hz, H_2) ppm.

^{13}C{1H} NMR (DMSO-*d*6, 101 MHz): δ_C 141.3, 139.8, 128.1, 126.9, 24.0, 15.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3293, 2889, 1375, 1190.

Melting point: 160 – 168 °C (decomposes). **Literature**: 170 – 172 °C.[212]

Preparation of (4a*R*,9a*S*)-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2*H*)-one.[213]



305

Scheme 145

NaH (1.31 g, 32.84 mmol) was added flame-dried, three-necked, round-bottom flask equipped with a stirrer bar and suspended in dry hexane (120 mL) before being stirred at rt for 30 min. The hexane was then removed *via* cannula and the solid was washed with a further 100 mL of dry hexane, suspended in dry THF (375 mL) and the resulting suspension was cooled to -10 °C. An internal thermometer was added to the reaction mixture and the mixture was allowed to stir at -10 °C for 30 min,after which time, (1*R,*2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (3.769 g, 25.26 mmol) was added in two batches and the reaction turned heterogeneous. The reaction mixture was heated to reflux for 1 h then cooled to –10 °C and ethyl chloroacetate (2.73 mL, 25.77 mmol) was added over 5 min. The reaction mixture was warmed to room temperature for 1 h then heated to reflux for a further 1 h before being cooled to room temperature and quenched by the addition of brine (11 mL). The THF was removed *in vacuo* and EtOAc (75 mL) was added followed by brine (75 mL) to create a biphasic mixture. The layers were separated and the aqueous layer was washed with EtOAc (2 x 75 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as an off white solid. The crude solid was dissolved in dry hexane (120 mL) and heated to 70 °C for 2 h then cooled to room temperature, filtered, and the solid was collected and dried under high vacuum for 1 h to give (4a*R*,9a*S*)-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2*H*)-one (3.46 g, 18.26 mmol, **72%**) as a white solid.

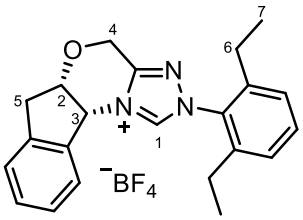
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.64 (1H, s, NH), 7.42 – 7.23 (4H, m, ArH), 4.80 (1H, t, *J* = 3.9 Hz, H_1), 4.56 (1H, t, *J* = 4.5 Hz, H_2), 4.19 (2H, s, H_3), 3.25 (1H, dd, ^2J = 16.8 Hz, ^4J = 4.8 Hz, H_4), 3.13 (1H, d, ^2J = 16.8 Hz, H_4) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 168.6, 140.1, 138.8, 127.9, 126.9, 124.7, 123.1, 75.6, 66.0, 58.3, 37.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3179, 3051, 2909, 1680, 1643, 1485.

Melting point: 180 – 186 °C (decomposes).

Preparation of (5a*S*,10b*R*)-2-(2,6-diethylphenyl)-2,5a,6,10b-tetrahydro-4*H*-indeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-11-ium tetrafluoroborate.[214]



292

Scheme 145

(4a*R*,9a*S*)-4,4a,9,9a-tetrahydroindeno[2,1-b][1,4]oxazin-3(2*H*)-one (0.349 g, 2.10 mmol) was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in dry DCM (5.5 mL). Me_3OBF_4 (0.285 g, 1.93 mmol) was added to this solution and the reaction was stirred until homogeneous. In a separate flask, 2-(2,6-diethylphenyl)hydrazin-1-ium chloride (0.365 g, 1.93 mmol) was reacted with 1 M NaOH (1.93 mL) and extracted with Et_2O (5 × 5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was added to the stirring mixture of substrate and Me_3OBF_4 as a solution in dry DCM (1 mL) and the resulting mixture was stirred at room temperature for 5 h. After this time, the solvent was removed *in vacuo* and the residue was dissolved in dry PhCl (7.00 mL). Triethyl orthoformate was added (1.6 mL, 9.66 mmol) and the resulting mixture was heated to 120 °C for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to give the crude material as a yellow oil. The crude material was purified by flash column chromatography (hexane:EtOAc, 50:50 – 10:90) and concentrated *in vacuo* to give an off-white solid, which was triturated using a 1:1 mixture of DCM:hexane (5 mL) to deliver (5a*S*,10b*R*)-2-(2,6-diethylphenyl)-2,5a,6,10b-tetrahydro-4*H*-indeno[2,1-b][1,2,4]triazolo[4,3-d][1,4]oxazin-11-ium tetrafluoroborate (0.465 g, 1.07 mmol, **56%**) as a white solid.

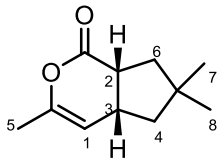
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 10.28 (1H, s, H_1), 7.60 – 7.23 (7H, m, ArH), 6.13 (1H, d, J = 3.9 Hz, H_2), 5.17 – 4.99 (3H, m, H_3, H_4), 3.16 (1H, d, ^2J = 17.0 Hz, H_5), 3.10 (1H, dd, ^2J = 17.1 Hz, J = 4.2 Hz, H_5), 2.60 – 2.06 (4H, m, H_6), 1.13 (6H, t, J = 7.4 Hz, H_7) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 149.6, 143.3, 141.0, 139.6, 134.9, 131.8, 131.6, 129.2, 127.5, 126.6, 125.0, 123.3, 77.0, 61.7, 59.8, 36.8, 23.5, 14.2 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3125, 2974, 2938, 1578.

Melting point: 192 – 194 °C.

Preparation of (4*aR*,7*aR*)-3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4*aH*)-one.[201]



290

Scheme 146

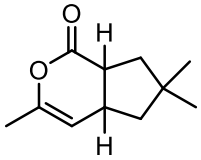
(2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal (2.5 g, 13.87 mmol) and (5*aS*,10*bR*)-2-(2,6-diethylphenyl)-2,5*a*,6,10*b*-tetrahydro-4*H*-indeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-11-ium tetrafluoroborate (0.3 g, 0.69 mmol) were dissolved in dry DCM (70 mL) in a flame-dried, round-bottom flask and degassed by five cycles of freeze-pump-thaw. In a separate flask, DIPEA (0.121 mL, 0.69 mmol) was dissolved in dry DCM (5 mL) and degassed by five cycles of freeze-pump-thaw and then added to the flask containing (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal and the azolium salt, followed by the addition of a stirrer bar. The reaction mixture was heated to 40 °C for 5 days and then cooled to room temperature and concentrated *in vacuo* to afford the crude product as a pale yellow oil. The crude material was purified by flash column chromatography (hexane:EtOAc, 95:5) and concentrated *in vacuo* to give (4*aR*,7*aR*)-3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4*aH*)-one (1.777 g, 9.86 mmol, **71%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.85 (1H, d, *J* = 3.7 Hz, H_1), 3.05 (1H, apparent q, *J* = 8.8 Hz, H_2), 2.96 – 2.85 (1H, m, H_3), 2.02 – 1.93 (2H, m, H_4), 1.88 (3H, s, H_5), 1.83 (1H, dd, ^{2}J = 12.8 Hz, *J* = 7.8 Hz, H_6), 1.35 (1H, dd, ^{2}J = 12.8 Hz, *J* = 7.9 Hz, H_6), 1.11 (3H, s, H_7), 1.03 (3H, s, H_8) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 171.3, 145.9, 102.9, 48.3, 44.3, 40.9, 37.4, 35.4, 29.3, 28.5, 18.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2866, 1753, 1701, 1464.

Preparation of 3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4a*H*)-one.[201]



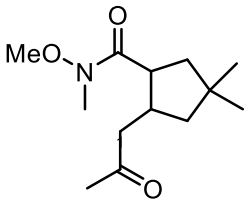
***rac*-290**

Scheme 147

(2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal (0.047 g, 0.258 mmol) and 1,3-dimesityl-1*H*-imidazol-3-ium chloride (0.088 g, 0.258 mmol) were dissolved in dry DCM (1.3 mL) in a flame-dried, round-bottom flask, and degassed by five cycles of freeze-pump-thaw. In a separate flask, DIPEA (0.044 mL, 0.258 mmol) was dissolved in dry DCM (0.3 mL), degassed by five cycles of freeze-pump-thaw, and then added, along with a stirrer bar, to the flask containing (2*E*,6*E*)-4,4-dimethyl-8-oxonona-2,6-dienal and the azolium salt. The reaction mixture was heated to 40 °C for 18 h and then cooled to room temperature and concentrated *in vacuo* to afford the crude product as a pale yellow oil. The crude material was purified by flash column chromatography (hexane:EtOAc, 95:5) and concentrated *in vacuo* to give 3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4a*H*)-one (0.024 g, 0.13 mmol, **52%**) as a colourless oil.

The characterisation data obtained was identical to that for (4*aR*,7*aR*)-3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4*aH*)-one **290**, as described on page 278.

Preparation of *N*-methoxy-*N*,4,4-trimethyl-2-(2-oxopropyl)cyclopentane-1-carboxamide.[201]



***rac*-308**

Scheme 147

3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4a*H*)-one (0.024 g, 0.133 mmol) was dissolved in dry DCM (1.3 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. *N*,*O*-dimethylhydroxylamine hydrochloride (0.03 g, 0.49 mmol) was added in one portion and the resulting mixture was cooled to 0 °C. Isopropylmagnesium chloride (2 M in toluene, 0.245 mL, 0.49 mmol) was added dropwise and the reaction was stirred at 0 °C for 3 h. After

this time, the reaction mixture was warmed to room temperature, quenched by the addition of sat. aqueous NH_4Cl (1 mL) and EtOAc (2 mL), and the layers separated. The aqueous phase was extracted with further quantities of EtOAc (3 x 2 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (hexane:EtOAc, 50:50) and concentrated *in vacuo* to give *N*-methoxy-*N*,4,4-trimethyl-2-(2-oxopropyl)cyclopentane-1-carboxamide (0.0213 g, 0.088 mmol, **66%**) as a colourless oil.

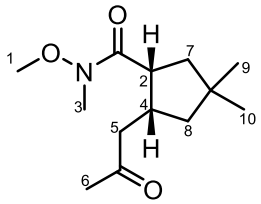
^{1}H NMR ($CDCl_3$, 400MHz): δ_H 3.70 (3H, s, H_1), 3.59 – 3.45 (1H, m, H_2), 3.16 (3H, s, H_3), 2.94 – 2.80 (1H, m, H_4), 2.69 (1H, dd, ^2J = 17.4 Hz, J = 6.8 Hz, H_5), 2.41 (1H, dd, ^2J = 17.4 Hz, J = 7.5 Hz, H_5). 2.10 (3H, s, H_6), 1.85 (1H, dd, ^2J = 12.7 Hz, J = 9.4 Hz, H_7), 1.68 (1H, ddd, ^2J = 12.4 Hz, J = 7.1 Hz, ^4J = 1.2 Hz, H_8), 1.60 (1H, ddd, ^2J = 12.8 Hz, J = 7.8 Hz, ^4J = 1.5 Hz, H_7), 1.31 (1H, dd, ^2J = 12.3 Hz, J = 9.9 Hz, H_8), 1.13 (3H, s, H_9), 1.03 (3H, s, H_{10}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.0, 175.8, 60.7, 47.1, 45.5, 43.5, 40.8, 37.9, 35.8, 31.5, 30.0, 29.2, 28.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2936, 2903, 2866, 1713, 1659, 1462, 1418.

Chiral HPLC analysis: Chiracel OD-H column, 2% IPA in ^{n}hexane, 0.75 mL/min flowrate, 254 nm detector, t_R = 20.70 min and 22.27 min, 50:50.

Preparation of (1*R*,2*R*)-*N*-methoxy-*N*,4,4-trimethyl-2-(2-oxopropyl)cyclopentane-1-carboxamide.[201]



308

Scheme 147

(4*aR*,7*aR*)-3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4*aH*)-one (0.024 g, 0.133 mmol) was dissolved in dry DCM (1.3 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. *N*,*O*-dimethylhydroxylamine hydrochloride (0.03 g, 0.49 mmol) was added in one portion and the resulting mixture was cooled to 0 °C. Isopropylmagnesium chloride (2 M in toluene, 0.245 mL, 0.49 mmol) was added dropwise and the reaction was stirred at 0 °C for 3

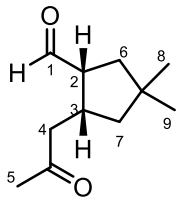
h. After this time, the reaction mixture was warmed to room temperature, quenched by the addition of sat. aqueous NH_4Cl (1 mL) and EtOAc (2 mL), and the layers separated. The aqueous phase was extracted with further quantities of EtOAc (3 x 2 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (hexane:EtOAc, 50:50) and concentrated *in vacuo* to give (1*R*,2*R*)-*N*-methoxy-*N*,4,4-trimethyl-2-(2-oxopropyl)cyclopentane-1-carboxamide (0.0209 g, 0.087 mmol, **65%**) as a colourless oil.

The characterisation data obtained matched that for *N*-methoxy-*N*,4,4-trimethyl-2-(2-oxopropyl)cyclopentane-1-carboxamide **308**, as described on page 280.

$[\alpha]^{20}_D$ = +184 ° (c = 0.005, $CHCl_3$).

Chiral HPLC analysis: Chiracel OD-H column, 2% IPA in ^{n}hexane, 0.75 mL/min flowrate, 254 nm detector, t_R = 22.93 min, >99:1.

Preparation of (1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentane-1-carbaldehyde.[201]



289

Scheme 148

(4*aR*,7*aR*)-3,6,6-trimethyl-5,6,7,7a-tetrahydrocyclopenta[c]pyran-1(4*aH*)-one (0.411 g, 2.28 mmol) was dissolved in dry Et_2O (5.3 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar and the solution was cooled to -78 °C. DIBAL-H (1.98 mL, 2.44 mmol) was added dropwise down the wall of the flask over 30 min and then the reaction mixture was stirred for 1 h at -78 °C. After this time, the reaction mixture was quenched by slow addition of a 5% aq. AcOH solution (10 mL) and warmed to room temperature and stirred for 1 h. The layers were then separated and the aqueous layer was extracted with Et_2O (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was dissolved in an acetone:H_2O 4:1 solvent mixture, cooled to 0 °C, and PPTS (0.573 g, 2.28 mmol) was added in one portion. The reaction was warmed to room temperature over 3 h by allowing the ice bath to melt. After this time, the reaction was poured into brine (10 mL) and the biphasic mixture was separated.

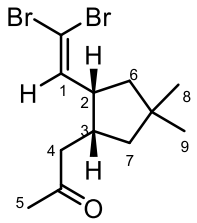
The aqueous layer was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give (1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (0.41 g, 2.25 mmol, **99%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.62 (1H, d, *J* = 2.7 Hz, H_1), 3.12 – 2.98 (1H, m, H_2), 2.86 – 2.72 (1H, m, H_3), 2.64 (1H, dd, ^2J = 17.7 Hz, *J* = 7.9 Hz, H_4), 2.46 (1H, dd, ^2J = 17.7 Hz, *J* = 6.8 Hz, H_4), 2.05 (3H, s, H_5), 1.74 (1H, dd, ^2J = 13.4 Hz, *J* = 7.1 Hz, H_6), 1.64 – 1.58 (1H, m, H_6), 1.58 – 1.51 (1H, m, H_7), 1.12 (1H, apparent t, *J* = 11.9 Hz, H_7), 1.03 (3H, s, H_8), 0.96 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.4, 204.4, 52.2, 47.0, 44.7, 40.2, 37.8, 36.0, 29.7, 29.3, 28.5 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2934, 2866, 1713.

Preparation of 1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-one.



309

Scheme 148

Carbon tetrabromide (6.05 g, 18.24 mmol) was dissolved in DCM (40 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar and the solution was cooled to 0 °C. PPh_3 (9.57 g, 36.49 mmol) was added portionwise over 30 min and then the mixture was stirred for a further 30 min. (1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentane-1-carbaldehyde (1.66 g, 9.12 mmol) was added slowly as a solution in DCM (40 mL) and the reaction mixture was warmed to room temperature and stirred for 1 h. At this point, the reaction was diluted with hexane (300 mL), filtered through a pad of silica, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (hexane:EtOAc, 80:20) and concentrated *in vacuo* to give 1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-one (2.85 g, 8.43 mmol, **92%**) as a colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.31 (1H, d, *J* = 10.0 Hz, H_1), 3.17 – 3.01 (1H, m, H_2), 2.86 – 2.73 (1H, m, H_3), 2.54 (1H, dd, ^2J = 16.7 Hz, *J* = 6.5 Hz, H_4), 2.32 (1H, dd, ^2J = 16.8 Hz, *J* = 8.2 Hz, H_4),

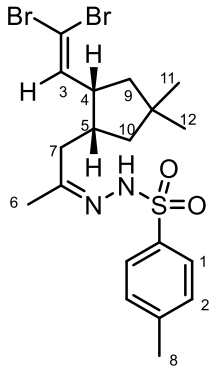
2.16 (3H, s, H_5), 1.82 – 1.75 (1H, m, H_6), 1.75 – 1.67 (1H, m, H_6), 1.37 (1H, dd, ^2J = 13.2 Hz, J = 6.6 Hz, H_6), 1.18 (1H, apparent t, J = 11.7 Hz, H_7), 1.10 (3H, s, H_8), 1.04 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.4, 140.2, 88.1, 46.5, 45.8, 45.1 (2C), 37.7, 36.9, 30.3, 29.9, 29.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2930, 2864, 1714, 1462, 1364, 1354.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{19}O_1Br_2$: 336.97971; **found:** 336.97770.

Preparation of *N*'-((*Z*)-1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-ylidene)-4-methylbenzenesulfonohydrazide.



310

Scheme 149

1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-one (0.034 g, 0.1 mmol) was dissolved in dry MeOH (0.8 mL) and $TsNHNH_2$ (0.037 g, 0.2 mmol) was added as a solid. The reaction mixture was stirred at room temperature for 16 h, after which time, a white precipitate had formed. The solvent was removed using a pipette and the white crystals were washing with hexane:ether (1:1, 1 mL) and dried *in vacuo*. The crystals were further purified by flash column chromatography (pet. ether:Et_2O, 50:50) and concentrated *in vacuo* to give *N*'-((*Z*)-1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-ylidene)-4-methylbenzenesulfonohydrazide (0.048 g, 0.095 mmol, **95%**) as a white crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.87 (2H, d, J = 7.6 Hz, H_1), 7.33 (2H, d, J = 7.7 Hz, H_2), 6.26 (1H, d, J = 9.8 Hz, H_3), 2.97 – 2.84 (1H, m, H_4), 2.64 – 2.53 (1H, m, H_5), 2.45 (3H, s, H_6), 2.30 – 2.19 (1H, m, H_7), 2.19 – 2.09 (1H, m, H_7), 1.78 (3H, s, H_8), 1.74 – 1.63 (1H, m, H_9), 1.45 – 1.36 (1H,

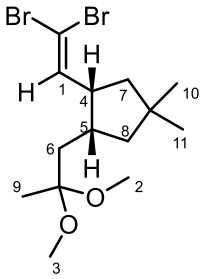
m, H_{10}), 1.36 – 1.26 (1H, m, H_9), 1.12 – 1.06 (1H, m, H_{10}), 1.03 (3H, s, H_{11}), 0.99 (3H, s, H_{12}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 143.5, 140.2, 135.0, 129.0, 127.8, 87.6, 46.6, 45.8, 45.6, 45.2, 40.0, 38.2, 37.5, 30.3, 29.3, 21.1, 15.6 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3206, 2949, 2920, 2862, 1340.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{27}O_2{}^{79}Br_2S$: 505.01545; **found:** 505.01420.

Preparation of (3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane.



311

Scheme 150

1-((1*R*,2*R*)-2-(2,2-dibromovinyl)-4,4-dimethylcyclopentyl)propan-2-one (2.85 g, 8.43 mmol) was dissolved in dry MeOH (420 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. Trimethylorthoformate (16.6 mL, 151.2 mmol) and PPTS (0.425 g, 1.69 mmol) were added sequentially, and the mixture was heated to reflux for 1 h. After this time, the reaction was cooled to room temperature the MeOH was removed *in vacuo*. The residue was dissolved in Et_2O (150 mL) and washed sequentially with water (70 mL) and brine (70 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give (3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane as a colourless oil (3.24 g, 8.43 mmol, **quant.**)

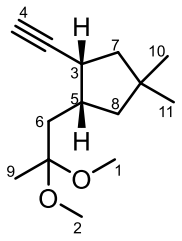
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.39 (1H, d, *J* = 10.1 Hz, H_1), 3.19 (3H, s, H_2), 3.18 (3H, s, H_3), 3.08 – 2.91 (1H, m, H_4), 2.37 – 2.22 (1H, m, H_5), 1.81 – 1.69 (3H, m, H_6, H_7, H_8), 1.55 (1H, dd, ^2J = 14.3 Hz, *J* = 8.6 Hz, H_6), 1.37 (1H, dd, ^2J = 13.5 Hz, *J* = 4.8 Hz, H_7), 1.30 (1H, apparent t, *J* = 12.1 Hz, H_8), 1.29 (3H, s, H_9), 1.09 (3H, s, H_{10}), 1.03 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 140.4, 101.2, 87.4, 47.9, 47.61, 47.56, 47.2, 45.9, 37.3 (2C), 37.2, 30.8, 30.0, 21.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2949, 2864, 1460.

HRMS (ESI/micrOTOF) m/z: $[M]^+$ calcd for $C_{14}H_{24}O_2Br_2$: 382.01375; **found:** 382.01501.

Preparation of (3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane *via* attempted preparation of 3-((1*R*,2*R*)-2-(2,2-dimethoxypropyl)-4,4-dimethylcyclopentyl)prop-2-yn-1-ol.



312

Scheme 151

Table 15, **Entry 1**: (3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane (0.067 g, 0.174 mmol) was dissolved in dry THF (4.4 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to -78 °C and 2.5 M ^{n}BuLi in hexanes (0.15 mL, 0.383 mmol) was added dropwise. The reaction mixture was stirred for 30 min then paraformaldehyde (0.006 g, 0.192 mmol) was added as a solid, and the reaction was warmed to room temperature and stirred for a further 15 min. After this time, the solvent was removed *in vacuo*, and the residue was dissolved in Et_2O (5 mL) and washed sequentially with H_2O (2 mL), brine (2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (hexane:EtOAc, 90:10) and concentrated *in vacuo* to give (3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane (0.033 g, 0.147 mmol, **85%**) as a colourless oil.

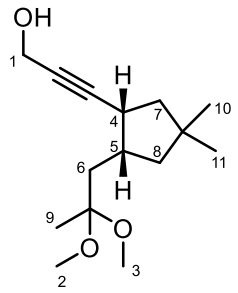
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.21 (3H, s, H_1), 3.20 (3H, s, H_2), 2.93 (1H, s, H_3), 2.14 (1H, s, H_4), 2.13 – 2.03 (2H, m, H_5, H_6), 1.81 – 1.70 (3H, m, H_6, H_7, H_8), 1.67 – 1.59 (1H, m, H_7), 1.52 – 1.46 (1H, m, H_8), 1.32 (3H, s, H_9), 1.17 (3H, s, H_{10}), 1.01 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 101.8, 86.7, 71.3, 48.1, 47.8, 47.7, 38.3, 38.2, 37.3, 35.8, 31.6, 31.1, 21.6 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2949, 2864, 1462.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{14}H_{24}O_2Na$: 247.16685; **found:** 247.16630.

Preparation of (3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane.



313

Scheme 151

Table 15, **Entry 2**: (3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane (1.90 g, 4.94 mmol) was dissolved in THF (25 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to -78 °C and 2.5 M ^{n}BuLi in hexanes (7.55 mL, 16.3 mmol) was added dropwise. The mixture was stirred for 30 min then paraformaldehyde (0.741 g, 24.7 mmol) was added and the mixture was warmed to room temperature and stirred for 15 min. After this time, the reaction was diluted with Et_2O (20 mL), H_2O (20 mL) was added, and the layers were separated. The aqueous phase was washed with Et_2O (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 50:50) and concentrated *in vacuo* to give 3-((1*R*,2*R*)-2-(2,2-dimethoxypropyl)-4,4-dimethylcyclopentyl)prop-2-yn-1-ol (1.17 g, 4.60 mmol **93%**) as a colourless oil.

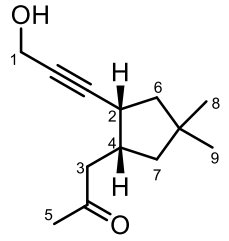
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.28 (2H, s, H_1), 3.21 (3H, s, H_2), 3.20 (3H, s, H_3), 3.01 – 2.90 (1H, m, H_4), 2.18 – 2.08 (1H, m, H_5), 2.03 (1H, dd, ^2J = 14.5 Hz, J = 5.6 Hz, H_6), 1.79 – 1.57 (4H, m, H_6, H_7, H_8), 1.47 (1H, apparent t, J = 12.0 Hz, H_8), 1.32 (3H, s, H_9), 1.16 (3H, s, H_{10}), 1.01 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 101.3, 88.0, 81.0, 51.0, 47.6 47.3, 47.25, 37.9, 37.8, 37.79, 35.5, 31.1, 30.5, 21.1 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3431, 2949, 2864, 1458, 1449, 1377.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{15}H_{26}O_3Na$: 277.17742; **found:** 277.17780.

Preparation of 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one.



314

Scheme 151

Table 15, **Entry 3**: (3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane (0.05 g, 0.13 mmol) was dissolved in THF (0.65 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to -78 °C and 2.16M ^{n}BuLi in hexanes (0.2 mL, 0.43 mmol) was added dropwise. The mixture was stirred for 30 min then paraformaldehyde (0.02 g, 0.65 mmol) was added, the mixture warmed to room temperature and stirred for 1 h. After this time, the reaction was diluted with Et_2O (2 mL), 6M HCl (2 mL) was added, and the layers were separated. The aqueous phase was washed with Et_2O (3 × 20 mL) and the combined organic phases were then washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 50:50 – 30:70) and concentrated *in vacuo* to give 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.022 g, 0.101 mmol, **78%**) as a colourless oil.

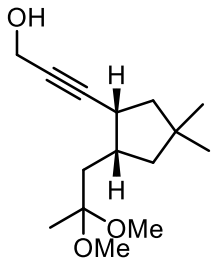
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.26 (2H, d, ^4J = 2.1 Hz, H_1), 3.12 – 3.00 (1H, m, H_2), 2.82 (1H, dd, ^2J = 17.1 Hz, J = 8.1 Hz, H_3), 2.69 – 2.56 (1H, m, H_4), 2.46 (1H, dd, ^2J = 17.1 Hz, J = 6.0 Hz, H_3), 2.18 (3H, s, H_5), 2.00 (1H, s, OH), 1.78 (1H, dd, ^2J = 12.9 Hz, J = 7.7 Hz, H_6), 1.66 – 1.55 (2H, m, H_6, H_7), 1.27 (1H, apparent t, J = 11.7 Hz, H_7), 1.11 (3H, s, H_8), 0.98 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.5, 87.4, 80.9, 50.8, 47.3, 46.2, 46.0, 37.4, 36.6, 33.0, 30.3, 29.9, 29.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3412, 2951, 2932, 2864, 1709.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{21}O_2$: 209.15361; **found:** 209.15440.

Preparation of (3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane.



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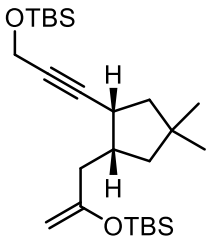
Scheme 152

(3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane (0.017 g, 0.08 mmol) was dissolved in THF (0.8 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to -78 °C and 2.5 M ^{n}BuLi in hexanes (0.04 mL, 0.11 mmol) was added dropwise. The mixture was stirred for 30 min then paraformaldehyde (0.048 g, 1.60 mmol) was added and the mixture was warmed to room temperature and stirred for a further 15 min. After this time, the solvent was removed *in vacuo*, the residue was dissolved in Et_2O (5 mL) and washed sequentially with H_2O (2 mL) and brine (2 mL). The organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10 – 50:50) and concentrated *in vacuo* to give (3*R*,4*R*)-3-(2,2-dimethoxypropyl)-4-ethynyl-1,1-dimethylcyclopentane (0.008 g, 0.03 mmol, **39%**) as a colourless oil.

The characterisation data for this compound matched that described on page 286.

Preparation of *tert*-butyl((3-((1*R*,2*R*)-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-4,4-dimethylcyclopentyl)prop-2-yn-1-yl)oxy)dimethylsilane



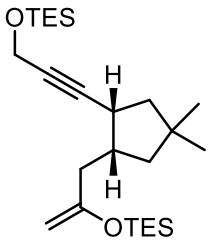
315

Scheme 153

Prepared according to **General Procedure A**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.11 g, 0.53 mmol); (b) DCE (4.8 mL); (c) DIPEA (0.1 mL, 0.58 mmol); (d) TBSOTf (0.12 mL, 0.58 mmol); (e) a complex mixture of compounds was obtained; and (f) N/A.

Preparation of ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane.



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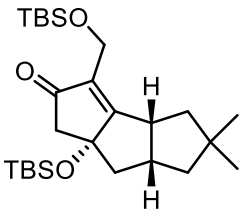
Scheme 153

Prepared according to **General Procedure A**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.028 g, 0.136 mmol); (b) DCE (1.4 mL); (c) DIPEA (0.053 mL, 0.299 mmol); (d) TESOTf (0.07 mL, 0.299 mmol); (e) a complex mixture of compounds was obtained; and (f) N/A.

Preparation of (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



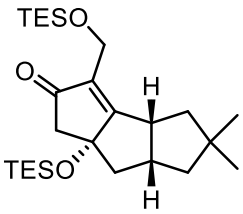
317

Scheme 154

Prepared according to **General Procedure B**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.100 g, 0.48 mmol); (b) DCE (4.8 mL); (c) DIPEA (0.18 mL, 0.106 mmol); (d) TBSOTf (0.22 mL, 0.96 mmol); (e) 92:8; (f) DCE (4.8 mL); (g) $Co_2(CO)_8$ (0.166 g, 0.485 mmol); (h) DodSMe (0.6 mL, 2.28 mmol); (i) 70 °C; (j) 16 h; (k) N/A; and (l) N/A.

Preparation of (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



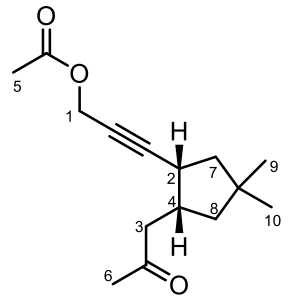
300

Scheme 154

Prepared according to **General Procedure B**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.05 g, 0.24 mmol); (b) DCE (2.4 mL); (c) DIPEA (0.09 mL, 0.52 mmol); (d) TESOTf (0.11 mL, 0.48 mmol); (e) 92:8; (f) DCE (2.4 mL); (g) $Co_2(CO)_8$ (0.083 g, 0.24 mmol); (h) DodSMe (0.3 mL, 1.14 mmol); (i) 70 °C; (j) 16 h; (k) N/A; and (l) N/A.

Preparation of 3-((1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentyl)prop-2-yn-1-yl acetate.



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Scheme 155

1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.04 g, 0.19 mmol) and DCE (1.9 mL) was added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and DIPEA (0.04 mL, 0.21 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and Ac_2O (0.055 mL, 0.58 mmol) was added dropwise. The reaction was stirred for 30 min at room temperature then an additional 1.1 eq. of DIPEA (0.04 mL, 0.21 mmol) was added and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction was quenched by the addition of 1 M HCl (1 mL). Et_2O (2 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 2 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (1 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to give 3-((1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentyl)prop-2-yn-1-yl acetate (0.037 g, 0.148 mmol, **78%**) as a colourless oil.

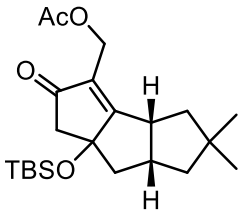
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.68 (2H, d, ^5J = 1.8 Hz, H_1), 3.16 – 3.00 (1H, m, H_2), 2.83 (1H, dd, ^2J = 17.2 Hz, J = 8.0 Hz, H_3), 2.70 – 2.56 (1H, m, H_4), 2.47 (1H, ^2J = 17.2 Hz, J = 6.1 Hz, H_3), 2.18 (3H, s, H_5), 2.10 (3H, s, H_6), 1.80 (1H, ^2J = 12.9 Hz, J = 7.8 Hz, H_7), 1.67 – 1.62 (1H, m, H_8), 1.62 – 1.57 (1H, m, H_7), 1.28 (1H, apparent t, J = 11.8 Hz, H_8), 1.11 (3H, s, H_9), 0.99 (3H, s, H_{10}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.9, 169.8, 86.6, 76.5, 52.2, 47.1, 45.96, 45.91, 37.4, 36.6, 33.0, 30.2, 29.9, 29.1, 20.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2864, 1744, 1715, 1437, 1375, 1360.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{15}H_{23}O_3$: 251.16417; **found:** 251.16450.

Preparation of ((3*bR*,6*aR*)-7*a*-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-2-oxo-2,3*b*,4,5,6,6*a*,7,7*a*-octahydro-2*H*-cyclopenta[a]pentalen-3-yl)methyl acetate



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Scheme 155

Prepared according to **General Procedure B**:

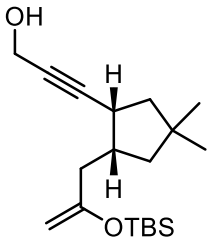
(a) 3-((1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentyl)prop-2-yn-1-yl acetate (0.037 g, 0.148 mmol); (b) DCE (1.5 mL); (c) DIPEA (0.03 mL, 0.163 mmol); (d) TBSOTf (0.034 mL, 0.148 mmol); (e) 88:12; (f) DCE (1.5 mL); (g) $Co_2(CO)_8$ (0.051 g, 0.15 mmol); (h) DodSMe (0.19 mL, 0.703 mmol); (i) 70 °C; (j) 18 h; (k) N/A; and (l) N/A.

Scheme 156

Prepared according to **kine**:

(a) 3-((1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentyl)prop-2-yn-1-yl acetate (0.193 g, 0.77 mmol); (b) DCE (7.7 mL); (c) DIPEA (0.15 mL, 0.85 mmol); (d) TBSOTf (0.18 mL, 0.77 mmol); (e) 88:12; (f) DCE (1.5 mL); (g) $Co_2(CO)_8$ (0.266 g, 0.78 mmol); (h) DodSMe (0.97 mL, 3.66 mmol); (i) reflux; (j) 18 h; (k) N/A; and (l) N/A.

Preparation of 3-((1*R*,2*R)*-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-4,4-dimethylcyclopentyl)prop-2-yn-1-ol.



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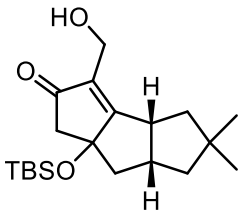
Scheme 156

3-((1*R*,2*R*)-4,4-dimethyl-2-(2-oxopropyl)cyclopentyl)prop-2-yn-1-yl acetate (0.034 g, 0.136 mmol) and DCE (1.4 mL) was added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to -10 °C and DIPEA (0.03 mL, 0.15 mmol) was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the reaction mixture was allowed to warm to room temperature and TBSOTf (0.03 mL, 0.136 mmol) was added dropwise. The reaction was stirred for 1 h at room temperature then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). Et_2O (2 mL) was added, the organic phase separated, and the aqueous phase washed with Et_2O (3 × 2 mL). The combined organic extracts were washed with brine (1 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as a yellow oil. The crude residue was dissolved in a chloroform:MeOH mixture (12:1, 0.5 mL) and K_2CO_3 was added in one portion (0.021 g, 0.15 mmol). The resulting mixture was stirred at room temperature for 1 h then diluted with Et_2O (2 mL) and washed with H_2O (1 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product as a yellow oil (as a mixture of kinetic:thermodynamic enol ether products, 88:12), which was used in the next reaction without further purification.

Preparation of (3*bR*,6*aR*)-7*a*-((*tert*-butyldimethylsilyl)oxy)-3-(hydroxymethyl)-5,5-dimethyl-1,3*b*,4,5,6,6*a*,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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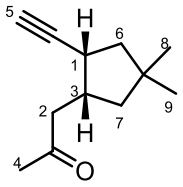
Scheme 156

The crude residue from the preparation of 3-((1*R*,2*R)*-2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-4,4-dimethylcyclopentyl)prop-2-yn-1-ol was dissolved in DCE (1.4 mL) and $Co_2(CO)_8$ (0.047 g, 0.137 mmol) was added. The solution was stirred at room temperature for 1 h, after which time, DodSMe (0.17 mL, 0.646 mmol) was added and the reaction was heated to 70 °C for 18 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude product as a black oil. The crude material was purified by flash column

chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* but, after ^1H NMR analysis, no desired product was obtained.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one.



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Scheme 157

(3*R*,4*R*)-3-(2,2-dibromovinyl)-4-(2,2-dimethoxypropyl)-1,1-dimethylcyclopentane (1.50 g, 3.904 mmol) was dissolved in THF (97.6 mL) in a flame-dried, round-bottom flask equipped with a stirrer bar. The mixture was cooled to -78 °C, 2.5 M ^{n}BuLi in hexanes (3.44 mL, 8.59 mmol) was added dropwise, and the mixture was stirred for 30 min before being warmed to room temperature and stirred for a further 1 h. After this time, the reaction was diluted with Et_2O (22 mL), 6M HCl (22 mL) was added, and the layers were separated. The aqueous phase was washed with Et_2O (3 × 20 mL) and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5 – 90:10) and concentrated *in vacuo* to give 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.597 g, 3.35 mmol, **86%**) as a colourless oil.

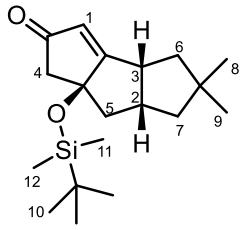
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.10 – 2.99 (1H, m, H_1), 2.87 (1H, dd, ^2J = 17.2 Hz, J = 7.8 Hz, H_2), 2.68 – 2.55 (1H, m, H_3), 2.50 (1H, dd, ^2J = 17.2 Hz, J = 6.1 Hz, H_2), 2.18 (3H, s, H_4), 2.13 (1H, d, ^4J = 2.6 Hz, H_5), 1.82 (1H, dd, ^2J = 12.8 Hz, J = 8.1 Hz, H_6), 1.66 (1H, dd, ^2J = 13.1 Hz, J = 5.5 Hz, H_6), 1.62 (1H, ^2J = 12.6 Hz, J = 6.9 Hz, H_7), 1.32 (1H, apparent t, J = 11.8 Hz, H_7), 1.13 (3H, s, H_8), 1.00 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.0, 85.8, 70.6, 47.3, 45.93, 45.85, 37.4, 36.4, 32.9, 30.4, 30.0, 29.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3293, 2951, 2897, 2866, 1717, 1464.

HRMS (ESI/micrOTOF) m/z: [M]$^+$ calcd for $C_{12}H_{18}O_1$: 178.13522; **found:** 178.13520.

Preparation of (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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Scheme 158

Prepared according to **General Procedure B**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.026 g, 0.15 mmol); (b) DCE (1.5 mL); (c) DIPEA (0.03 mL, 0.16 mmol); (d) TBSOTf (0.034 mL, 0.146 mmol); (e) 91:9; (f) DCE (1.5 mL); (g) $Co_2(CO)_8$ (0.05 g, 0.148 mmol); (h) DodSMe (0.18 KmL, 0.69 mmol); (i) 70 °C; (j) 18 h; (k) (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.018 g, 0.056 mmol, **38%**); and (l) colourless oil.

Scheme 159

Prepared according to **General Procedure B**:

Table 16, **Entry 1**: (a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.075 g, 0.42 mmol); (b) DCE (4.2 mL); (c) DIPEA (0.08 mL, 0.46 mmol); (d) TBSOTf (0.1 mL, 0.42 mmol); (e) 91:9; (f) DCE (4.2 mL); (g) $Co_2(CO)_8$ (0.15 g, 0.425 mmol); (h) DodSMe (0.53 mL, 2.0 mmol); (i) 70 °C; (j) 16 h; (k) (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.058 g, 0.181 mmol, **43%**); and (l) colourless oil.

Table 16, **Entry 2**: (a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.03 g, 0.168 mmol); (b) DCE (1.7 mL); (c) DIPEA (0.032 mL, 0.185 mmol); (d) TBSOTf (0.042 mL, 0.185 mmol); (e) 91:9; (f) DCE (1.7 mL); (g) $Co_2(CO)_8$ (0.058 g, 0.17 mmol); (h) DodSMe (0.21 mL, 0.798 mmol); (i) 70 °C; (j) 64 h; (k) (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.03 g, 0.094 mmol, **56%**); and (l) colourless oil.

Table 16, **Entry 3**: (a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.061 g, 0.342 mmol); (b) DCE (3.4 mL); (c) DIPEA (0.066 mL, 0.376 mmol); (d) TBSOTf (0.086 mL, 0.376 mmol); (e) 91:9 (f) DCE (0.34 mL); (g) $Co_2(CO)_8$ (0.118 g, 0.345 mmol); (h) DodSMe (0.43 mL, 1.62 mmol); (i) 70 °C; (j) 18 h; (k) (3b*R*,6a,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.019 g, 0.059 mmol, **17%**); and (l) colourless oil.

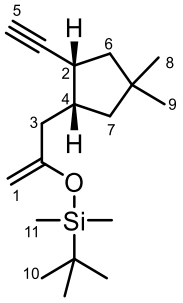
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.79 (1H, d, ^4J = 2.0 Hz, H_1), 3.63 – 3.42 (1H, m, H_2), 3.42 – 3.15 (1H, m, H_3), 2.53 (1H, d ^2J = 18.1 Hz, H_4), 2.47 (1H, d, ^2J = 17.9 Hz, H_4), 2.47 (1H, dd, ^2J = 13.1 Hz, J = 7.7 Hz, H_5), 1.91 (1H, ddd, ^2J = 12.2 Hz, J = 8.9 Hz, ^4J = 1.6 Hz, H_6), 1.79 (1H, ddd, ^2J = 12.5 Hz, J = 8.2 Hz, ^4J = 1.5 Hz, H_7), 1.35 – 1.29 (1H, m, H_6), 1.24 – 1.18 (1H, m, H_7), 1.11 – 1.07 (1H, m, H_5), 1.06 (3H, s, H_8), 1.04 (3H, s, H_9), 0.87 (9H, s, H_{10}), 0.11 (3H, s, H_{11}), 0.06 (3H, s, H_{12}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.8, 192.0, 124.0, 89.1, 48.3, 47.5, 46.2, 44.1, 43.9, 43.6, 43.0, 28.4, 26.9, 25.1, 17.5, -3.5, -3.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2930, 2899, 2857, 1717, 1638.

HRMS (ESI/micrOTOF) m/z: [M+H]$^+$ calcd for $C_{19}H_{33}O_2Si$: 321.22444; **found:** 321.22520.

Preparation of *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane.



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Scheme 160

Prepared according to **General Procedure C.**

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.15 g, 0.84 mmol); (b) DCE (8.4 mL); (c) DIPEA (0.16 mL, 0.93 mmol); (d) TBSOTf (0.21 mL, 0.93

mmol); (e) *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane (0.133 g, 0.45 mmol, **54%**); (f) 86:14; and (g) colourless oil.

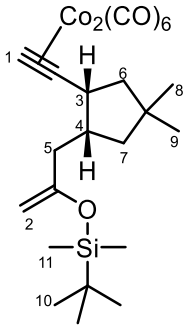
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.07 (2H, d, ^2J = 15.1 Hz, H_1), 2.99 – 2.86 (1H, m, H_2), 2.47 – 2.39 (1H, m, H_3), 2.40 – 2.31 (1H, m, H_4), 2.16 – 2.11 (1H, m, H_5), 2.11 – 2.02 (1H, m, H_3), 1.87 – 1.56 (4H, m, H_6, H_7), 0.95 (9H, s, H_{10}), 0.20 (6H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 158.2, 89.9, 86.0, 70.3, 47.4, 45.4, 39.1, 38.7, 37.1, 33.7, 30.9, 30.2, 25.2, 17.6, -5.1, -5.2 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2930, 2859, 1256.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{33}OSi$: 293.22952; **found:** 293.22830.

Preparation of *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane dicobalt hexacarbonyl complex.



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Scheme 160

Prepared according to **General Procedure D**:

(a) *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane (0.131 g, 0.45 mmol); (b) pet. ether (4.5 mL); (c) $Co_2(CO)_8$ (0.161 g, 0.47 mmol); (d) *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane dicobalt hexacarbonyl complex (0.247 g, 0.427 mmol, **95%**); (e) 89:11; and (f) red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.08 (1H, s, H_1), 4.09 (1H, s, H_2), 4.03 (1H, s, H_2), 3.73 – 3.55 (1H, m, H_3), 2.60 – 2.42 (1H, m, H_4), 2.29 (1H, dd, ^2J = 13.8 Hz, J = 3.1 Hz, H_5), 1.97 (1H, apparent t,

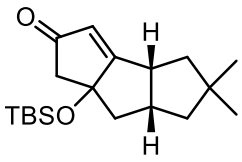
J = 13.1 Hz, H_5), 1.84 (1H, dd, ^2J = 12.3 Hz, *J* = 6.8 Hz, H_6), 1.72 – 1.63 (3H, m, H_6, H_7), 1.16 (3H, s, H_8), 1.11 (3H, s, H_9), 0.93 (9H, s, H_{10}), 0.19 (6H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.7, 157.8, 95.6, 90.1, 73.0, 50.9, 48.1, 44.5, 40.5, 37.0, 36.5, 31.2, 30.9, 25.1, 17.6, -5.0, -5.4 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2930, 2860, 2089, 2045, 1996.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{24}H_{32}O_7Co_2NaSi$: 601.04735; **found:** 601.04430.

Preparation of (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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Scheme 160

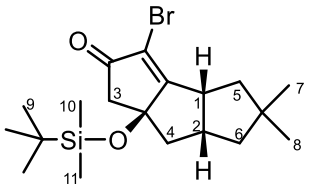
Prepared according to **General Procedure E**:

Table 17, **Entry 1** (a) *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane dicobalt hexacarbonyl complex (0.112 g, 0.194 mmol); (b) DCE (1.9 mL); (c) DodSMe (0.24 mL, 0.92 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.028 g, 0.086 mmol, **44%**); and (g) colourless oil.

Table 17, **Entry 2**: (a) *tert*-butyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)dimethylsilane dicobalt hexacarbonyl complex (0.126 g, 0.218 mmol); (b) DCE (2.2 mL); (c) DodSMe (0.55 mL, 2.07 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.037 g, 0.115 mmol, **53%**); and (g) colourless oil.

The characterisation data for this compound matched that described on page 295.

Preparation of (3b*R*,6a*R*,7a*S*)-3-bromo-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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Scheme 161

(3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.12 g, 0.374 mmol) and distilled DCM (3.74 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to 0 °C and Br_2 (0.066 g, 0.412 mmol) was added dropwise as a solution in DCM (0.5 mL). The resulting mixture was stirred at 0 °C for 2 h then Et_3N (0.26 mL, 1.87 mmol) was added slowly and the reaction mixture was warmed to rt. After 3 h, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude product as a brown oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 95:5) and concentrated *in vacuo* to give (3b*R*,6a*R*,7a*S*)-3-bromo-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.117 g, 0.293 mmol, **78%**) as a pale yellow oil.

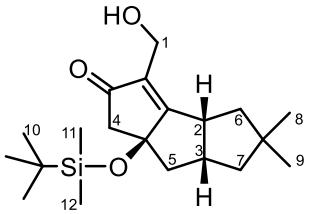
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.60 – 3.47 (1H, td, *J* = 10.6 Hz, *J* = 8.5 Hz, H_1), 3.35 – 3.19 (1H, m, H_2), 2.68 (1H, d, ^2J = 18.1 Hz, H_3), 2.59 (1H, d, ^2J= 18.1 Hz, H_3), 2.50 (1H, dd, ^2J = 13.2 Hz, *J* = 7.5 Hz, H_4), 2.07 (1H, ddd, ^2J = 12.5 Hz, *J* = 8.4 Hz, ^4J = 1.9 Hz, H_5), 1.82 (1H, ddd, ^2J = 12.6 Hz, *J* = 8.4 Hz, ^4J = 1.8 Hz, H_6), 1.49 (1H, dd, ^2J = 12.3 Hz, *J* = 10.9 Hz, H_5), 1.29 (1H, dd, ^2J = 13.2 Hz, *J* = 9.9 Hz, H_4), 1.10 (1H, dd, ^2J = 12.6 Hz, *J* = 8.6 Hz, H_6), 1.099 (3H, s, H_7), 1.04 (3H, s, H_8), 0.87 (9H, s, H_9), 0.08 (3H, s, H_{10}), 0.04 (3H, s, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.9, 185.2, 118.3, 88.8, 47.2, 46.9, 46.8, 44.2, 43.7, 41.6, 28.2, 26.4, 25.0, 17.5, -3.4, -3.9 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2930, 2857, 1726, 1641, 1462.

HRMS (ESI/micrOTOF) m/z: [M+H]$^+$ calcd for $C_{19}H_{32}O_2BrSi$: 399.13495; **found:** 399.14036.

Preparation of (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-3-(hydroxymethyl)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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Scheme 161

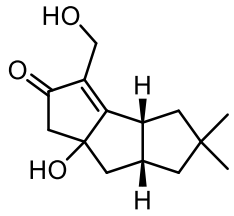
(3b*R*,6a*R*,7a*S*)-3-bromo-7a-((*tert*-butyldimethylsilyl)oxy)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.058 g, 0.145 mmol) and dry THF (2.1 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar and stirring was commenced. LiCl (0.012 g, 0.29 mmol), a solution of (tributylstannyl)methanol (0.093 g, 0.29 mmol) in THF (0.22 mL), and $Pd(PPh_3)_4$ (0.017 g, 0.0145 mmol) were added sequentially, and the reaction mixture was heated to 65 °C for 24 h. After this time, the reaction was concentrated *in vacuo* and purified by flash column chromatography (pet. ether:Et_2O, 80:20) to give (3b*R*,6a*R*,7a*S*)-7a-((*tert*-butyldimethylsilyl)oxy)-3-(hydroxymethyl)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.018 g, 0.051 mmol, **35%**) as a pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 3.96 (1H, m, H_1), 3.78 (1H, dd, ^2J = 11.0 Hz, J = 6.8 Hz, H_1), 3.54 (1H, td, J = 15.8 Hz, J = 8.7 Hz, H_2), 3.38 – 3.23 (1H, m, H_3), 2.78 (1H, t, ^4J = 6.5 Hz, H_4), 2.30 (1H, dd, ^2J = 13.2 Hz, J = 7.5 Hz, H_5), 2.19 (1H, s, OH), 2.06 (1H, ddd, ^2J = 12.5 Hz, J = 8.4 Hz, ^4J = 1.7 Hz, H_6), 1.83 (1H, ddd, ^2J = 12.6 Hz, J= 8.4 Hz, J = 1.7 Hz, H_7), 1.52 – 1.47 (1H, m, H_5), 1.48 – 1.45 (1H, m, H_6), 1.12 (1H, dd, ^2J = 12.7 Hz, J = 8.1 Hz, H_7), 1.10 (3H, s, H_8), 1.04 (3H, s, H_9), 0.87 (9H, s, H_{10}), 0.11 (3H, s, H_{11}), 0.07 (3H, s, H_{12}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.9, 186.1, 117.0, 91.0, 60.3, 56.9, 46.8, 44.1, 43.7, 43.6, 41.9, 41.6, 28.1, 26.5, 25.0, 17.5, -3.3, -3.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3391, 2951, 2928, 2857, 1719, 1641.

Preparation of (3b*R*,6a*R*)-7a-hydroxy-3-(hydroxymethyl)-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



1

Scheme 162

Table 18, **Entry 1**:

Prepared according to **General Procedure F**:

(a) (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.023 g, 0.066 mmol); (b) THF (0.36 mL); (c) 0.59375 M HCl (0.042 mL); (d) rt; (e) 18 h; (f) N/A; and (g) N/A. To note, starting material was recovered (0.013 g, 0.038 mmol, **58%**).

Table 18, **Entry 2**:

(3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.013 g, 0.038 mmol) was added to a round-bottom flask equipped with a stirrer bar and dissolved in a mixture of AcOH:THF:H_2O (0.64 mL:0.21 mL:0.21 mL). The resulting solution was heated to 50 °C for 16 h. TLC analysis at this point showed no reaction, therefore, the mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) was added. Et_2O (3 mL) was added, the organic phase separated, and the aqueous phase was washed with Et_2O (3 × 3 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to return the starting material (0.011 g, 0.031 mmol, **82%**).

Table 18, **Entry 3**:

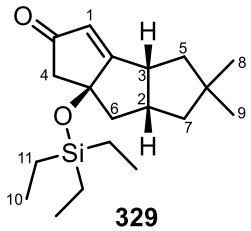
(3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.019 g, 0.054 mmol) was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in a mixture of DMF:H_2O (0.07 mL:0.07 mL). KF (0.016 g, 0.27 mmol) was added in one portion

and the resulting mixture was stirred at rt for 5 h. TLC analysis at this point showed undesired reactivity, therefore, the mixture was diluted with H_2O (1 mL). Et_2O was added (1 mL), the organic phase separated, and the aqueous phase was washed with Et_2O (3 × 1 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide the crude product as a yellow oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to return the starting material(0.015 g, 0.043 mmol, **80%**).

Table 18, **Entry 4**:

(3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.015 g, 0.043 mmol) was added to a flame-dried, round-bottom flask equipped with a stirrer bar and dissolved in dry DCM (0.25 mL). TBAF (1 M in toluene, 0.06 mL, 0.06 mmol) was added dropwise and the resulting mixture was stirred at rt for 1 h. TLC analysis at this point showed undesired reactivity, with no starting material remaining, therefore, the reaction was abandoned.

Preparation of (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one



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Scheme 163

Prepared according to **General Procedure B**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.149 g, 0.84 mmol); (b) DCE (8.4 mL); (c) DIPEA (0.16 mL, 0.92 mmol); (d) TESOTf (0.21 mL, 0.92 mmol); (e) 91:9; (f) DCE (8.4 mL); (g) $Co_2(CO)_8$ (0.29 g, 0.848 mmol); (h) DodSMe (1.06 mL, 3.99 mmol); (i) 70 °C; (j) 16 h; (k) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-

1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.053 g, 0.165 mmol, **20%**); and (l) pale yellow oil.

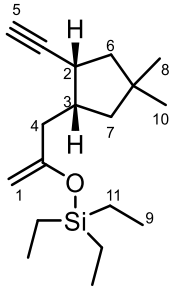
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.79 (1H, d, ^4J = 2.0 Hz, H_1), 3.62 – 3.52 (1H, m, H_2), 3.32 – 3.19 (1H, m, H_3), 2.54 (1H, d, ^2J = 18.0 Hz, H_4), 2.48 (1H, d, ^2J = 18.2 Hz, H_4), 2.48 (1H, dd, ^2J = 13.3 Hz, J = 7.9 Hz, H_5), 1.92 (1H, ddd, ^2J = 12.3 Hz, J = 9.0 Hz, ^4J = 1.5 Hz, H_6), 1.78 (1H, ddd, ^2J = 12.5 Hz, J = 8.5 Hz, ^4J = 1.4 Hz, H_7), 1.32 – 1.26 (1H, m, H_6), 1.24 – 1.19 (1H, m, H_7), 1.10 – 1.07 (1H, m, H_5), 1.06 (3H, s, H_8), 1.03 (3H, s, H_9), 0.95 (9H, t, J = 7.9 Hz, H_{10}), 0.59 (6H, q, J = 7.9 Hz, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.7, 192.1, 123.8, 89.0, 48.4, 47.5, 46.3, 44.1, 43.9, 43.6, 43.0, 28.3, 26.9, 6.4, 5.5 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2938, 2913, 2874, 2047, 1715, 1636.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{33}O_2Si$: 321.22444; **found:** 321.22480.

Preparation of triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane.



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Scheme 164

Prepared according to **General Procedure C**:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.126 g, 0.71 mmol); (b) DCE (7.1 mL); (c) DIPEA (0.14 mL, 0.777 mmol); (d) TESOTf (0.18 mL, 0.777 mmol); (e) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane (0.152 g, 0.52 mmol, **74%**); (f) 85:15; and (g) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.06 (2H, d, ^2J = 4.0 Hz, H_1), 2.99 – 2.86 (1H, m, H_2), 2.46 – 2.38 (1H, m, H_3), 2.38 – 2.29 (1H, m, H_4), 2.13 (1H, d, ^4J = 2.6 Hz, H_5), 2.11 – 2.05 (1H, m, H_4), 1.78

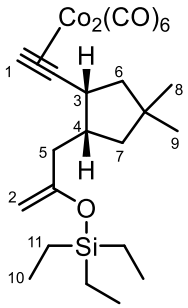
(1H, dd, ^2J = 12.9 Hz, J = 6.4 Hz, H_7), 1.70 (1H, dd, ^2J = 12.9 Hz, J = 5.0 Hz, H_6), 1.58 (1H, dd, ^2J = 12.8 Hz, J = 6.4 Hz, H_7), 1.43 (1H, ^2J = 12.5 Hz, J = 10.6 Hz, H_6), 1.16 (3H, s, H_8), 1.01 (9H, t, J = 7.9 Hz, H_9), 1.00 (3H, s, H_{10}), 0.72 (6H, q, J = 7.8 Hz, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 158.2, 89.4, 86.0, 70.3, 47.3, 45.5, 39.3, 38.7, 37.1, 33.8, 30.9, 30.2, 6.2, 4.4 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2876, 1458.

HRMS (ESI/micrOTOF) m/z: [M]$^+$ calcd for $C_{18}H_{32}O_1Si$: 292.22170; **found:** 292.22122.

Preparation of triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex.



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Scheme 164

According to General Procedure D:

(a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane (0.105 g, 0.359 mmol); (b) pet. ether (3.9 mL); (c) $Co_2(CO)_8$ (0.129 g, 0.377 mmol); (d) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.196 g, 0.339 mmol, **94%**); (e) 95:5; and (f) red oil.

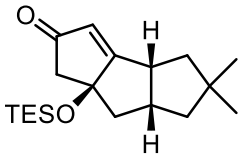
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.08 (1H, d, ^4J = 1.0 Hz, H_1), 4.08 (1H, s, H_2), 3.99 (1H, s, H_2), 3.67 – 3.56 (1H, m, H_3), 2.55 – 2.41 (1H, m, H_4), 2.27 (1H, dd, ^2J = 13.7 Hz, J = 3.7 Hz, H_5), 1.95 (1H, dd, ^2J = 13.5 Hz, J = 12.6 Hz, H_5), 1.82 (1H, dd, ^2J = 12.2 Hz, J = 6.6 Hz, H_6), 1.72 – 1.62 (3H, m, H_6, H_7), 1.15 (3H, s, H_8), 1.10 (3H, s, H_9), 0.98 (9H, t, J = 7.9 Hz, H_{10}), 0.69 (6H, q, J = 7.8 Hz, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 200.3, 158.3, 90.0, 73.5, 51.3, 48.8, 45.0, 41.3, 37.4, 37.0, 31.8, 31.5, 30.3, 6.6, 4.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2914, 2878, 2359, 2342, 2089, 2045, 1998.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{24}H_{32}O_7Co_2NaSi$: 601.04735; **found:** 601.04760.

Preparation of (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one



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Scheme 165

Prepared according to **General Procedure E**:

Table 19, **Entry 1**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.049 g, 0.085 mmol); (b) DCE (0.85 mL); (c) DodSMe (0.11 mL, 0.404 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.006 g, 0.019 mmol, **22%**); and (g) pale yellow oil.

Table 19, **Entry 2**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.044 g, 0.076 mmol); (b) DCE (0.76 mL); (c) DodSMe (0.096 mL, 0.36 mmol); (d) 70 °C; (e) 8 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0035 g, 0.011 mmol, **14%**); and (g) pale yellow oil.

Table 19, **Entry 3**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.112 g, 0.194 mmol); (b) DCE (1.9 mL); (c) DodSMe (0.49 mL, 1.84 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0235 g, 0.0733 mmol, **38%**); and (g) pale yellow oil.

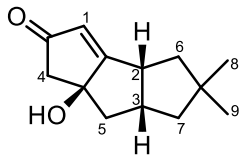
Table 19, **Entry 4**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.097 g, 0.168 mmol); (b) DCE (1.7 mL); (c) DodSMe (0.89 mL, 3.35 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0239 g, 0.0745 mmol, **44%**); and (g) pale yellow oil.

Table 19, **Entry 5**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.099 g, 0.171 mmol); (b) DCE (1.7 mL); (c) DodSMe (0.43 mL, 1.63 mmol); (d) 70 °C; (e) 24 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0279 g, 0.087 mmol, **51%**); and (g) pale yellow oil.

Table 19, **Entry 6**: (a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobalt hexacarbonyl complex (0.10 g, 0.17 mmol); (b) DCE (1.7 mL); (c) none; (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.013 g, 0.0405 mmol, **24%**); and (g) pale yellow oil

The characterisation data for this compound matched that described on page 302.

Preparation of (3b*R*,6a*R*,7a*S*)-7a-hydroxy-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



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Scheme 166

Prepared according to **General Procedure F**:

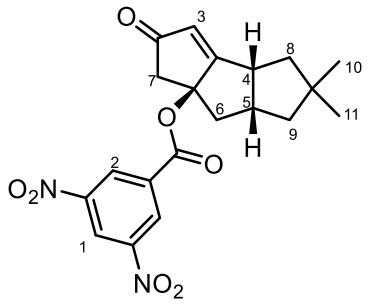
(a) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.029 g, 0.09 mmol); (b) THF (0.49 mL); (c) 0.6M HCl (0.06 mL, 0.0297 mmol); (d) rt; (e) 18 h; (f) (3b*R*,6a*R*,7a*S*)-7a-hydroxy-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.014 g, 0.068 mmol, **76%**); and (g) colourless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.81 (1H, d, ^4J = 2.2 Hz, H_1), 3.67 – 3.55 (1H, m, H_2), 3.39 – 3.25 (1H, m, H_3), 2.57 (1H, d, ^2J = 18.2 Hz, H_4), 2.51 (1H, d, ^2J = 18.1 Hz, H_4), 2.48 (1H, dd, ^2J = 13.6 Hz, J = 8.1 Hz, H_5), 2.14 (1H, s, OH), 1.94 (1H, ddd, ^2J = 12.3 Hz, J = 8.9 Hz, ^4J = 1.7 Hz, H_6), 1.82 (1H, ddd, ^2J = 12.5 Hz, J = 8.2 Hz, ^4J = 1.7 Hz, H_7), 1.36 – 1.33 (1H, m, H_6), 1.32 – 1.29 (1H, m, H_5), 1.10 (1H, dd, ^2J = 12.4 Hz, J = 8.7 Hz, H_7), 1.07 (3H, s, H_8), 1.03 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.3, 191.6, 124.8, 88.3, 49.0, 48.2, 45.1, 44.5, 44.4, 44.2, 43.3, 28.8, 27.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3387, 2951, 2934, 2862, 1711, 1699, 1632.

Preparation of (3a*R*,6a*S*,7a*R*)-2,2-dimethyl-5-oxo-1,2,3,3a,5,6,7,7a-octahydro-6a*H*-cyclopenta[a]pentalen-6a-yl 3,5-dinitrobenzoate.



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Scheme 167

(3b*R*,6a*R*,7a*S*)-7a-Hydroxy-5,5-dimethyl-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.015 g, 0.0713 mmol) was dissolved in dry DCM (0.79 mL) in a vial. Et_3N (0.1 mL, 0.71 mmol), 3,5-dinitrobenzoyl chloride (0.083 g, 0.36 mmol), and a single crystal of *N*,*N*-dimethylaminopyridine were added sequentially. The resulting mixture was stirred at room temperature for 1 h. After this time the reaction was filtered through a pad of silica using Et_2O:pet. ether as the eluent (75:25, 45 mL). The mixture was then concentrated *in vacuo* to give (3a*R*,6a*S*,7a*R*)-2,2-dimethyl-5-oxo-1,2,3,3a,5,6,7,7a-octahydro-6a*H*-cyclopenta[a]pentalen-6a-yl 3,5-dinitrobenzoate (0.028 g, 0.07 mmol, **98%**) as colourless crystals.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 9.24 (1H, apparent t, ^4J = 2.1 Hz, H_1), 9.08 (2H, d, ^4J = 1.9 Hz, H_2), 6.12 (1H, d, ^4J = 1.8 Hz, H_3), 3.76 – 3.62 (1H, m, H_4), 3.28 – 3.15 (1H, m, H_5), 3.11 (1H, dd, ^2J = 14.6 Hz, J = 7.9 Hz, H_6), 2.91 (1H, d, ^2J = 18.8 Hz. H_7), 2.84 (1H, d, ^2J = 19.2 Hz, H_7), 2.05 (1H,

dd, ^2J = 12.2 Hz, J = 8.9 Hz, H_8), 1.85 (1H, dd, ^2J = 12.3 Hz, J = 8.2 Hz, H_9), 1.53 (1H, dd, ^2J = 14.6 Hz, J = 9.1 Hz, H_6), 1.44 (1H, dd, ^2J = 12.0 Hz, J = 9.2 Hz, H_8), 1.17 (1H, dd, ^2J = 12.5 Hz, J = 9.0 Hz, H_9), 1.11 (3H, s, H_{10}), 1.05 (3H, s, H_{11}) ppm.

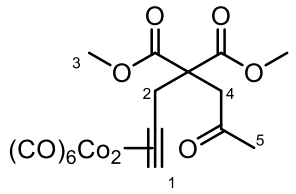
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.6, 185.1, 161.2, 148.2, 133.5, 128.9, 127.9, 122.1, 96.9, 47.6, 45.4, 44.2, 43.9, 43.9, 43.3, 42.1, 28.3, 26.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3102, 2953, 2936, 2862, 1717, 1628, 1541, 1460, 1343.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}N_2O_7$: 401.13433; **found:** 401.13220.

Melting point: 152 – 154 °C.

Preparation of dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobalt hexacarbonyl complex.



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Scheme 168

Prepared according to **General Procedure D**:

(a) dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate (0.117 g, 0.52 mmol); (b) pet. ether (5.2 mL); (c) $Co_2(CO)_8$ (0.186 g, 0.54 mmol); (d) dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobalt hexacarbonyl complex (0.231 g, 0.45 mmol, **87%**); (e) N/A; and (f) red crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.93 (1H, s, H_1), 3.87 (2H, s, H_2), 3.78 (6H, s, H_3), 3.30 (2H, s, H_4), 2.21 (3H, s, H_5) ppm.

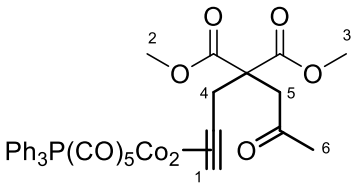
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.3, 199.2, 169.5, 76.7, 72.3, 55.4, 52.6, 45.1, 37.7, 29.6 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2093, 2050, 2016, 1989, 1736, 1715.

HRMS (ESI/micrOTOF) m/z: $[M]^+$ calcd for $C_{17}H_{14}O_{11}Co_2$: 512.92728; **found:** 512.92510.

Melting point: 84 – 86 °C.

Preparation of dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex.



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Scheme 168

Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobalt hexacarbonyl complex (0.05 g, 0.0976 mmol) and dry toluene (0.9 mL) were added to a flame-dried, round-bottom flask. PPh_3 (0.026 g, 0.0976 mmol) was added to the solution and the resulting mixture was heated to 65 °C for 3 h. After this time, the reaction was concentrated *in vacuo* to give the crude product as a red oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to give dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobalt pentacarbonyltriphenylphosphine complex (0.056 g, 0.075 mmol, **77%**) as a red crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.59 – 7.34 (15H, s, ArH), 5.05 (1H, s, H_1), 3.72 (3H, s, H_2), 3.62 (3H, s, H_3), 3.53 (1H, d, ^2J = 15.8 Hz, H_4), 3.12 (1H, ^2J = 18.0 Hz, H_5), 2.88 (1H, d, ^2J = 15.7 Hz, H_4), 2.61 (1H, d, J = 18.0 Hz, H_5), 2.05 (3H, s, H_6) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 204.3, 201.2, 170.1, 169.6, 133.5 (d, $^1J_{C\text{-}P}$ = 41.3 Hz), 132.5 (d, $^2J_{C\text{-}P}$ = 10.9 Hz), 129.8, 128.1 (d, $^3J_{C\text{-}P}$ = 9.9 Hz), 76.7, 72.9, 55.4, 52.2, 52.1, 45.1, 37.3, 29.6 ppm.

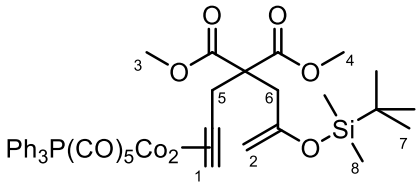
^{31}P NMR ($CDCl_3$, 202 MHz): δ_P 53.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2058, 1996, 1958, 1740, 1715.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{34}H_{29}O_{10}Co_2NaP$: 769.00545; **found:** 769.00590.

Melting point: >300 °C.

Preparation of dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex.



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Scheme 168

Prepared according to **General Procedure A**:

(a) dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex (0.054 g, 0.072 mmol); (b) DCE (0.7 mL); (c) DIPEA (0.015 mL, 0.087 mmol); (d) TBSOTf (0.02 mL, 0.087 mmol); (e) dimethyl 2-(2-((*tert*-butyldimethylsilyl)oxy)allyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex (0.045 g, 0.052 mmol, **73%**); and (f) as a red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.44 (15H, s, ArH), 5.07 (1H, s, H_1), 4.00 (1H, s, H_2), 3.89 (1H, s, H_2), 3.64 (3H, s, H_3), 3.61 (3H, s, H_4), 3.57 – 3.36 (2H, m, H_5), 2.73 (1H, d, ^{2}J = 15.2 Hz, H_6), 2.37 (1H, d, ^{2}J = 14.6 Hz, H_6), 0.90 (9H, s, H_7), 0.14 (6H, s, H_8) ppm.

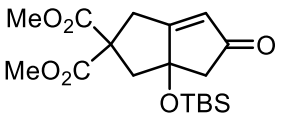
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.5, 170.2, 169.8, 154.3, 133.9 (d, $^{1}J_{C\text{-}P}$ = 40.7 Hz), 132.5 (d, $^{2}J_{C\text{-}P}$ = 10.9 Hz), 129.7, 128.1 (d, $^{3}J_{C\text{-}P}$ = 9.8 Hz), 93.0, 72.2, 57.1, 51.6, 41.0, 36.9, 25.4, 25.2, -3.4, -5.0, -5.1 ppm.

^{31}P NMR ($CDCl_3$, 202 MHz): 53.2 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2058, 1998, 1956, 1736.

HRMS (ESI/micrOTOF) m/z: [M+Cl]- calcd for $C_{40}H_{43}O_{10}ClCo_2Si$: 895.07211; **found:** 895.07160.

Preparation of dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate from dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex.



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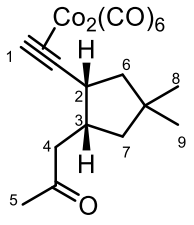
Scheme 169

Prepared according to **General Procedure E**:

(a) dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex (0.0356 g, 0.041 mmol); (b) DCE (0.4 mL); (c) DodSMe (0.05 mL, 0.196 mmol); (d) 70 °C; (e) 16 h; (f) dimethyl 3a-((*tert*-butyldimethylsilyl)oxy)-5-oxo-3,3a,4,5-tetrahydropentalene-2,2(1*H*)-dicarboxylate (0.011 g, 0.034 mmol, **84%**); and (g) white solid.

The characterisation data for this compound matched that described on page 115.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex.



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Scheme 170

Prepared according to **General Procedure D**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one (0.099 g, 0.557 mmol); (b) pet. ether (5.6 mL); (c) $Co_2(CO)_8$ (0.200 g, 0.585 mmol); (d) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.256 g, 0.552 mmol, **99%**); (e) N/A; and (f) a red oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.04 (1H, s, H_1), 3.73 – 3.59 (1H, m, H_2), 2.83 – 2.68 (1H, m, H_3), 2.60 (1H, dd, ^2J = 16.3 Hz, J = 3.6 Hz, H_4), 2.51 (1H, dd, ^2J = 16.3 Hz, J = 11.0 Hz, H_4), 2.16 (3H, s, H_5), 1.89 (1H, dd, ^2J = 12.3 Hz, J = 6.9 Hz, H_6), 1.83 (1H, dd, ^2J = 13.3 Hz, J = 7.1 Hz, H_7), 1.62

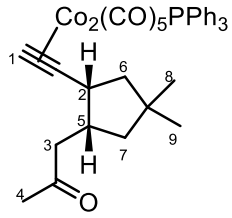
(1H, apparent t, J = 12.0 Hz, H_7), 1.39 (1H, dd, ^2J = 13.3 Hz, J = 4.3 Hz, H_6), 1.15 (3H, s, H_8), 1.11 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.4, 199.5, 96.4, 72.6, 50.6, 47.3, 46.1, 44.8, 39.0, 36.8, 31.1, 30.5, 29.7 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2963, 2934, 2089, 2043, 1991, 1713.

HRMS (ESI/micrOTOF) m/z: [M+Na]$^+$ calcd for $C_{18}H_{18}O_7Co_2Na$: 486.96087; **found:** 486.95950.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriphenylphosphine complex.



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Scheme 170

Dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobalt hexacarbonyl complex (0.100 g, 0.215 mmol) and dry toluene (1.96 mL) were added to a flame-dried, round-bottom flask. PPh_3 (0.057 g, 0.215 mmol) was added to the solution and the resulting mixture was heated to 65 °C for 3 h. After this time, the reaction was concentrated *in vacuo* to give the crude product as a red oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 70:30) and concentrated *in vacuo* to give dimethyl 2-(2-oxopropyl)-2-(prop-2-yn-1-yl)malonate dicobaltpentacarbonyltriphenylphosphine complex (0.113 g, 0.162 mmol, **75%**, as a 86:14 mixture of diastereomers) as a red oil.

Major Isomer

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.46 (15H, s, ArH), 5.10 (1H, s, H_1), 2.63 (1H, s, H_2), 2.31 (1H, d, ^2J = 15.5 Hz, H_3), 2.24 – 2.10 (1H, m, H_3), 2.02 (3H, s, H_4), 1.97 – 1.88 (1H, m, H_5), 1.48 – 1.42 (1H, m, H_6), 1.42 – 1.36 (1H, m, H_7), 1.21 – 1.12 (1H, m, H_6), 1.12 – 1.07 (1H, m, H_7), 1.05 (3H, s, H_8), 0.82 (3H, s, H_9) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.2, 201.8, 133.8 (d, $^1J_{C\text{-}P}$ = 41.7 Hz), 132.5 (d, $^2J_{C\text{-}P}$ = 10.8 Hz), 129.8, 128.1 (d, $^3J_{C\text{-}P}$ = 9.7 Hz), 84.9, 71.0, 50.8, 46.6, 45.2, 43.0, 37.3, 36.6, 30.1, 28.8 ppm.

^{31}P NMR ($CDCl_3$, 202 MHz): 55.6 ppm.

Minor Isomer

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.49 – 7.36 (15H, m, ArH), 5.21 (1H, d, ^4J = 5.9 Hz, H_1), 3.07 (1H, d, ^2J = 15.9 Hz, H_3), 2.55 – 2.41 (2H, m, H_2, H_5), 2.14 – 2.31 (1H, m, H_3), 2.13 (3H, s, H_4), 1.60 – 1.49 (1H, m, H_6/H_7), 1.20 – 1.10 (3H, m, H_6/H_7), 0.94 (3H, s, H_8), 0.76 (3H, s, H_9) ppm.

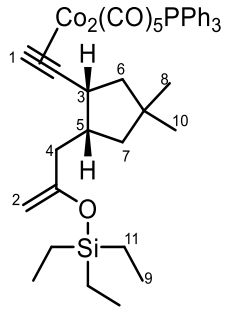
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.6, 201.8, 134.2 (d, $^1J_{C\text{-}P}$ = 42.0 Hz), 132.5 (d, $^2J_{C\text{-}P}$ = 10.7 Hz), 129.8, 128.0 (d, $^3J_{C\text{-}P}$ = 9.8 Hz), 93.0, 74.3, 49.4, 45.9, 44.7, 43.5, 37.8, 36.5, 31.0, 30.2, 29.7 ppm.

^{31}P NMR ($CDCl_3$, 202 MHz): 54.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2930, 2052, 1987, 1950, 1711.

HRMS (ESI/micrOTOF) m/z: $[M+Na]^+$ calcd for $C_{35}H_{33}O_6Co_2PNa$: 721.05709; **found:** 721.05360.

Preparation of triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silanedicobaltpentacarbonyltriphenylphosphine complex.



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Scheme 170

Prepared according to **General Procedure G**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.106 g, 0.152 mmol); (b) DCE (1.5 mL); (c) DIPEA (0.03 mL, 0.182 mmol); (d) TESOTf

(0.042 mL, 0.182 mmol); (e) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silanedicobaltpentacarbonyltriphenylphosphine complex (0.082 g, 0.10 mmol, **66%**); (f) 89:11; (g) 100:0; and (h) red oil. To note, starting material (0.023 g, 0.049 mmol, 32%) was recovered.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.66 – 7.35 (15H, m, ArH), 5.23 (2H, d, ^{4}J = 5.2 Hz, H_1), 3.96 (1H, s, H_2), 3.83 (1H, s, H_2), 2.54 – 2.44 (1H, m, H_3), 2.05 (1H, dd, ^{2}J = 13.4 Hz, J = 3.0 Hz, H_4), 1.94 (1H, dd, ^{2}J = 12.5 Hz, J = 7.5 Hz, H_4), 1.89 – 1.76 (1H, m, H_5), 1.64 (1H, apparent t, J = 12.8 Hz, H_6), 1.45 (1H, apparent t, J = 11.6 Hz, H_7), 1.28 (1H, s, H_7), 1.26 (1H, s, H_6), 1.06 (3H, s, H_8), 0.98 (9H, t, J = 7.8 Hz, H_9), 0.81 (3H, s, H_{10}), 0.69 (6H, q, J = 7.8 Hz, H_{11}) ppm.

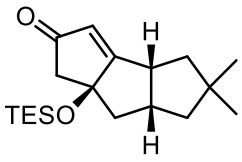
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 201.7, 158.5, 134.0 (d, $^{1}J_{C\text{-}P}$ = 41.1 Hz), 132.5 (d, $^{2}J_{C\text{-}P}$ = 11.0 Hz), 129.7, 128.0 (d, $^{3}J_{C\text{-}P}$ = 9.9 Hz), 95.8, 89.3, 71.1, 50.8, 45.4, 43.3, 39.4, 37.6, 36.3, 30.2, 20.1, 6.2, 4.4 ppm.

^{31}P NMR (202 MHz): δ_P 56.2 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2936, 2876, 2054, 1991, 1952.

HRMS (ESI/micrOTOF) m/z: [M+Cl]- calcd for $C_{41}H_{47}O_6Co_2ClSiP$: 847.12375; **found:** 847.12260.

Preparation of (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one



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Scheme 171

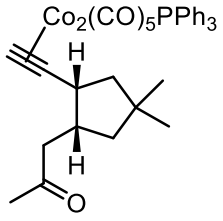
Prepared according to **General Procedure E**:

(a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silanedicobaltpentacarbonyltriphenylphosphine complex (0.081 g, 0.1 mmol); (b) DCE (1 mL); (c) DodSMe (0.251 mL, 0.947 mmol); (d) 70 °C; (e) 24 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-

7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0158 g, 0.049 mmol, **49%**); and (g) pale yellow oil.

The characterisation data for this compound matched that described on page 302.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriphenylphosphine complex.



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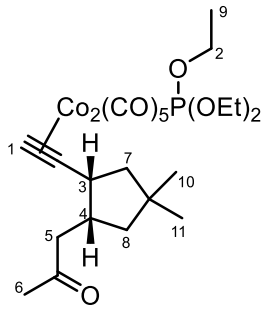
Scheme 172

Prepared according to **General Procedure H**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.121 g, 0.236 mmol); (b) acetone (23.6 mL); (c) -10 °C; (d) PPh_3 (0.062 g, 0.236 mmol); (e) TMANO.$2H_2O$ (0.026 g, 0.236 mmol); (f) 7 h; (g) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriphenylphosphine complex (0.147 g, 0.210 mmol, **89%**); (h) red oil; and (i) 52:48.

Characterisation data for this compound on page 312.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriethylphosphite complex.



339

Scheme 173

Prepared according to **General Procedure H**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.025 g, 0.054 mmol); (b) acetone (5.4 mL); (c) -10 °C; (d) TMANO.2H_2O (0.006 g, 0.054 mmol); (e) $P(OEt)_3$ (0.009 g, 0.054 mmol); (f) 7 h; (g) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriethylphosphite complex (0.0298 g, 0.049 mmol, **92%**); (h) red oil; and (i) 61:39.

Thermodynamic isomer:

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.44 (1H, s, H_1), 3.97 (6H, s, H_2), 3.77 – 3.65 (1H, m, H_3), 2.87 – 2.77 (1H, m, H_4), 2.76 – 2.65 (1H, m, H_5), 2.53 – 2.37 (1H, m, H_5), 2.16 (3H, s, H_6), 2.04 – 1.92 (1H, m, H_7), 1.84 – 1.72 (1H, m, H_8), 1.72 – 1.50 (2H, m, H_7, H_8), 1.33 (9H, apparent s, H_9), 1.13 (3H, s, H_{10}), 1.06 (3H, s, H_{11}) ppm.

Kinetic isomer:

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.51 (1H, s, H_1), 3.97 (6H, s, H_2), 3.63 – 3.54 (1H, m, H_3), 2.99 – 2.86 (1H, m, H_4), 2.76 – 2.65 (1H, m, H_5), 2.53 – 2.37 (1H, m, H_5), 2.15 (3H, s, H_6), 1.84 – 1.72 (1H, m, H_7), 1.72 – 1.50 (3H, m, H_7, H_8), 1.33 (9H, apparent s, H_9), 1.11 (3H, s, H_{10}), 1.06 (3H, s, H_{11}) ppm.

The following data are related to the mixture of diastereomers:

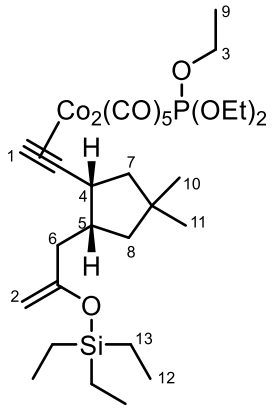
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.7, 208.4, 202.4, 94.6, 92.7, 76.8, 76.5, 76.2, 71.3, 69.2, 60.5, 50.5, 49.5, 46.7, 459, 45.7, 45.3, 44.9, 44.0, 38.8, 37.7, 36.8, 36.6, 31.3, 30.7, 30.3, 30.1, 29.5, 29.4, 15.6, 15.6 ppm.

^{31}P NMR ($CDCl_3$, 202 MHz): δ_P 158.2 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2982, 2953, 2934, 2058, 1987, 1962, 1715.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{34}O_9Co_2P$: 603.05989; **found:** 603.05550.

Preparation of triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobaltpentacarbonyltriethylphosphite complex.



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Scheme 174

Prepared according to **General Procedure G.**

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.0298 g, 0.049 mmol); (b) DCE (0.49 mL); (c) DIPEA (0.009 mL, 0.054 mmol); (d) TESOTf (0.012 mL, 0.054 mmol); (e) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobaltpentacarbonyltriethylphosphite complex (0.0189 g, 0.026 mmol, **54%**); (f) 69:31; (g) 100:0; and (h) red oil.

Thermodynamic isomer:

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.55 (1H, dd, $^3J_{H\text{-}P}$ = 3.6 Hz, ^4J = 0.78 Hz, H_1), 4.06 (1H, s, H_2), 3.98 (7H, m, H_2, H_3), 3.69 (1H, dt, *J* = 10.3 Hz, *J* = 8.1 Hz, H_4), 2.65 – 2.51 (1H, m, H_5), 2.46 – 2.43 (1H, m H_6), 2.00 (1H, dd, ^2J = 12.6 Hz, *J* = 7.6 Hz, H_6), 1.87 (1H, dd, ^2J = 13.7 Hz, *J* = 11.9 Hz, H_7), 1.68 (1H, dd, ^2J = 16.2 Hz, H_8), 1.63 – 1.58 (1H, m, H_7), 1.48 (1H, dd, ^2J 13.0 Hz, *J* = 7.2 Hz, H_8), 1.32 (9H, t, *J* = 7.0 Hz, H_9), 1.14 (3H, s, H_{10}), 1.05 (3H, s, H_{11}), 1.01 (9H, t, *J* = 7.9 Hz, H_{12}), 0.72 (6H, q, *J* = 7.6 Hz, H_{13}) ppm.

Kinetic isomer:

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.52 (1H, dd, $^3J_{H\text{-}P}$ = 6.0 Hz, ^4J = 0.91 Hz, H_1), 4.07 (1H, s, H_2), 3.98 (7H, m, H_2, H_3), 3.63 – 3.55 (1H, dt, *J* = 10.3 Hz, *J* = 8.1 Hz, H_4), 2.52 – 2.45 (1H, m, H_5), 2.42 – 2.38 (1H, m H_6), 1.97 – 1.90 (1H, m, H_6), 1.76 (1H, dd, ^2J = 12.5 Hz, *J* = 6.6 Hz, H_7), 1.63 – 1.53 (4H, m, H_7, H_8) 1.33 (9H, t, *J* = 7.0 Hz, H_9), 1.12 (3H, s, H_{10}), 1.07 (3H, s, H_{11}), 1.01 (9H, t, *J* = 7.9 Hz, H_{12}), 0.72 (6H, q, *J* = 7.6 Hz, H_{13}) ppm.

The following data are related to the mixture of diastereomers:

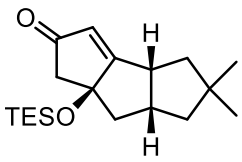
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 202.2, 158.7, 158.6, 95.3, 89.5, 89.2, 70.7, 69.5, 60.4, 60.37, 60.3, 60.26, 50.5, 49.3, 47.5, 45.6, 44.6, 44.3, 40.8, 39.7, 37.8, 36.8, 36.4, 36.36, 31.4, 31.1, 30.5, 29.7, 15.6, 15.57, 6.2, 6.16, 4.4, 4.35 ppm.

^{31}P NMR (202 MHz): δ_P 159.3 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2058, 1993, 1964.

HRMS (ESI/micrOTOF) m/z: [M+Cl]$^-$ calcd for $C_{29}H_{47}O_9Co_2PSiCl$: 751.10850; **found:** 751.10930.

Preparation of (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one



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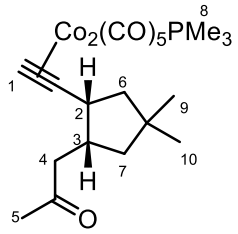
Scheme 174

Prepared according to **General Procedure E**:

(a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silanedicobaltpentacarbonyltriethylphosphite complex (0.018 g, 0.025 mmol); (b) DCE (0.25 mL); (c) DodSMe (0.06 mL, 0.238 mmol); (d) 70 °C; (e) 24 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one, trace; and (f) N/A.

The characterisation data for this compound matched that described on page 302.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltrimethylphosphine complex.



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Scheme 175

Prepared according to **General Procedure H**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.02 g, 0.043 mmol); (b) acetone (4.3 mL); (c) -10 °C; (d) PMe_3 (1M in toluene) (0.043 mL, 0.043 mmol); (e) TMANO.$2H_2O$ (0.005 g, 0.047 mmol); (f) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltrimethylphosphine complex (0.0213 g, 0.0418 mmol, **97%**); (g) a red oil; and (h) 76:24.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.11 (1H, s, H_1), 3.56 – 3.53 (1H, m, H_2), 2.88 – 2.76 (1H, m, H_3), 2.49 (1H, d, ^2J = 16.2 Hz, H_4), 2.21 (3H, s, H_5), 2.17 – 2.08 (1H, m, H_6), 1.70 – 1.62 (1H, m, H_7), 1.58 – 1.44 (1H, m, H_6/H_7), 1.42 – 1.38 (1H, m, H_6/H_7), 1.37 (9H, d, $^2J_{H\text{-}P}$ = 9.0 Hz, H_8), 1.14 (3H, s, H_9), 1.06 (3H, s, H_{10}) ppm.

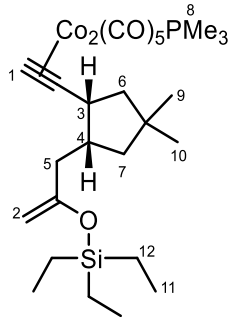
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.6, 202.7, 94.3, 59.6, 50.6, 46.3, 44.8, 43.0, 37.2, 36.8, 29.9, 29.6, 28.7, 18.9 (d, $^1J_{C\text{-}P}$ = 27.3 Hz) ppm.

^{31}P NMR (202 MHz): δ_P 12.9 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2930, 2910, 2048, 1979, 1966, 1946, 1713.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{28}O_6Co_2P$: 513.0209; **found:** 513.02820.

Preparation of triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobaltpentacarbonyltrimethylphosphine complex.



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Scheme 175

Prepared according to **General Procedure G**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.057 g, 0.111 mmol); (b) DCE (1.11 mL); (c) DIPEA (0.02 mL, 0.122 mmol); (d) TESOTf (0.03 mL, 0.122 mmol); (e) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silane dicobaltpentacarbonyltrimethylphosphine complex (0.057 g, 0.091 mmol, **82%**); (f) 81:19; (g) 100:0; and (h) red oil.

^{1}H NMR (CDCl$_3$, 400 MHz): δ_H 5.40 (1H, dd, ^4J = 4.4 Hz, ^5J = 0.8 Hz, H_1), 4.08 (1H, s, H_2), 4.03 (1H, s, H_2), 3.49 – 3.40 (1H, m, H_3), 2.66 – 2.52 (1H, m, H_4), 2.41 (1H, dd, ^2J = 14.0 Hz, J = 4.3 Hz, H_5), 2.05 (1H, dd, ^2J = 12.7 Hz, J = 7.7 Hz, H_6), 1.94 (1H, dd, ^2J = 14.0 Hz, J = 11.1 Hz, H_5), 1.65 (1H, dd, ^2J = 12.8 H, J = 10.0 Hz, H_6), 1.56 (1H, d, J = 7.0 Hz, H_7), 1.53 (1 H, d, J = 7.7 Hz, H_7), 1.34 (9H, s, H_8), 1.15 (3H, s, H_9), 1.05 (3H, s, H_{10}), 1.01 (9H, t, J = 7.9 Hz, H_{11}), 0.72 (6H, q, J = 7.9 Hz, H_{12}) ppm.

^{13}C{1H} NMR (CDCl$_3$, 101 MHz): δ_C 202.4, 158.4, 89.7, 69.3, 50.7, 45.5, 45.2, 39.8, 37.6, 36.4, 30.4, 29.8, 19.2, 18.9, 6.2, 4.4 ppm.

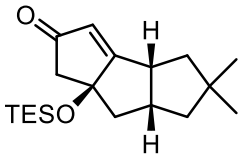
The following data relates to the mixture of isomers:

^{31}P NMR (202 MHz): δ_P 11.6 (major), 6.5 (minor) ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 2876, 2052, 1983, 1973, 1950**.**

HRMS (ESI/micrOTOF) m/z: [M+Cl]$^-$ calcd for $C_{26}H_{41}O_6Co_2PSiCl$: 661.07680; **found:** 661.07640.

Preparation of (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one



329

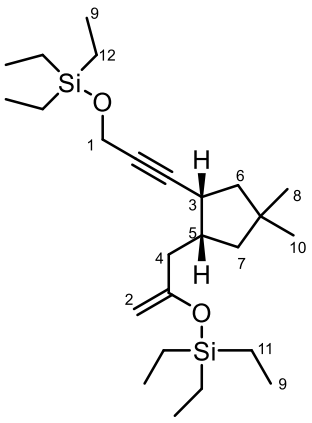
Scheme 175

Prepared according to **General Procedure E**:

(a) triethyl((3-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)prop-1-en-2-yl)oxy)silanedicobaltpentacarbonyltrimethylphosphine complex (0.057 g, 0.091 mmol); (b) DCE (0.9 mL); (c) DodSMe (0.23 mL, 0.863 mmol); (d) 70 °C; (e) 24 h; (f) (3b*R*,6a*R*,7a*S*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0121 g, 0.038 mmol, **42%**); and (g) pale yellow oil.

The characterisation data for this compound matched that described on page 302.

Preparation of ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane.



316

Scheme 176

Prepared according to **General Procedure C:**

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.028 g, 0.136 mmol); (b) DCE (1.4 mL); (c) DIPEA (0.053 mL, 0.299 mmol); (d) TESOTf (0.07 mL, 0.299 mmol); (e) ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane (0.043 g, 0.097 mmol, **72%**); (f) 89:11; and (g) colourless oil.

*The following data refers to the desired kinetic silyl enol ether **306**.*

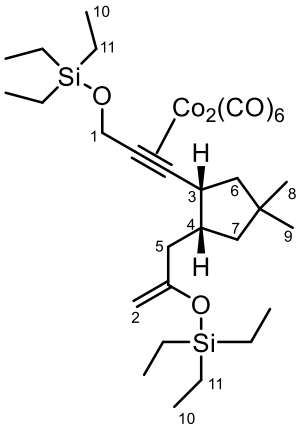
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.35 (2H, d, ^5J = 2.1 Hz, H_1), 4.04 (2H, s, H_2), 3.03 – 2.89 (1H, m, H_3), 2.40 (1H, dd, ^2J = 13.4 Hz, J = 5.87 Hz, H_4), 2.37 – 2.29 (1H, m, H_5), 2.05 (1H, dd, ^2J = 13.5 Hz, J = 8.5 Hz, H_4), 1.75 (1H, dd, ^2J = 7.4 Hz, H_6), 1.66 (1H, ^2J = 12.8 Hz, J = 5.6 Hz, H_6), 1.57 (1H, dd, ^2J = 12.7 Hz, J = 6.5 Hz, H_7), 1.40 (1H, dd, ^2J = 12.6 Hz, J = 10.2 Hz, H_7), 1.14 (3H, s, H_8), 1.00 (18 H, t, J = 7.9 Hz, H_9), 0.99 (3H, s, H_{10}), 0.71 (6H, q, J = 7.8 Hz, H_{11}), 0.67 (6H, q, J = 7.8 Hz, H_{12}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 158.4, 89.3, 86.4, 80.8, 51.1, 47.2, 45.6, 39.5, 38.9, 37.0, 34.1, 30.8, 30.1, 6.23, 6.2, 4.4, 4.0 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2951, 2911, 2876, 1653, 1634.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{49}O_2Si_2$: 437.32656; **found:** 437.35850.

Preparation of ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane dicobalt hexacarbonyl complex.



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Scheme 176

Prepared according to **General Procedure D**:

(a) ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane (0.022 g, 0.05 mmol); (b) pet. ether (0.5 mL); (c) $Co_2(CO)_8$ (0.018 g, 0.053 mmol); (d) ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane dicobalt hexacarbonyl complex (0.032 g, 0.044 mmol, **89%**); (e) 86:14; and (f) red oil.

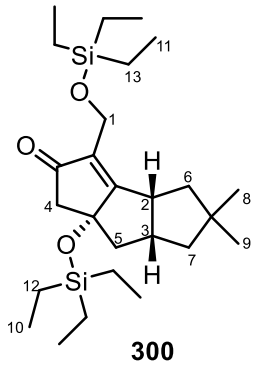
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.95 – 4.71 (2H, m, H_1), 4.08 (1H, s, H_2), 3.98 (1H, s, H_2), 3.70 – 3.45 (1H, m, H_3), 2.67 – 2.39 (1H, m, H_4), 2.21 (1H, d, ^2J = 12.6 Hz, H_5), 1.95 (1H, d, ^2J = 12.9 Hz, H_5), 1.87 – 1.59 (4H, m, H_6, H_7), 1.17 (3H, s, H_8), 1.10 (3H, s, H_9), 1.07 – 0.89 (18H, m, H_{10}), 0.78 – 0.56 (12H, m, H_{11}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 199.8, 157.8, 97.7, 96.8, 89.4, 63.2, 49.7, 48.7, 44.3, 42.1, 36.8, 36.5, 31.4, 31.2, 6.2, 6.1, 4.3, 3.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2955, 2914, 2878, 2087, 2045, 2004.

HRMS (ESI/micrOTOF) m/z: [M+Cl]$^-$ calcd for $C_{31}H_{48}Co_2O_8Si_2Cl$: 757.12540; **found:** 757.12457.

Preparation of (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



300

Scheme 177

Prepared according to **General Procedure E**:

(a) ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane dicobalt hexacarbonyl complex (0.032 g, 0.044 mmol); (b) DCE (0.4 mL); (c) DodSMe (0.11 mL, 0.42 mmol); (d) 70 °C; (e) 16 h; (f) (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-

cyclopenta[a]pentalen-2-one (0.002 g, 0.0043 mmol, **10%**, as a single diastereomer); and (g) colourless oil.

Scheme 178

Table 20, **Entry 1**:

1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.042 g, 0.202 mmol) and DCE (2.0 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to -10 °C and DIPEA (0.077 mL, 0.444 mmol) was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the TESOTf (0.102 mL, 0.444 mmol), was added dropwise. The reaction was stirred for 1 h at -10 °C then quenched by the addition of water. Et_2O was added, the organic phase separated, and the aqueous phase washed with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product (as a mixture of kinetic:thermodynamic enol ether products, 92:8) as a yellow oil. The crude residue was dissolved in DCE (5.2 mL), $Co_2(CO)_8$ (0.07 g, 0.204 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. After this time, DIPEA (0.035 mL, 0.202 mmol) and DodSMe (0.51 mL, 1.919 mmol) were added sequentially and the reaction was heated to 70 °C for 40 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude product as a black oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to give (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.0237 g, 0.051 mmol, **25%**, as a single diastereomer) as a colourless oil.

Table 20, **Entry 2**:

1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.108 g, 0.518 mmol) and distilled DCE (5.2 mL) were added to a flame-dried round-bottom flask equipped with a stirrer bar. The solution was cooled to -10 °C and DIPEA (0.199 mL, 1.14 mmol) was added dropwise. The mixture was stirred at -10 °C for 1 h. At this point, the TESOTf (0.27 mL, 1.14 mmol) was added dropwise. The reaction was stirred for 1 h at -10 °C then quenched by the addition of water. Et_2O was added, the organic phase separated, and the aqueous phase washed with Et_2O. The combined organic extracts were washed with

saturated aqueous $NaHCO_3$ solution, brine, dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product (as a mixture of kinetic:thermodynamic enol ether products, 92:8) as a yellow oil. The crude residue was dissolved in DCE (5.2 mL), 4 Å powdered molecular sieves (oven-dried at 220 °C for 2 h, 1.8 g) and $Co_2(CO)_8$ (0.179 g, 0.523 mmol) were added, and the reaction mixture was stirred for 1 h at room temperature. After this time, DIPEA (0.09 mL, 0.518 mmol) and DodSMe were added sequentially and the reaction was heated to 70 °C for 68 h. At this point, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the crude product as a black oil. The crude material was purified by flash column chromatography (pet. ether:Et_2O, 90:10) and concentrated *in vacuo* to give (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.036 g, 0.078 mmol, **15%**, as a single diastereomer) as a colourless oil.

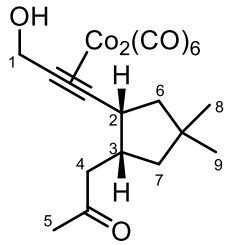
^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.46 (1H, dd, ^2J = 14.6 Hz, ^5J = 0.75 Hz, H_1), 4.41 (1H, d, ^2J = 14.6 Hz, H_1), 3.71 (1H, apparent q, J = 9.3 Hz, H_2), 2.97 (1H, apparent dq, J = 9.0 Hz, J = 8.5 Hz, H_3), 2.65 (1H, d, ^2J = 17.8 Hz, H_4), 2.36 (1H, d, ^2J = 17.8 Hz, H_4), 2.07 (1H, d, ^2J = 13.6 Hz, H_5), 1.92 – 1.63 (5H, m, H_5, H_6, H_7), 1.10 (3H, s, H_8), 0.993 (3H, s, H_9), 0.99 (9H, t, J = 7.8 Hz, H_{10}), 0.95 (9H, t, J = 7.8 Hz, H_{11}), 0.65 (6H, q, J = 8.0 Hz, H_{12}), 0.61 (6H, q, J = 8.1 Hz, H_{13}) ppm.

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.0, 183.3, 134.1, 86.0, 56.8, 48.9, 47.7, 45.8, 45.2, 42.9, 42.6, 42.3, 27.5, 25.8, 6.5, 6.2, 5.9, 3.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 2953, 1711, 1672.

HRMS (ESI/micrOTOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{49}O_3Si_2$: 465.32148; **found:** 465.32320.

Preparation of 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex.



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Scheme 179

According to General Procedure D:

(a) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one (0.05 g, 0.24 mmol); (b) pet. ether (2.4 mL); (c) $Co_2(CO)_8$ (0.086 g, 0.252 mmol); (d) 1-((1*R*,2*R*)-2-(3-hydroxyprop-1-yn-1-yl)-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.107 g, 0.22 mmol, **90%**); (e) N/A; and (f) red solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 4.85 (2H, d, *J* = 6.1 Hz, H_1), 3.63 (1H, dt, ^2J = 11.8 Hz, *J* = 6.9 Hz, H_2), 2.84 – 2.72 (1H, m, H_3), 2.61 (1H, dd, ^2J = 16.3 Hz, *J* = 4.1 Hz, H_4), 2.52 (1H, dd, ^2J = 16.3 Hz, *J* = 10.9 Hz, H_4), 2.16 (3H, s, H_5), 1.87 (1H, dd, ^2J = 9.8 Hz, *J* = 7.0 Hz, H_6), 1.84 (1H, dd, *J* = 10.8 Hz, *J* = 6.9 Hz, H_7), 1.68 (1H, apparent t, *J* = 12.2 Hz, H_7), 1.42 (1H, dd, ^2J = 13.5 Hz, *J* = 4.3 Hz, H_6), 1.17 (3H, s, H_8), 1.11 (3H, s, H_9) ppm.

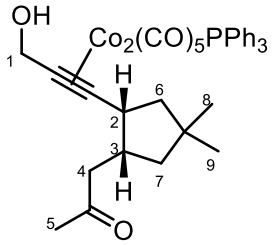
^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 207.8, 199.4, 96.9, 63.2, 49.7, 47.4, 46.1, 44.6, 39.9, 36.8, 31.2, 30.7, 29.8 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3449, 2953, 2934, 2866, 2087, 2043, 2043, 1991, 1707.

HRMS (ESI/micrOTOF) m/z: [M-H]$^-$ calcd for $C_{19}H_{19}O_8Co_2$: 492.97384; **found:** 492.97370.

Melting point: 74 – 76 °C.

Preparation of 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriphenylphosphine complex.



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Scheme 179

Prepared according to **General Procedure H**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.05 g, 0.101 mmol); (b) acetone (10 mL); (c) -10 °C; (d) 7 h; (e) TMANO.2H_2O (0.011 g, 0.101 mmol); (f) PPh_3 (0.027 g, 0.101 mmol); (g) 1-((1*R*,2*R*)-2-ethynyl-4,4-

dimethylcyclopentyl)propan-2-one dicobaltpentacarbonyltriphenylphosphine complex (0.067 g, 0.092 mmol, **91%**); (h) red solid; and (i) N/A.

Major isomer

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.52 – 7.39 (15H, s, ArH), 4.29 – 4.03 (2H, m, H_1), 2.81 – 2.60 (1H, m, H_2), 2.38 – 2.27 (2H, m, H_4), 2.23 – 2.16 (1H, m, H_3), 2.03 (3H, s, H_5), 1.92 – 1.78 (1H, m, H_6), 1.36 – 1.19 (3H, m, H_6, H_7), 0.99 (3H, s, H_8), 0.77 (3H, s, H_9) ppm.

Minor Isomer

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.80 – 7.52 (15H, s, ArH), 4.47-4.24 (2H, m, H_1), 3.61 – 3.42 (1H, m, H_2), 3.24 – 3.05 (1H, m, H_3), 2.53 – 2.39 (2H, m, H_4), 2.14 (3H, s, H_5), 1.56 – 1.36 (4H, m, H_6, H_7), 1.94 – 1.87 (1H, m, H_6), 0.99 (3H, s, H_8), 0.76 (3H, s, H_9) ppm.

Mixture of diastereomers

^{13}C{1H} NMR ($CDCl_3$, 101 MHz): δ_C 208.5, 208.4, 201.4, 134.2, 134.1, 133.7, 133.65, 132.5, 132.4, 132.3, 130.0, 129.95, 128.3, 128.2, 128.1, 92.4, 62.9, 62.6, 50.1, 47.6, 46.3, 45.8, 44.7, 44.6, 44.5, 42.4, 9.2, 37.9, 36.6, 35.7, 31.4, 31.1, 30.7, 30.4, 30.1 ppm.

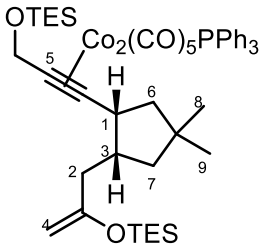
^{31}P NMR ($CDCl_3$, 202 MHz): δ_P 53.2, 52.7 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3424, 2951, 2930, 2864, 2359, 2342, 2052, 1989, 1950, 1707.

HRMS (ESI/micrOTOF) m/z: [M+Cl]- calcd for $C_{36}H_{35}O_7Co_2PCl$: 763.04784; **found**: 763.04690.

Melting point: 40 °C – 50 °C (decomposes).

Preparation of ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane dicobaltpentacarbonyltriphenylphosphine complex.



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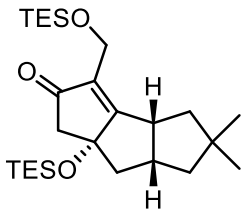
Scheme 179

Prepared according to **General Procedure G**:

(a) 1-((1*R*,2*R*)-2-ethynyl-4,4-dimethylcyclopentyl)propan-2-one dicobalt hexacarbonyl complex (0.263 g, 0.361 mmol); (b) DCE (3.6 mL); (c) DIPEA (0.14 mL, 0.794 mmol); (d) TESOTf (0.18 mL, 0.794 mmol); (e) N/A; (f) N/A; (g) N/A; and (h) red oil.

Isolated material could not be purified to achieve sufficiently clear characterisation data and so was subjected to the subsequent reaction without further purification.

Preparation of (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one.



300

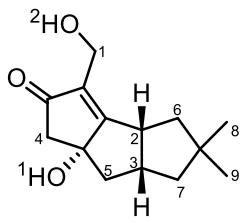
Scheme 179

Prepared according to **General Procedure E**:

(a) ((3-((1*R*,2*R*)-4,4-dimethyl-2-(2-((triethylsilyl)oxy)allyl)cyclopentyl)prop-2-yn-1-yl)oxy)triethylsilane dicobaltpentacarbonyltriphenylphosphine complex (0.183 g, 0.191 mmol); (b) DCE (1.9 mL); (c) DodSMe (0.48 mL, 1.82 mmol); (d) 70 °C; (e) 64 h; (f) (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.011 g, 0.024 mmol, **7%** over 2 steps, as a single diastereomer); and (g) colourless oil.

The characterisation data for this compound matched that described on page 325.

Preparation of Xeromphalinone C.[5]



1

Scheme 180

Prepared according to **General Procedure F**:

(a) (3b*R*,6a*R*,7a*R*)-5,5-dimethyl-7a-((triethylsilyl)oxy)-3-(((triethylsilyl)oxy)methyl)-1,3b,4,5,6,6a,7,7a-octahydro-2*H*-cyclopenta[a]pentalen-2-one (0.067 g, 0.144 mmol); (b) THF (0.77 mL); (c) 0.6M HCl (0.08 mL); (d) rt; (e) 36 h; (f) Xeromphalinone C (0.015 g, 0.064 mmol, **44%**); and (g) white powder.

^{1}H NMR (MeCN-*d*3, 400 MHz): δ_H 4.21 (1H, dd, ^{2}J = 13.6 Hz, J = 5.6 Hz, H_1), 4.17 (1H, dd, ^{2}J = 13.6 Hz, J = 5.7 Hz, H_1), 3.56 (1H, q, J = 9.3 Hz, H_2), 3.11 (1H, d, ^{4}J = 1.2 Hz, OH^1), 3.07 – 2.94 (1H, m, H_3), 2.87 (1H, t, J = 5.8 Hz, OH^2), 2.42 (1H, d, ^{2}J = 17.7 Hz, H_4), 2.36 (1H, d, ^{2}J = 17.7 Hz, H_4), 1.96 – 1.95 (1H, m, H_5), 1.85 – 1.66 (5H, m, H_5, H_6, H_7), 1.07 (3H, s, H_8), 1.00 (3H, s, H_9) ppm.

^{13}C{1H} NMR (MeCN-*d*3, 101 MHz): δ_C 209.0, 183.9, 135.9, 85.3, 55.8, 51.3, 49.2, 47.2, 46.6, 43.5, 43.3, 42.1, 28.7, 26.7 ppm.

IR (FTIR, ν_{max}/cm^{-1}): 3387, 2928, 1700, 1665, 1437.

Melting point = 170 – 172 °C.

$[\alpha]^{20}_D$ = -108 ° (MeCN, c=0.22) **Literature**: **$[\alpha]^{24}_D$** = -156 ° (MeCN, c=0.28).

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